**Nutrition and Health**
*Series Editor:* Adrianne Bendich

Gerard E. Mullin
Lawrence J. Cheskin
Laura E. Matarese *Editors*

# Integrative Weight Management

## A Guide for Clinicians

Humana Press

# Nutrition and Health

Adrianne Bendich, PhD, FACN, FASN, Series Editor

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*To our families and loved ones for their unwavering support.*

*To those who struggle with weight-related health problems, the clinicians who care for them, the researchers who are dedicated to pursue a cure, and the organizations and individuals who promote awareness and support research.*

*To our colleagues, administrators, and staff who support our careers.*

# Foreword

Obesity is a chronic disease that has become a major public health problem throughout the world because of its high prevalence, causal relationship with serious medical illnesses, adverse effect on quality of life, and considerable economic consequences. The current obesity crisis represents an adverse gene–environment interaction. The innate drive to eat and store excess energy as fat made it possible for our ancestors to survive harsh environments and periods of food deprivation. However, in our modern environment that requires minimal daily physical activity and provides an abundance of pleasurable foods, the same genes that were initially advantageous now have harmful consequences.

The cornerstone of obesity therapy is to alter lifestyle behaviors to consume less energy than expended in order to burn endogenous triglyceride stores for fuel. Diet and physical activity education, behavioral therapy, pharmacotherapy, and bariatric surgery represent the current treatment options used to generate a negative energy balance and induce weight loss. However, obesity therapy requires constant vigilance, and nonsurgical therapy is often characterized by weight regain. *Integrative Weight Management*, compiled by Gerard E. Mullin, Lawrence J. Cheskin, and Laura E. Matarese, presents an integrated weight management approach that involves expertise from different disciplines. This multilevel approach is needed to target the multilevel complexity of this disease and represents the most effective therapeutic strategies for implementing effective regulation of energy balance and body weight.

St. Louis, MO

Samuel Klein, MD

# Preface

For many years I have witnessed those in my community and clinics being victimized by socioeconomic forces ultimately resulting in obesity and its untoward manifestations. As a teen in the mid-1970s, I found myself severely overweight, but back then I was a rarity and was quite easily stigmatized by society. My personal experience with Eastern principles through martial arts coupled with diet and lifestyle modifications was highly successful. This "integrative" approach toward achieving effective weight loss motivated me to help others flourish. As a practitioner of integrative medicine for many years, I have witnessed an ever expanding literature which supports the application of principles I experienced as a young man to manage weight disorders and its adverse consequences; however, a comprehensive resource guide for healthcare practitioners was lacking.

As a contributing editor and complementary medicine expert for the journal Nutrition in Clinical Practice, I was asked to team up with weight management experts who were working on a review paper on complementary herbs and nutritional supplements for obesity. The authors were from the Johns Hopkins Weight Management Center headed by Dr. Larry Cheskin. The manuscript piqued the interest of Dr. Adrianne Bendich who is a "Nutrition and Health" Series Editor for over 15 years overseeing the 60+ well-respected and highly recommended volumes. Dr. Bendich spoke with Dr. Cheskin about the paper and its potential to serve as the foundation for a textbook for her series and he recommended that I be consulted as a first measure. Dr. Bendich then approached me at the annual meeting of the American College of Nutrition in 2009 to discuss this idea. After a period of intense investigation of textbooks and original research papers on weight management matters, the evidence supporting the need for this textbook was compelling. We began to move forward outlining the project but realized that a critical member was missing, an academic nutritionist with experience in the field with impeccable credentials who is a team player—Dr. Laura E. Matarese. This unique alliance and blend of expertise and chemistry led to the definitive textbook for healthcare practitioners who oversee or manage the well-being for the two-thirds of Americans who are overweight or obese-now labeled as a disease by the American Medical Association. The 32 chapters of *Integrative Weight Management* is organized into four sections: epidemiology and pathophysiology of adults and children, manifestations and complications of disease, major therapies, and integrative approaches. *Integrative Weight Management* is the work product of a powerful collaboration of dozens of leading experts in the fields of nutrition, weight management, and integrative medicine who have managed countless numbers of patients and summarized the research from 1,000 of articles to create an up-to-date state-of-the-art guide for healthcare practitioners, allied health professionals, and public health authorities who manage those who are overweight/obese along with the associated metabolic consequences. We hope that our encyclopedic work provides guidance and ultimately improves the quality of life for those all of those who suffer from weight and eating disorders.

My sincere thanks to my coeditors Drs. Larry Cheskin and Laura E. Matarese for their friendship, fortitude, support, and outstanding editorial management. I big thank you to Dr. Adrianne Bendich for choosing me to coedit this first textbook on integrative weight management. My deepest appreciation to Mr. Michael Wilt from Springer publishing for his tireless efforts and keeping us on track. I would like to express my gratitude to the many experts whose exceptional contributions made this book possible. There are many individuals I would like to recognize who have guided my career and sparked my interest in nutrition, integrative medicine, and weight management. To my mentors who have guided my career over the years, in particular, Drs. Anthony Kalloo, Andrew Weil, Victoria Maizes, and Ben Caballero. To the nutritionists whose collaborations have fostered career development and friendships over the years: Drs. Laura E. Matarese, Carol Irenton-Jones, Mark DeLegge, Steve McClave, Kelly Tappenden, Jeanette Hasse, Deborah Rubin, Alan Buchmann, Tim Lipman, Ron Koretz, and Amy Brown. A special thank you to those who have supported my clinical practice at Johns Hopkins: my medical office assistants Julie McKenna-Thorpe, Ms. Erin O'Keefe, and Ms. Abena Carr-Walker; nurse clinician Kimberly Kidd-Watkins; administrators Ms. Lisa Bach-Burdsall and Mr. Nathan Smith; administrative director of the Johns Hopkins Division of Gastroenterology and Hepatology Ms. Tiffany Boldin and Dr. Myron L. Weisfeldt; chairman of medicine at Johns Hopkins and Dr. Linda A. Lee; and clinical director of the Johns Hopkins Division of Gastroenterology and Hepatology.

Baltimore, MD Gerard E. Mullin, MD

# Series Editor Page

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

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter and in the choice of chapter authors. The editor(s), whose training(s) is (are) both research and practice oriented, has the opportunity to develop a primary objective for their book, defines the scope and focus, and then invites the leading authorities to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

"Integrative Weight Management" edited by Gerard E. Mullin, MD; Lawrence J. Cheskin, MD, FACP; and Laura E. Matarese, PhD, RD, LDN, CNSC, FADA, FASPEN, clearly exemplifies the goals of the Nutrition and Health Series. The major objective of this comprehensive and up-to-date text is to review the body of research and practice measures used to enhance the potential for successful and long-term weight loss. This volume could not be timelier as obesity was recently labeled as a disease by the American Medical Association in 2013 and the prevalence of obesity, metabolic syndrome, and nonalcoholic liver disease either individually or in the same patient continues to increase every year throughout the world. Fortunately, this volume includes methods that provide the potential to enhance weight loss and maintain a healthier body weight.

The three editors are well-recognized leaders in the critical field of integrative weight management. Each has a successful academic career and clinical practice which has resulted in their acknowledgement by their peers as leaders in the clinical obesity field. Dr. Gerard E. Mullin, MD, is an Associate Professor in the Department of Medicine at the Johns Hopkins Hospital where he is the Director of Integrative Nutrition Services for the Division of Gastroenterology. He also holds a faculty appointment at the Johns Hopkins Bloomberg School of Public Health in Baltimore, MD. Dr. Mullin is board certified by the American Board of Internal Medicine in Internal Medicine and Gastroenterology, the American Board of Integrative Holistic Medicine, and is additionally boarded by three separate nutrition societies (NBNSC, CBNS, ABPNS). Dr. Mullin has specialized expertise in obesity/weight loss, inflammatory bowel disease, functional bowel disorders including GERD, and

small bowel imaging-capsule endoscopy. He is a Fellow of the American College of Physicians, the American Gastroenterology Association, and the American College of Nutrition. Dr. Mullin is nationally and internationally renowned for his work in integrative gastroenterology and nutrition, and he was twice won young investigator awards from the Crohn's and Colitis Foundation of America. Dr. Mullin has over 20 years of clinical experience in the field of integrative gastroenterology and earned his master's degree in nutrition while in practice. In 2009 Dr. Mullin was honored by the American Dietetic Association and was elected as an honorary member. In 2010 he was recognized by the American College of Nutrition with the Grace A. Goldsmith Award. He is an Associate Editor of several nutrition and integrative medicine journals and serves on several certification exam committees and medical boards. Dr. Mullin has authored/edited several authoritative books on nutrition and integrative medicine. He has served as a reliable and objective resource for radio, television, and print media. Dr. Mullin is listed in Marquis and Covington's Who's Who and continues to be one of America's Top Physicians since 2004. Dr. Lawrence J. Cheskin, MD, FACP, FACG, is Director of the Johns Hopkins Weight Management Center which he founded in 1990 and Associate Professor of Health, Behavior, and Society, with a joint appointment in Human Nutrition and in Medicine at Johns Hopkins, and also holds a faculty appointment at the Johns Hopkins Bloomberg School of Public Health in Baltimore, MD. He is also Associate Director of the Johns Hopkins Global Center on Childhood Obesity and Director of its Rapid Response Project Core, which awards pilot grants nationally and internationally, utilizing a systems-science approach to studying childhood obesity. Dr. Cheskin is a Fellow of the American College of Physicians as well as a Fellow of the American College of Gastroenterology. Among his honors and awards are his recognition as a finalist for a National Merit Scholarship, Dr. Jonas E. Salk Scholarship Certificate of Recognition, DHHS John Hartford Scholar in Geriatric Medicine Young Investigator Award, and NATO-NIH Research Workshop: Obesity Treatment. Dr. Laura E. Matarese, PhD, RD, LDN, CNSC, FADA, FASPEN, is an Associate Professor of Medicine in the Division of Gastroenterology, Hepatology, and Nutrition in the Department of Internal Medicine at the Brody School of Medicine at East Carolina University in Greenville, North Carolina. She is the author of numerous books and peer-reviewed journal articles and currently serves on the editorial boards of several journals. She has held numerous positions within the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition. Dr. Matarese is the Past President of the National Board of Nutrition Support Certification. She currently serves on the Board of Trustees of the Oley Foundation and as a Commissioner for the Commission on Dietetic Registration. She is the recipient of the American Dietetic Association's Medallion Award and their Award for Excellence in the Practice of Clinical Nutrition; she has also received the American Society for Parental and Enteral Nutrition's Award for Distinguished Achievement in Nutrition Support Dietetics and Excellence in Nutrition Support Education, and she is the first recipient of the Advanced Clinical Practice Award as well as the Dietitians in Nutrition Support Distinguished Service Award. These distinguished editors have engaged the very best colleagues to develop the chapters in this objective, data-driven volume.

This timely volume includes 32 informative reviews of the current thinking about associations between obesity and diseases, systemic health and diet/nutrition, as well as the relationship between diet quality and assuring the overall health of the individual. Of great importance, there are in-depth reviews by the leading researchers on the associations between obesity and metabolic diseases and chronic and infectious diseases and a balanced perspective on the potential for diet and nutrition to reduce body weight. Practicing health professionals, researchers, and academicians can rely on the chapters in this volume for objective data-driven resources about the complex interactions between integrative medicine, current therapy choices, and physical activity/nutritional interventions. This new comprehensive volume includes unique chapters including separate chapters on topics such as the global consequences of maternal obesity, the effects of obesity on the treatment of the patient in the intensive care unit, and the potential for mind-body interventions in obesity treatment. Thus, the book contains valuable chapters that are of great importance to health professionals who have to

answer patient, client, or graduate student questions about the newest clinical research on interactions and relationships between weight management, diet, nutrition, gastrointestinal health, surgical options, and a broad overview of the overall health consequences of obesity during the different life stages that can impact both sexes.

"Integrative Weight Management" is organized into four sections. The first chapter provides an overview of the volume and indicates the major areas reviewed in each chapter and points out the related chapters. The first section contains nine chapters and provides in-depth introductions to the key aspects of obesity, metabolic syndrome, and nonalcoholic fatty liver disease (NAFLD). The first chapter in this section (Chap. 2) reviews the definitions, terminology, and measurements used in the clinic, by the media and by numerous national and international health-related organizations to describe the obese patient's status. It is clear that simply measuring a patient's height and weight and calculating their body mass index (BMI) is not sufficient to determine either the overall health status of the patient or the universality of the diagnosis. Examples are provided that sensitize us to the complexities of diagnosis and treatment such as in the elderly where BMI may not be predictive of total body fat. Differences between the sexes and ethnic groups are included to further provide evidence of the problems with generalizations made by using the terms currently available to describe the obese patient as well as methods of weight management. Chapter 3 reviews the epidemiology of obesity. Standards used by the World Health Organization (WHO), individual nations, and organizations are not the same and continue to be updated as the prevalence of obesity increases around the world. Growth standards for children have been altered by the WHO to reflect increased body weights in growing children. Examples of changes in the rate of obesity in children and adults in Europe, China, and other nations over the past decades are included in excellent tables and figures. The author documents the finding that "Obesity has become one of the most serious global public health challenges of the 21st century." The fourth chapter includes an introduction to the usefulness of animal models to study complex conditions such as the metabolic syndrome. Although the metabolic syndrome is often seen in the obese patient, it may occur in the non-obese person. The author clearly points out the major differences between the criteria, genetics, and symptoms of the metabolic syndrome in rat and mouse models compared to humans and discusses the value and limitations of the animal models.

The fifth chapter, that includes almost 100 relevant references, reviews the pathophysiology of obesity and the metabolic syndrome leading to the dysregulation of energy balance, appetite, and metabolism in humans. There is a detailed discussion of the interactions between the hormones, other regulatory molecules, the central nervous system, and the gastrointestinal tract in the control of energy intake and expenditure. The sixth chapter examines the animal models currently available to study obesity-related liver disease with emphasis on NAFLD. NAFLD is considered a hepatic manifestation of the metabolic syndrome and is increasing globally with the increased prevalence of obesity. Animal models of NAFLD and the related, more complex, and serious disease, nonalcoholic steatohepatitis (NASH), can yield important information about the pathogenesis of these liver diseases and are required in the development of new pharmacological treatments for the diseases. Genetic and dietary models as well as combinations of these two are reviewed, and the author clearly indicates that currently there is no animal model that is equivalent to the human diseases; however, the models are of use in evaluation of potential treatment modalities as well as examination of disease progression. The seventh chapter is a comprehensive review concerning the microbiome, its effects on immune function, gut homeostasis, potential to interact with the nervous system, role in obesity, and effects of diet and specific dietary factors on microbiome health. The chapter includes 179 relevant references for the reader. Chapter 8 reviews the tools available to assess the nutritional status of the obese patient. This is particularly important when bariatric surgery is being considered. The chapter includes a discussion of possible nutritionally related adverse effects following bariatric surgery in the acute as well as chronic stages and also includes seven informative tables. The last chapter in this section examines the current status of childhood obesity and includes over 150 up-to-date references. The chapter focuses on an analysis of the environmental factors influencing childhood obesity, weight-loss-specific

nutrition and exercise recommendations, and methods of improving patient health through dietary and physical activity behavioral changes at home and in the school environment.

The second section contains six chapters that look at the serious consequences of obesity including NAFLD, cancer, diabetes, and cardiovascular complications. NAFLD is described in detail in the first chapter in this section and reminds us that this disease is considered as a potential component of the metabolic syndrome. Diagnosis is made histologically and the disease can be benign or can progress to cirrhosis and even liver cancer. No pharmacological treatment is currently available. Specific recommendations for macronutrient and micronutrient intakes, based upon an extensive review of the literature (218 references included in the chapter), weight loss options, and exercise programs, are recommended. The author indicates that over 90 % of morbidly obese patients undergoing bariatric surgery have confirmed NAFLD. Chapter 11 reviews the growing literature that associates obesity with increased risk of several cancers including breast (in postmenopausal women), cervical, colon, endometrial, esophageal, gallbladder, multiple myeloma, non-Hodgkin's lymphoma, rectal, renal, thyroid, and pancreatic. The chapter includes review of the potential mechanisms linking obesity and cancer, a summary of the available studies of weight control in cancer survivors, and guidelines for cancer survivors regarding diet and physical activity for risk reduction and weight control.

Diabesity is the topic reviewed in the next chapter that describes the spectrum of the condition, the dietary and stress factors implicated in its development as well as other environmental and genetic factors, and the role of functional medicine in reducing the causes of metabolic imbalances. The chapter describes the systemic approach to reducing the risk of obesity and diabesity by adopting newer tested methodologies that support behavior change with regular feedback metrics and the development of social networks that should be incorporated into national health policies and medical practice. Chapter 13 examines the interrelationship between obesity and cardiovascular disease. The chapter reviews the data linking insulin resistance to the formation of proinflammatory and prothrombic factors and oxidative stress. Resultant effects discussed include hypertension, atherogenic dyslipidemia, and impaired glycemic control, vascular endothelial dysfunction, and the potential for the development of atherosclerosis. As is clear from the above chapters, obese individuals have greater risk of developing serious illnesses that can result in their hospitalization and admission to intensive care units. The next chapter informs us that in the USA more than one third of patients in the intensive care unit (ICU) are obese and 7 % of patients are morbidly obese. Detailed descriptions of recommended assessment tools and dietary/nutrient intakes are provided. The last chapter in this section reviews the importance of quality-of-life (QoL) assessments in the obese population. The chapter includes a discussion of the concept of QoL; the measurement of QoL using both obesity-specific and general questionnaires; the mechanisms by which obesity may influence the physical, social, mental, and sexual aspects of QoL; and the effects of weight loss interventions on QoL. There is also an informative discussion of how health professionals can use QoL measures to improve the quality of their treatment of the obese patient.

The third section of this volume contains ten chapters that describe the major therapies available for the treatment of obesity and its associated health conditions. The first chapter in this section (Chap. 16) describes the numerous behavioral programs that are used to assist obese patients in losing weight and usually result in a 7–10 % weight loss. The major difficulty with behavioral therapies is weight maintenance. The pros and cons of these and other psychologically based therapies are reviewed. Exercise programs are reviewed in the next objective chapter. The authors acknowledge that exercise alone does not contribute substantially to weight loss; however, any type of exercise is important in maintaining a lowered body mass after weight loss. Both weight loss and weight maintenance programs should include both exercise and dietary interventions for optimal results. Any level of exercise is preferable to a sedentary lifestyle. Chapter 18 provides a historical perspective and up-to-date review of the currently approved prescription drugs for the treatment of obesity in both the USA and Europe. The usefulness of these approved drugs as well as other relevant drugs in the treatment of diabetes is also reviewed. There is also a discussion of drugs that are in clinical trials and may be approved in the future.

The next chapter on weight loss diets reminds us that there are about 1,000 weight loss diets that have been developed and more appear on a regular basis. The focus of the chapter is on weight loss diets with the most supporting scientific evidence and includes a review of the randomized, controlled studies of both academically developed and popular diet regimes. Commercial weight loss programs, such as Weight Watchers, are described in Chap. 20. There is also a discussion of e-dieting plans and objective suggestions for improving these plans for the consumer who wants to lose weight and maintain the weight loss. Academic weight loss programs are examined in Chap. 21. The hospital-, university-, or clinic-based programs are medically supervised, provide personalized behavioral management, involve collaboration between different health practitioners, and are generally not for profit. The chapter includes a discussion of the differences in the health status of patients that enter academic weight loss programs as they may have additional health issues and/or failed at losing weight using other programs. The next chapter examines the potential for pharmaconutrients to affect certain adverse effects of obesity such as inflammation. Compounds reviewed include green tea, green coffee extract, soy protein, L-leucine, and other bioactive dietary components. Both animal and clinical data are discussed. The last three chapters in this section describe the currently available surgical approaches to obesity management. Chapter 23 reviews the endoscopic and transoral approaches for the treatment of obesity. Endoscopic approaches primarily include intragastric balloons, gastric stapling, and the duodenal-jejunal sleeve procedures. These techniques that are illustrated in the figures provided are less invasive than gastric surgery and can be performed on patients with comorbidities and older age who may be excluded from surgical procedures. At present certain endoscopic approaches are available worldwide but not in the USA. The next chapter describes the surgical approaches used in the treatment of obesity and type 2 diabetes mellitus. The impact of bariatric surgery on hypertension, polycystic ovary syndrome, dyslipidemias, nonalcoholic steatotic hepatitis (NASH), gastroesophageal reflux disease, degenerative arthritis of weight-bearing joints, depression, stress incontinence, cardiopulmonary failure, and certain cancers is examined. In this chapter there is a comprehensive review of the indications, surgical approaches, outcomes, and complications of bariatric surgery. The final chapter in this section provides an in-depth analysis of the acute (within the first 30 days following surgery) and long-term adverse effects that may occur with bariatric surgeries. It is commendable that there is this separate chapter in light of the fact that globally almost half a million such surgeries are performed annually. Potential early adverse effects discussed include venous thromboembolism, infection, bleeding, gastrointestinal leaks, nausea, vomiting dehydration, and dumping syndrome. Long-term adverse effects reviewed include ulcers, fistulas, nutritional deficiencies, and weight loss failure.

The fourth section and final section contains seven chapters that examine the value of integrative medicine in the treatment of obesity. Preventive strategies that are applicable to children as well as adults are the topic for the first chapter in this section (Chap. 26). Obesity prevention interventions in the clinical, school, worksite, and community settings in at-risk populations are reviewed. The largest body of evidence of benefit is in the school setting that combines intervention approaches that include nutrition and physical activity as well as a reduction in sedentary activities. Worksite studies and community setting studies are compared to recommended guidelines. Federal guidelines for obesity prevention programs are discussed and tabulated. Chapter 27 examines the evidence for safety and efficacy of dietary supplements sold in the USA that make weight loss claims.

The chapter evaluates the supplements utilizing published data. The chapter strongly urges healthcare providers to provide an environment where patients will understand the importance of their being monitored during the use of these products to ensure safety. Data indicate that many patients do not meet the criteria for recommended use and the supplement users may also be taking prescription medications; thus, the potential for drug/nutrient interactions needs to be considered. The 178 references cited are integrated into the overall review of the data concerning the use of the most popular weight loss supplement ingredients and their modes of action including certain dietary fibers such as psyllium, konjac root fiber, and guar gum and other substances including caffeine, chitin, green tea, ginseng, chromium, hydroxycitric acid, and conjugated linoleic acid.

There are numerous stresses that affect the obese patient including physical and emotional stresses. The next chapter examines the physiological consequences of stress and how these affect the obese patient. The author indicates that stress plays a role in potentiating obesity, maintaining obesity, and undermining the obese person's power to reduce weight. The mind-body modalities reviewed include visualization, breathing exercises, hypnosis and guided imagery, cognitive-behavioral therapy, therapeutic journaling, affirmations and self-talk, meditation, mindfulness techniques, therapeutic social and group support, and mindful exercises like yoga and qigong. The use of acupuncture in the treatment of obesity and the treatment of certain adverse effects of obesity such as arthritis pain are discussed in Chap. 29. The rationale behind traditional East-Asian medicine is explained and the three most popular types of acupuncture treatments are outlined (and illustrated in the included figures) including manual acupuncture, electroacupuncture, and auricular acupuncture. The next chapter reviews the commonalities between obesity and serious eating disorders. The author informs us that eating disorders such as anorexia, bulimia, and binge eating can include individuals who are overweight or obese. We learn that dieting is a known trigger for the development of all the eating disorders. Obese individuals and those with eating disorders share negative body images and body dissatisfaction, often have a history of being victims of weight-related teasing, and are negatively affected by the media's emphasis on the desire to be thin. Eating disorders have the highest mortality of any psychiatric disorder. The chapter includes a detailed description and table outlining the most common nutritional consequences of eating disorders.

The final two chapters of this comprehensive book examine the importance of religious, cultural, and social aspects of eating on the potential to develop obesity, lose weight, as well as maintain a healthy body weight. Chapter 31 outlines the evidence-based research that indicates that making cultural accommodations to weight management interventions has the potential to dramatically improve outcomes. The author indicates that practitioners have a professional responsibility to assess their cultural competence and develop action plans to strengthen knowledge and skills especially as related to Hispanic and Asian cultures as these are the fastest growing populations in the USA. The unique cultural aspects of obesity in African American women are reviewed in depth. References to online resources are provided that can assist the practitioner in assessing cultural competence and improve outcomes for the obese patient. A number of patient-centered strategies that have been shown to be effective in weight management are discussed in the final chapter. The final chapter authors explain the concept of patient-centered care and the use of a number of strategies that have been successful in treating other adverse health conditions such as cigarette smoking. There is a comprehensive discussion of the data concerning the counseling technique called the five As (Ask, Advise, Agree/Assess, Assist, and Arrange). This framework has been used for smoking cessation and may be familiar to primary care providers and is currently being applied to weight counseling. As noted by the author, although patient-centered strategies for weight management are in its infancy, there are indications of success.

The logical sequence of the sections in the volume as well as the chapters within each section enhances the understanding of the latest information on the current standards of practice in weight management and the role of nutrition considerations in patient care. This comprehensive resource has great value for academicians involved in the education of graduate students and postdoctoral fellows, medical students and practicing healthcare professionals, allied health professionals and public health nutritionists, and dietitians who plan to improve the diet quality for patients at risk for obesity and its metabolic consequences. Moreover, many of the chapters provide unique resources including lists of relevant websites, professional organizations, and other references that are of value to any health professional interested in the field of integrative weight management.

The volume contains over 100 detailed tables and figures that assist the reader in comprehending the complexities of obesity treatment and prevention, quantification of intake and availability of essential nutrients, composition of diets and the nutritional needs of children, pregnant women, other adults and seniors who may be at risk for obesity, its metabolic consequences including diabetes and cardiovascular disease, and/or eating disorders. There are in-depth discussions of the behavioral

aspects of eating and dieting and the effects of religious, ethnic, and community expectations. The overriding goal of this volume is to provide health professionals including physicians and nutrition professionals with balanced documentation and awareness of the newest research and technical approaches to assessing the nutritional as well as psychological and pathological consequences of obesity throughout the lifespan. A number of the chapters broaden one's appreciation of the complexity of the interactions between genetics, health and disease, nutrient deficiencies and excesses, and new issues involving psychological aspects of food choice in the obese. Hallmarks of the 32 chapters include key words and bulleted key points at the beginning of each chapter, complete definitions of terms with the abbreviations fully defined for the reader, and consistent use of terms between chapters. There are over 2,400 up-to-date references; all chapters include a conclusion to highlight major findings. The volume also contains several case studies, a valuable appendix that contains lists of relevant websites and academic weight loss programs, as well as a highly annotated index. This unique text provides practical, data-driven resources based upon the totality of the evidence to help the reader understand the basics of determining the best-practice opportunities for the obese patient with or without comorbidities. The volume provides fully referenced information to health professionals who treat obese patients, patients with obesity-related acute or chronic diseases, and/or those with eating disorders who often are overweight or obese.

In conclusion, "Integrative Weight Management" edited by Gerard E. Mullin, MD; Lawrence J. Cheskin, MD, FACP; and Laura E. Matarese, PhD, RD, LDN, FADA, CNSC, provides health professionals in many areas of research and practice with the most up-to-date, well-referenced, and comprehensive volume on the current state of weight management with emphasis on the role of the health practitioner. Additionally, practice-oriented recommendations for the determination of diet and nutritional status using validated assessment tools are included along with relevant discussions of the management of clients' and patients' nutritional requirements when they are obese, on weight loss diets, or in a weight maintenance program. This carefully organized volume, edited by well-respected leaders in the integrative weight management field, will serve the reader as the most authoritative resource in the field to date and is very welcome addition to the Nutrition and Health Series.

Morristown, NJ

Adrianne Bendich, PhD, FACN, FASN
Series Editor

# About Series Editor

**Dr. Adrianne Bendich**, **PhD, FASN, FACN** has served as the "Nutrition and Health" Series Editor for over 15 years and has provided leadership and guidance to more than 100 editors that have developed the 50+ well respected and highly recommended volumes in the Series.

In addition to "Fructose, High Fructose Corn Syrup, Sucrose and Health" edited by James M. Rippe, MD—major new editions in 2013–2014 include:

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2. *Handbook of Food Fortification and Health, volume II* edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
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5. *The Handbook of Clinical Nutrition and Stroke*, edited by Mandy L. Corrigan, MPH, RD Arlene A. Escuro, MS, RD, and Donald F. Kirby, MD, FACP, FACN, FACG, 2013
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14. *Nutritional Health, Strategies for Disease Prevention, Third Edition*, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr., 2012
15. *Chocolate in Health and Nutrition*, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
16. *Iron Physiology and Pathophysiology in Humans*, edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren, 2012

Earlier books included *Vitamin D, Second Edition* edited by Dr. Michael Holick; "Dietary Components and Immune Function" edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi and Dr. Victor R. Preedy; "Bioactive Compounds and Cancer" edited by Dr. John A. Milner and Dr. Donato F. Romagnolo; "Modern Dietary Fat Intakes in Disease Promotion" edited by Dr. Fabien De Meester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson; "Iron Deficiency and Overload" edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; "Nutrition Guide for Physicians" edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple and Dr. Mary Struble; "Nutrition and Metabolism" edited by Dr. Christos Mantzoros and "Fluid and Electrolytes in Pediatrics" edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include: "Handbook of Drug-Nutrient Interactions" edited by Dr. Joseph Boullata and Dr. Vincent Armenti; "Probiotics in Pediatric Medicine" edited by Dr. Sonia Michail and Dr. Philip Sherman; "Handbook of Nutrition and Pregnancy" edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch and Dr. Elliot Philipson; "Nutrition and Rheumatic Disease" edited by Dr. Laura Coleman; "Nutrition and Kidney Disease" edited by Dr. Laura Byham-Grey, Dr. Jerrilynn Burrowes and Dr. Glenn Chertow; "Nutrition and Health in Developing Countries" edited by Dr. Richard Semba and Dr. Martin Bloem; "Calcium in Human Health" edited by Dr. Robert Heaney and Dr. Connie Weaver and "Nutrition and Bone Health" edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

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

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

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

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**Dr. Gerard E. Mullin, MD,** is an associate professor in the department of medicine at the Johns Hopkins Hospital. He is an internist, gastroenterologist, and nutritionist. Dr. Mullin is nationally and internationally renowned for his work in integrative gastroenterology and nutrition. Mullin has accumulated over 20 years of clinical experience in the field of integrative gastroenterology and earned his master's degree in nutrition while in practice.

In 2009 he was named by the American Dietetic Association's as an honorary member. He is an associate editor of several nutrition and integrative medicine journals and serves on several certification exam committee's and boards. Dr. Mullin has authored/edited several books in nutrition and integrative medicine (http://thefoodmd.com/books). He has been interviewed on radio and television and has contributed to many stories in print media. Dr. Mullin's biography has been included in Marquis and Covington's Who's Who numerous times and continues to be selected as one of America's Top Physicians since 2004.

**Lawrence J. Cheskin, MD,** graduated from Dartmouth Medical School and completed a fellowship in gastroenterology at Yale-New Haven Hospital. He is associate professor of Health, Behavior, and Society at the Johns Hopkins Bloomberg School of Public Health, with a joint appointment in International Health-Human Nutrition, and in Medicine (GI) at the Johns Hopkins University School of Medicine. Dr. Cheskin is also founder and director of the Johns Hopkins Weight Management Center, a comprehensive treatment program for obesity.

In his research, Dr. Cheskin has studied the effects of medications on body weight, the gastrointestinal effects of olestra, how cigarette smoking relates to dieting and body weight, and the effectiveness of lifestyle and dietary changes in weight loss and weight maintenance.

He is also the author of four books: Losing Weight for Good, New Hope for People with Weight Problems, Better Homes and Gardens' 3 Steps to Weight Loss, and Healing Heartburn. Dr. Cheskin has appeared on television news programs and lectured both professional and lay audiences on the topics of obesity and weight control.

**Dr. Laura E. Matarese, PhD, RD, LDN, CNSC, FADA, FASPEN,** is an Associate Professor of Medicine in the Division of Gastroenterology, Hepatology, and Nutrition, Department of Internal Medicine, the Brody School of Medicine at East Carolina University in Greenville, North Carolina. She is the author of numerous books, chapters, manuscripts, abstracts, and videos and currently serves on the editorial boards of several journals. She has lectured extensively, both nationally and internationally, and has held numerous positions within the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition. Dr. Matarese is the Past President of the National Board of Nutrition Support Certification. She currently serves on the Board of Trustees of

the Oley Foundation and as a Commissioner for the Commission on Dietetic Registration. She is the recipient of numerous honors and awards including the American Dietetic Association Medallion Award, the American Dietetic Association Foundation Award for Excellence in the Practice of Clinical Nutrition, the American Society for Parental and Enteral Nutrition Award for Distinguished Achievement in Nutrition Support Dietetics, Excellence in Nutrition Support Education, and the first recipient of the Advanced Clinical Practice Award as well as the Dietitians in Nutrition Support Distinguished Service Award.

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Laura E. Matarese, PhD, RD, LDN, CNSC, FADA, FASPEN

I would like to thank my coeditors of this volume, Drs. Gerry Mullin and Laura E. Matarese, for their support and encouragement all along the multistep path of turning an idea into reality. Truly a team effort, this work would not likely have happened had any member of the team not been present and enthusiastic about what we set out to accomplish. Equally important to making this volume happen was the expert editorial assistance and occasional needed prodding from Michael Wilt at Springer. He kept us focused; to no small extent is this book a result of his skillful work.

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# Chapter 1
# Introduction to Integrative Weight Management

**Gerard E. Mullin, Lawrence J. Cheskin, and Laura E. Matarese**

**Abstract** Obesity has become a global pandemic with over one billion people world-wide are presently overweigh and/ or obese which surpasses malnutrition as the world's most serious health problem. The number of Americans who are overweight and/or obese has doubled in adults and more than tripled in children and adolescents. Two-thirds of adults and one-third of children in the United States are overweight and obese. In June 2013, the American Medical Association (AMA) declared obesity a disease. Weight management is a branch of medicine that helps individuals achieve and maintain a healthy body weight. Integrative medicine embraces all evidence-based complementary and alternative medicine (CAM), conventional and traditional treatment modalities. *Integrative Weight Management* offer practitioners a weight management textbook that integrates the evidence about CAM-based therapies along with conventional and traditional weight management methods. This first chapter provides an overview of the entire book to assist the reader.

**Keywords** Obesity • Weight management • Complementary alternative medicine • Alternative medicine • Dietary supplements • Therapeutic diets • Commercial weight-loss diets • Surgery

Over the past three decades, the prevalence of obesity has risen dramatically in the United States and worldwide. Obesity has become a global pandemic that now surpasses malnutrition as the world's most serious health problem. The number of Americans who are overweight and/or obese has doubled in adults and more than tripled in children and adolescents. Two-thirds of adults and one-third of children in the United States are overweight and obese. In June 2013, the *American Medical Association* (AMA) declared obesity a disease [1].

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Weight management is a branch of medicine that helps individuals achieve and maintain a healthy body weight. The practice of weight management has evolved from the solo practitioner providing diet and exercise plans to a multidisciplinary team approach that utilizes an array of tools to implement to deliver best practice. Weight management centers have grown in magnitude, number, and popularity and are compelled to keep up with demand and deliver reasonable results. Consumers are becoming more educated and savvy about risk-reward strategies of care and are favoring the use of complementary and alternative modalities (CAM) such as yoga, meditation, and nutraceuticals, either alone or in conjunction with conventional medicine therapies [2]. Reports show that one-quarter to one-third of Americans employ CAM therapies with utilization being much higher for those afflicted with a chronic illness [3]. Given the utilization and patient satisfaction reported with CAM therapies, providers should become more familiar with their risks and proven benefits as not all modalities are effective and/or safe to use and many are not covered by health insurance in the United States. The editors and publisher recognize the need to offer practitioners a weight management textbook that integrates the evidence about CAM-based therapies. The textbook is categorized into four sections: the introduction, morbidity and mortality, therapy, and the role of integrative medicine for weight management disorders.

## Introduction

The definition and terminology used in the field of weight management as well as the tools used to assess body composition are discussed by Dr. Dalton in Chap. 2. Weight management, broadly defined, is the practice of aiming for and achieving a healthy body weight with the goal of preventing disease and improving quality of life (QOL). Obesity (a body mass index (BMI) of 30 or higher) itself has been categorized as a disease by the AMA, the National Institutes of Health, and the Academy of Dietetics and Nutrition. The US Internal Revenue Service has permitted income tax deductions for monies utilized for weight loss programs for diseases, including obesity. Medicare parts A and B also provide limited benefits for weight loss counseling, but improved coverage is mandated under the affordable care act of 2014 [4]. Dr. Dalton (Chap. 2) and Dr. Compher and colleagues (Chap. 8) discuss assessment tools for identifying and staging those who are overweight and/or obese. The assessment of patients with obesity begins with calculation of the BMI in weight (kg)/height ($m^2$). Physical measurements provide a means of identifying those who are obese and are at risk for comorbidities. BMI is the ratio of weight to height, calculated as weight (kg)/height ($m^2$) or weight (lb)/height ($in^2$) multiplied by 703. Several levels of obesity have been described by NHLBI [5] and are used globally to identify obesity: BMI 30–34.9 (Class I obesity), BMI 35–39.9 (Class II obesity), and BMI $\geq$ 40 (Severe obesity). The techniques to measure body fat such as waist and hip circumference measurements, skinfold thickness, bioelectric impedance (BIA), and dual-energy X-ray absorptiometry (DXA) were defined and discussed in terms of techniques and applications. The gold standard to measure body composition including the amount of body fat (or called adiposity) is underwater weighing or DXA. These techniques are expensive and are impractical to use in clinical setting; thus the current consensus is to use BMI (BMI = weight [kg]/height $[m]^2$) as a good measure of adiposity. Dr. Wang in Chap. 3 presents the epidemiology of obesity from a global perspective. In 2009–2010, 66.8 % of adults in the United States were overweight or obese (BMI $\geq$ 25) and 35.9 % were obese (BMI $\geq$ 30) [6]. According to the data, in 2011, by state, obesity prevalence ranged from 20.7 % in Colorado to 34.9 % in Mississippi [7]. No state had a prevalence <20 %; 39 states had a prevalence of $\geq$25 %; obesity has become a global epidemic, but the prevalence has varied dramatically between world regions, countries, and population groups within counties. Worldwide, more than 1.4 billion adults are overweight; of these over 200 million men and nearly 300 million women are obese. The Region of the Americas (approximately 25–30 %) and Eastern Mediterranean Region (approximately 20–40 %) have a higher prevalence of obesity than the South East Asian and Western Pacific Regions such as Malaysia, Vietnam, China, and Japan [8]. The African region has the lowest prevalence rate

of obesity. Some developing countries, such as China, Brazil, and Mexico, have experienced rapid increases in overweight and obesity prevalence over the past three decades. Jason Schaub in Chap. 9 discusses the growing obesity epidemic in children and adolescents. The Centers for Disease Control and Prevention (CDC) now estimates the current net childhood obesity rate at 17 %, up from 16.4 % between 2007 and 2010 [8–10]. Obese children are at risk for the same gamut of complications as their adult counterparts and, due to their developmental stage in life, are particularly vulnerable to the establishment of poor lifestyle habits associated with physical and mental health complications [11].

Chapters 4 and 5 discuss the pathophysiology of obesity and the metabolic syndrome in animal models and humans, respectively. Dr. Palmer in Chap. 10 discusses the pathogenesis and treatment of nonalcoholic fatty liver disease (NAFLD), the most common liver disease worldwide. Dr. Takahashi and colleagues provide details of the various animal models of NAFLD in Chap. 5. NAFLD occurs in individuals who do not drink excessive alcohol, yet have hepatic histology that mimics alcoholic liver disease. NAFLD is often associated with type 2 diabetes mellitus, central obesity, dyslipidemia, and/or hypertension—conditions which comprise the metabolic syndrome. Currently, the criteria for diagnosing metabolic syndrome in adults are those established by the Adult Treatment Panel III (ATP III), by the World Health Organization (WHO), and those established by the International Diabetes Federation (IDF), with latter the most commonly used [9]. According to the IDF [10], the diagnosis will be based on the existence of three or more of the criteria listed below: obesity central dominance, triglycerides ≥150 mg/dL, men HDL <40 mg/dL, women HDL <50 mg/dL, systolic blood pressure (SBP) ≥130 mmHg, diastolic blood pressure (DBP) ≥85 mmHg, fasting glucose ≥100 mg/dL.

In Chap. 4, Stephens et al. describe the mouse models used for the study of metabolic syndrome which include leptin-deficient ($Lep^{ob/ob}$ or *ob*/*ob*) and leptin receptor-deficient ($LepR^{db/db}$ or *db*/*db*) mice, agouti lethal yellow obese ($A^{y}$) mice, fat (*fat*/*fat or* $Cpe^{fat}$) mice, and tubby (tub/tub) mice. Rodent models of the metabolic syndrome include the Zucker fatty rat (defect in the leptin receptor gene (Ob-R)), the obese spontaneously hypertensive rat (SHROB) (a nonsense mutation of *Ob-R* gene), the low-capacity runner (LCR) rat, the Wistar Ottawa Karlsburg W (WOKW) rat, and the Otsuka Long-Evans Tokushima fatty (OLETF) rat.

In Chap. 5, the pathophysiology of obesity and the metabolic syndrome is described as an intricate array of genetic, environmental, and biochemical events that creates a pathological cascade of adiposity and systemic disease. One of the key hormones involved in the pathogenesis of obesity is leptin, which is an adipose tissue-derived hormone that is released into the circulation proportional to increased energy stores in fat. Leptin stimulates neural circuits that decrease food intake and increase energy expenditure. Leptin is a product of the OB (or LEP) gene that plays an important role in food intake and body weight regulation [11]. Resistance to the anorectic actions of leptin plays an important role in the pathogenesis of obesity. The delicate circuitry of leptin's inhibition of appetite via its inhibition of neuropeptide Y (a potent appetite stimulant) production by the arcuate nucleus and via its stimulation of melanocorticotropins modulates energy expenditure and insulin sensitivity. Other hormones come into play such as α-melanocyte-stimulating hormone (an anorectic peptide closely involved in the regulation of food intake), agouti-related protein along with several other circulating appetite modulators including the only known orexigenic gut hormone ghrelin, and a suite of anorexigenic gut hormones including cholecystokinin (CCK), pancreatic polypeptide (PP), peptide YY (PYY), glucagon-like peptide (GLP)-1, and oxyntomodulin (OXM) [12, 13]. The law of thermodynamics dictates that energy intake greater than energy utilization results in energy excess—which leads to storage in the form of fat. Clearly, overconsumption of calorie-rich convenience foods and decreased physical activity play a key role in the growing prevalence of obesity worldwide.

There may be other factors at play in the development of obesity beyond imbalances in thermodynamics. For instance, disruptions in the gut microbiota is one of newest emerging factors that may portend towards fat accumulation in part via increased energy extraction from food and disruption in lipid metabolism and hormonal regulation (Chap. 7). Recent work has shown obesity to be associated with a shift in the representation of the dominant phyla of bacteria in the gut, both in humans and animal models. Studies of the effect of excess body fat on the abundances of different bacteria taxa in

the gut generally show alterations in the gastrointestinal microbiota and change during weight loss. The gastrointestinal microbiota has been shown to impact insulin resistance, inflammation, and adiposity via interactions with epithelial and endocrine cells. The gut microbiota modulates adiposity by changing the expression of host genes that are involved in fat storage and oxidation, in gastrointestinal hormone production and barrier function, and in the inflammatory response. Restoration of the gut microbiota to a healthy state may ameliorate the conditions associated with obesity and help maintain a healthy weight as has been shown in animal models. For instance, the bacterial communities of ob/ob mice ceca have an altered composition of the two dominant phyla (Bacteroidetes, Firmicutes) when compared to lean genetically normal mice or those possessing only one gene deletion for leptin [14]. A greater representation of Firmicutes and fewer Bacteroidetes characterizes the obese host microbiota. The Firmicutes-dominant microbiota in obese mice has been found to be enriched in genes involved in energy extraction from food relative to that of the lean host's microbiome. Diet may not only regulate energy consumption but also shift the gut microbiota to either an obesogenic or non-obesogenic composition [15]. Certain fermentable carbohydrates with prebiotic properties can counteract the overexpression of several host targets that are involved in the development of adiposity, metabolic disorders, and inflammation and have been found to decrease appetite, fat mass, and hepatic insulin resistance by regulating gut hormones [16]. Fecal transplant data in mice show that obesity is transferrable to highlight the role of the microbiota in disease pathogenesis [17]. Compelling data obtained in animals and humans provide evidence that changing the gut microbiota by using prebiotics or probiotics has a salutary effect on the development of liver diseases by restoring gut permeability which restricts hepatic endotoxin and inflammation [18]. Probiotic food and supplements appear to be a promising adjunct to weight management but more rigorous trials are needed [19–22].

The morbidity and mortality of obesity and the metabolism syndrome are discussed extensively in part II. NAFLD is a comorbidity of obesity and metabolic syndrome and is the most common liver disease worldwide. The spectrum of NAFLD ranges from simple steatosis, which is typically nonprogressive, to nonalcoholic steatohepatitis (NASH), which may progress to cirrhosis and its complications. The prevalence of NAFLD in the United States is approximately 35 %, while NASH occurs in 6–12 % of Americans [23]. Overall, NASH can occur in as many as 12 % of the US population [23]. Over 90 % of morbidly obese people undergoing bariatric surgery have NAFLD. Management includes lifestyle modifications comprising weight reduction, nutritional alterations, and exercise, in addition to aggressive treatment of other components of the metabolic syndrome. Cancer is a serious comorbidity of obesity. There are numerous cancers that have been associated with obesity including but not limited to breast (in postmenopausal women), cervical, colon, endometrial, esophageal, gallbladder, multiple myeloma, non-Hodgkin's lymphoma, rectal, renal, thyroid, and pancreatic cancer. A variety of biological mechanisms involving the adipocyte via the production of obesity-related hormones and alterations in insulin pathways leading to a state of chronic subclinical inflammation have been implicated in tumorigenesis. A number of substrates including sex steroid hormones, cytokines, adipokines, growth factors, and insulin have been noted to influence cellular reactions and affect cell signaling in such ways leading to dysregulation and neoplasia. Moreover, poorer outcomes in terms of worsened disease survival have been reported for obese patients. Diabetes complicating obesity is extensively discussed in Chap. 12, which presents a systems-based approach to its pathogenesis and management. The cardiovascular complications of obesity are discussed in Chap. 13 by Ashen and Blumenthal. The authors outline the adverse impact of obesity on cardiovascular risk factors such as hypertension, atherogenic dyslipidemia, and diabetes-related insulin and leptin resistance to the underlying pathogenesis. For instance, leptin has been linked to HTN through (1) upregulating renal Na, K-ATPase activity and enhancing renal sodium reabsorption [24]. As was emphasized by Dr. Hyman in Chap. 12, Drs. Ashen and Blumenthal highlight the adverse effect that inflammation and oxidative stress have on the vasculature. For example, a number of proinflammatory cytokines by adipocytes (IL-6, TNF-alpha, resistin) attract macrophages to the endothelium which, in turn, produce more proinflammatory cytokines and enhance the expression of numerous tissue factors (i.e., intracellular adhesion molecule-1 (ICAM-1))

which ultimately promotes endothelial injury and cardiovascular stress [25]. The authors also present strategies to maintain insulin sensitivity and prevent cardiovascular disease.

The approach to the metabolic support of the obese patient in the intensive care unit is covered by Wichansawakun et al. in Chap. 14. The importance of this topic is underscored by the prevalence of obesity in the US intensive care units more than one-third [26]. The assessment of energy requirements, nutritional management of the obese patient in the critical care setting, monitoring, and role of pharmaconutrients in the intensive care unit setting are reviewed. Obesity had an unfavorable impact upon the QOL. Disease-specific as well as generic measuring tools are provided along with the challenges involved in their implementation. A multitude of physical challenges such as musculoskeletal pain, difficulty walking long distances, trouble bending down, difficulty getting up from chairs, and inability to climb stairs etc. limit self-care for those with a BMI > 40 kg/m$^2$ and ultimately dependence upon others and even social isolation. A very important issue raised in this chapter deals with discrimination in the workplace. One effect of stigma and prejudice is that obese individuals as a group have more problems in job settings than normal weight individuals [27, 28]. Beyond the adverse economic impact and stigmatization is the mental health cruelty experienced by the obese. Reduction in body weight and morphology improves QOL as prospective studies have shown in those who undergo obesity surgery [29, 30].

Therapy of obesity is presented in parts III and IV of *Integrative Weight Management*. The medical, endoscopic, and surgical approaches to obesity are discussed in part III with the role for complementary and alternative strategies in part IV. The therapy of obesity is complex and requires a multidisciplinary approach. Fortunately, many of the chronic and life-threatening health conditions associated with obesity are potentially reversible in response to weight loss, whereby losing even 5–10 % of total body weight range can greatly improve obesity-related morbidities [31]. Unhealthy behaviors become ingrained in many requiring behavioral reprogramming. The approaches outlines by the Frutchey et al. include physiological, dietary goals, exercise prescriptions, self-monitoring, and additional behavioral techniques such as stimulus control, goal setting, social support, contingencies, habit disruption, self-care promotion, and relapse prevention strategies. Motivational interviewing, mindfulness, and acceptance commitment therapy were presented as treatment advances. Relating back to the principles of thermodynamics discussed by Drs. Gonzales-Jiménez and Mullin in Chap. 5, JM Maples and JA Hourmard devoted Chap. 17 to provide details of how to use physical activity through aerobic exercise and how resistance training can enhance energy expenditure and create a calorie deficit for weight loss. Programs consisting of dietary reduction of caloric intake alone without physical activity are more prone to failure; thus any weight management program should incorporate both exercise and dietary interventions for optimal results. Such program should incorporate both aerobic and resistance-oriented exercise training which consistently reduce the risk for cardiovascular and metabolic disease. In Chap. 18, Drs. De Rosa and Maffioli discuss in depth the pharmacology available for obesity. The authors evaluated the evidence for their efficacy, mechanisms of action, and adverse reactions. Their review is up to date as of September 2013 and includes the two new medications approved by the FDA of lorcaserin and the phentermine-topiramate extended release preparation along with phentermine, orlistat, exenatide, and liraglutide. The authors also review several drugs in development including the central-acting drugs tesofensine bupropion-zonisamide combination; gut hormone-based therapies such as ghrelin, PYY, and OXM; and the pancreas peptide-based treatments such as pancreatic polypeptide and amylin.

Drs. Matarese and Kandil carefully weighed the evidence about the weight loss diets that are popular among consumers in Chap. 19. The diets that were evaluated for their advantages and disadvantages recommended exercise and behavioral modification along with clinical trials if applicable. The types of diets included in their analysis included the low glycemic index/load diets (Zone, South Beach, Sugar Busters, NutriSystem), low fat and very low fat diets (Ornish, LEARN (lifestyle, exercise, attitudes, relationships, and nutrition), Mediterranean diet, Weight Watchers), and very low carbohydrate (Atkins Diet). In response to an obesity epidemic and the prevalence of dieting in women

(40 %) and men (24 %), the entire industry related to weight loss has emerged. The programs for weight control were segregated into two subchapters: a review of commercial programs, Chap. 20 by Drs. Redmond and Kahan, and academic programs, Chap. 21 by D. FLug and L. Cheskin. Chapter 20 provided a detailed analysis of the commercial weight loss programs including Weight Watchers, NutriSystem, Optifast, Medifast/Take Shape for Life, Jenny Craig, LA Weight Loss, and eDiets. The programs are analyzed according to the prescribed diet, physical activity, behavioral components, and support provided. The evidence to support their use, recommendations by the Institute of Medicine for upfront disclosures, and advice for understanding what consumers need and programs offer are provided. Chapter 21 provides evidence to support the interdisciplinary approach to weight management in the academic setting. The team of professionals often includes a combination of dietitians, exercise physiologists, medical doctors, and behavioral therapists as well as surgeon if surgery is required. There is a preponderance of dietary supplement use in the United States—with estimates show that approximately two-thirds of adults use dietary supplements [32]. *Integrative Weight Management* devotes two chapters to the use of dietary supplements as weight loss aids. In Chap. 22, Dr. Hurt and colleagues discuss the pathogenesis of obesity as an inflammatory condition and provides the rationale for the use of anti-inflammatory nutraceuticals aka pharmaconutrients in its management. The evidence from clinical trials about the use of green tea, green coffee extract, specialized proteins, and branched-chain amino acids for weight loss is analyzed and presented. Dr. Poddar and colleagues discuss a number of dietary supplements in part IV Integrative Medicine Chap. 27.

When dietary and lifestyle interventions and medical therapy for obesity are unsuccessful, invasive means are required in order to mechanically induce a state of decreased gastric accommodation of food and/or bypass the absorptive lining of the proximal small intestine. There is a growing branch of endoscopy that assists the obese patient in accomplishing their weight loss goals via transoral and endoscopic approaches. Endoscopic approaches primarily include restrictive (i.e., intragastric balloons, gastric plication-suturing/sewing) or malabsorptive (i.e., duodenal-jejunal bypass) devices and procedures. These less invasive approaches allow for outpatient or short-stay procedures and allow for treatment of individuals with comorbidities, older age, and super or mild obesity that are often excluded from surgical procedures. Efficacy observed with endoscopic methods typically lies between that observed for conservative and surgical approaches, with an improved safety profile over surgical procedures. Dr. Bermudez and colleagues review the four major bariatric operations that are now commonly performed for obesity in Chap. 24. The operations are (1) adjustable gastric banding (AGB), (2) sleeve gastrectomy (SG), (3) Roux-en-y gastric bypass (RYGB), and (4) biliopancreatic bypass with duodenal switch (DS). The indications, technique, safety, and outcomes including complications are presented. The four operations are far safer than other routine abdominal operations with a 90-day mortality rate of 0.3 %, the same as routine cholecystectomy in part due to the rigorous certification process established by the American Society for Metabolic and Bariatric Surgery (ASMBS); however, complications do occur as are discussed by Dr. Bermudez and colleagues and in more depth in Chap. 25 by Drs. Claros and Shikora. Patient selection along with the preoperative evaluation (patient education, nutritional, and psychological assessment) is discussed.

Part IV of Integrative Weight Management incorporates complementary-alternative medicine as well as preventive strategies for weight loss. The origin of *Integrative Weight Management* began with an interest of Springer's Nutrition and Health Series, Dr. Adrianne Bendich, in a review article by Dr. Poddar and colleagues on the use of dietary supplements for weight loss [33]. Dr. Bendich desired to build a weight management text that incorporated the best evidence from all disciplines of conventional and traditional medicine. To this end, part IV begins with strategies for prevention of obesity. Dr. Bleich and colleagues present the framework for obesity prevention in adults and children in Chap. 26. The Federal guidelines for obesity prevention are provided along with the evidence on obesity prevention interventions in clinics, schools, workplace, and the community. The nutrition series editor for Springer Publishing was interested in a review article Dr. Poddar and colleagues in Chap. 27 extend the discussion began in Chap. 22 by Dr. Hurt and coauthors on the use of dietary

supplements for obesity and extend it to the metabolic syndrome. The supplements discussed are categorized according to those that increase satiety such as dietary fiber, supplements that block fat and carbohydrate absorption, those that accelerate metabolism, modulate carbohydrate processing, and reduce fat synthesis. Drs. Gurgevich and Nicolai devote Chap. 28 to provide guidance for rendering mind-body therapies for weight control. The pathophysiology of obesity and its connection to stress are elaborated. A number of techniques are discussed such as breathwork, breathwalking, clinical hypnosis, guided imagery, cognitive behavioral therapy (CBT), mindfulness meditation, and therapeutic journaling. Drs. Lee and Lee provide the rationale and evidence about the use of acupuncture for weight management in Chap. 29. A number of different acupuncture techniques are reviewed including manual, auricular, and electroacupuncture. Eating disorders along with an integrative approach to their management are presented by Dr. Ross in Chap. 30. Anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), and eating disorder not otherwise specified (ED-NOS) are reviewed in terms of their definition, epidemiology, recognition, and management using an integrative approach. The medical risks and complications are provided along with the root psychological causes. The evidence for the use of dietary supplements that influence mood and behavior such as amino acid therapies, omega-3 fatty acids, B vitamins, vitamin D, and zinc (not provided in Chaps. 22 and 27) is discussed. An expanding critical mass of evidenced-based research indicates that making cultural accommodations to weight management interventions has the potential to dramatically improve outcomes. Dr. Collaizzo-Anas (Chap. 31) presents a critical piece to *Integrative Weight Management*—the religious cultural and social aspects of eating that are largely not addressed in weight management counseling. The social influences affecting food patterns, cultural and food practices, professional cultural competence along with many other related issues are discussed in depth. The cultural attitudes about health care and its implications for weight management along with the role of religion and food practices are highlighted in this chapter. Dr. Kolasa discusses the patient-centered strategies for effective weight management in Chap. 32 using the 5As framework: for ask, advise, agree/assess, assist, and arrange. The role of motivational interviewing and the socio-ecological model in the clinical care setting are discussed.

Overall, we the editors of *Integrative Weight Management* hope that you find this unique textbook from international authorities highly beneficial in the care of your patients.

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# Part I
# Introduction to Weight Management Disorders

# Chapter 2
# Definitions, Terminology, and Measurement

**Sharron Dalton**

**Abstract** Weight management is the practice of aiming for and achieving a healthy body weight, a major tool in the prevention and treatment of chronic diseases. An expanded definition determines the line between a healthy and unhealthy weight considering absence of disease, body size and shape, and physical and psychological ability to function. The definition of body weight standards is important to health professionals in planning and providing guidance for lifestyle choices about food, eating, physical activity, and using weight-related products and services as are mind-body influences, natural healing power, and cultural beliefs and preferences. Many terms, "obesity," "overweight," "fat," and "big," are used by health professionals and the media.

Is obesity a disease? Since 2002, many key agencies have changed their position on the question which involves discussions of the cost, cost-effectiveness, and safety of interventions employed in weight management; questions remain about public perception and the role of personal and collective responsibility for prevention and treatment.

Standard definitions based on body mass index (BMI) do not distinguish between body fat and other body tissues (muscle, bone, water). BMI is used by government and international health organizations to establish weight standards for given heights. Measurements of waist circumference, waist-to-hip ratio, skinfold thickness, and bioelectrical impedance are useful in clinics and community settings to determine percentage of weight that is body fat.

Weight management intervention includes physical and psychological screening, dietary assessment, intensive behavioral therapy, and monitoring weight-loss maintenance. Measurable indicators of effectiveness include improved quality of life with increased functional and physical activity, qualitative changes in food consumption, and overall health regardless of body size.

**Keywords** Healthy weight • Obesity as disease • Weight-/fat-related measurements • Weight management intervention • Weight intervention effectiveness • Weight as individual or environmental responsibility

### Key Points

- Weight management is the practice of aiming for and achieving a healthy body weight, which is a major tool in the prevention and treatment of chronic diseases and determines the line between a

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healthy and unhealthy weight considering absence of disease, body size and shape, and physical and psychological ability to function.
- The definition of body weight standards is important for providing guidance for lifestyle choices about food, eating, physical activity, and using weight-related products and services.
- Many key agencies have changed their position on the question of whether obesity is a disease, which involves discussions of the cost, cost-effectiveness, and safety of interventions employed in weight management.
- Standard definitions based on body mass index (BMI) do not distinguish between body fat and other body tissues (muscle, bone, water).
- Weight management intervention includes physical and psychological screening, dietary assessment, intensive behavioral therapy, and monitoring weight-loss maintenance.
- Measurable indicators of effectiveness include improved quality of life with increased functional and physical activity, qualitative changes in food consumption, and overall health regardless of body size.

Weight management, broadly defined, is the practice of aiming for and achieving a healthy body weight. As a branch of health care, weight management, like nutrition, is a major tool in the prevention and treatment of chronic diseases such as cardiology, pediatrics, and other medical specialties. Ideally, weight management would simply describe the process of maintaining a "healthy weight." Yet an expanded definition is needed to determine the line between a healthy and unhealthy weight. Is it the absence of disease? Is it a specific body size? A body shape? A physical ability to function in daily living activities? A psychological ability to cope with social and cultural body size standards? Measurements of body weight at a given height are categorized according to the absence or degree of biological disease risk, in each category, for heart disease, hypertension, and diabetes, all leading causes of death. Weight management aims to prevent disease, whether the goal is attaining and/or maintaining a healthy weight or reducing burdensome excess weight. The definition of body weight standards is important to health professionals in planning and providing guidance for lifestyle choices about food, eating, physical activity, and using weight-related products and services. The framework of traditional weight management embraces a whole person approach with emphasis on eating and physical activity behaviors and less attention to mind-body influences and natural healing power. The support of health-care practitioners who consider social and cultural factors and relationships (beliefs and preferences) that affect a person's weight, size, and shape is recommended but often overlooked in traditional weight management.

## Defining Obesity

Health professionals and the media often dance around the term "obesity." They may talk about the "obese person" or the "obesity epidemic," yet are very cautious about labeling an individual "obese." Apparently "overweight" is an acceptable label, "obese" is less so. Terms such as "big" or "large" are common in conversation and popular media. "Fat" is a common pejorative description often used by family, friends, and playmates. However, with the exception of a few muscular athletes, most overweight people are fat because fat is what they "have too much of." The standard definitions of "overweight" and "obesity" do not distinguish between body fat and other body tissues (muscle, bone, water).

Is obesity a disease? Are we in the midst of an "obesity epidemic" among adults and children in the United States and worldwide? The traditional definition of an epidemic refers to a rapidly spreading disease that affects many individuals at the same time. Over the past three decades—about one generation—obesity has dramatically increased among Americans, doubling in adults.

The prevalence has more than tripled in children and adolescents. Two thirds of adults and one third of children in the United States are overweight and obese [1].

Globally, obesity affects nearly as many children as does undernutrition. The World Health Organization (WHO) predicts that nearly half of the children in North and South America will be overweight in the next decade and 38 % of all children will be overweight in the European Union [2]. These figures represent both "rapid" and "widespread" characteristics—certainly an epidemic. Yet language, ethnicity, and varying perceptions of weight—some that stigmatize and discriminate against obese people—make defining obesity as a disease less simple than it may seem.

Since 2002, many key agencies have changed their position on the question: Is obesity a disease? The decision involves discussions of the cost, cost-effectiveness, and safety of interventions employed in weight management; questions remain about public perception and the role of personal and collective responsibility for prevention and treatment. Summarized here are responses to the question: Is obesity a disease?

National Institute of Health (NIH): Obesity is a disease with enormous negative effects on health and survival; health-care costs caused by obesity are estimated at $150 billion a year, about 10 % of the national medical budget [3]. This represents direct costs (treatment services, pharmaceuticals, etc.) and indirect costs (decreased productivity) [4].

Academy of Nutrition and Dietetics (AND): Obesity should be classified as a disease; it is a significant risk factor for poor health. The goal of obesity intervention is health improvement that should be measured in heart and lung performance, rates of admission to hospitals, and reduction in medication use [5].

Internal Revenue Service (IRS): Deductible medical expenses may include payments to participate in a weight-loss program for a specific disease or diseases, *including obesity*, diagnosed by a physician, but not payments for diet food items or the payment of health club dues [6]. Surgical interventions are deductible for those qualifying by BMI and comorbidity.

Centers for Medicare and Medicaid Services (CMS): The evidence is adequate that intensive behavioral therapy for *obesity* (a BMI of 30 or higher) is reasonable and necessary for the prevention or early detection of illness or disability. For those entitled to benefits under Part A or enrolled under Part B, payment is allowed for one counseling session a week for the first month and five more monthly sessions. By the end of the sixth month, a loss of at least 6.6 lb allows for six more monthly sessions. Otherwise, a wait of 6 months is required before coverage includes another weight-loss attempt. Sessions must be conducted by a qualified practitioner in a primary care setting [7].

American Medical Association (AMA): During discussion in 2008, member advocates for this designation said it will mean that this problem will be taken more seriously. Those opposed said it will negate personal and societal responsibility [8]. A 2009 news report stated that AMA objects to calling obesity a disability. "Under a new policy…the AMA formally opposes efforts by advocacy groups to define obesity as a disability. Doctors fear using that definition makes them vulnerable under disability laws to lawsuits from obese patients who don't want their doctors to discuss their weight." [9] As of 2012, physicians bill Medicare using code GO447, *intensive behavioral counseling for obesity.*

National Association to Advance Fat Acceptance (NAFFA): Fat people can be healthy and are therefore not suffering from a disease. NAFFA's goal is to help build a society in which people of every size are accepted with dignity and equality in all aspects of life [10]. A physician stated one view, "We have to take into account how patients actually feel, and the vast majority, even people who are morbidly obese, do not think they're sick" [8].

Obesity is officially recognized as a disease by most health agencies, yet viewing our country as a "diseased nation" or referring to whole populations with a term like "sick society" strips it of meaning. The continuing debate on terminology has important consequences. If we label obesity a disease, the implied remedy is medical, pharmaceutical, and/or surgical treatment. These may not be viable remedies for many individuals, especially children, or even health-care systems.

## Measurements in Weight Management

Body mass index (BMI) is used by government and international health organizations to establish weight standards for given heights. Measurements of waist circumference, waist-to-hip ratio (WHR), skinfold thickness, and bioelectrical impedance are useful in clinics and community settings to determine percentage of weight that is body fat.

The medical or clinical definition of healthy or unhealthy body weight for height uses measurement "cut points" to determine categories labeled *underweight, healthy weight, overweight, obese, very obese*. The categories are based on a variety of physical and biochemical measurements and statistical estimates of disease risk. A practical definition is less precise, incorporating elements of medical, social, and psychological measurement. Effectiveness in individual weight management is usually based on changes in weight or size but may also reflect psychological or social responses to weight, such as coping, resilience, and motivation, valuable in determining overall health status, guiding goal setting and care, as well as evaluating change and progress.

### *Physical Measurements*

Body mass index is the ratio of weight to height, calculated as weight (kg)/height ($m^2$) or weight (lb)/height ($in^2$) multiplied by 703. The terms *overweight* and *obese* describe ranges of weight that are greater than what is considered healthy for a given height, while underweight describes a weight that is lower than what is considered healthy for a given height. The adult BMI categories are age independent and the same for both men and women. Examples of the cut points for adults in the obesity range: 5′4″ in height is 174 lb or more; 5′9″ in height is 203 lb or more. These categories are a guide, and some people at a healthy weight also may have weight-responsive health conditions. Because children and adolescents are growing, their BMI is plotted on growth charts for sex and age. The percentile indicates the relative position of the child's BMI among children of the same sex and age (Table 2.1).

A high BMI predicts a higher risk of chronic disease and early death. For many people, BMI is strongly correlated with body fat levels. However, although easy to measure and inexpensive, BMI does not accurately predict body fat in elderly people compared to middle-aged adults. At the same BMI, women generally have more body fat than men, as do Asians compared to Caucasians.

The term "morbid obesity" usually indicates a level of obesity above a BMI of 30 combined with one or more risk factors (comorbidities) determined by measuring blood pressure, lipids, glucose, insulin sensitivity, and symptoms such as sleep apnea.

In the NIH 1998 publication (revised edition due 2013), *The clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults*, three subclasses are included in the obese category: Obese Class I (30.0–34.9 BMI), Class II (35.0–39.9 BMI), and Class III (≥40 BMI) [11]. The WHO guidelines concur with the NIH [12]. Because severe obesity is frequently surgically treated, NIH guidelines specify a BMI of 40 without or 35 with significant obesity-related comorbidity, in screening candidates for bariatric surgery. The gastric banding system was approved by FDA in 2011 for patients with a BMI as low as 30.

Children's BMI is calculated from measured height and weight and is plotted on a growth chart according to age and gender and then compared to recommended values for growth and BMI based on percentile ranges. Adult standards use arbitrary cutoff points to assign weight categories; childhood standards use percentiles. The BMI changes dramatically during childhood and adolescence. For example, the average BMI for age 6 or 7 is about 16; at age 17 the BMI is close to 22. Thus the BMI must always relate to age. Differences between boys and girl are most striking in the high percentiles.

**Table 2.1** Weight definitions by BMI categories for children, adolescents, and adults

| Category | Children and adolescents (BMI for age percentile range) | Adults (BMI) |
|---|---|---|
| Underweight | Less than the fifth percentile | Less than 18.5 $g/m^2$ |
| Healthy weight | Fifth percentile to less than the 85th percentile | 18.5–24.9 $kg/m^2$ |
| Overweight | 85th percentile to less than the 95th percentile | 25.0–29.9 $kg/m^2$ |
| Obese | Equal to or greater than the 95th percentile | 30.0 $kg/m^2$ or greater |

*Source*: U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, December 2010
Adult BMI can be calculated at http://www.nhlbisupport.com/bmi/
A child and adolescent BMI calculator is available at http://apps.nccd.cdc.gov/dnpabmi/
Growth charts are available at http://www.cdc.gov/growthcharts

The BMI and corresponding growth charts do not show the whole picture. First, they do not account for variation in amount of body fat. Second, one BMI value provides only a snapshot of a child's weight-for-height, not the rate of growth. A series of measures over time are essential to determine growth rate. Ignoring these two factors may result in identifying a disproportionate number of tall, apparently overweight children while overlooking short overweight ones. In judging a child's body size, parents and caregivers often use comparisons to siblings and other relatives. These comparisons influence opinions about the "right size" for their children. Many studies indicate that cultural expectations differ from one ethnic group to another along with pride and protective instincts that result in a parental definition of a "normal size."

## *Body Fat Measurements*

A waist circumference measurement of adults is the most simple and common way to measure "abdominal obesity"—the extra fat found around the middle, an important indicator of health risk, even independent of BMI. A waist measurement of greater than 94 cm (>40 in.) for men or 80 cm (>35 in.) for women is an indicator of internal (visceral) fat deposits, which can impair the heart, kidneys, liver, and pancreas, thus increasing the risk of chronic disease. Visceral fat is strongly linked to increased markers of inflammation, insulin resistance, and nonalcoholic fatty liver disease. A combination of (BMI) and waist circumference is recommended for the clinical measurement of adult overweight and obesity. A 2012 study reported that 29 % of people classified as healthy weight and 80 % of those classified as overweight according to BMI had body fat measures, according to waist circumference, within the obesity range (defined as over 25 % body fat for men and 35 % for women) [13]. This suggests that waist circumference is the more accurate method of determining risk for disease.

Although the waist is easy to measure, the procedure is difficult to standardize. The variability can be high when following the guidelines: "measure at the natural waist (in between the lowest rib and the top of the hip bone), the umbilicus (belly button), or at the narrowest point of the midsection" [11]. Waist circumference should only be used for adults to check the risk of developing a chronic disease. Waist measurements that indicate increased risks for children and teenagers have not been developed.

The WHR measures central or abdominal obesity as well as the distribution of subcutaneous or truncal fat; both contribute to body shape. Persons with central fat are commonly referred to as "apple shaped" or android (male). Those with peripheral fat are called "pear shaped" or gynoid (female). Waist to hip ratio $\geq 1.0$ for men and $\geq 0.8$ for women is associated with increased risk. The increased amount and metabolic turnover of visceral fat, compared to subcutaneous fat, increase the risk of cardiovascular disease, stroke, and insulin resistance.

### *Other Body Fat Methods of Measurement*

Skinfold thickness, a "pinch" of skin and the fat beneath it in selected areas of the body (trunk, thighs, upper arm, under shoulder blade) are measured with a special caliper. Equations are used to predict body fat percentage based on these measurements. Equations are also used with bioelectric impedance (BIA). The rate of resistance to a safe electric current through body fat, lean mass, and water estimates body fat percentage. Dual-energy X-ray absorptiometry (DEXA), typically used to measure bone mineral density from X-ray beans passing through different body tissues at different rates, also estimates fat body mass.

## Functional Measures of Overweight and Obesity

Ability to perform activities of daily living is important to an individual and caregivers. Other measures include number of hospitalizations, excessive physician visits, work-loss day, and restricted activity days. This type of definition is important in estimating health-care costs and an individual's concerns regarding daily living and social and financial well-being.

In addition to physical and functional measurements, a comprehensive definition in weight management may include an individual's perceived body image based on a socially acceptable body size and shape. Some measurements of psychological and emotional perceptions are necessary in setting goals and evaluating progress in weight management. Measurement tools may include current and desired body size comparisons, assessment of disordered eating, and motivational readiness to change behavior.

## Weight Management Intervention

As defined by Medicare and Medicaid Services [7], "intensive behavioral therapy" for obesity consists of the following:

1. Screening for obesity in adults using measurement of BMI calculated by dividing weight in kilograms by the square of height in meters (expressed in $kg/m^2$)
2. Dietary (nutritional) assessment
3. Intensive behavioral counseling and behavioral therapy to promote sustained weight loss through high intensity interventions on diet and exercise

The intensive behavioral intervention for obesity should be consistent with the 5A framework that has been highlighted by the US Preventive Services Task Force (USPSTF):

1. *Assess*: Ask about/assess behavioral health risk(s) and factors affecting choice of behavior change goals/methods.
2. *Advise*: Give clear, specific, and personalized behavior change advice, including information about personal health harms and benefits.
3. *Agree*: Collaboratively select appropriate treatment goals and methods based on the patient's interest in and willingness to change the behavior.
4. *Assist*: Using behavior change techniques (self-help and/or counseling), aid the patient in achieving agreed-upon goals by acquiring the skills, confidence, and social/environmental supports for behavior change, supplemented with adjunctive medical treatments when appropriate.

5. *Arrange*: Schedule follow-up contacts (in person or by telephone) to provide ongoing assistance/support and to adjust the treatment plan as needed, including referral to more intensive or specialized treatment.

## Weight-Loss Maintenance

Weight maintenance is often defined as "not gaining or losing" weight over a period of time. Weight-loss maintenance definitions vary by amount and duration of weight loss and the amount and duration of weight regain after weight loss. The Institute of Medicine (IOM): Losing at least 5 % of body weight or reducing BMI by at least 1 unit, and keeping weight below this level for at least 1 year [14]. The NIH: A weight regain of less than 3 kg in 2 years after weight loss and a sustained reduction in waist circumference of at least 4 cm [11].

Other programs use significant weight loss (5 or 10 %) and focus on the end point by allowing some regain by a 1- or 2-year mark. There is little data about successful weight-loss maintenance because, in part, the definition of success varies widely among programs and interventions. Measuring risk factors may be the most useful. Research studies have shown that a modest 5 % weight loss and maintenance can greatly improve blood pressure, glucose, and lipid control [15].

### *Measuring Effectiveness of Intervention*

A definition of successful weight management is more inclusive than a given weight or fat loss—or even a long-term decrease in health risk. Maintenance of a healthier weight, improved quality of life with increased functional and physical activity, qualitative changes in food consumption, and overall health regardless of body size are measureable indicators of effectiveness. Quality of life measures inform the degree of progress that indicates a lifelong approach to weight management marked by interaction with family, community, and most environmental and social structures.

A whole person approach to weight management calls for identifying and attending to the environmental forces, whether real or perceived, in an individual's life. This involves addressing beliefs about personal responsibility and control.

A 2012 IOM report and accompanying documentary, *The Weight of the Nation,* present a strong case that the obesity epidemic has been driven, not solely by individuals making poor decisions, but largely by structural changes in our environment. The report asks for accelerated change through an approach of "shared responsibility across sectors and levels," for modification of external factors such as excessive exposure to energy dense foods in the media and the marketplace and the limited availability of affordable healthy foods [16]. However, public opinion surveys report that 64 % of Americans identify personal factors (overeating, lack of exercise, watching too much television) as individual choices causing the epidemic. These respondents believe that addressing weight problems is an individual responsibility, not one of schools, workplaces, communities, media, or food and beverage systems [17].

A classic 1930 medical view of obesity stated that "obesity results not from 'gland dysfunction' or other 'endogenous' problems but rather from various human weaknesses such as over-indulgence and ignorance and lessened activity" [18]. Increased understanding about the role of genetics, counter-regulatory mechanisms and the forces of our environment challenge the notion that weak willpower is the defining root cause of obesity. We do know that traditional weight management for individuals and groups has not prevented increased prevalence of overweight and obesity. Weight management in a living environment that is itself integrated with the goal to provide healthy foods and living spaces, safe activity, and supportive health care may be successful.

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# Chapter 3
# Epidemiology of Obesity: The Global Situation

**Youfa Wang and Hyunjung Lim**

**Abstract** Obesity has become a serious public health threat in many industrialized and developing countries worldwide, and the problem continues to grow. Obesity has many health and financial consequences to individuals and society. Different measures have been used to classify overweight and obesity in adults and children, while body mass index (BMI) cut points have been widely used to define overweight and obesity. Different BMI cutoff point are being used over time and across countries at present. It is estimated in 2008 worldwide 35 % of adults aged ≥20 years were overweight and 11 % were obese; more than 1.4 billion adults were overweight. Of these, over 200 million men and nearly 300 million women were obese. It is projected, except for the World Health Organization's (WHO) African region (lack of data), the overall combined prevalence of overweight and obesity in adults and children is about 20–40 % in the WHO regions. In the United States, based on 2009–2010 national survey data, 66.8 % of adults were overweight or obese (BMI ≥ 30), and 35.9 % were obese (BMI ≥ 25). The prevalence of obesity varied across ethnic groups: ranging from 34.9 % in non-Hispanic whites to 49.6 % in non-Hispanic blacks. In the US children aged 2–19 years old, the combined prevalence is 31.8 % but varies by age and ethnicity. The US children aged 2–5 (26.7 %) and non-Hispanic whites (27.9 %) had the lowest prevalence among the age and ethnic groups, respectively. Overweight and obesity are largely preventable by having healthy lifestyles. The development of population-based intervention programs and related national policies is crucial to combat the obesity epidemic and promote public health globally.

**Keywords** Obesity • Overweight • Prevalence • Trends • World • Global • Body mass index

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## Abbreviations

| | |
|---|---|
| AMA | American Medical Association |
| BMI | Body mass index |
| BRFSS | Behavioral Risk Factor Surveillance System |
| CDC | Centers for Disease Control and Prevention |
| IASO | The International Association for the Study of Obesity |
| IOTF | The International Obesity Task Force |
| NHANES | National Health and Nutrition Examination Survey |
| WHO | World Health Organization |

### Key Points

- Obesity has become a serious public health threat in many industrialized and developing countries worldwide, and it has many health and financial consequences to individuals and society.
- Different measures have been used to classify overweight and obesity in adults and children, while body mass index (BMI) cut points have been widely used to define overweight and obesity.
- It is estimated in 2008 worldwide 35 % of adults aged ≥20 years were overweight and 11 % were obese; more than 1.4 billion adults were overweight.
- It is projected that the overall combined prevalence of overweight and obesity in adults and children is about 20–40 % in the World Health Organization (WHO) regions.
- In the United States, 66.8 % of adults were overweight or obese (BMI ≥ 30), and 35.9 % were obese (BMI ≥ 25).
- Overweight and obesity are largely preventable by having healthy lifestyles.
- The development of population-based intervention programs and related national policies is crucial to combat the obesity epidemic and promote public health globally.

## Introduction

According to a 2000 World Health Organization (WHO) report, obesity is a disease [1]. Most recently in June 2013, the *American Medical Association* (AMA) declared obesity as a disease [2]. The obesity epidemic has become a serious public health problem in many countries worldwide, and it is a major public health challenge of the twenty-first century [3–6].

Obesity has many health and social consequences. Obesity increases the risks for developing other chronic diseases such as hypertension, dyslipidemia, type 2 diabetes, heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and certain cancers [7]. Childhood obesity has long-term effects on mortality and morbidity [8, 9]. Overweight and obese children are likely to maintain their status into adulthood and are at higher risks for developing chronic diseases [7]. The prevalence of type 2 diabetes has also been increasing among young people in many countries during recent years, largely due to obesity.

Obesity also causes huge financial burden to society. Taking the United States as an example, it is estimated that annual medical costs for people who are obese were $1,429 higher than those with a normal weight. Obesity adds 9.1 % to the nation's personal health spending or about $222 billion in 2013 [10, 11]. Obesity is already responsible for 2–8 % of total health costs and 10–13 % of deaths in parts of Europe. Previously, we projected in the United States that obesity and overweight might account for 17 % of health costs by 2030 if the trend in the prevalence observed over the past three decades continues [12].

Obesity has become a global epidemic, but the prevalence has varied dramatically between world regions, countries, and population groups within counties. In 2008, worldwide, more than 1.4 billion adults aged ≥20 years were overweight or obese. Of these, over 200 million men and nearly 300 million women were obese; 35 % of adults aged 20 and over were overweight in 2008, and 11 % were obese [13]. In 2011, more than 40 million children under the age of five were overweight or obese [13]. Recent studies indicate that approximately 20 % of school-age children in European countries are overweight or obese and 5 % are obese. In North America, these figures are 30 % and 15 %, respectively. It is estimated that 155 million, or one in ten school-age (5–17 years old) children, are overweight or obese [14]. During the most recent two decades, rates of overweight and obesity have been increasing dramatically in many countries, in particular those with rapid economic development. Obesity is largely preventable, but is difficult to cure once developed; thus, prevention is the key [7].

## Definition and Classification of Overweight and Obesity for Adults and Children

### *What Are Overweight and Obesity?*

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. Over the past two to three decades, various measures and references have been used to define the conditions in adults and children. Also, various terms have been used to describe the conditions, in particular, in children. For example, previously "at risk of overweight" has been used for "overweight," and it was recommended not to use the term of "obesity" for children, but to use "overweight."

The gold standard to measure body composition including the amount of body fat (or adiposity) is underwater weighing or dual-energy X-ray absorptiometry (DXA). However, such measures are expensive and infeasible to be used in clinical settings or population-based studies. Current consensus is to use body mass index (BMI = weight [kg]/height [m]$^2$) as a good surrogate measure of adiposity in children and adults [1, 15–18]. However, BMI varies substantially by age and gender during childhood. Thus, unlike in adults, BMI cutoff points used to classify obesity in children and adolescents should be sex–age specific. For adults, BMI of 25 and 30 are widely used to define overweight and obesity, respectively. In children, BMI changes by age and varies by gender; thus, age–sex-specific BMI cutoff points are used to classify obesity [1].

Abdominal obesity or called "central obesity" is excessive abdominal fat around the stomach and abdomen. In recent years, it is classified using waist circumference (WC) cut points. Previously, other measures such as waist/hip ratio were used in adults. Different WC cut points have been recommended for use and varied by country. Age–sex-specific percentiles have been developed and used in some countries such as the United States. WC has been found to be a better predictor of future health risks than BMI.

### *Classification of Overweight and Obesity for Adults*

Various BMI cutoff points have been recommended to classify weight status, which include some recommended by the WHO for international use and some used by individual countries. BMI of 25 and 30 have been recommended by the WHO since 1995 and have been widely used since then; however, other BMI cutoff points have been recommended and are being used, e.g., for overweight, 23

(e.g., WHO Asian cut point), 24 (China), and 26 (for Maori and Pacific ethnic groups in the New Zealand), and for obesity, 25 (2000 WHO Asian cut point), 27 (Congo and Taiwan), 27.5 (Malaysia), 28 (China), and 32 (for Maori and Pacific ethnic groups in the New Zealand).

The recommended WC cut points (in centimeters, cm) also varied considerably across countries and by international health organizations. For example, in men, these included 85 (Japan), 90 (by IDF for Asian and in countries like China), and 102 (in the United States), and in women, 80 (e.g., by IDF), 88 (WHO), and 95 (Iran). Note that most countries or health organizations recommended different cut points for men and women, but a few countries use the same cut points (e.g., Congo and Iran).

## *Classification of Overweight and Obesity for Children*

The classification of overweight and obesity in children is more complex than that in adults. Different references based on weight-for-height indexes, such as BMI and weight for height, have been used to classify the conditions for children. However, application of these measures varies considerably over time and across countries [15–19]. For example, in the United States, the sex–age-specific 85th and 95th BMI percentiles have been used. Other countries, such as China, France, the United Kingdom, Singapore, and the Netherlands, have developed their own BMI references using local data. The corresponding BMI cutoff points to these references differ considerably. The use of different references will provide different estimates of the prevalence of the conditions. An international reference would be useful to facilitate international comparisons. The following are a few references that have been used widely:

1. The International Obesity Task Force (IOTF) BMI reference: The IOTF endorses a series of sex–age-specific BMI cutoff points for children aged 2–18 years for international use [18]. It is developed based on large data sets from six countries—Brazil, Britain, Hong Kong, the Netherlands, Singapore, and the United States. The cutoff points are linked to adult BMI cutoff points, which are established indicators of risks for adverse health outcomes. It is also simple to use and consistent for children and adolescents. However, there are also some concerns about the IOTF reference [20].
2. The 2006 WHO Growth Standards for preschool children: In 2006, the WHO released new growth standard for children from birth to the age of 60 months (5 years old) [21]. In order to establish growth standards for different races/ethnicities, the Multicentre Growth Reference Study (MGRS) recruited affluent, breast-fed, and healthy infants/children whose mothers did not smoke during or after delivery from six cities in Brazil, Ghana, India, Norway, Oman, and the United States. These standards include anthropometric indicators such as height-for-age (length-for-age), weight-for-age, weight-for-height (weight-for-length), and BMI-for-age. BMI *Z*-score $\geq 2$ was recommended to classify "obesity" and BMI *Z*-score $\geq 1$ to classify "overweight."
3. The 2007 WHO growth reference for school-age children and adolescents: In 2007, the WHO released another set of growth references for children and adolescents aged 5–19 years [22]. To our knowledge, these have not been widely used. The references were derived based on the same US data set for the 1978 WHO/NCHS growth references but used different growth curve smoothing techniques. The references include three indicators: BMI-for-age, weight-for-age, and height-for-age. Overweight and obesity cut points were based on BMI-for-age *Z*-scores. A *Z*-score of 1 was found to be equivalent to a BMI-for-age of 25.4 for boys and 25.0 for girls in 19-year-olds. As these values are equal or close to the WHO BMI cutoff points of 25 used in adults, it was recommended to use a *Z*-score of 1 to classify "overweight" and a *Z*-score $\geq 2$ to classify "obesity." BMI-for-age *Z*-scores $<-2$ and $<-3$ were set as the cut points for thinness and severe thinness, respectively.
4. BMI references used in the United States: Two sets of different BMI 85th and 95th percentiles have been used in the United States to classify children's weight status. In 2000, the US National Center

for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC) updated growth charts using data from five national health examination surveys from 1963 to 1994. The resultant 2000 CDC Growth Charts provided new BMI percentiles [15] and recommended the use of sex- and age-specific 85th and 95th BMI percentiles to classify childhood overweight and obesity, respectively, in children over age 2 years old. Before the release of the 2000 CDC Growth Charts, the sex–age-specific 85th and 95th percentiles developed by Dr. Aviva Must and her colleagues based on the First National Health and Nutrition Examination Survey (NHANES, 1971–1974) data were used in the United States and many other countries to classify childhood overweight and obesity [23, 24]. The BMI cutoff points of the two sets of percentiles differ.

## The Global Epidemic of Overweight and Obesity

### *In Adults*

#### Worldwide

It is estimated that in 2008, worldwide overall 35 % of adults aged 20 and over were overweight and 11 % were obese [13]. Despite for the overall high combined prevalence of overweight and obesity in many countries around the world, large variations exist across world regions, between countries and across population groups within countries. In general, the combined prevalence is much higher in developed countries than developing countries. For example, in 2010, the combined prevalence was 68.8 % in US adults [25], while it was <15 % in many developing countries [26]. In the recent two decades, the prevalence has increased at a much faster rate in some developing countries, such as China, Brazil, and Mexico, compared to other industrialized countries such as the United States and European countries. In developing countries, urban groups and higher social economic status (SES) groups have higher rates of overweight and obesity than their counterparts.

A comprehensive examination identified sex- and age-specific prevalence of overweight and obesity in representative population samples from 106 countries, which cover approximately 88 % of the world population. They estimated that in 2005, overall, 23.2 % of the world adult population was overweight (24.0 % in men and 22.4 % in women) and 9.8 % was obese (7.7 % in men and 11.9 % in women). The estimated total numbers of overweight and obese adults were 937 million and 396 million, respectively. They projected that if the secular trends would continue, by 2030 2.16 billion would be overweight or obese and 1.12 billion obese [27].

Figure 3.1 shows the country-specific obesity (BMI ≥ 30) prevalence in men that the International Association for the Study of Obesity (IASO) released in 2012. The maps highlight to top five countries in each WHO region based on the data available to IASO. There is a big variation of the prevalence by WHO region. The prevalence was the highest region in South East Asia and Pacific region (e.g., Nauru 56 %, Tonga 47 %) and followed by Eastern Mediterranean (e.g., Kuwait 36 %, Qatar 35 %) and Americas region (e.g., the United States 35 %, Panama 28 %). The WHO African region had the lowest prevalence rate. The patterns in women are similar to those in men.

Some developing countries especially those with swiftly expanding economies, such as China, Brazil, and Mexico, have experienced rapid increases in overweight and obesity prevalence over the past three decades. Figure 3.2 shows the example in China. The combined prevalence (BMI ≥ 24) among Chinese adults increased from 20 % in 1992 to 30 % in 2002. The prevalence in major cities like Beijing is much higher than the national average, where over half of the adults are overweight or obese [28].

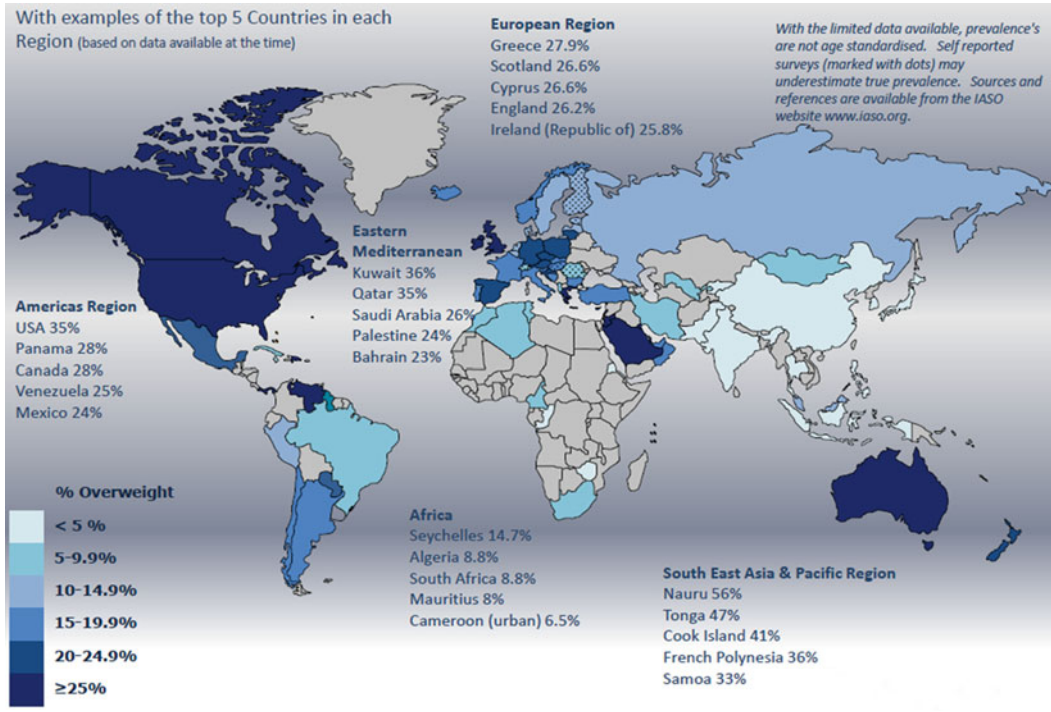


**Fig. 3.1** Global prevalence of obesity (BMI ≥ 30) in adult males. With examples of the top five countries in each region. (*Data Source*: International Obesity Task Force (IOTF) [26])

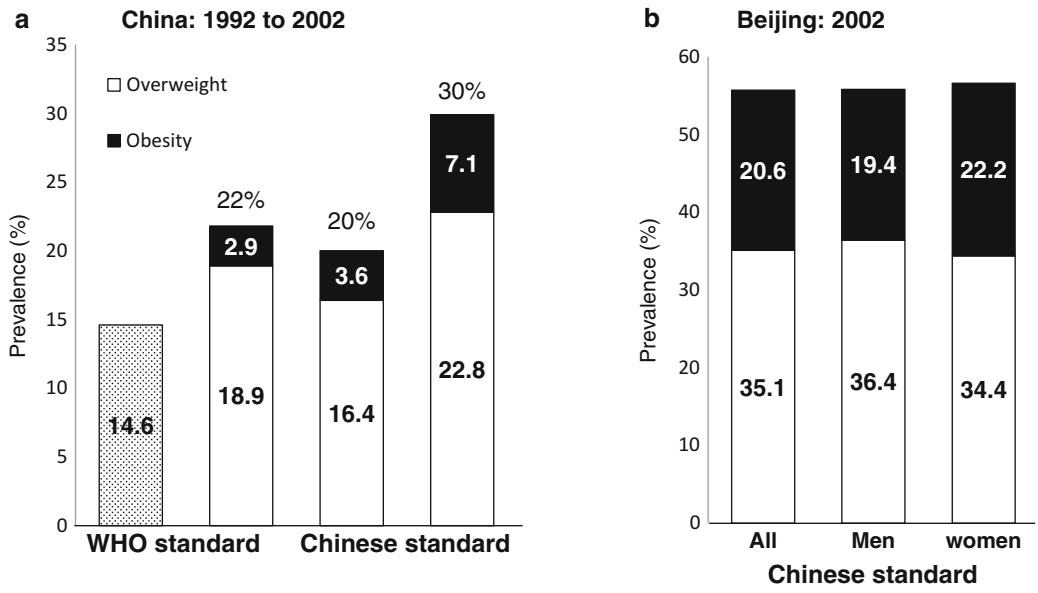


**Fig. 3.2** Changes in prevalence (%) of overweight and obesity among adults (≥18 years) based on WHO or Chinese BMI standard in China and Beijing: 1992–2002. Based on data from the 1992 and 2002 China National Nutrition Surveys. In the WHO standard, obesity was defined as BMI ≥ 30 and overweight 25 ≤ BMI < 30; in Chinese standard, obesity BMI ≥ 28 and overweight 24 ≤ BMI < 28. *The combined prevalence; prevalence of obesity was not reported. (*Data Source*: Wang et al. [28]. Used with permission)

**Table 3.1** Prevalence of obesity (BMI ≥ 30) and of overweight and obesity combined (BMI ≥ 25) in adults aged ≥20 years in the United States in 2009–2010[a]

| | All[b] | Non-Hispanic white | Non-Hispanic black | Hispanic[c] | Mexican American |
|---|---|---|---|---|---|
| Obesity, BMI ≥ 30 | | | | | |
| *Men and women* | | | | | |
| ≥20 years | 35.9 | 34.9 | 49.6 | 37.9 | 39.6 |
| Age adjusted ≥20 years[d] | 35.7 | 34.3 | 49.5 | 39.1 | 40.4 |
| *Men* | | | | | |
| ≥20 years | 35.5 | 36.4 | 38.8 | 35.3 | 35.6 |
| Age adjusted ≥20 years[d] | 35.5 | 36.2 | 38.8 | 37.0 | 36.6 |
| *Women* | | | | | |
| ≥20 years | 36.3 | 33.4 | 58.6 | 40.7 | 44.3 |
| Age adjusted ≥20 years[d] | 35.8 | 32.2 | 58.5 | 41.4 | 44.9 |
| Overweight or obese, BMI ≥ 25 | | | | | |
| *Men and women* | | | | | |
| ≥20 years | 69.2 | 68.0 | 76.6 | 77.3 | 80.0 |
| Age adjusted ≥20 years[d] | 68.8 | 66.7 | 76.7 | 78.8 | 81.2 |
| *Men* | | | | | |
| ≥20 years | 74.1 | 75.0 | 69.9 | 79.9 | 81.3 |
| Age adjusted ≥20 years[d] | 73.9 | 74.0 | 69.9 | 81.7 | 82.4 |
| *Women* | | | | | |
| ≥20 years | 64.5 | 61.3 | 82.1 | 74.4 | 78.5 |
| Age adjusted ≥20 years[d] | 63.7 | 59.5 | 82.1 | 75.7 | 79.8 |

[a]These are based on the 2009–2010 National Health and Nutrition Examination Survey (NHANES) data
[b]Includes all race/ethnicity groups
[c]Includes Mexican American participants
[d]Age adjusted by the direct method to the year 2000 Census population using the age groups 20–39 years, 40–59 years, and 60 years and older
*Data source*: Flegal [29]

## The United States

The NHANES, conducted in the United States since the 1970s, provides good data regarding trends of obesity in the United States. In 2009–2010, about two-thirds (68.8 %) of the US adults were overweight or obese and one-third (35.7 %) were obese (Table 3.1). Obesity affects some ethnic groups more than others: Non-Hispanic blacks have the highest age-adjusted rates of obesity (49.5 %) compared with Mexican Americans (40.4 %), all Hispanics (39.1 %), and non-Hispanic whites (34.3 %) [29].

Obesity prevalence varied across states and regions in the United States. Although the NHANES sample sizes are not adequate to examine between-region differences in obesity rates, self-reported weight and height collected in the national Behavioral Risk Factor Surveillance System (BRFSS) survey conducted by the CDC allow for this. According to the data, in 2011, by state, obesity prevalence ranged from 20.7 % in Colorado to 34.9 % in Mississippi (see Table 3.2). No state had a prevalence of <20 %; 39 states had a prevalence of ≥25 %; 12 states had a prevalence of ≥30 %, which were Alabama, Arkansas, Indiana, Kentucky, Louisiana, Michigan, Mississippi, Missouri, Oklahoma, South Carolina, Texas, and West Virginia. The South had the highest prevalence (29.5 %), followed by the Midwest (29.0 %), the Northeast (25.3 %), and the West (24.3 %) [30].

**Table 3.2** State-specific prevalence of obesity (BMI ≥ 30) in the United States based on self-reported weight and height, BRFSS 2011[a]

| State | Prevalence | Confidence interval | State | Prevalence | Confidence interval |
|---|---|---|---|---|---|
| Alabama | 32 | (30.5, 33.5) | Montana | 24.6 | (23.3, 26.0) |
| Alaska | 27.4 | (25.3, 29.7) | Nebraska | 28.4 | (27.6, 29.2) |
| Arizona | 24.7 | (22.7, 26.9) | Nevada | 24.5 | (22.5, 26.6) |
| Arkansas | 30.9 | (28.8, 33.1) | New Hampshire | 26.2 | (24.7, 27.7) |
| California | 23.8 | (22.9, 24.7) | New Jersey | 23.7 | (22.7, 24.8) |
| Colorado | 20.7 | (19.7, 21.8) | New Mexico | 26.3 | (25.1, 27.6) |
| Connecticut | 24.5 | (23.0, 26.0) | New York | 24.5 | (23.2, 25.9) |
| Delaware | 28.8 | (26.9, 30.7) | North Carolina | 29.1 | (27.7, 30.6) |
| District of Columbia | 23.7 | (21.9, 25.7) | North Dakota | 27.8 | (26.3, 29.4) |
| Florida | 26.6 | (25.4, 27.9) | Ohio | 29.6 | (28.3, 31.0) |
| Georgia | 28 | (26.6, 29.4) | Oklahoma | 31.1 | (29.7, 32.5) |
| Hawaii | 21.8 | (20.4, 23.4) | Oregon | 26.7 | (25.2, 28.3) |
| Idaho | 27 | (25.3, 28.9) | Pennsylvania | 28.6 | (27.3, 29.8) |
| Illinois | 27.1 | (25.4, 28.9) | Rhode Island | 25.4 | (23.9, 27.0) |
| Indiana | 30.8 | (29.5, 32.3) | South Carolina | 30.8 | (29.6, 32.1) |
| Iowa | 29 | (27.6, 30.3) | South Dakota | 28.1 | (26.3, 30.1) |
| Kansas | 29.6 | (28.7, 30.4) | Tennessee | 29.2 | (26.8, 31.7) |
| Kentucky | 30.4 | (28.9, 31.9) | Texas | 30.4 | (29.1, 31.8) |
| Louisiana | 33.4 | (32.0, 34.9) | Utah | 24.4 | (23.4, 25.5) |
| Maine | 27.8 | (26.8, 28.9) | Vermont | 25.4 | (24.1, 26.8) |
| Maryland | 28.3 | (26.9, 29.7) | Virginia | 29.2 | (27.5, 30.9) |
| Massachusetts | 22.7 | (21.8, 23.7) | Washington | 26.5 | (25.3, 27.7) |
| Michigan | 31.3 | (30.0, 32.6) | West Virginia | 32.4 | (30.9, 34.0) |
| Minnesota | 25.7 | (24.6, 26.8) | Wisconsin | 27.7 | (25.8, 29.7) |
| Mississippi | 34.9 | (33.5, 36.3) | Wyoming | 25 | (23.5, 26.6) |
| Missouri | 30.3 | (28.6, 32.0) | | | |

[a]The actual prevalence rates are likely to be higher considering underreport in people's weight and overreport in height by some individuals. BRFSS, Behavioral Risk Factor Surveillance System
*Data source*: CDC http://www.cdc.gov/obesity/data/adult.html [30]

## *In Children*

### Worldwide

The situation in children is similar to that in adults. Large variations exist across regions, between countries and across population groups within countries. In general, the combined prevalence is much higher in developed countries than in developing countries. For example, in 2010, the combined prevalence was 31.8 % in the US children and adolescents [25], while it was <5 % in many developing countries [31]. Nevertheless, overweight and obesity rates have been increasing dramatically in many countries and population groups. In recent years, the prevalence has increased at a much faster rate in some developing countries, such as China, compared to other industrialized countries, such as the United States. Often, the increase in children is more dramatic than that in adults.

Table 3.3 shows overweight and obesity prevalence in WHO-defined regions. Our previous work projected combined prevalence for 2006 and reported a range from 17 % in South East Asia to 40 % in the Americas [5]. In general, combined prevalence is much higher in developed countries than in developing countries. Approximately 26 % of school-age children in European countries were overweight or obese in 2006, and 5 % were obese. In Americas, these figures were 28 % and 10 %, respectively.

**Table 3.3** Prevalence (%) of overweight and obesity in school-age children based on available data and IOTF criteria and estimated for 2006 and 2010

| WHO region (dates of most recent surveys) | Most recent surveys | | Projected 2006[a] | | Projected 2010[a] | |
|---|---|---|---|---|---|---|
| | Overweight and obesity | Obesity | Overweight and obesity | Obesity | Overweight and obesity | Obesity |
| Africa (1987–2003) | 1.6 | 0.2 | [b] | [b] | [b] | [b] |
| Americas (1988–2002) | 27.7 | 9.6 | 40.0 | 13.2 | 46.4 | 15.2 |
| Eastern Mediterranean (1992–2001) | 23.5 | 5.9 | 35.3 | 9.4 | 41.7 | 11.5 |
| Europe (1992–2003) | 25.5 | 5.4 | 31.8 | 7.9 | 38.2 | 10.0 |
| South East Asia (1997–2002) | 10.6 | 1.5 | 16.6 | 3.3 | 22.9 | 5.3 |
| West Pacific (1993–2000) | 12.0 | 2.3 | 20.8 | 5.0 | 27.2 | 7.0 |

[a]Based on population-weighted annualized increases in prevalence
[b]There were insufficient data on school-age children in the WHO African region to make estimates of projected prevalence rates
*Data source*: Wang and Lobstein [5]. Used by permission

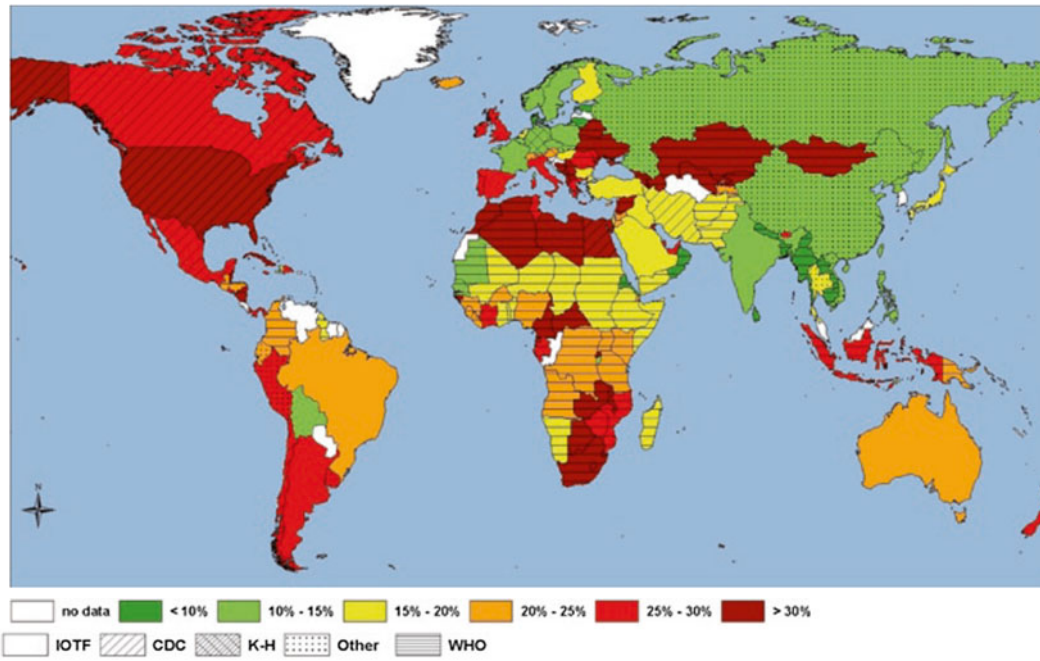


**Fig. 3.3** Worldwide combined prevalence of overweight and obesity in children and adolescents. The prevalence estimates were calculated as the arithmetic mean of the age-specific estimates (*Data Source*: Pigeot et al. [32], Used by permission)

Figure 3.3 shows the variation in childhood overweight and obesity prevalence worldwide. The combined prevalence is high in Western and industrialized countries and some nations in the Middle East [32]. The region of the Americas (approximately 25–30 %) and Eastern Mediterranean region (approximately 20–40 %) had higher prevalence than the South East Asian and Western Pacific regions such as Malaysia, Vietnam, China, and Japan. In contrast, the African region had the lowest prevalence rate (about 10 %) [32]. Self-reported information in a 2001–2002 international school survey from 35 countries in Europe and North America ($N = 162{,}305$) showed large variation in the adolescent overweight prevalence rates in these countries, which ranged from 3.5 % in Lithuanian girls to 31.7 % in boys from Malta [33].

**Table 3.4** Combined overweight and obesity prevalence (%) in children based on data collected since around the year 2000 for selected countries by WHO region[a]

| | Year of survey | Age (years) | Boys | Girls | BMI reference |
|---|---|---|---|---|---|
| *WHO Africa region* | | | | | |
| Algeria | 2006 | 6–10 | 7.4 | 7.4 | IOTF |
| Seychelles | 2004/5 | 9–15 | 16.5 | 21.0 | IOTF |
| South Africa | 2001–2004 | 6–13 | 13.6 | 17.7 | IOTF |
| *WHO Americas region* | | | | | |
| Brazil | 2002 | 7–10 | 23.1 | 21.1 | IOTF |
| Canada | 2004 | 2–19 | 28.9 | 26.6 | 2000 CDC |
| Chile | 2002 | 6 | 28.6 | 27.1 | IOTF |
| Mexico | 2006 | 2–19 | 28.4 | 27.3 | 2000 CDC |
| United States[b] | 2009–2010 | 2–19 | 33.0 | 30.4 | 2000 CDC |
| *WHO Eastern Mediterranean region* | | | | | |
| Egypt | 2005 | 10–17 | 23.4 | 29.6 | 85th percentile |
| Iran | 2003/2004 | 6–18 | 14.4 | 14.0 | IOTF |
| Kuwait | 1999–2000 | 10–14 | 44.7 | 44.9 | NCHS |
| Saudi Arabia | 2002 | 1–18 | 16.7 | 19.4 | IOTF |
| United Arab Emirates (UAE) | 1998–1999 | 5–17 | 32.4 | 32.4 | IOTF |
| *WHO European region* | | | | | |
| England | 2007 | 5–17 | 22.7 | 26.6 | IOTF |
| France | 2006/2007 | 3–17 | 13.1 | 14.9 | IOTF |
| Germany | 2008 | 4–16 | 22.6 | 17.7 | IOTF |
| Netherlands | 2003 | 5–16 | 14.7 | 17.9 | IOTF |
| Switzerland | 2007 | 6–13 | 16.7 | 13.1 | IOTF |
| *WHO South East Asia region* | | | | | |
| India[c] | 2007–2008 | 2–17 | 20.6 | 18.3 | IOTF |
| India[d] | 2005–2006 | <5 | 1.7 | 1.4 | 2006 WHO Growth Standard |
| Malaysia | 2002 | 7–10 | 9.7 (obesity) | 7.1 (obesity) | WHO |
| Sri Lanka | 2003 | 10–15 | 1.7 | 2.7 | IOTF |
| Vietnam | 2004 | 11–16 | 11.7 (boys and girls) | | IOTF |
| *WHO Western Pacific region* | | | | | |
| Australia | 2007 | 2–16 | 22.0 | 24.0 | IOTF |
| China[e] | 2005 | 7–18 | 14.9 | 8.9 | Chinese ref. |
| Japan | 1996–2000 | 6–14 | 16.2 | 14.3 | IOTF |
| New Zealand | 2007 | 5–14 | 28.2 | 28.8 | IOTF |
| South Korea[f] | 2005 | 10–19 | 21.7 | 17.1 | Korean ref. |

[a]Some prevalence data was limited by data availability; many rates presented here may not be nationally representative. Only data collected since 2000 were used, and we report statistics for those countries with large population sizes within each region as examples. We also added some additional data (Main data Source: IASO [36])
[b]We updated the rates based on more recent results [25]
[c]The rates were higher than other reported prevalence (Wang et al. 2009), and this might be due to sample differences
[d]We added the rates based on results from a large nationwide sample (International Institute for Population Sciences and Macro International, 2007)
[e]We added the rates based on results from a large nationwide sample [34]
[f]We updated the rates based on more recent results of a nationwide survey (Song et al. 2010)

Table 3.4 shows the combined prevalence for countries in the six WHO regions (IASO, 2011). The following countries had the highest combined rate in each region: the United States (32 %), Kuwait (44 %), England (25 %), New Zealand (28 %), India (19 %), and Seychelles (18 %).

Obesity and overweight rates have increased very rapidly over the past 2–3 decades in some countries. In a comprehensive meta-analysis of studies published between January 1980 and October 2005, from

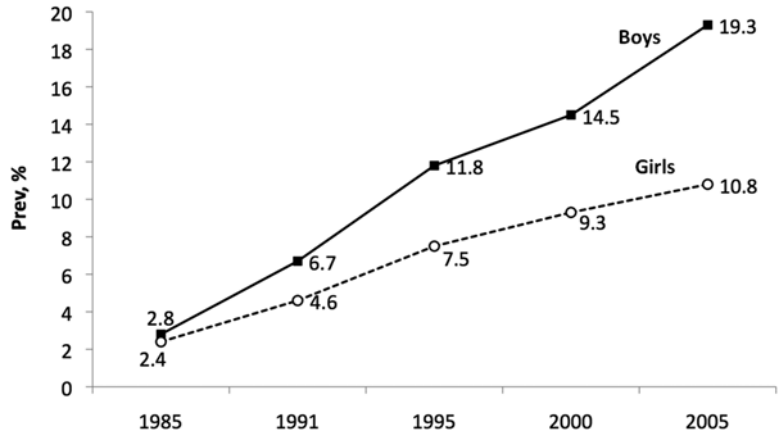


**Fig. 3.4** Trends in the prevalence (%) of overweight and obesity in Chinese school-age children, by gender: 1985–2005. Based on Chinese BMI cutoff points and data reported by Ji and Cheng [34]

over 60 countries, we studied the global trends in childhood obesity [5]. Russia and Poland during the 1990s were exceptions to this trend. From the 1970s to the end of the 1990s, the combined prevalence doubled or tripled in several large countries in North America (i.e., Canada and the United States), the Western Pacific region (i.e., Australia), and Europe (i.e., Finland, France, Germany, Italy, and Spain).

Take China as an example. Nationally representative data collected in China has allowed examining national time trends in childhood obesity. Data from large nationwide school-based surveys showed that although less than 3 % of school-age children were overweight or obese in 1985, by 2005 the combined prevalence reached about 15 %, and in urban areas it reached 32.5 % in boys and 17.6 % in girls aged 7 years or older [34], which was similar to that in some industrialized countries. Figure 3.4 shows overall trends in prevalence based on data collected through a representative school-based surveys that collects health data among school-age children in China [34]. The combined prevalence has increased approximately tenfold during 1985–2005. In boys, the prevalence increased more dramatically than in girls.

One recent study examined time trends in the combined prevalence in children aged 0–5 years from 1990 to 2010 and projected worldwide rates for 2015 and 2020 [31]: 43 million children (35 million in developing countries) were estimated to be overweight or obese in 2010, and 92 million were at risk of overweight. This represents an estimated increase in global combined prevalence from 4.2 in 1990 to 6.7 % in 2010. If such trends continue, these numbers may reach 9.1 % (or approximately 60 million children) in 2020. For developing countries alone, the combined prevalence was estimated at 6.1 % in 2010 and is expected to rise, perhaps as high as 8.6 % by 2020. 2010 rates were lower in Asian than in Africa (4.9 % vs. 8.5 %), but a much larger number of children are affected (17.7 million vs. 13.3 million) in Asia compared to Africa. Given the dramatic increases in combined prevalence since 1990, the study concluded that effective interventions starting as early as infancy are necessary to reverse anticipated trends.

### The United States

In 2009–2010, 31.8 % of children 2–19 years old were overweight or obese (BMI ≥ 85th percentile), and 16.9 % were obese (BMI ≥ 95th percentile) [25]. The combined prevalence was lower in preschool-age children compared to older children (approximately 27 vs. 33 %). Large disparities existed across ethnic groups, with lower prevalence in non-Hispanic whites (28 %) compared to non-Hispanic blacks (39 %) and Hispanics (39 %) [25].

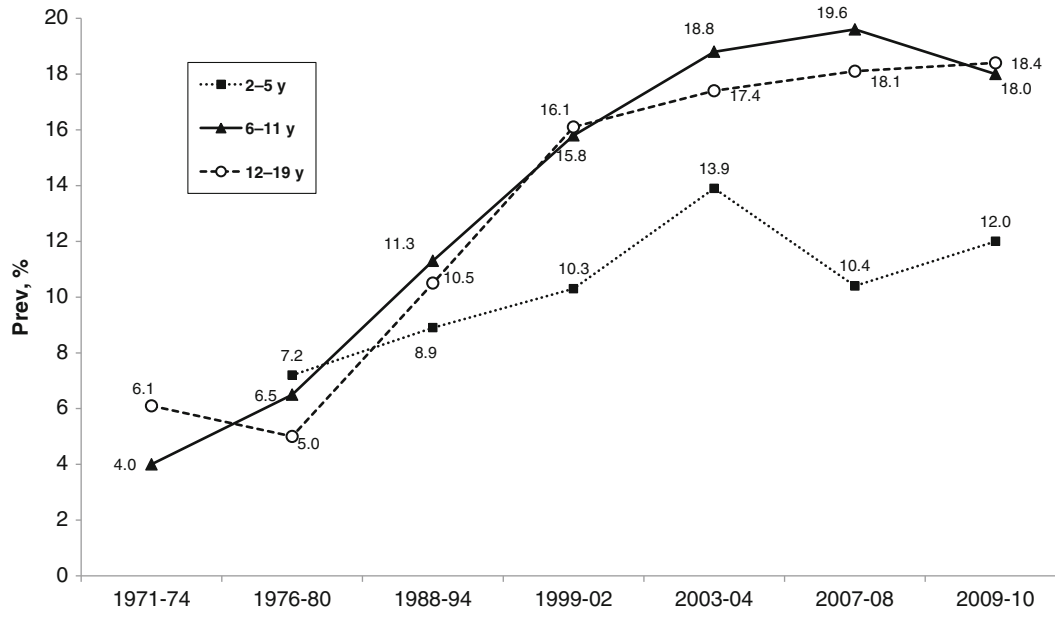


**Fig. 3.5** Trends in the prevalence (%) of obesity (BMI ≥ 95th percentile) in the US children and adolescents, by age: 1971–1974 to 2009–2010. Based on national data collected in NHANES. (*Data Source*: Wang and Beydoun [4]; Ogden et al. [25])

Since the late 1970s, the combined prevalence in children has increased for all ages, but the increase in obesity leveled off in some age groups in recent years. Figure 3.5 shows time trends in the prevalence of obesity by age between 1971–1974 and 2009–2010. Between NHANES II (1976–1980) and 2003–2004 NHANES, the average annual rate of increase in obesity prevalence was approximately 0.5 percentage point in children aged 2–19. However, this rate was slower in younger children. For example, during this period, the prevalence of overweight only increased from 7.2 to 13.9 % in children aged 2–5 years but almost tripled in children aged 6–11 (from 6.5 to 18.8 %). In adolescents (12–19 years), the prevalence more than tripled, increased from 5.0 to 17.4 %. In contrast, data from NHANES 2007–2008 shows a decrease in the prevalence of obesity among children aged 2–5 years, from 13.9 in NHANES 2003–2004 to 10.4 %. During the same time period, the prevalence in both children aged 6–11 years and adolescents only increased slightly [35] (Table 3.5).

## Discussion

Obesity has become one of the most serious global public health challenges of the twenty-first century. The combined prevalence has tripled in many countries worldwide since the 1980s, and the number of people affected is expected to continue to rise. Obesity has many short- and long-term health and financial consequences for individuals, families, and society. Obesity is already responsible for 2–8 % of health costs and 10–13 % of deaths in parts of Europe, and it is projected to be even worse in the United States and may reach 17 % of deaths in 2030 [12].

The fundamental cause of obesity and overweight is a prolonged positive energy imbalance between energy intake (food and beverage consumption) and expenditure (physical activity). The growing global obesity epidemic is a result of the following factors: an increased intake of

**Table 3.5** Prevalence of overweight and obesity in the US children and adolescents (2–19 years old) in 2009–2010[a]

| By BMI percentile | 2–19 years | 2–5 years | 6–19 years | 6–11 years | 12–19 years |
|---|---|---|---|---|---|
| Boys and girls | | | | | |
| *All racial/ethnic groups* | | | | | |
| ≥85th | 31.8 | 26.7 | 33.2 | 32.6 | 33.6 |
| ≥95th | 16.9 | 12.1 | 18.2 | 18.0 | 18.4 |
| ≥97th | 12.3 | 9.7 | 13.0 | 13.0 | 13.0 |
| *Hispanic*[b] | | | | | |
| ≥85th | 39.1 | 33.1 | 41.2 | 39.7 | 42.4 |
| ≥95th | 21.2 | 16.2 | 22.9 | 22.5 | 23.2 |
| ≥97th | 15.6 | 13.0 | 16.4 | 16.4 | 16.4 |
| *Mexican American* | | | | | |
| ≥85th | 39.4 | 33.3 | 41.4 | 39.0 | 43.4 |
| ≥95th | 21.2 | 15.5 | 23.1 | 22.1 | 23.9 |
| ≥97th | 15.5 | 11.9 | 16.7 | 17.5 | 16.1 |
| *Non-Hispanic white* | | | | | |
| ≥85th | 27.9 | 23.8 | 29.0 | 27.6 | 30.0 |
| ≥95th | 14.0 | 9.2 | 15.2 | 13.9 | 16.1 |
| ≥97th | 9.8 | 7.5 | 10.4 | 9.1 | 11.3 |
| *Non-Hispanic black* | | | | | |
| ≥85th | 39.1 | 28.9 | 41.8 | 42.7 | 41.2 |
| ≥95th | 24.3 | 18.9 | 25.7 | 28.6 | 23.7 |
| ≥97th | 18.6 | 14.4 | 19.7 | 22.2 | 18.0 |
| Boys | | | | | |
| *All racial/ethnic groups* | | | | | |
| ≥85th | 33.0 | 29.7 | 34.0 | 33.1 | 34.6 |
| ≥95th | 18.6 | 14.4 | 19.8 | 20.1 | 19.6 |
| ≥97th | 13.9 | 11.5 | 14.7 | 14.6 | 14.7 |
| Girls | | | | | |
| *All racial/ethnic groups* | | | | | |
| ≥85th | 30.4 | 23.4 | 32.4 | 32.1 | 32.6 |
| ≥95th | 15.0 | 9.6 | 16.5 | 15.7 | 17.1 |
| ≥97th | 10.5 | 7.9 | 11.2 | 11.3 | 11.2 |

[a]These are based on the 2009–2010 National Health and Nutrition Examination Survey (NHANES) data
Percentiles are from the Centers for Disease Control and Prevention's 2000 Growth Charts
[b]Includes Mexican American participants
*Data source*: Ogden et al. [25]

energy-dense foods that are high in fat and sugar and reduced physical activity and increased physical inactivity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and leisure activities, associated with increasing urbanization. Changes in dietary and physical activity patterns are often the result of environmental and societal changes associated with development and lack of supportive policies in sectors such as health, agriculture, transport, urban planning, environment, food processing, distribution, marketing, and education [13].

Although still not very well studied, there are many drivers for the current obesity epidemic, including globalization and the resultant and profound changes in society, living environments, and individual behavioral patterns. Economic growth, modernization, urbanization, and the globalization of food markets are additional forces. The impact of global exchanges of trade, information, and culture, made possible by new information technologies, on health-related behaviors such as dietary intakes is likely considerable as well, though not yet well understood.

Several key international health organizations, such as IASO and WHO, have been calling on nations to invest and develop effective programs to fight the epidemic [36, 37]. In the United States, over the past decade, a number of federal and nongovernment agencies have been making great efforts to fight the epidemic, which include the efforts made by First Lady Michelle Obama [38]. The recent 2013 June AMA declaration that obesity is a disease will help focus more attention on obesity. This could increase research funding allocated toward obesity, expand obesity-related public health initiatives, and help improve reimbursement and services for obesity treatment, including counseling and education.

As the largest industrialized country that has been struggling with the obesity epidemic, the United States has invested heavily in fighting the epidemic, especially in the past decade. One example is the comprehensive initiative, "Let's Move!," launched by the First Lady on *February 9*, *2010*. It is dedicated to solving the problem of obesity within a generation [38]. Combining comprehensive strategies with common sense, the program is about putting children on the path to a healthy future at a young age. At the launch of the initiative, President Barack Obama signed a Presidential Memorandum creating the first-ever Task Force on Childhood Obesity to conduct a review of every single program and policy relating to child nutrition and physical activity and develop a national action plan to maximize federal resources and set concrete benchmarks toward the First Lady's national goal. The Task Force recommendations focus on the five pillars of the Let's Move! initiative: (1) creating a healthy start for children; (2) empowering parents and caregivers; (3) providing healthy food in schools; (4) improving access to healthy, affordable foods; and (5) increasing physical activity.

More future research is needed to better understand how to classify overweight and obesity, their health, and other consequences and how to most effectively combat the problem [39, 40]. Nevertheless, everyone has an important role to play in reducing obesity, including individuals, parents and caregivers of children, government agencies, schools, health care professionals, community-based organizations, and private sector companies including the food industry.

In conclusion, obesity has many health and financial consequences to individuals, their families, and to society. Obesity is a serious public threat in many industrialized and developing countries worldwide, and the problem continues to grow. The epidemic calls for timely and effective population-based approaches to prevent the condition. Meanwhile, treatment is also important as a large number of people have developed the condition. Obesity is largely preventable by having healthful lifestyles that include healthy eating and adequate physical activity. However, once developed, obesity is difficult to treat. Therefore, prevention of obesity, especially in young people, should be a priority. The development of new national and regional policies, along with effective population-based intervention programs to promote a healthful living environment and healthful lifestyles, is crucial to combat this epidemic and promote public health around the world.

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# Chapter 4
# Pathophysiology of Obesity and the Metabolic Syndrome: Rodent Models

**David Sanchez-Infantes, Carrie M. Elks, and Jacqueline M. Stephens**

**Abstract** Metabolic syndrome (MetS) affects one in three Americans and is a strong predictor of cardiovascular disease risk; therefore, understanding the pathophysiological mechanisms that contribute to MetS is of great priority. While rodent models can only reproduce certain aspects of human diseases, they remain useful tools in our examination of the mechanisms contributing to the development of MetS. This chapter will provide a brief review of some of the more common mouse and rat MetS models. In addition to brief descriptions of the models, the advantages and disadvantages of using each model will be addressed.

**Keywords** Metabolic syndrome • Adipocyte • Adipose tissue • Obesity

**Key Points**

- Metabolic syndrome (MetS) is diagnosed if "cut points" for a minimum of three of the following criteria are met: waist circumference, hypertriglyceridemia, reduced HDL cholesterol, hypertension, and hyperglycemia.
- The prevalence of MetS has reached epidemic proportions, with one in three (34 %) of individuals in the United States affected.
- MetS greatly increases the risk of coronary artery disease and stroke and can lead to type 2 diabetes mellitus (T2DM).
- Rodents are the most commonly used animal models in the study of MetS and, as in humans, this disease can occur in rodents in the absence of obesity.
- Despite clear differences between rodents and humans, rat and mouse models can be used to study MetS.
- Although there is no ideal rodent model with which human MetS can be reproduced, these models can provide us with valuable information regarding the pathophysiology of and interactions among components of MetS.
- MetS in rodents will be defined by the presence of obesity along with dyslipidemia, hyperglycemia, and/or hypertension.

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# Animal Models

## *Introduction*

Metabolic syndrome (MetS) is diagnosed if "cut points" for a minimum of three of the following criteria are met: waist circumference, hypertriglyceridemia, reduced HDL cholesterol, hypertension, and hyperglycemia. Although the criteria for MetS can vary, the prevalence of MetS has reached epidemic proportions, with one in three (34 %) of individuals in the United States affected [1]. MetS greatly increases the risk of coronary artery disease and stroke and can lead to type 2 diabetes mellitus (T2DM) [2]. Rodents are the most commonly used animal models in the study of metabolic MetS. Like MetS in humans, this disease can occur in rodents in the absence of obesity. Although the majority of the rodent models used to study MetS are obese, some are not. A number of animal models traditionally used to study obesity and T2DM are currently being used to study MetS. In several of these rodent models, other phenotypic features that are not always associated with MetS are often present. These features should be considered when choosing an appropriate animal model for MetS studies.

The focus of this chapter will be to present both rat and mouse models that can be used to study MetS. As rodents and humans are clearly different in many regards, it is not appropriate to use the same criteria for MetS diagnosis when studying rodents. For example, waist circumference cannot be used as a MetS criterion for rodents. In addition, the lipid profiles of normal rodents differ drastically from those of humans; therefore, alterations in these profiles in the obese condition may differ drastically between species. Lastly, the majorities of rodent models of MetS result from single-gene mutations, while the majority of human MetS cases are polygenic and have strong environmental and epigenetic components. Thus, there is no ideal rodent model with which human MetS can be reproduced, although these models can provide us with valuable information regarding the pathophysiology of and interactions among components of MetS. For the purpose of this book chapter, MetS in rodents will be defined by the presence of obesity along with dyslipidemia, hyperglycemia, and/or hypertension. Brief descriptions of all models discussed in this chapter appear in Table 4.1.

# Mouse Models of Metabolic Syndrome

## *Leptin-Deficient (Lep$^{ob/ob}$ or* ob/ob*) and Leptin Receptor-Deficient (LepR$^{db/db}$ or* db/db*) Mice*

In 1949, the obese (*ob*) mutation spontaneously arose in a strain at Jackson Laboratories. Yet, the obese gene that codes for leptin would not be identified until 1994 [3, 4]. A nonsense mutation in codon 105, resulting from a C to T point mutation, is responsible for the leptin deficiency in *ob/ob* mice [4]. As demonstrated by Coleman and colleagues, the genetic background of mice with the *ob/ob* mutation can greatly influence phenotype [5, 6]. They transferred the *ob* genome from its normal C57BL/6 background to the C57BLKS background and found a severe T2DM phenotype [5, 6]. Regardless of genetic background, *ob/ob* mice exhibit hyperphagia, extreme obesity, hyperglycemia, hyperinsulinemia, and hypothermia. In *ob/ob* mice on a C57BL/6 background, despite early-onset obesity, hyperglycemia is transient and resolves by approximately 16 weeks of age due to a compensatory increase in insulin levels [7]. However, *ob/ob* mice on a C57BLKS background have overt early-onset hyperglycemia that leads to severe T2DM and death by approximately 6 months of age [8].

**Table 4.1** Rodent models for the study of metabolic syndrome

| Model | Characteristics | Advantages (+)/disadvantages (–) |
|---|---|---|
| *Rat models of metabolic syndrome* | | |
| Zucker fatty rats | • Monogenic obesity (*fa* mutation) | – Hormonal and reproductive abnormalities |
| | • Extreme obesity, glucose intolerance, insulin resistance, dyslipidemia, mild hypertension | – No leptin signaling |
| SHROB | • Monogenic obesity ($fa^k$ mutation) | – Severe kidney disease; short life span |
| | • Obesity, insulin resistance, glucose intolerance, hyperlipidemia, fatty liver, hypertension, vascular disease | – Reproductive abnormalities<br>– No leptin signaling |
| Low-capacity runner rats | • Artificial selection | + Polygenic model |
| | • Obesity, hypertension, insulin resistance, hypertriglyceridemia | + Intact leptin signaling |
| WOKW | • Polygenic obesity | + Polygenic model |
| | • Obesity, dyslipidemia, impaired glucose tolerance, hyperinsulinemia | + Intact leptin signaling |
| OLETF | • CCK-1 receptor deficient | – Progression to T2DM |
| | • Obesity, hyperglycemia, dyslipidemia in males | – Females not affected<br>+ Intact leptin signaling |
| *Mouse models of metabolic syndrome* | | |
| Leptin and leptin receptor deficient | • Monogenic obesity (*ob* or *db* mutation) | – Differences in phenotype severity with varying genetic backgrounds |
| | – *ob*: extreme obesity, glucose intolerance, insulin resistance, mild hypertension | – No leptin signaling |
| | – *db*: hyperglycemia, polydipsia, polyuria, glucosuria | – Hormonal and reproductive abnormalities |
| Agouti lethal yellow | • Monogenic obesity ($A^y$ or $A^{vy}$ mutations) | – Differences in phenotype severity with varying genetic backgrounds |
| | • Delayed-onset obesity, insulin resistance, hyperglycemia, hypertension | + Intact leptin signaling |
| Fat | • Monogenic obesity (*fat* mutation); CPE defect | – Differences in phenotype severity with varying genetic backgrounds |
| | • Obesity, hyperglycemia, insulin resistance | – Defective prohormone processing<br>– Decreased fertility<br>– Females only mildly affected<br>+ Intact leptin signaling |
| Tubby | • Monogenic obesity (*tub* mutation) | – Severe sensory deficits (blindness, deafness) and other nervous system defects |
| | • Obesity, dyslipidemia, insulin resistance | – Decreased fertility<br>+ Intact leptin signaling |

The obese phenotype of *ob/ob* mice is first recognizable at about 4 weeks of age [6, 9]. These mice exhibit rapid weight gain and can easily reach weights that are up to four times those of wild-type littermates [6, 9]. Obesity in the *ob/ob* mouse is characterized by increases in both adipocyte size and number [6]. In addition to obesity, *ob/ob* mice exhibit hyperglycemia, glucose intolerance, hyperinsulinemia, impaired wound healing, and an increase in hormone production from both pituitary and adrenal glands [6]. Homozygous animals are infertile.

The spontaneous recessive diabetes (*db*) mutation was first observed in a C57BLKS mouse colony at Jackson Laboratories. Homozygous *db/db* mice, regardless of genetic background, become obese

around 4 weeks of age [6]. Plasma insulin begins to rise at approximately 2 weeks of age, and blood glucose begins to increase between 4 and 8 weeks of age [9]. These mice become polydipsic and polyuric. As with the *ob* mutation, phenotypic severity depends heavily on genetic background, and mice on the C57BLKS background exhibit a more severe phenotype than mice on the C57BL/6 background [9]. While they exhibit most of the characteristics of MetS, the lack of functional leptin signaling along with the strain-specific phenotypic variations and reproductive abnormalities in *ob/ob* and *db/db* mice should be taken into account when considering the use of these mice as models for MetS.

## *Agouti Lethal Yellow Obese (*$\mathbf{A^y}$*) Mice*

Several mutations of the agouti locus on mouse chromosome 2 have been reported [10]. As the agouti gene is a coat-color determinant, each mutation has its own effect on the coat color of affected mice [6, 10, 11]. In addition to yellow coat color, two of the most dominant agouti alleles (lethal yellow, $A^y$; viable yellow, $A^{vy}$) lead to obesity, hyperinsulinemia, insulin resistance, hyperleptinemia, and eventually hyperglycemia [6, 10, 12]. In mice carrying the $A^y$ or $A^{vy}$ alleles, these symptoms are collectively referred to as the yellow obese syndrome.

In the mouse hypothalamus, the agouti protein competes against α-melanocyte-stimulating hormone for binding to the melanocortin 4 receptor, whose activity is critical to energy homeostasis and acts as an antagonist of this signaling pathway; thus, agouti mutants exhibit hyperphagia and obesity [13–15]. The obesity that develops in $A^y$ and $A^{vy}$ heterozygotes is of mature onset, peaking between 8 and 17 months of age [10]. Interestingly, the amount of yellow pigmentation in mutants correlates with degree of obesity. Hyperinsulinemia is detected as early as 6 weeks of age, with insulin levels becoming up to 20-fold higher than those of lean controls. Adipocyte hypertrophy, decreased basal lipolysis, and higher caloric efficiency are all considered contributors to the obese phenotype in these mice [10]. As observed with the mouse models mentioned above, genetic background also affects the severity of yellow obese syndrome. The two most commonly used backgrounds are C57BL/6 and KK, with a more severe phenotype in KK mice that includes hypertension and diabetes [9]. The agouti yellow obese mouse develops most of the components of MetS, but the monogenic adult-onset obesity and variable strain-dependent phenotype seen in these mice are two caveats to using them as a model for MetS.

## *Fat (*fat/fat or $\mathbf{Cpe^{fat}}$*) Mice*

In 1973, obese mice were observed in an inbred mouse colony. Genetic analyses demonstrated the presence of a spontaneous autosomal recessive mutation, which was named *fat*. The *fat* gene was compared in allelism tests with the *db* and *ob* genes, which established that *fat* was a new mutation and not an additional mutation of *db* or *ob* [16]. The *fat* spontaneous mutation was later found to occur within the gene for carboxypeptidase E (CPE), an enzyme involved in the cleavage of prohormones including intermediates derived from proinsulin [17]. The overall quantity and activity of CPE in the tissues of *fat/fat* mice are greatly reduced and cause accumulation of incompletely processed proinsulin (less active than fully processed insulin) in pancreatic beta cells, leading to increased physiologic demand [17].

*Fat* mutants develop obesity more slowly than *db* and *ob* mutants, usually between 6 and 8 weeks of age, and can be easily distinguished from lean littermates by 12 weeks of age [16]. By 6 months of age, *fat* homozygotes weigh between 60 and 70 g. Interestingly, there are no sex differences in the rate of weight gain in *fat* mutants when compared to lean littermates. The excess weight in *fat/fat* mice is adipose tissue, with all adipose depots equally affected [16]. Homozygous *fat* mutants are infertile

after their obesity develops, but successful matings can occur if mice are paired before the development of the obesity. If on the same genetic background on which the *fat* mutation was first discovered, male homozygotes experience a transient hyperglycemia between 6 and 8 weeks of age. Homozygous *fat* mice on a C57BLKS genetic background are severely hyperglycemic, with blood glucose levels reaching a plateau between 400 and 600 mg/dL [16]. The hyperglycemia in *fat/fat* mice is primarily restricted to males and is more severe than the phenotype on the original background. Female homozygotes from both backgrounds remain normoglycemic, but both sexes are consistently hyperinsulinemic [16]. Although they are a monogenic obesity model with several MetS characteristics, *fat/fat* mice are not as widely used as the three mouse models of MetS mentioned above.

### *Tubby (*tub/tub*) Mice*

The tubby (*tub*) mutation spontaneously occurred in a C57BL/6J mouse and was later found to be a G-to-T transversion in a splice site at the junction of the 3′ end of exon 11 which resulted in a larger transcript that contained the unspliced intron [18, 19]. Mice homozygous for the *tub* mutation exhibit a mature-onset obesity that progresses more slowly than that of *ob/ob*, *db/db*, and *fat/fat* mice [16]. Tubby mice also exhibit severe sensory deficits in the forms of blindness and deafness [18, 20]. Body weights of homozygotes begin to diverge at approximately 12 weeks of age, and ultimately, the homozygotes can have body weights double those of their wild-type littermates [19]. This excess weight is composed of adipose tissue which, as in the *fat* mutation, is distributed throughout all adipose depots [16]. Food intake in tubby mice increases with age but only surpasses that of normal littermates after the tubby mice have significantly higher body weights [20]. In addition to being obese, tubby mice are also insulin resistant, hyperinsulinemic, and mildly hyperglycemic; however, these mice never become overtly diabetic [16, 19, 20]. The hyperinsulinemia in these animals is mild at the time of weaning and increases with age. Male tubby mice develop hypertriglyceridemia and hypercholesterolemia but to a much lesser degree than *ob/ob* and *db/db* mice [21]. Tubby homozygotes are infertile after obesity develops but can produce litters if mated before severe obesity develops, up to approximately 12 weeks of age [16].

The expression of *tub* is primarily in the central and peripheral nervous systems, with very low levels found in the liver [20, 22]. Before the onset of obesity, when homozygotes are only 7–8 weeks old, some hypothalamic mediators of the central control of food intake are found to be upregulated (orexin, neuropeptide Y, agouti-related peptide) [20]. Metabolic defects also become apparent even before the onset of obesity. Tubby mice have defective carbohydrate utilization and rely primarily on lipid metabolism and β-oxidation for energy [20]. Although the tubby mouse develops obesity, insulin resistance, and dyslipidemia, the severity of the sensory defects found in this genetic model make them a less desirable model of MetS, which is a likely reason they are not as commonly used as the *ob/ob*, *db/db*, or yellow obese agouti mice.

## Rat Models of Metabolic Syndrome

### *The Zucker Fatty Rat*

The “fatty” (*fa*) mutation was discovered by Lois Zucker over 50 years ago in a crossing experiment [23]. The mutation consists of a defect in the leptin receptor gene (*Ob-R*) that produces a substitution of a single amino acid, glutamine, to a proline [24–26]. This mutation is present on all three isoforms

of the leptin receptor and greatly decreases the binding affinity of leptin. Rats homozygous for this autosomal recessive mutation are known as Zucker fatty (*fa/fa*) rats and develop extreme obesity of juvenile onset [23]. Obesity may be observed as early as 3 weeks of age but is readily apparent by 5 weeks of age. Adipocyte proliferation in the fatty rat is hypertrophic and hyperplastic and is often evident before the animals reach sexual maturity [27]. This phenomenon is thought to be due in part to elevated adipose lipoprotein lipase (LPL) activity, which causes excessive triglyceride shunting into adipose tissue [28]. Elevations in LPL activity in fatty rats can be seen in the first week of life, with increased body fat detectable as early as 14 days of age [29]. The largest changes in adipocyte number and size are seen in the subcutaneous fat of these animals, with rates of lipogenesis being higher in young rats [30]. By 14 weeks of age, around 40 % of the body weight of the Zucker fatty rat comprises lipid, and as adults, homozygotes for the *fa* mutation can have body weights that are almost double those of lean littermates [31].

Zucker fatty rats, in addition to their extreme obesity, also possess a variety of endocrine abnormalities, including decreased energy expenditure, hypothyroidism, decreased glucagon levels, dyslipidemia, glucose intolerance, and hyperinsulinemia; however, these rats generally remain euglycemic [30–33]. The fatty rat also exhibits severe peripheral and hepatic insulin resistance. Conversely, heterozygous lean Zucker rats (*fa/?*) have similar lipid profiles, glucose tolerance, and insulin sensitivity to Sprague–Dawley and Wistar rats [34–36]. Fatty rats are hyperphagic and as early as 3 weeks of age can exhibit food intakes that are greater than those of their lean littermates [25]. The hyperphagia is most apparent during the rapid growth period in the first 16 weeks of life [37]. Interestingly, hyperphagia in the *fa/fa* rat is not necessary for the development of extreme obesity. Food restriction can reduce body weight in fatty rats, but the percentage of body composition that comprises fat remains considerably higher than that of lean Zucker rats (50 % vs. 20 %) [38].

Male Zucker fatty rats have normal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels and respond normally to LH-releasing hormone [39]. Testosterone levels are significantly lower in fatty rats than in lean littermates [39]. However, there is no apparent correlation between fertility and testosterone levels, as male *fa/fa* rats are only occasionally infertile while female homozygotes are consistently sterile. Female homozygotes exhibit decreased LH surge during proestrus and slower decline of FSH and prolactin levels accompanied by elevated progesterone concentrations during estrus [40]. These hormonal differences paired with decreased expression of estradiol and progestin receptors in the hypothalamus of the female *fa/fa* rat are considered partial contributors to the infertility seen in these animals [40].

The mean arterial pressure of the Zucker fatty rat is significantly higher than that of lean Zucker rats [41, 42]. This hypertension is not dependent on increases in body weight or hyperphagia, as pair-fed calorie-restricted fatty rats exhibit decreased weight gain but remain hypertensive [42]. Elevated blood pressure in these fatty rats also does not seem to be a result of sodium retention in the kidney since pair-fed fatty rats retained less sodium than lean counterparts, while still exhibiting hypertension [42]. The most probable explanation for the increased blood pressure in these rats is an enhanced pressor response to the effector peptide of the renin-angiotensin system, angiotensin II, although a modest role for the adrenergic system has also been proposed [41]. Interestingly, the hypertension in the Zucker fatty rat is only associated with the *fa/fa* genotype; lean littermates are normotensive throughout life.

A substrain of Zucker fatty rats exhibiting severe hyperglycemia/diabetes was developed in 1980 at Indiana University School of Medicine; these rats are referred to as Zucker diabetic fatty rats, and they develop marked hyperglycemia by 6–8 weeks of age, glucosuria, and polyuria. More recently, a congenic rat strain was created where a segment of the mutant leptin receptor *fa* gene from heterozygous Zucker rats was introduced into the genetic background of stroke-prone spontaneously hypertensive rats (SHRSP); these rats are referred to as stroke-prone SHR fatty rats (SHRSP *fa/fa*) [43]. These animals develop obesity and hypertension simultaneously, and they show elevated glucose, insulin, total cholesterol, and triglyceride levels when compared with SHRSP rats [43]. For additional

background on these two strains of rats, the reader is referred to Clark et al. (1983) (Zucker diabetic fatty) and Hiraoka-Yamamoto et al. [43] (SHRSP *fa/fa*).

## *The Obese Spontaneously Hypertensive Rat (SHROB)*

The SHROB rat, also known as the Koletsky rat, arose spontaneously in 1969 when a spontaneously hypertensive (SHR) female rat was mated with a normotensive male Sprague–Dawley rat [44]. The obesity mutation in the SHROB rat is a recessive trait, designated $fa^k$, which is a nonsense mutation of the *Ob-R* gene, resulting in a premature stop codon in the extracellular domain of the leptin receptor at position 763, causing a complete lack of the membrane-bound segments of all *Ob-R* isoforms in these rats [45]. This is in contrast to the missense mutation (*fa*) in Zucker fatty rats, which is at position 269 of the *Ob-R* and causes reduced receptor functionality resulting in lack of leptin action [46]. SHROB rats, although not overweight at 4–6 weeks of age, can be identified from their SHR littermates by a rounding of the lower trunk. After 6 weeks of age, the SHROB begin to gain weight rapidly and exhibit food intakes that are about 40 % higher than those of their lean SHR littermates [47]. Fat deposition in the SHROB occurs at a dramatic rate, with some fat depots being 10–20-fold larger than those of lean SHR. Peak body weights in male SHROB routinely reach 750–1,000 g [44].

Lean siblings of the SHROB, which can carry one $fa^k$ allele or no $fa^k$ allele, are SHR which exhibit hypertension but are only mildly insulin resistant relative to normotensive rats [48]. The SHROB rat exhibits insulin resistance, glucose intolerance, hyperlipidemia (with triglycerides affected more so than cholesterol), fatty liver, and hypertension [49]. In response to an oral glucose challenge, SHROB are glucose intolerant and have a delayed, exaggerated insulin response. Although they are normoglycemic, SHROB rats exhibit fasting insulin concentrations over 40-fold higher than those of lean SHR, which implies severe insulin resistance [48, 50]. These animals also have increased serum free fatty acid levels, fasting hyperglucagonemia, and impaired suppression of glucagon secretion and free fatty acids in response to an oral glucose challenge [48]. There are lower expression levels of glucose transport and insulin-signaling proteins in SHROB rats, which may mechanistically explain the insulin resistance and hyperinsulinemia in this strain. Serum lipid levels in SHROB are increased as early as 5 weeks of age and are characterized by severe hypertriglyceridemia and mild hypercholesterolemia, while triglycerides and cholesterol remain at normal levels in lean SHR littermates [44]. Interestingly, lipid profiles do not differ between sexes in the SHROB.

Homozygous SHROB ($fa^k/fa^k$) are infertile and the $fa^k/fa^k$ genotype can only be inherited when both parents are heterozygous for the recessive allele [44]. Male SHROB are consistently infertile even when treated with daily testosterone injections. Koletsky reported decreased levels of spermatogenesis and a lower number of mature follicles containing ova in the testes and ovaries, respectively, of SHROB when these tissues were microscopically examined [51].

In contrast with the Zucker fatty rat, which only exhibits a mild degree of hypertension, the SHROB rat will consistently develop hypertension, with systolic blood pressure reaching 150 mmHg beginning at approximately 3 months of age and progressively rising between 6 and 9 months of age and lasting the entire life span [44]. Unlike their SHR littermates, there is no gender difference in the severity of the hypertension seen in SHROB. Proteinuria is detectable in these rats as early as 6 weeks of age and accelerates in an exponential manner [44]. Severe proteinuria is noted in SHROB by 6 months of age, and these rats develop focal segmental glomerulosclerosis and nephrosclerosis, which resemble the kidney and vascular damage seen with human diabetes and hypertension. As with the Zucker fatty rat, angiotensin II is thought to have a role in the development and maintenance of kidney disease and hypertension in the SHROB [52]. The SHROB rat can also exhibit vascular disease and lesions mimicking human atherosclerosis, although this has not been a consistent finding across all

SHROB colonies [44, 53]. The severe kidney disease and protein wasting found in the SHROB are responsible for its shorter life span; these animals only live to 10–12 months of age [44, 54].

Several substrains of the SHROB rat exist, with two of the most common being the SHR/N-corpulent (*cp*) and LA/N-*cp* rats. SHROB rats were sent by Koletsky to Hansen at NIH in 1982, who then crossed them with two inbred NIH strains; the results of these crossings were the congenic SHR/N-*cp* and LA/N-*cp* rats. These rats only retain the *cp* gene from the original SHROB rat. Obese homozygous (*cp/cp*) LA/N-*cp* and SHR/N-*cp* rats exhibit metabolic alterations similar to those seen in human T2DM, including hyperinsulinemia, hyperlipidemia, glucosuria, and proteinuria [55], while *cp* heterozygotes (*cp/+*) exhibit a completely normal lean phenotype. These substrains are more commonly used for the study of T2DM as opposed to MetS.

## *The Low-Capacity Runner Rat*

Koch and Britton used artificial selection for aerobic endurance running capacity in genetically heterogeneous N:NIH rats to create animals with low and high running capacities [56]. This selection was based upon distance run to exhaustion on a motorized treadmill. Rats capable of running long distances were classified as high-capacity runner (HCR) rats and were bred together. Rats with a low intrinsic aerobic capacity for running short distances were classified as low-capacity runner (LCR) rats [56].

After 11 generations of breeding, the LCR rats began to show divergent metabolic characteristics in comparison with the HCR rats [57]. LCR rats had higher mean arterial pressures than HCR, and when endothelial function in carotid arteries was assessed via nitric oxide-mediated vascular relaxation, the LCR exhibited less vessel relaxation, implying a degree of endothelial dysfunction. Further, LCR rats were insulin resistant when compared to HCR, as demonstrated by hyperinsulinemia and impaired glucose tolerance. These rats also had reduced cardiovascular function, higher plasma triglycerides and free fatty acids, and increased visceral adiposity. When mitochondrial biogenesis proteins were measured in skeletal muscles of LCR and HCR rats, these proteins were found to be markedly reduced in the LCR rats, which correlated with their decreased aerobic capacity [57]. Interestingly, in 5-week-old male pups, although body and fat weights were similar, LCR rats had elevated glucose and triglycerides, demonstrating that the metabolic alterations in these rats precede the increases in body weight and adiposity [57]. Later studies demonstrated that the LCR rats, when fed a high-fat diet, gained more weight and body fat and had more severe insulin resistance than HCR rats, despite the consumption of similar amounts of metabolizable energy [58]. The LCR rat therefore seems to be a suitable model of polygenic MetS.

## *The Wistar Ottawa Karlsburg W Rat*

The Wistar Ottawa Karlsburg W (WOKW) rat is an inbred rat strain developed in 1995 and is derived from a cross between the spontaneously diabetic BioBreeding (BB) rat and Wistar rat outbred stock [59]. The BB rat is homozygous for the $RT1^u$ haplotype of the major histocompatibility complex, which is considered a predisposing factor to development of diabetes in these rats. After crossing BB rats with Wistar outbred rats, two inbred strains were developed: the diabetes-resistant Wistar Ottawa Karlsburg A rat and the diabetes-prone WOKW (which possessed the $RT1^u$ haplotype) [59]. After 35 generations of inbreeding, researchers noticed decreased fertility and increased pup survival in the WOKW; this prompted the first studies of the metabolic phenotype of these animals [59, 60]. In comparison with control dark agouti rats, the WOKW rat was subsequently found to develop obesity, dyslipidemia, hyperinsulinemia, hyperleptinemia, proteinuria, and mild hypertension but did not

develop diabetes [59]. These phenotypic characteristics seem to manifest between 8 and 10 weeks of life. WOKW rats exhibit severe adipose tissue insulin resistance and altered expression of key adipocyte genes, such as adiponectin, fatty acid synthase, peroxisome proliferator-activated receptor gamma, and others [61]. Subsequent genetic analyses of the MetS phenotype in the WOKW rat revealed that it was polygenic in nature [62]. The polygenic basis for the components of MetS seen in this model more closely resembles the basis for human MetS, making it a very useful model.

### *The Otsuka Long-Evans Tokushima Fatty Rat*

In 1984, a spontaneously diabetic rat exhibiting obesity, polydipsia, and polyuria was discovered in an outbred colony of Long-Evans rats housed at the Tokushima Research Institute in Japan [63, 64]. Selective breeding from the Tokushima colony produced a strain of rat that exhibited obesity, hyperglycemia of adult onset, and, eventually, diabetes mellitus; this rat strain is known as the Otsuka Long-Evans Tokushima Fatty (OLETF) rat [63]. From the same colony, the control strain for the OLETF rat, the Long-Evans Tokushima Otsuka (LETO) rat, was also created. The OLETF rat exhibits hyperphagia and significantly increased body weight when compared to control LETO rat. This trend fades with the development of glucosuria and diabetes in male OLETF beginning at about 30 weeks of age. The obesity in the OLETF rat becomes evident in both sexes only a few weeks after birth [65]. In contrast to the Zucker fatty rat, which accumulates mostly subcutaneous fat, the accumulation of fat in the OLETF rat is predominantly visceral [43]. Male OLETF rats develop late-onset hyperglycemia, starting at about 18 weeks of age. Interestingly, female OLETF rats never develop hyperglycemia and exhibit glucose levels similar to those of female LETO rats, even at advanced age. Male rats develop hypertriglyceridemia and hypercholesterolemia, with triglyceride and cholesterol levels increasing with age. Females experience increased triglycerides with age, but levels remain normal. Cholesterol does not increase with age in female OLETF rats.

Studies of pancreatic function in the OLETF rat revealed that this strain was nonresponsive to cholecystokinin (CCK) subsequent studies revealed that the OLETF rat lacked CCK-1 receptors, which are considered significant contributors to the hyperphagia in this model [66, 67]. This aberrant CCK pathway along with the progression to overt T2DM may decrease the suitability of the OLETF rat as a MetS model.

## Concluding Remarks

Any of the rodent models discussed in this chapter could be used to study MetS. When choosing an appropriate model, it is important to remember that MetS is a constellation of risk factors that do not manifest themselves in a consistent pattern across humans, as their severity can vary greatly. All the models discussed here have health profiles that are similar to those present in many MetS patients. However, it is important to recognize that the phenotypes of many of the models described result from single-gene mutations, while MetS in humans is polygenic. The monogenically obese Zucker rat, *ob/ob* mouse, and *db/db* mouse have been studied extensively and are the most widely used MetS models. A more translationally appropriate MetS model may be the LCR rat, which exhibits polygenic obesity. Potential advantages and disadvantages of the models discussed in this chapter are indicated in Table 4.1.

In addition to the rodent models discussed in this chapter, there are also a variety of transgenic mouse models that exhibit features of MetS. However, like most of the models described above, the majority of phenotypes result from defects in one or two specific genes. High-fat feeding in mice and rats can produce MetS-like features without altering the genetic makeup of the animal and therefore can also be used as an animal model to study MetS. The limitations of any model chosen should be considered in order to avoid misinterpretation of experimental results. Although no ideal rodent model exists from which human MetS can be recapitulated, these models do provide us with valuable information regarding the pathophysiology of MetS, which may help in the treatment or prevention of this modern epidemic.

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# Chapter 5
# Obesity and Metabolic Syndrome: Etiopathogenic Analysis

**Emilio González-Jiménez and Gerard E. Mullin**

**Abstract** Obesity is a global pandemic and has become a serious health problem worldwide by producing considerable morbidity and mortality. Thus it is imperative for the scientific community to become familiar with the key etiological factors that are ultimately responsible for the development of obesity. The objective of this chapter is to review the important events involved in the pathophysiology of obesity leading to the dysregulation of energy balance, appetite, and metabolism.

**Keywords** Obesity • Physiology • Pathophysiology • Metabolic syndrome

**Key Points**

- Obesity is a global pandemic and has become a serious health problem worldwide by producing considerable morbidity and mortality.
- It is imperative for the scientific community to become familiar with the key etiological factors that are ultimately responsible for the development of obesity.
- Several important events are involved in the pathophysiology of obesity leading to the dysregulation of energy balance, appetite, and metabolism.

## Introduction

According to the World Health Organization (WHO), more than one billion people worldwide are overweight, of which 300 million can be considered obese. In Europe, one in six children and adolescents are overweight (17 %) today while 1 in 20 are obese (5 %) [1].

This increase in the prevalence of obesity is related to dietary factors and an increase in sedentary lifestyle [2]. The increased consumption of saturated fats and carbohydrates with decreased intake of fruits and vegetables and low levels of physical activity are the most important dietary factors in the

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development of this global health problem [3]. Moreover, the consequences of obesity have far-reaching consequences. Cardiovascular disease, disorders of lipid metabolism, insulin resistance resulting in risk of type II diabetes mellitus, arterial hypertension with the risk of stroke (CVA) which can now make their appearance at 6 years of age in obese children [4].

Investigations over the last few years have revolutionized our understanding of the physiological and molecular mechanisms that regulate body weight. The discovery of certain hormonal mediators involved in the maintenance of body weight such as leptin has contributed to the understanding of the physiological processes involved in the development of obesity [5].

## Etiology of Obesity

Current knowledge on genetics and molecular biology would support the notion that the pathogenesis of obesity is a complex series of events that leads to a vicious cycle of appetite dysregulation and energy imbalance. In this regard, the theory of increased intake together with deficient energy expenditure is an overly simplistic theory because obesity is a very heterogeneous disorder in origin, involving a variety of genetic and nutritional factors [6, 7].

### *Genetic Factors*

Recent studies suggest that the development of obesity may have originated in the earliest stages of life, i.e., during the fetal period. Accordingly, in the fetal period a programming mechanism activates nutritional, hormonal, physical, and psychological processes which act at critical periods of life, controlling specific physiological functions [8]. The existence of one or more members in a family with severe obesity at an early age has raised the likely involvement of genetic factors [9].

According to the seventh revision of the map of human obesity with data collected through 2005, there are 47 published cases of monogenic obesity, 24 cases of Mendelian disorders, and 115 different loci involved in polygenic obesity [10]. In this regard, the map of obesity indicates that all chromosomes are potential genes involved in the onset and development of obesity except for the Y chromosome [11]. There have been 71 genes identified as being potential inducers in the development of obesity [12]. Of these, 15 genes are associated intimately with the amount of body fat [13]. One of the genes identified for their potential implication in the development of obesity at an early age is fat mass obesity-associated gene (FTO) [14]. FTO overexpression is found in subjects with progressive weight gain [15]. Usually, FTO expression is higher in hypothalamic areas involved in the process of feeding [16]. Along these lines, acute food deprivation behavior expression is modified by the FTO gene suggesting its possible relationship to appetite and satiety [17]. Children who were carriers of two risk FTO alleles showed a significantly lower satiety response [18].

For decades there are a number of gene mutations that have been shown to be responsible for the onset of morbid obesity [19]. Among them is the Prader–Willi syndrome (PWS), an autosomal dominant condition. In 70 % of cases, PWS patients show abnormalities in several genes located in the paternal chromosome 15 [20]. PWS in children is accompanied by the development of a cadre of obesity, muscular hypotonia, mental retardation, hypogonadism, cryptorchidism, and stunting accompanied by small hands and feet. In certain cases, PWS is often associated with the presence of diabetes mellitus [21]. This syndrome is one of the most prevalent examples dysmorphic obesity in humans.

Alstrom syndrome (also known as Alstrom–Hallgren syndrome) is an autosomal recessive disorder characterized by the appearance of nerve deafness and diabetes mellitus without polydactyl or

mental retardation [22]. In this syndrome, obesity usually appears after 2 years of age, highlighting an increase in weight figures that often exceed by 100 % of the normal values for age and sex of the child [23]. Dermatological manifestations include acanthosis nigricans [24].

## *Gut Microbiota and Its Influence on the Development of Obesity*

At present there is some controversy over whether the microbiota that colonizes the human intestine is involved in the development of obesity. The gut microbiota plays an integral role in appetite regulation, thermodynamics, and metabolism by facilitating the extraction of energy from food, synthesizing vitamins and regulating the production of gut-derived hormones (note to publisher: please cross-reference to the gut microbiota-obesity chapter) [25]. However, imbalances in the composition of the intestinal microbiota have been associated with the development of insulin resistance and weight gain [26]. Numerous studies have analyzed the composition of the intestinal microbiota in obesity. Sato et al. [27] reported that the administration of milk fermented with *Lactobacillus gasseri* reduced the size of adipocytes mesenteric adipose tissue while reducing leptin levels in serum. This study demonstrated the potential regulatory effect of commensal enteric bacteria on the growth of adipose tissue in obesity. In another study by Ma et al. [28] in mice fed with a diet rich in fat, dietary administration of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* improved steatosis and insulin resistance, linking the possible relationships between metabolism and certain components of the microbiota. While it is necessary to continue with further studies to clear all the unknown factors involved in the development of obesity and associated metabolic diseases.

## *Changes in Dietary Patterns and Physical Activity*

In the Western world, the emergence of food biotechnology has enabled the consumption of processed and convenience foods throughout the year. In this regard there has been an increase in the consumption of high-calorie low-nutrient-dense animal foods and carbonated soft drinks which accounts for 20–30 % of total daily energy intake [29]. Excessive consumption of fruit juice (greater than 350 mL/day) in preschool can favor the development of obesity [29, 30]. González and colleagues present evidence that the total calories, composition, portability of food, variety, size, and number of meals also represent factors closely linked to obesity [31]. Many parents are not engaging in the daily task of preparing food for the family and are instead opting for high-calorie ready meals [32]. Beverages rich in refined carbohydrates such as artificial fruit juices and carbonated soft drinks are increasingly preferred instead of water [33]. Thus, the habit of eating out contributes to the progressive increase in adipose tissue of subjects as these foods are often high in fat and calorie dense. In the USA, most meals are eaten outside of the home during the work week. For many children, school lunches and snacks do not meet the criteria of a healthy diet [34].

In addition to excess caloric consumption, a progressive decline in physical activity over the past 25 years is another major reason for the obesity pandemic. In the case of adolescents, it has been possible to predict whether they choose to use public transportation when the distance exceeds 15 min walking time [35]. Research has shown a 37 % decrease in the number of adolescents walking and a 20 % reduction in the number of miles walked per year [35]. Serra-Majem et al. showed that only 32.2 % of boys and 17.8 % of girls aged 6–9 years old play sports more than 2 days a week [36]. The prevalence of physical inactivity in Spain is highest in communities of Andalusia (64 %) and the Canary Islands (68 %) [31]. According to Stefanick et al. [37], daily physical activity is the main factor in the maintenance of body weight and is therefore essential for weight loss to be successful [37].

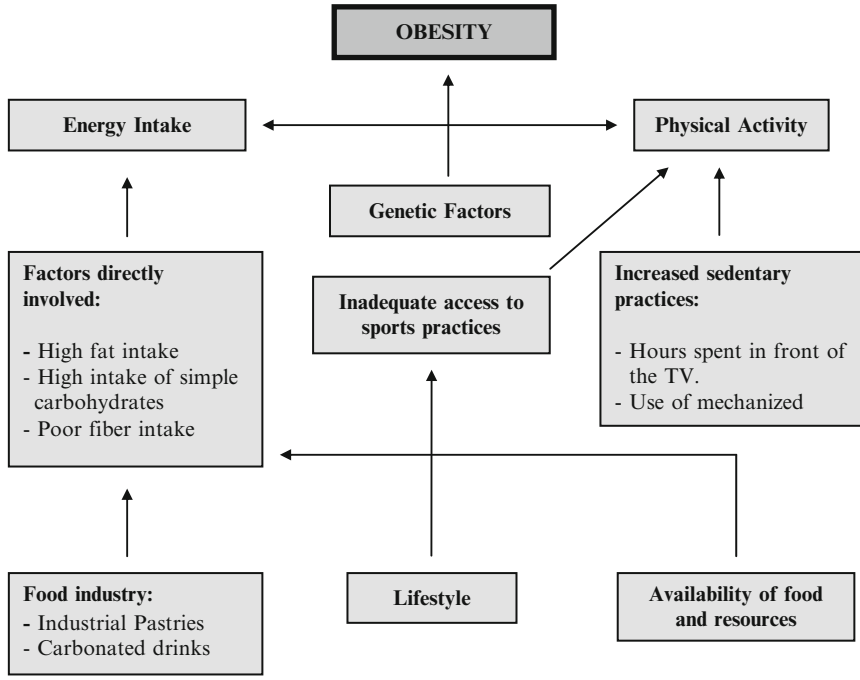


**Fig. 5.1** Factors involved in the development of obesity. Conceptual framework of the main factors involved in obesity. Adapted from: González E, 2010 [37]

All forms of physical activity should be encouraged throughout the day such as stair climbing at work since the sum of all energy expenditures facilitates weight balance. The factors involved in the development of obesity are depicted in Fig. 5.1.

## Pathophysiology of Obesity

According to the first law of thermodynamics, obesity is the result of an imbalance between expenditure and energy intake. Excess energy intake comes in the form of carbohydrates, proteins, and fats [38]. Carbohydrates are the first step as fuel in the power supply. When carbohydrate intake exceeds the requirements, they become metabolized and stored as fat. In the setting of nil or very low levels of carbohydrates and energy needs, fat is mobilized for the production of energy. This process is known as lipolysis whereby fat is converted into fatty acids and glycerol. Thus, the human body meets the first law of thermodynamics which states that energy can be neither created nor destroyed, only transformed. Excess energy consumption changes the internal energy of the body and is transformed into chemical energy whereby the main warehouse is adipose tissue [39]. When energy intake (EI) is greater than total energy expenditure (CET), adipose tissue will accumulate. Excess EI relative to CET results in gains in total fat mass, lean body mass (which facilitates energy expenditure), and body weight [40]. Accordingly, body weight may vary in relation to overall energy intake (EI) and total energy expenditure (CET). The amount of daily energy expenditure is the sum of the resting (REE) or basal energy expenditure (BEE) plus energy expenditure during physical activity (GEA) plus the energy expenditure from thermogenic processes (GET) [41]. This would be defined in the energy balance equation: CET = REE + GEA + GET.

A number of body systems regulate energy intake and expenditure such as the nervous system and digestive tract organs such as the liver and pancreas and adipocytes [42]. The adipocyte is a highly differentiated cell which stores and releases fat and regulates energy metabolism via hormone secretion. The adipocyte can change its size up to 20 times and its volume a thousandfold. Each adipocyte is capable of storing a maximum volume of 1.2 μg of triglycerides which are formed by the esterification of a glycerol backbone and three free fatty acids. Esterification is catalyzed by two enzymes, lipoprotein lipase (LPL) and acylation-stimulating protein (ASP); both are activated from the action of insulin and chylomicrons. The quantity of triglycerides stored inside the adipocyte normally does not exceed 0.6 μg per cell. Considering that the average number of adipocytes present in each subject is 30 to $60 \times 109$ and each of these contains therein 0.5 μg of triglycerides can infer a total fat mass of 15 kg = 135,000 kcal [43].

Leptin is an adipose tissue-derived hormone that is released into the circulation proportional to increased energy stores in fat. Leptin stimulates neural circuits that decrease food intake and increase energy expenditure. Leptin, a product of the OB (or LEP) gene, plays an important role in food intake and body weight regulation [44]. Both humans and rodents with mutations in the leptin gene or leptin receptor gene are obese. Defective leptin signaling due to either leptin deficiency, as in ob/ob mice, or mutation in the leptin receptor, as in db/db mice, leads to development of obesity (note to publisher: please cross-reference the animal model chapter in this textbook). The discovery of leptin and the genes that regulate hormone production from adipocytes have caused a great revolution in our understanding of the regulation of energy intake-expenditure and thus the study of obesity. Leptin synthesis is regulated by the OB gene which is located on chromosome 7q 51. The ob gene is 650 kb in length and consists of three exons separated by two introns 51. The coding region of the leptin gene (501 nucleotides in length) is contained in exons 2 and 3, which are separated by an intron of approximately 2 kb.

Leptin is a peptide composed of 167 amino acids whose sequence is similar in different species. For instance, mouse leptin has 84 % homology to human leptin while rat leptin has 83 % homology to human leptin [45]. Leptin influences the hypothalamus which regulated energy homeostasis by modulating food intake and energy balance [46]. Overall, leptin causes an activation of catabolic effector systems [47]. Leptin reduces adiposity via the inhibition of appetite (anorexigenic effect) which reduces caloric intake while disabling anabolic effector systems designed to increase body fat. The net result is a gain in energy expenditure, lipolysis of adipose tissue, and reduction of fat mass.

The anorectic action of leptin is exerted through its receptor located in the arcuate nucleus neurons of the hypothalamus. Once activated the receiver will set up a complex network of mechanisms. The binding of leptin to its receptor induces the activation of a series of signaling pathways, including the Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated kinase-like protein (MAPK), insulin responsive substrate 1 (IRS1), and suppressor of cytokine signaling 3 (SOCS3) pathways, which mediate its effects. The JAK/STAT pathway serves as the primary leptin signal transduction pathway in the hypothalamus. In this signaling cascade, Jak2 activation leads to phosphorylation of the STAT3 transcription factor, which dimerizes and translocates to the nucleus where it regulates gene transcription [48]. Alternatively, leptin signaling can alter neuronal activity without altering gene transcription through alternative pathways such as IRS—phosphoinositide 3-kinase (PI3K) signaling.

Leptin causes a decrease in the secretion of appetite stimulants. Leptin decreases the hypothalamus-derived neuropeptide Y which is the most potent endogenous appetite stimulant [49]. The aforementioned arcuate nucleus of the hypothalamus is an important relay center for leptin's effects. The hypothalamic arcuate nucleus integrates and distributes peripheral information from hormonal and neural signals that reflect metabolic status further into the brain. Within the arcuate nucleus, neurons containing melanocortins (MCs), products of the pro-opiomelanocortin (POMC) gene, are activated by leptin which ultimately suppresses appetite in part via this pathway (in addition to neuropeptide Y). Fasting results in loss of adipose tissue and low leptin levels, which causes diminished activation of POMC neurons, whereas overfeeding (high leptin levels) results in a stimulation of POMC

neurons. The activity of the MC system is not only regulated by the endogenous MC receptor agonists, α-melanocyte-stimulating hormone (α-MSH), β-MSH, and γ-MSH, which are all derived from the POMC precursor, but also by agouti-related protein (AgRP). AgRP is also expressed in the arcuate nucleus but in a different subset of neurons than those expressing POMC. In contrast to POMC neurons, AgRP neurons are inhibited by leptin and activated during negative energy balance. Although often described as a competitive antagonist, AgRP acts in fact as an inverse agonist on constitutively active MC3 and MC4 receptors, the main brain MC receptors [50]. The MC system modulates energy expenditure and insulin sensitivity. Spontaneous mutations of the MC receptor in humans and gene knockout in animals result in obesity [50, 51]. The unique presence of an endogenous agonist and an inverse agonist acting at the same receptor system implicates a tight regulation of MC function in the brain. Thus, during a negative energy balance, AgRP neurons are activated, and AgRP acts to suppress MC receptor activity, thus raising appetite. The opposite is true in obesity whereby leptin suppresses appetite by decreasing AgRP which disinhibits MC3 and MC4, thereby increasing POMC expression and appetite suppression [52]. Leptin also acts to increase energy expenditure through the hypothalamus to utilize the sympathetic nervous system to stimulate the release of thyrotropin [53]. Furthermore, leptin noradrenergic receptors also modulate body weight by stimulation of the alpha 1 and beta 3 receptors to decrease food intake and increase energy expenditure. For its part, the efferent parasympathetic nervous system modulates hepatic metabolism, insulin secretion, and gastric emptying, thus participating in the control and regulation of body weight.

Olfactory and taste stimuli produced by food also participate in the regulation of food intake. These stimuli are peripheral signals that in turn will be integrated and processed in the nervous system by releasing neurotransmitters which modulates our food intake. The best studied neurotransmitter is serotonin whose receptors are involved in regulating food intake and macronutrient selection. The neural pathways through which central serotonergic systems regulate food intake and body weight remain to be fully elucidated. Heisler et al. reported that serotonin, via action at serotonin1B receptors (5-HT1BRs), modulates the endogenous release of the aforementioned melanocortin receptors (MC4), which are a core component of the central circuitry controlling body weight homeostasis [54]. There are other mechanisms elucidated for serotonin's regulation of appetite that have therapeutic implications. The role of serotonin in regulating hypothalamic appetite circuitry is extensively reviewed by Yadav et al. [55].

The aforementioned α-MSH is an anorectic peptide closely involved in the regulation of food intake. α-MSH is synthesized in the arcuate nucleus where it is distributed widely in the central nervous system (CNS) with a high concentration at the paraventricular nucleus. α-MSH administration into the ventricular system of the brain causes decreased appetite and increased thermogenesis [56]. α-MSH's actions on the CNS are via its interactions with MC3 and MC4. There is mounting research to support the contention that α-MSH may play a key role in antiobesity therapy in the near future [57]. As previously mentioned above, another neuropeptide that is involved in the modulation of food intake is neuropeptide Y. The main function of neuropeptide Y is to increase food intake via appetite stimulation, thus constituting the most powerful anabolic neurotransmitter [58]. Leptin suppresses appetite in part by decreasing neuropeptide Y [59].

There is increasing recognition and understanding of the intricate interplay between gut hormones and the CNS and the regulation of food intake through appetite modulation [60, 61]. Several of these circulating appetite modulators have been shown to influence appetite in humans including the only known orexigenic gut hormone ghrelin and a suite of anorexigenic gut hormones including cholecystokinin (CCK), pancreatic polypeptide (PP), peptide YY (PYY), glucagon-like peptide (GLP)-1, and oxyntomodulin (OXM) [62, 63]. Specifically, CCK, PP, PYY, glucose-dependent insulinotropic polypeptide (GIP), gastrin-releasing peptide (GRP), and bombesin all decrease food intake, thus providing the basis for potential antiobesity intervention. Overall, gastrointestinal peptides possess powerful modulating actions upon appetite, motility, and metabolism following food intake.

Ghrelin, discovered by Kojima et al. [64], is the first peptide described as having an orexigenic effect. Ghrelin acts upon the hypothalamus in three possible ways: accessing the arcuate nucleus following gastric secretion and circulation through the blood brain barrier. A second way is via the vagal afferents arriving from the stomach to the hypothalamus via the vagus nerve. Third is by intrahypothalamic synthesis [65]. Other studies have shown that plasma ghrelin levels rise during periods of negative energy balance (i.e., fasting) then normalize by eating food [66].

Gastrointestinal peptides are also involved in the satiety process. Glucagon-like peptide-1 (GLP-1) and GIP are also known for being involved in the "incretin effect" whereby oral glucose induces greater insulin levels compared with an equivalent intravenous challenge. Both of these hormones are insulinotropic and increase insulin sensitivity. Studies have shown that GLP-1 and GIP levels and actions may be perturbed in obesity, T2DM, and metabolic syndrome [67]. There is evidence to suggest that impairments in secretion and/or action of incretin hormones arise secondarily to the development of insulin resistance, glucose intolerance, and/or increases in body weight rather than being causative factors [68]. GIP induces satiety by delaying gastric emptying [69]. Studies from mice deficient in the receptor GIP-R (GIP-R deletion knockout) demonstrated a resistant phenotype of diet-induced obesity; thus, GIP may be involved in the pathogenesis of abdominal obesity. GLP-1 peptide is secreted by the L-cells of the ileum and colon. Secretion occurs after the ingestion of nutrients (carbohydrates and fatty acids) and in proportion to the caloric content. GLP-1 decreases gastric emptying and appetite while increasing satiety. Exogenous GLP-1 and GLP-1 R agonists used clinically have been associated with body weight loss [70]. Näslund et al. provided subcutaneous administration of GLP-1 to obese subjects before each meal for 5 days which was associated with a 15 % reduction in food intake per meal and generating a weight loss of 0.5 kg [71]. A subsequent study using a long-acting GLP-1 analogue liraglutide was evaluated for its safety, tolerability, and efficacy over a 2-year period of time [72]. A total of 564 adults with a body mass index 30–40 kg m (−2) were enrolled with 268 completing the 2-year trial. Participants received diet (500 kcal deficit per day) and exercise counseling during a 2-week run-in, before being randomly assigned to once-daily subcutaneous liraglutide, placebo, or open-label orlistat. After 1 year, liraglutide/placebo recipients switched to liraglutide. From randomization to year 1, liraglutide 3.0 mg recipients lost 5.8 kg (95 % confidence interval 3.7–8.0) more weight than those on placebo and 3.8 kg (1.6–6.0) more than those on orlistat. At year 2, participants on liraglutide for the full 2 years (pooled group, $n = 184$) lost 3.0 kg (1.3–4.7) weigh more than those on orlistat. Completers on liraglutide ($n = 92$) maintained a 2-year weight loss of 7.8 kg from screening. The 20-week body fat decreased by 15.4 % and lean tissue by 2.0 % with liraglutide. The most frequent drug-related side effects were mild to moderate transient nausea and vomiting. The 2-year prevalence of prediabetes and metabolic syndrome decreased by 52 and 59 %, with improvements in blood pressure and lipids in the liraglutide group. The result of this clinical trial shows promise for the use of GLP-1 agonists in the management of obesity and the metabolic syndrome.

Peptide YY (PYY) or tyrosine-tyrosine in the family of pancreatic polypeptide (PP) is a 36-amino acid peptide that is synthesized and released by specialized enteroendocrine cells called L-cells of the distal gastrointestinal tract (colon and rectum) but is also present in stomach, pancreas, and certain regions of the CNS [73]. Two main endogenous forms of PYY have been identified, PYY1–36 and PYY3–36, the latter being the predominant circulating form. PYY is secreted in response to the proportion of caloric intake [73]. In situations of fasting, plasma values are low, rising 15–30 min before food even reaches the distal intestines indicating neural regulation [74]. Its secretion and release into the blood allow the absorption of nutrients by delaying gastric emptying and intestinal transit [74]. PYY 3–36 has been shown to reduce feeding in obese rodents and humans fueling interest in the role of PYY3–36 in body weight regulation [75]. Peptide YY(PYY 3–36) and pancreatic polypeptide (PP) released from endocrine cells of the pancreas directly act on and increase cytosolic Ca(2+) in vagal afferent nodose ganglion neurons and finally suppress food intake via vagal afferents [76]. Therefore, peripheral terminals of vagal afferents sense gastrointestinal and pancreatic hormones and regulate food intake.

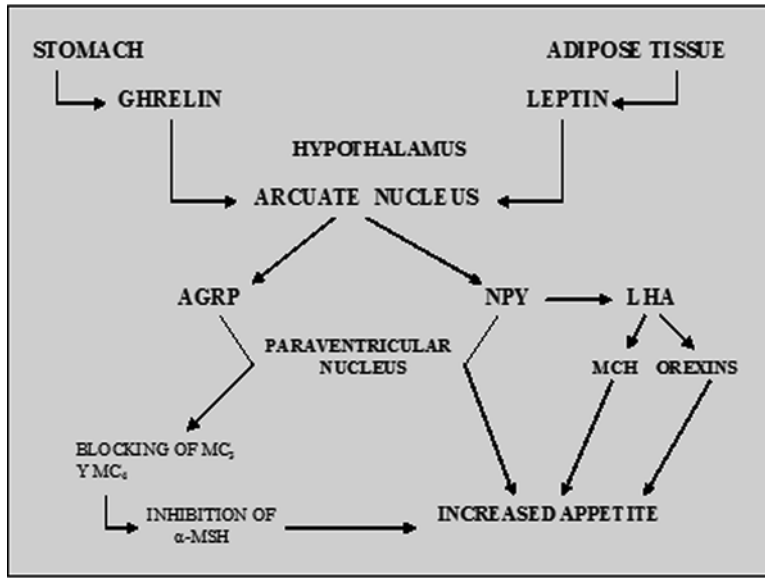


**Fig. 5.2** Mechanisms, major biomolecules, and nervous system structures involved in appetite regulation

Other non-gastrointestinal hormones that influence weight regulation include testosterone which increases lean body weight relative to the fat, while estrogens do the opposite [77]. In the case of adrenal glucocorticoids, they develop an important action in the neuroendocrine control of food intake and energy consumption [77]. Finally, the autonomic nervous system represents the last link in the chain of processes and its biomolecules carry out the control of body weight by regulating hormonal secretions and thermogenesis [78]. Figure 5.2 shows more clearly the mechanisms, major biomolecules, and nervous system structures involved in appetite regulation.

## Metabolic Syndrome and Obesity

Since its first description by Reaven et al. [79], metabolic syndrome (MS) is defined as the association of various risk factors and precursors of cardiovascular disease.

The increase in the prevalence of metabolic syndrome is a cause of concern among the international scientific community [79]. In the study by Ford et al. [80] from a population of 8,814 American adults, the prevalence of metabolic syndrome was reported to be 42 % for ages 20–29, 60–69, and over 70 years, respectively. Other American [81–83] and European studies [84] have verified these findings. In Spain the data on its prevalence are scarce. One of the first studies was the Canary Nutrition Survey. This study included a total of 578 adult subjects aged between 18 and 74 years. The result revealed a 24.4 % prevalence of metabolic syndrome with no differences between the sexes [85].

The factors associated with an increased risk of metabolic syndrome are postmenopausal status, obesity, states of hypertension, dyslipidemia, a diet rich in carbohydrates, physical inactivity, and the existence of a family history of metabolic syndrome [86]. From the point of view of its pathogenesis, obesity and insulin resistance are the major risk factors in the etiology of metabolic syndrome. One of the first studies to investigate the risk factors of metabolic syndrome in childhood was The Cardiovascular Risk in Young Finns Study [87]. In this study subjects consisting of a group of 1,865 children and adolescents between 6 and 18 years old were followed for the evolution of metabolic syndrome over a 6-year period. The results showed that baseline serum insulin levels were higher

among children who subsequently developed the metabolic syndrome, thus suggesting the idea that insulin resistance precedes and predicts the development of the syndrome [86]. More recently, The Bogalusa Heart Study examined the relative contribution of childhood adiposity and insulin to the adulthood risk of developing metabolic syndrome in a biracial (black–white) community-based longitudinal cohort ($n = 745$; baseline age, 8–17 years; mean ± SD follow-up period, 11.6 ± 3.4 years) [88]. Childhood levels of adiposity along with insulin, blood pressure, and lipoprotein variables showed significant adverse changes with increasing number of metabolic syndrome risk factors in adulthood. Children in the top quartile of BMI and insulin versus those in the bottom quartile were 11.7 and 3.6 times more likely to develop metabolic syndrome as adults. In a logistic regression model, childhood BMI and insulin were significant predictors of adulthood metabolic syndrome, with BMI being the strongest predictor and showing a curvilinear relationship. Using an insulin resistance index instead of insulin did not change the above findings. These results indicate that childhood obesity is a powerful predictor of development of metabolic syndrome and underscores the importance of weight control early in life.

The prevalence of the metabolic syndrome is highest among Hispanic adults. However, studies exploring the metabolic syndrome in overweight Hispanic youth are lacking. For his part, Cruz and colleagues [89] studied the influence of insulin resistance on the development of the metabolic syndrome. These investigators demonstrated that insulin sensitivity was independently associated with negative and triglyceride and blood pressure levels and positively with the levels of cholesterol and high density lipoprotein (HDL-C), thus suggesting that adiposity effects on blood pressure and dyslipidemia are mediated by insulin resistance. Hispanic youth with a family history for type II diabetes are at increased risk for cardiovascular disease and type II diabetes, and this appears to be due to decreased insulin sensitivity. Therefore, both obesity and insulin resistance contribute substantially to the development of the metabolic syndrome.

### *Diagnosis of Metabolic Syndrome*

Currently, the criteria for diagnosing MS in adults are those established by the Adult Treatment Panel III (ATP III) by the WHO and those established by the International Diabetes Federation (IDF), with latter the most commonly used [90]. According to the International Diabetes Federation (IDF) [91], the diagnosis will be based on the existence of three or more of the criteria listed below:

- Obesity central dominance
- Triglycerides ≥150 mg/dL
- Men HDL <40 mg/dL
- Women HDL <50 mg/dL
- Systolic blood pressure (SBP) ≥130 mmHg
- Diastolic blood pressure (DBP) ≥85 mmHg
- Fasting glucose ≥100 mg/dL

In the case of children and adolescents, there is no established consensus for diagnosis [92]. Different rates reported by different studies confirm the need to unify criteria to reach a consensus diagnosis among children and adolescents [92].

## Conclusions

Whatever the etiology of obesity, the route for development is the same with an increase in food intake parallel to decreased energy expenditure. In this sense a proper understanding of the mechanisms involved in the regulation of energy balance is the key to understanding the pathogenesis of the

growing pandemic of obesity. The major efferent system of weight control is the endocrine system with growth hormone, thyroid hormones, gonadal, glucocorticoids, and insulin by the autonomic nervous system all contribute to the maintenance of energy balance and equilibrium. The breakthrough in the understanding of the major biomolecules that regulate body weight and food intake has important implications for clinical management and therapeutic approach to obesity. Although diet and exercise are still the central pillar in the management of obesity, there are more patients who require pharmacological support to achieve or maintain a reduced body weight. In this sense, the intervention at certain processes or phases of energy homeostasis system could be the key to improving the health and nutritional status of these patients. The adoption of a healthy lifestyle will be a deciding factor in the fight against obesity and the metabolic syndrome. In this regard, it is essential that health care from primary care screening processes is conducted in the general population in order to detect early those subjects at risk of obesity and the metabolic syndrome. Only in this way can we reduce health consequences resulting from this condition.

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# Chapter 6
# Animal Models for Nonalcoholic Fatty Liver Disease

**Yoshihisa Takahashi, Yurie Soejima, and Toshio Fukusato**

**Abstract** Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by excessive fat accumulation in the liver of a patient without a history of alcohol abuse. Nonalcoholic steatohepatitis (NASH), a severe form of NAFLD, may progress to liver cirrhosis and hepatocellular carcinoma. NAFLD/NASH is considered a hepatic manifestation of metabolic syndrome and is increasing globally with the increased prevalence of obesity. Animal models of NAFLD/NASH yield important information for elucidating the pathogenesis of NAFLD/NASH and for developing new treatments for the disease. An ideal animal model of NAFLD/NASH should correctly reflect both the histopathology and pathophysiology of human NAFLD/NASH. Animal models of NAFLD/NASH are classified into genetic models, nutritional models, and combination models of genetic and nutritional factors. In this chapter, we review representative animal models of NAFLD/NASH, referring to their advantages and disadvantages.

**Keywords** Animal model • Nonalcoholic fatty liver disease • Nonalcoholic steatohepatitis • Metabolic syndrome • Histopathology • Pathophysiology

## Abbreviations

| | |
|---|---|
| ALT | Alanine aminotransferase |
| HF | High fat |
| IL | Interleukin |
| MCD | Methionine and choline deficient |
| NAFLD | Nonalcoholic fatty liver disease |
| NASH | Nonalcoholic steatohepatitis |
| PTEN | Phosphatase and tensin homologue deleted on chromosome 10 |
| VLDL | Very low-density lipoprotein |

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**Key Points**

- Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by excessive fat accumulation in the liver of a patient without a history of alcohol abuse.
- Nonalcoholic steatohepatitis (NASH), a severe form of NAFLD, may progress to liver cirrhosis and hepatocellular carcinoma.
- NAFLD/NASH is considered a hepatic manifestation of metabolic syndrome and is increasing globally with the increased prevalence of obesity.
- Animal models of NAFLD/NASH yield important information for elucidating the pathogenesis of NAFLD/NASH and for developing new treatments for the disease.
- An ideal animal model of NAFLD/NASH should correctly reflect both the histopathology and pathophysiology of human NAFLD/NASH.
- Animal models of NAFLD/NASH are classified into genetic models, nutritional models, and combination models of genetic and nutritional factors.

## Introduction

Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by excessive fat accumulation in the liver of a patient without a history of alcohol abuse. NAFLD is classified into two types: simple steatosis in which only hepatocellular steatosis is observed and nonalcoholic steatohepatitis (NASH) in which not only steatosis but also necroinflammatory reaction is observed. Long-standing NASH may progress to liver cirrhosis, which may be accompanied by hepatocellular carcinoma [1, 2]. NAFLD/NASH is considered a hepatic manifestation of metabolic syndrome, and conditions associated with metabolic syndrome, such as central obesity, type 2 diabetes, hypertension, and hypertriglyceridemia, are well-known risk factors of NAFLD [3, 4]. Globally, NAFLD is increasing with the increased prevalence of obesity, and NAFLD/NASH is currently considered the most common chronic liver disease. Among the adult population, it is estimated that about 20 % have NAFLD and 2–3 % have NASH [5].

The pathogenesis of NAFLD/NASH has not been completely elucidated, and treatments for NASH other than lifestyle improvement through diet and exercise have not been fully established [2]. Studies of NAFLD/NASH on human subjects are limited by the long period (several decades) of the development and progression of this disease. Moreover, ethical problems exist in administering drugs to or obtaining liver tissues from human patients. Therefore, many researchers have been using animal models to study NAFLD/NASH. Animal models of NAFLD/NASH yield important information in elucidating the pathogenesis of and developing new treatments for the disease. An ideal animal model of NAFLD/NASH should correctly reflect both the histopathology and pathophysiology of the human disease. Ideally, it should show progressive fibrosis and tumorigenesis in the liver. Animal models of NAFLD/NASH are classified into genetic models, nutritional models, and combination models of genetic and nutritional factors. In this chapter, we review representative animal models of NAFLD/NASH, referring to their advantages and disadvantages.

## Genetic Models

### *Ob/ob Mice*

Ob/ob mice possess a spontaneous mutation of the leptin gene (leptin deficient). Leptin is an adipokine produced by white adipose tissue and exerts a marked anorexic effect by acting on the

hypothalamic ventral median nucleus [6]. Ob/ob mice are hyperphagic, inactive, and extremely obese and show hyperglycemia, insulin resistance, hyperinsulinemia, and hyperlipidemia [7, 8]. Ob/ob mice develop hepatic steatosis spontaneously; however, this does not progress to steatohepatitis spontaneously [9]. Secondary insults such as a methionine- and choline-deficient (MCD) diet, a high-fat (HF) diet, or low-dose lipopolysaccharide (endotoxin) are needed to induce steatohepatitis in ob/ob mice [10, 11]. Another feature of these mice is that they are resistant to liver fibrosis [12]; thus, leptin is considered an essential mediator of hepatic fibrogenesis [12, 13]. Mutations of the *Ob* gene are not prevalent in obese subjects or NASH patients, and serum leptin levels and the occurrence of NASH correlate poorly in humans [14].

## *Db/db Mice*

Db/db mice possess a natural mutation in the leptin receptor (*Ob-Rb*) gene [15]. Therefore, these mice are resistant to the effects of leptin despite having normal or increased leptin levels. These mice are hyperphagic and obese and show insulin resistance, type 2 diabetes, hyperlipidemia, and hepatic steatosis. They develop NASH when a second hit such as an MCD diet is added [16]. When fed an MCD diet, db/db mice exhibit greater histological inflammation and higher serum alanine aminotransferase (ALT) level than ob/ob mice. In addition, db/db mice fed an MCD diet develop marked pericellular fibrosis in the liver, while ob/ob mice develop no significant fibrosis [17]. In our laboratory, db/db mice fed an HF diet for 6 weeks developed NASH; however, the degree of fibrosis was mild (personal communication). The advantage of ob/ob and db/db mice is that their phenotype is consistent with metabolic syndrome in many aspects; however, the disadvantage of both of these models is that they develop neither steatohepatitis nor liver fibrosis spontaneously.

## *KK-A$^y$ Mice*

KK-A$^y$ mice possess a heterozygous mutation of the agouti gene (*KK-Ay/a*). As a result, these mice show a loss of melanocortin and an obese phenotype due to hyperphagia from impaired hypothalamic appetite suppression [18]. These mice possess a characteristically yellowish fur. They develop hepatic steatosis, as well as obesity, insulin resistance, hyperglycemia, and hypertriglyceridemia; however, they do not develop steatohepatitis spontaneously [18, 19]. In addition, these mice show leptin resistance and hyperleptinemia without defects in the *ObR* gene, while their expression of adiponectin is reduced [20–22]. KK-A$^y$ mice exhibit increased susceptibility to MCD diet-induced steatohepatitis, where hypoadiponectinemia most likely plays a key role in exacerbation of both inflammatory and profibrogenic responses [21]. Lipopolysaccharide-induced liver injury is more pronounced in KK-A$^y$ mice than in control mice [22]. Although the phenotype of KK-A$^y$ mice resembles that of humans with metabolic syndrome, the disadvantage of these mice is that they do not develop steatohepatitis spontaneously.

## *Phosphatase and Tensin Homologue Deleted on Chromosome 10 (PTEN) Null Mice*

*PTEN* is a tumor suppressor gene encoding a lipid phosphatase whose major substrate is phosphatidylinositol-3,4,5-triphosphate. PTEN is a negative regulator of the phosphatidylinositol 3-kinase/Akt signaling pathway [23]. Liver-specific *Pten* knockout (*AlbCrePten flox/flox*) mice show

extensive hepatomegaly and steatohepatitis, and their hepatic histopathology resembles that of human NASH [24]. Steatosis is observed at 10 weeks of age, and steatohepatitis with fibrosis is observed at 40 weeks of age. Hepatocellular adenomas occur at a 47 % incidence by 44 weeks of age, and by 74–78 weeks of age, hepatocellular adenomas and carcinomas occur at an incidence of 100 % and 66 %, respectively [25]. The advantage of this model is that its hepatic histopathology resembles that of human NASH; however, its disadvantage is its hypersensitivity to insulin [25].

## Dietary Models

### *Methionine and Choline Deficiency*

The MCD diet contains high sucrose (40 %) and fat (10 %) but lacks methionine and choline, which are essential for hepatic β-oxidation and very low-density lipoprotein (VLDL) production [6]. In addition, it is hypothesized that choline deficiency impairs hepatic VLDL secretion [26]. These mechanisms result in deposition of lipids on the liver. In addition, oxidative stress [27] and changes in cytokines and adipokines [28] induce hepatic injury.

Serum ALT level is consistently increased after MCD diet feeding in mice [29]. Steatohepatitis occurs at day 10 [29], and pericellular fibrosis occurs by 8–10 weeks in mice [27, 30]. Extensive macrovesicular steatosis at all areas except the periportal region and many necroinflammatory foci containing lymphocytes and neutrophils are observed after 10 weeks of MCD diet feeding in mice [27].

The advantages of the MCD diet model are that the hepatic histopathology resembles that of human NASH, and the degree of necroinflammatory reaction and fibrosis is more severe than that of other nutritional models. In addition, the MCD diet is easy to obtain and use. However, the disadvantage of this model is that the metabolic profile is opposite to that of typical human NASH. Namely, rodents fed the MCD diet were found to show significant weight loss (often >20 % weight loss after 3 weeks), low plasma triglyceride and cholesterol levels, low fasting blood sugar, peripheral insulin sensitivity, low serum insulin and leptin levels, and unchanged or increased serum adiponectin level [28, 31–35]. To overcome these problems, genetically obese mice, such as ob/ob or db/db mice, are occasionally used as the MCD diet-fed animal.

### *High-Fat Diet*

Lieber et al. [36] reported a NASH model induced by a high-fat (HF) diet (71 % energy from fat, 11 % from carbohydrates, and 18 % from proteins). The plasma insulin levels of rats fed this diet for 3 weeks ad libitum were increased, reflecting insulin resistance. Rats fed the HF diet showed marked panlobular steatosis, and their hepatic lipid concentrations were approximately twice those of control rats fed the standard diet. Like human NASH, oxidative stress occurred in the liver of HF diet-fed rats. Thereafter, several authors also reported that HF diets induced NASH in rodents [37, 38]. The advantage of the HF diet model is that its pathophysiology resembles that of human NASH. However, this model seems to produce variable results with regard to the degree of steatosis, inflammation, and fibrosis, and the results depend on the rodent species and strain, the fat content in the diet, the composition of dietary fat, and the duration of treatment. In general, the degree of liver injury in the HF diet

model is milder than that in the MCD diet model [34]. Several methods have been tested to induce a more severe hepatic histopathology with an HF diet (e.g., addition of cholesterol and fructose to an HF diet [39], intragastric overfeeding of an HF diet [40], or pretreatment with gold thioglucose to induce hyperphagia [41]). The histopathology and pathophysiology of the intragastric overfeeding method closely resemble those of human NASH. However, this method is difficult to implement because it requires specific equipment and expertise.

### *Cholesterol and Cholate (Atherogenic Diet)*

Matsuzawa et al. [42] fed mice with the atherogenic diet containing 1.25 % cholesterol and 0.5 % cholate and observed a time-dependent and progressive formation of hepatic steatosis, inflammation, and fibrosis over 6–24 weeks. In the model, hepatocellular ballooning, which is characteristic to human NASH, was observed at 24 weeks. When 60 % fat (cocoa butter) was added to the diet, the occurrence of these histological characteristics was accelerated, and hepatocellular ballooning was observed at 12 weeks. Furthermore, the atherogenic diet induced oxidative stress. Thus, it is conceivable that this diet induces in mice a hepatic histopathology that resembles that of human NASH. However, mice fed the atherogenic diet were systemically insulin sensitive. In fact, mice fed with this diet had lower body weight, epididymal fat pad weight, and plasma triglyceride level compared with control mice. Therefore, it seems that the metabolic status of this model is different from that of human NASH. In addition, the atherogenic diet has the disadvantage that it requires a long period to induce NASH in animals. Lately, high-fat plus high-cholesterol diet is occasionally used to induce NAFLD/NASH in experimental animals [43, 44].

### *Fructose*

We [45] found that Wistar rats fed a high-fructose (70 %) diet for 5 weeks showed significantly higher macrovesicular steatosis (Fig. 6.1a) and intralobular inflammation (Fig. 6.1b) grades, liver-to-body weight ratios, and hepatic triglyceride concentrations than control rats. In this study, hepatic steatosis induced by the high-fructose diet was characteristically predominant in zone 1. This distribution pattern of steatosis was different from that of human adult NAFLD, in which steatosis is usually predominant in zone 3. Rats fed the high-fructose diet showed significantly higher expression levels of interleukin (IL)-6 and tumor necrosis factor-α proteins in the liver than control rats (unpublished data). Addition of plant leaf extract to the high-fructose diet completely suppressed hepatic steatosis (Fig. 6.2) and IL-6 protein expression in the liver (unpublished data).

Other groups also reported that NAFLD was induced in experimental animals by adding fructose to the diet or the drinking water [46–48]. In mice, the onset of fructose-induced NAFLD is hypothesized to be associated with intestinal bacterial overgrowth and increased intestinal permeability, subsequently leading to an endotoxin-dependent activation of hepatic Kupffer cells [48]. The advantage of the high-fructose model is that its pathophysiology is similar to that of human NAFLD, including insulin resistance; however, the disadvantage of this model is that the hepatic lesion does not necessarily progress to NASH and fibrosis is not observed [35]. Lately, the high-fat plus high-fructose model is occasionally used to induce NAFLD in experimental animals [49–51].

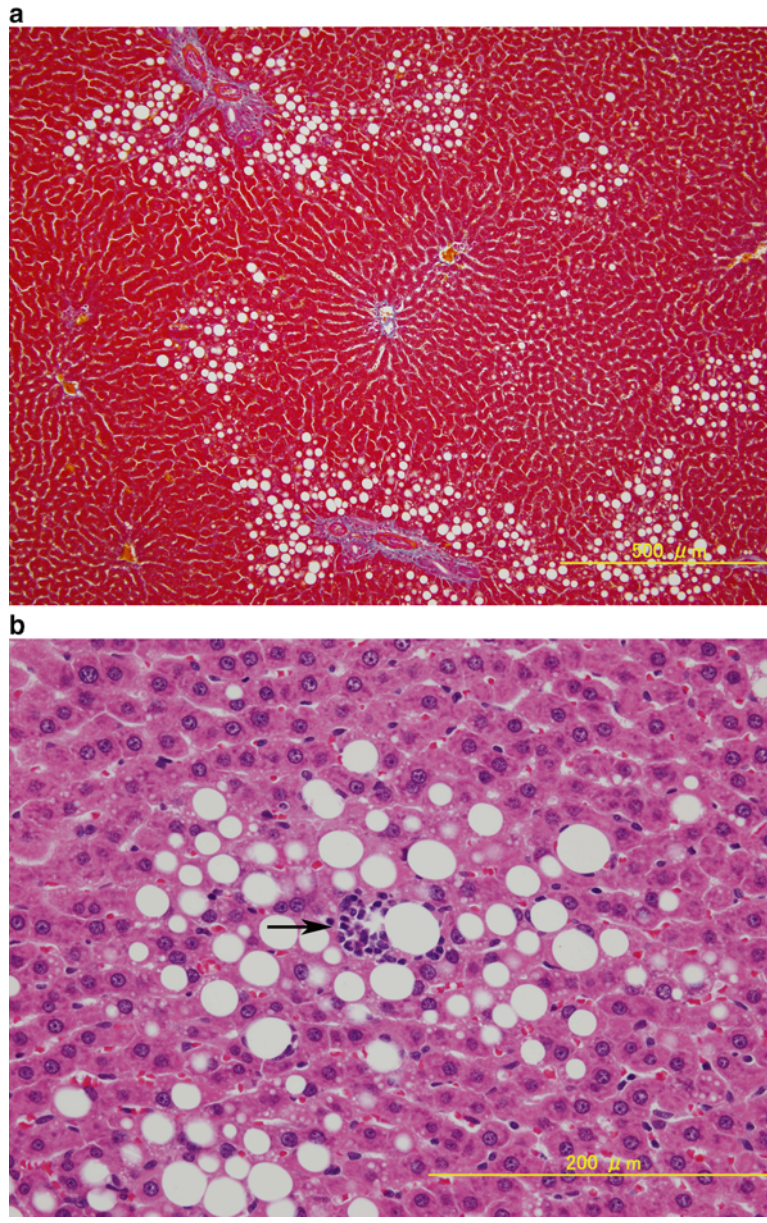


**Fig. 6.1** Liver histology of rats fed a high-fructose diet. (**a**) Macrovesicular steatosis distributed predominantly in zone 1 (Azan stain). (**b**) An intralobular necroinflammatory focus (*arrow*) and hepatic steatosis (H&E stain)

## *Combined Model of Genetic Modification and Nutritional/Dietary Challenges*

Various models that combine genetic abnormalities and dietary or chemical challenges have been developed to induce a pathophysiology closer to that of the human disease and induce a more severe hepatic histopathology [52–54]. One of the most commonly used animal models is db/db mice fed an MCD diet. As mentioned above, when fed an MCD diet, db/db mice show significantly higher serum ALT level and more severe hepatic inflammation and fibrosis than ob/ob or control mice [17].

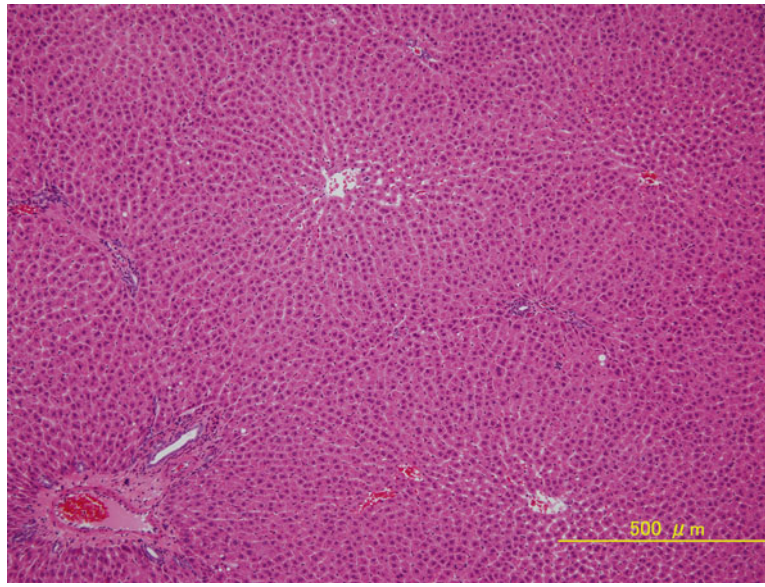


**Fig. 6.2** Liver histology of rats fed a high-fructose diet plus plant leaf extract. Hepatic steatosis was completely suppressed by the plant leaf extract (H&E stain)

## Conclusion

In this chapter, we reviewed representative animal models of NAFLD/NASH. These animal models are useful in elucidating the pathogenesis of NAFLD/NASH and in developing new treatments for the disease. Numerous genetic models have already been developed, and we hope that interested readers refer to other detailed review articles on this topic [20]. Currently, no animal model completely replicates the full spectrum of the human condition. It is important that researchers choose the animal model that best matches the objective of the study, considering the advantages and disadvantages of each model. We hope that animal models that more accurately replicate the pathogenesis, histopathology, and clinical course of human NAFLD/NASH will be developed in the future.

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# Chapter 7
# The Human Gut Microbiome and Its Role in Obesity and the Metabolic Syndrome

**Gerard E. Mullin and Nathalie M. Delzenne**

**Abstract** The gut microbiota helps balance key vital functions for the host, including immunity and nutritional status. Studies have also linked the microbiome to human mood and behavior, as well as many gut disorders, eczema, and a number of systemic disorders (Azad et al., CMAJ 185:385–394, 2013). Changes in the gut microbiota composition and/or activity may be implicated in the control of inflammation, fat storage, and altered glucose response in obese patients. Dietary short-chain fatty acids appear to be "indirect nutrients" produced by the gut microbiota that can modulate adiposity and immunity as well as send signals to the gut to produce hormones that regulate appetite, permeability, and inflammation. Numerous data have been published regarding differences in the composition of the gut microbiota in obesity. Taken together, the data currently published suggest that specific changes in the gut microbiota occur in overweight or obese patients and are either positively or negatively linked with adiposity, inflammation, and glucose or lipid homeostasis. Manipulation of the microbiota though diet can promote healthy weight loss by altering gut function and metabolism. Probiotics and prebiotics are interesting research tools to assess the relevance of specific bacteria in obesity. Prebiotics may lessen obesity and related metabolic stress by modulating gut peptides involved in the control of appetite and gut barrier function.

**Keywords** Obesity • Gut microbiome • Dysbiosis • Diet • Prebiotics • Probiotics • Fecal bacteriotherapy

### Key Points

- The gut microbiota helps balance key vital functions for the host, including immunity and nutritional status.
- Studies have also linked the microbiome to human mood and behavior, as well as many gut disorders, eczema, and a number of systemic disorders [1].
- Changes in the gut microbiota composition and/or activity may be implicated in the control of inflammation, fat storage, and altered glucose response in obese patients.

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- Dietary short-chain fatty acids appear to be "indirect nutrients" produced by the gut microbiota that can modulate adiposity and immunity as well as send signals to the gut to produce hormones that regulate appetite, permeability, and inflammation.
- The available data regarding differences in the composition of the gut microbiota in obesity suggest that specific changes in the gut microbiota occur in overweight or obese patients and are either positively or negatively linked with adiposity, inflammation, and glucose or lipid homeostasis.
- Manipulation of the microbiota through diet can promote healthy weight loss by altering gut function and metabolism.
- Probiotics and prebiotics are interesting research tools to assess the relevance of specific bacteria in obesity; prebiotics may lessen obesity and related metabolic stress by modulating gut peptides involved in the control of appetite and gut barrier function.

## The Human Microbiome: A Newly Discovered Organ

There is an ongoing resurgence of interest in the role of gut microbiota (flora)—host interactions in health and disease. Much of this renewed interest is due to advances in technology that permit a molecular analysis of the microbiota—much like the mapping of the human genome project. There is also another area of rapidly expanding research—the influence of the gut microbiota upon human physiology in health and disease.

The human microbiome is the aggregate of all gut microbial genes, whereas microbiota refers to all microbial organisms present in an ecosystem. There has been a concerted effort to characterize the bacterial genes within the human body. An effort to better describe the microbiota of the gut and other body locations using newly developed molecular-based technologies has been termed the Human Microbiome Project. This $173 million National Institutes of Health project has a mission of generating resources enabling comprehensive characterization of the human microbiota and analysis of its role in human health and disease [2, 3]. Not all the microbial species in the gut have been identified because most cannot be cultured [4].

The human superorganism is a conglomerate of mammalian and microbial cells, with the latter estimated to outnumber the former by ten to one and the microbial genetic repertoire (microbiome) to be approximately 100 times greater than that of the human host. Given the ability of the immune response to rapidly counter infectious agents, it is striking that such a large density of microbes can exist in a state of synergy within the human host. This is particularly true of the human digestive system which contains approximately 100 trillion bacteria from more than 1,000 distinct species having 70 divisions. The microbiome is highly organized as biology recognizes about 100 large groups of bacteria, known as phyla, that each has a different repertoire of biochemical capabilities. Human microbiomes are dominated by just four of these phyla: the Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria. Approximately 90 % of the human microbiome is composed of the Bacteroidetes (majority) and the Firmicutes phyla.

The human gut microbiome encompasses 3.3 million bacterial genes which is about 150 times the 20,000–25,000 genes in the human genome. In fact the microbial genes have cross talk among themselves and also with the host human genes. Thus our microbiota is an integral part of our genetic landscape and evolution. Gut bacteria can even exchange genes and they can also "sense" each other's presence through cell-to-cell signaling molecules—a process called quorum sensing.

The gut microbiota is mixed within the unabsorbed by-products of digestion and detoxification to form the feces that we eliminate. A specialized microbiota with a distinct composition from feces coats the lining of our intestines to form a specialized three-dimensional bacterial community encased within an exopolysaccharide. This slimy mucus layer of 100–200 μm thick is a biofilm—a dynamic

matrix of bacteria and carbohydrate-based mucins that forms a viscoelastic gel and provides us a layer of protection from invasion of harmful microbes and other damaging agents in the gut lumen. However, there is evidence showing that mucosal bacteria growing in biofilms on surfaces lining the gut differ from luminal populations and that due to their proximity to the epithelial surface, these organisms may be important in modulating the host's immune system in health and contributing to some chronic inflammatory diseases. The microbial cells of the human microbiome outnumber ours 10 to 1; thus, 90 % of the cells in our body are bacterial. What is more fascinating is that the DNA of the human microbiome has tremendous cross talk and can exchange DNA among themselves and has governance over our own DNA.

Early colonization of the gut microbiome has four phases. Phase 1 is the sterile gut in the womb. Phase 2 is the initial acquisition of flora from the mother's vagina canal and feces and while in the hospital setting—by the end of the first week of life bacterial communities can be cultured. Phase 3 is the influence of feeding upon the expansion of the gut microbiome. Phase 4 is the commencement of solid foods that further expands and diversifies the gut microbiome. The complexity of the bacterial community increases during infancy so that an adult-like complexity is attained by the end of the first year of life, and large fluctuations of bacterial populations occur during this first year.

The complexity and quantity of microbes in the gut is greatest at the orifices. The mouth and colon are heavily populated with trillions of anaerobic bacteria; however, the stomach is relatively sterile containing 100–10,000 bacteria per milliliter as gastric acid severely restricts the growth of bacteria. This is why the chronic use of acid blockers (i.e., proton pump inhibitors) favors the overgrowth of unfriendly bacteria in the gut and places individuals at risk for community-acquired pneumonia and deadly *Clostridium difficile* infection.

To highlight this point, a study in canines showed that those who were administered the proton pump inhibitor omeprazole had an overgrowth of bacteria in the small intestine and their gut microbiota shifted towards a higher proportion of "unfriendly" bacteria such as Fusobacterium and Firmicutes [5]. Interestingly, overpopulation of the Firmicutes phyla of bacteria has been linked to weight gain, insulin resistance, and obesity in mice [6].

The predominate species of the upper digestive tract include lactobacilli, streptococci, and *Helicobacter pylori*. As one travels down the digestive tube from the relatively sterile environment of the upper digestive tract towards the colon, the species become more abundant and diverse with anaerobic species such as Bacteroides and Fusobacterium. The distal colon is the most biodense, complex, and diverse natural ecosystem known having ten billion to ten trillion cells per milliliter. The distal colon comprises most of our bacterial biomass.

Intestinal bacteria are key to promoting the early development of the gut's mucosal immune system, both in terms of its physical components and function, and continue to play a role later in life in the system's operation. The bacteria stimulate the lymphoid tissue associated with the gut mucosa to produce antibodies to pathogens. Bacteria can influence the phenomenon known as oral tolerance, in which the immune system is less sensitive to innocuous particulate matter that we ingest or is present in our gut (i.e., food, friendly bacteria). Loss of oral tolerance can cause exaggerated immune responses to "harmless" luminal substances seen in allergies and autoimmune disease.

Diet, sanitation, and other lifestyle factors appear to have profound effects particularly on early intestinal colonization. For example, breast-feeding bolsters infant immunity and fosters development of the gut microbiota with friendly bacteria such as *Bifidobacterium* spp. which normally constitutes 90 % of an infant's flora and remains a key species into adulthood. Bottle-fed infants have been shown to have more undesirable Clostridia species and a higher prevalence of allergic and autoimmune conditions when compared to breast-fed infants [7]. Infants who are breast-fed are conferred a level of protection from the development of inflammatory bowel disease (IBD) when compared to bottle-fed infants [8].

### *Factors Impacting Upon the Development of the Gut Microbiome*

The human microbiome may be a vast, malleable genome that can be modified by dietary, medical, and hygienic practices. There are a number of factors that may impact the composition of the gut microbiome such as mode of birth, diet, antibiotic exposure, ethnicity, sanitation, hygiene, genetics, geography, and climate.

## Hygiene

Research has shown that children raised in a more rural environment, where playing in the dirt and being around farm animals are more common, have lower incidences of allergies and other autoimmune conditions. These bugs play a key role in training the immune system and influence many other aspects of biology. The immune system recognizes and fights harmful bacteria but leaves the helpful species, a tolerance developed in infancy and sometimes termed the "hygiene or old friends" hypothesis. There is an emerging theory initiated by D.P. Strachan in 1989 called the "hygiene hypothesis" which purports that vaccination and early antibiotic use in children have led to an increase in the prevalence of allergic and autoimmune diseases [9–11]. Strachan observed an inverse correlation between hay fever and the number of older siblings.

This aforementioned hygiene hypothesis proposes that these microorganisms—our old friends—have coevolved with humans and play an essential role in the establishment of the immune system. The microorganisms and the host have evolved codependence: the most relevant organisms are those that coevolved with mammals. These microorganisms interact with other modern lifestyle and environmental changes, such as inappropriate diet, obesity, psychological stress, and pollution leading to enhanced inflammatory responses. Other investigators have extended the findings of D.P. Strachan to allergic disorders and autoimmune diseases such as type 1 diabetes [12].

## Antibiotics

We live in a culture where we give antibiotics to our children at record rates and there is a can of Lysol in every home. In the United States, the average child now receives one antibiotic course per year despite evidence that antibiotics are no more effective for relieving coughs than a sugar pill [13]. The average child in the United States and other developed countries has received 10–20 courses of antibiotics by the time he or she is 18 years old [14]. Antibiotics have potent effects by suppressing up to one-third of the gut microbiome with a simple 5-day course of a single antimicrobial agent, ciprofloxacin. Gut communities are dynamic in nature such that most microbes returned to baseline levels within weeks post treatment, but several bacterial taxa remained undetectable. However, Jernberg et al. found that antibiotics have a detrimental long-term impact on the human intestinal microbiome, remaining for up to 2 years after treatment [15]. What is most concerning is that there is some evidence to suggest that each course of antibiotics may produce permanent alterations in the composition of our microbiome [16]. Some of the collateral damage of antibiotic overuse in children may account for the steep increase in conditions such as obesity, type 1 diabetes, IBD, allergies, and asthma, which have more than doubled in many populations. There is research to support that alterations of the gut microbiome contribute to each of these conditions [17–19]. In support of this view is the recent research showing that the risk of IBD in children rises with the number of courses of antibiotics taken [20].

Our meats are loaded with detectable levels of antibiotics which adversely impact the balance and diversity of our gut microbiome. The federal and drug administration has estimated that the livestock industry uses 20 million pounds of antibiotics annually [21]. Why do farmers use antibiotics in the feed of livestock? Antibiotics were used by the meat industry since World War II to prevent infections to livestock, but then the farmers noticed that they also fatten up livestock while needing less food. Farmers have used low nontherapeutic doses of antibiotics to increase the body weight of cows, sheep, pigs, and chickens since the 1950s [22]. Dr. Cho at New York University Medical Center suggests that antibiotic overuse in livestock is a contributing factor to the obesity epidemic. Cho and colleagues administered common antibiotics to weaning mice at similar doses as those used in agriculture and were able to generate a model of obesity [23]. By administering low doses of antibiotics in animal feeds, there were significant changes to the composition of the gut microbiome, resulting in modifications in copies of key genes involved in the metabolism of carbohydrates to short-chain fatty acids (SCFAs). Increases in colonic SCFA levels harvested additional energy from carbohydrates. Other metabolic changes that were observed included alterations in the regulation of hepatic metabolism of lipids and cholesterol. The antibiotic treatment altered the composition of gut bacteria in the mice which in turn led to metabolic changes, such as increased production of fatty acids. After about 6 weeks, the mice had gained about 10–15 % more fat mass than the untreated mice. Thus the antibiotic treatment altered the composition of gut bacteria in the mice which in turn led to metabolic changes. In this model, these investigators demonstrate the alteration of early-life murine metabolic homeostasis through antibiotic manipulation.

Disrupting this finely balanced ecosystem clearly has consequences for host metabolism and weight gain. Later in this chapter we will discuss other research which describes specific subgroups of gut bacteria that play a role in energy extraction from the diet and influence the production of hormones in the host. Antibiotics in livestock foster drug-resistant superbugs in their gut microbiome and these bacteria and antibiotics are present in manure for swine and other produce consumed by humans. The diversity of microbes within a given body habitat can be defined as the number and abundance distribution of distinct types of organisms, which has been linked to several human diseases: low diversity in the gut to obesity and IBD. The sudden shift of our gut microbiome away from a healthy mixture like those seen with antibiotic use weakens the diversity of our microbial friends and reduces our ability to adapt. The greater the diversity of an ecosystem, the better its health.

## Early Microbial Exposure: Mode of Delivery

Research has shown that there are several antenatal and perinatal events that affect the development of the intestinal microbiota. The mode of delivery influences the establishment of healthy flora after birth. There is also accumulating evidence that intestinal bacteria play an important role in the postnatal development of the immune system. The first time that we acquire friendly bacteria is while passing through the vaginal canal—this is why some researchers now believe that Caesarean birth may set the stage for illness and autoimmunity later in life.

In further support of the hygiene hypothesis, there is strong evidence that children developed via Caesarean section (C-section) have underdeveloped gut immunity from a less diverse microbiome—placing them at risk for subsequent allergic diseases. Birth by Caesarean section has recently been shown to be a risk factor for development of IBD, celiac disease, and type 1 diabetes—highlighting that improper development of the gut microbiome in early infancy is a risk for subsequent autoimmunity [24]. Studies have shown that allergic disorders such as asthma and allergic rhinitis occur more often in infants after Caesarean section than after vaginal delivery [25].

Therapy with broad-spectrum antibiotics is a common practice for mothers who go into premature labor or who have a Caesarean section. This treatment can reduce the biodiversity of the fecal microbiota

and may be a factor in the cause of life-threatening condition seen in some neonates—necrotizing enterocolitis. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants [26]. Antibiotics are now given routinely to between one-third and one-half of all women during pregnancy or nearing childbirth in the United States and other developed countries.

Babies acquire their founding bacterial populations from their mothers while passing through the vagina at birth. So each generation—particularly the 30 % or so of infants born via Caesarean section in the United States, 50 % in rural China, and up to 80 % in Brazil—could be beginning life with a smaller endowment of gut microbes and be at higher risk for developing serious disease [27]. In support of this view, researchers have shown that the primary gut flora in infants born by Caesarean section may be disturbed for up to 7 years after delivery [28].

A new study has found that C-sections and formula-feeding disrupt the development of microbial communities in infants. Caesarean sections (C-section) and strict formula-based feeding disrupt the development of microbial communities that promote lifelong health in an infant's digestive tract, according to a new study by researchers at the University of Alberta. In the study published in the *Canadian Medical Association Journal*, the researchers evaluated the composition of gut microbiomes of twenty-four 4-month-old infants [1]. When compared to vaginally delivered children, infants delivered by C-section were deficient in a specific genus of bacteria called Bacteroides that helps breakdown complex molecules in the intestine. Furthermore, the researchers found significant differences in the gut microbes of infants who were strictly formula-fed and those of infants who were breast-fed. For example, formula-fed infants had an overrepresentation of *Clostridium difficile* bacteria, which has been associated with allergies and asthma.

The compositions of the microbiota are established early in life but are subject to variations in our environment and lifestyle which determines our susceptibility to disease. Our environment, lifestyle and perhaps most importantly our diet influences the composition of out gut ecology and where they live because each of us lives in a slightly different environment, eats different foods, etc.

## Diet

Domestic hygiene, the aforementioned antibiotic usage, diet, and urbanization all play a role in modifying the composition and activity of the microbiome throughout life. There are a number of factors which shift the microbiota unfavorably over time such as antibiotic overuse, gastrointestinal infections, starvation, systemic illness, stressful lifestyles, dietary changes, and aging. We have discussed how antibiotics can have a long-term adverse impact upon the constitution of the gut microbiota. Aside from eating meats that were raised without hormones or antibiotics, what other measures can we take to influence the composition of our gut microbiome?

The unabsorbed foodstuff is metabolized by gut bacteria into a myriad of nutrients and biochemicals that have a diverse influence on bodily functions while becoming fertilizer for the growth of the gut microbiome. The high fiber content of plant foods therefore provides large amounts of substrate for fermentation by the gut microbiota that, in turn, through direct and indirect effects, modulate the health of its host. Western diets are low in dietary fiber and radically different from those of our ancestors. They are most likely mismatched with our archaic genome and gut microbiota since there has been little time or evolutionary pressure to adapt to the modern diet that followed the agricultural revolution. This suggests that dietary changes over time that have shaped our modern diet have occurred much more rapidly than any genetic changes, especially during the industrial and postindustrial revolution, as foods became much more convenient and accessible with advances in food processing, preservation (canning and refrigeration), and transportation. Consequentially, the current

underutilization of the gut microbiota may contribute to less than optimal health and may provide some explanation as to the rise of chronic diseases over time in Western nations.

There are numerous studies which have evaluated the impact of diet upon the composition of the gut microbiome. There are two worth mentioning here that highlight this point. The diet in Africa simulated the early human settlements at the time of the birth of agriculture—rich in fiber which "fertilizes" the growth of friendly bacteria. The prevalence of colorectal cancer and diverticular diseases are reduced in Africa when compared to the United States and Europe. In contrast, the Western diet in the United States and Europe is lower in fiber and higher in refined carbohydrates and saturated fats (i.e., red meats, dairy). A group of investigators compared the composition of the microbiota from children who ate a modern Western diet versus a rural diet. The microbiota from children of the Boulpon rural village of Burkina Faso (BF) in Africa and Florence, Italy, were analyzed using molecular techniques [29]. These researchers found significant differences in gut microbiota between the two groups. BF children showed a significant enrichment in the Bacteroidetes and depletion in Firmicutes (a phyla that is associated with obesity as we will discuss later in this chapter), while the European (EU) children showed the opposite pattern. Furthermore, the BF children's gut microbiota contained significantly less harmful bacterial species such as Enterobacteriaceae (*Shigella* and *Escherichia*) than those from EU. These data suggest that the consumption of sugar, animal fat, and calorie-dense foods in industrialized countries is rapidly limiting the adaptive potential of the microbiota. The second study looked at the stool composition of individuals after eating a high-fat, low-fiber (Western-based) diet compared to a high-fiber, low-fat consumption. There was a significant shift in the composition of the microbiota. The biodiversity of the Western-diet was reduced within only 24 hours [30].

Diet may also direct the microbiota to cluster into discrete patterns. The study of the configuration of bugs in your gut is part of the emerging science of enterotyping. The idea here is the types of species present in the gut microbiome that people fall into three categories—akin to blood typing. An analysis of gut microbial communities proposed three predominant variants, or "enterotypes," dominated by *Bacteroides*, *Prevotella*, and *Ruminococcus*, respectively [31]. The basis for enterotype clustering is unknown but appears independent of nationality, sex, age, or body mass index (BMI); however, diet may play a role in partitioning individuals into enterotypes. For example, individuals consuming a diet high in fat/low fiber/high protein are clustered into a *Bacteroides* enterotype whereas high-carbohydrate foods favored *Prevotella* [30].

## Ethnicity and Geography

Just as ecosystems such as forests, grasslands, and coral reefs differ from place to place, so it is with microbiomes. As mentioned above, the gut microbiota of children from Burkina Faso contain cellulases and xylan hydrolases that can digest fibers while these enzymes are lacking in the US and European children. Furthermore, children in Malawi and rural Venezuela contain more riboflavin-producing bugs than do those of North Americans.

Bacteria are quite smart for single-cell creatures. They develop resistant genes to antibiotics for avert extinction, but they also can induce the gut microbiota to make enzymes breakdown food for its survival. Gut microbes supply the human body with energy from dietary polysaccharides through carbohydrate-active enzymes which are absent in the human genome. These enzymes target polysaccharides from terrestrial plants that dominated diet throughout human evolution. Carbohydrate-active enzymes have been found to be transferred from algae to Japanese individuals who ate seaweed—which is absent in the microbiome from Western populations [32].

## Functions of the Gut Microbiota

The genetic makeup of your gut microbiome and how they influence your genes and metabolism may have more to determine your health than previously thought. The gut microbiota are a hidden metabolic organ of bacterial biomass that influence a number of important metabolic functions that are not conducted by the host that are discussed in detail below (Table 7.1).

### *Metabolic Regulation*

#### Microbiota and Carbohydrate Metabolism

The gut microbiome possesses a fascinating array of enzymes that can degrade complex dietary substrates that are unable to be digested by the human host. Certain colonic bacteria are able to metabolize a remarkable variety of substrates while other species carry out more specialized activities, including primary degradation of plant cell walls. Major substrates available for colonic fermentation are starches and soluble dietary fibers. Other carbohydrate sources available for fermentation in lower concentrations essentially include oligosaccharides and portions of nonabsorbable sugars and sugar alcohols.

Certain bacterial species in the colon survive by cross-feeding—a process by which one strain partially degrades the primary energy resource and excretes an intermediate that is used as an energy resource by a second strain. For example, a bacterial strain may ferment complex carbohydrates to lactic acid for growth of other species.

Another fascinating feature of the gut microbiome is the ability to ferment the breakdown products of fibrous plant material into SCFAs, acetate, propionate, and butyrate, and gases. There are many benefits to us that are conferred by SCFAs such as preventing the development of colon cancer, regulating immunity, combating intestinal inflammation, and maintaining the health and integrity of the gut by becoming an energy source for the lining cells of the colon. The colonic epithelium derives up

**Table 7.1** Physiological functions of the gut microbiota

| Functions | Mechanisms/effects |
|---|---|
| Protective functions against pathogenic bacteria | Pathogen displacement |
| | Nutrient competition |
| | Production of antimicrobial factors |
| | Activation of local immune response |
| | Contribute to the intestinal barrier function |
| Immune development | Immunoglobulin A production |
| | Control of local and general inflammation |
| | Tightening of junctions |
| | Induction of tolerance to foods |
| Digestive and metabolic functions | Vitamin production |
| | Fermentation of nondigestible carbohydrates |
| | Control of energy metabolism |
| | Dietary carcinogens metabolism |
| | Biotransformation of toxins |
| Neuronal development | Modulation of brain–gut axis during neuronal development |
| | Motor control and anxiety behavior |

to 70 % of its energy needs directly from butyrate. These SCFAs are also weak acids which influence the microbial composition and directly affect host health [33]. SCFAs regulate energy metabolism and drive adipose tissue expansion which influences the development of obesity [34].

### Microbiota and Protein Metabolism

In contrast to carbohydrates, little attention has been paid to the relationship between the intestinal microbiota and nitrogen balance in humans. The intestinal microbiota also produces essential amino acids and participates in the salvaging of nitrogen through the urea cycle. In contrast to carbohydrates, protein digestion by the microbiota yields a greater diversity of end products, including SCFAs, amines, phenols, indoles, thiols, hydrogen sulfite, carbon dioxide, and hydrogen gas, many of which have toxic properties [33].

### Microbiota and Lipid Metabolism

There is exciting new research to suggest that the body's supply of triglycerides is tightly linked to the intestinal microbiota. These findings have enormous potential relevance for research in a wide range of disease states, including metabolic disorders such as obesity and cardiovascular disease (CVD).

Animals that are germfree are lighter in weight and have 42 % less body fat than those who have their gut flora (wild type) despite their having a higher metabolism and eating less food [35]. Transfer of the microbiota from wild-type animals into the germfree animals resulted in obesity and affected lipid metabolism. It has been proposed that the presence of the gut microbiota modulates a key factor (fasting-induced adipose factor) that controls fat storage, by regulating lipoprotein lipase activity. This would be one mechanism by which the gut microbiota may have effect "at distance," namely in the adipose tissue. Gut microbes improve blood lipoprotein profiles and modulate lipid metabolism.

### Manufacture of Vitamins

Most human diets provide a robust supply of vitamins, the essential human nutrients that must be obtained from exogenous sources. However, it has long been recognized that gut microbes also contribute to vitamin synthesis. The magnitude of this contribution in healthy and unhealthy patients is poorly understood.

Several bacterial genera that are common in the distal intestine (e.g., *Bacteroides*, *Bifidobacterium*, and *Enterococcus*) are known to synthesize vitamins. Thiamine, folate, biotin, riboflavin, and pantothenic acid are water-soluble vitamins that are plentiful in diet, but that are also synthesized by gut bacteria. Likewise, it has been estimated that up to half of the daily vitamin K requirement is provided by gut bacteria. Other B vitamins that have been found to be produced by *Lactobacillus acidophilus* bacteria used in yogurt, cheese, and fermentations include vitamin B12, niacin, and pyridoxine [36]. Interestingly, germfree animals not only need 30 % more energy to maintain their weight but require the administration of B vitamins and vitamin K.

### Protection Against Pathogenic Bacteria

The gut microbiota is our first line of defenses against potential pathogens prior to their attempted invasion of the host. Gut microbiota provides its host with a physical barrier to incoming pathogens by competitive exclusion, such as occupation of attachment sites, consumption of nutrient sources, and

production of antimicrobial substances. It also stimulates the host to produce various antimicrobial compounds. Members of the *Lactobacillus* genus produce lactic acid which provides an inhibitory environment to the growth of many bacteria. The physical presence of the microbiota in the luminal biofilm also serves as a deterrent to pathogen colonization and attachment to the gut lining. Enteric flora also stimulates the production of immunoglobulin A which binds to potential invaders and tags them for elimination by the gut's immune system. The gut microbiota antagonizes the adherence of potential pathogens to the gut lining by promoting the propulsion of the flow of luminal contents of the gastrointestinal tract.

### Maintenance of Immunity and Gut Integrity

Commensal bacteria are necessary for the development and maintenance of a healthy immune system [37]. The gut microbiota help regulate immune responses and maintains a state tolerance to foods and ubiquitous materials. The bacterial genes of the microbiome send signals to the immune system to control local and systemic inflammatory responses.

By maintaining the integrity of the gut barrier through the preservation of tight junctions, the gut microbiome helps seal off the intestinal lining from the seepage of harmful bacterial toxins throughout the body [38]. The absorption of bacterial toxins into the circulation is felt to contribute towards a number of conditions such as atherosclerosis and chronic liver disease [39, 40]. Harnessing the ability of microbiota to affect host immunity is considered an important therapeutic strategy for many immune-related conditions, such as IBDs, celiac disease, metabolic syndrome, diabetes, and microbial infections.

### Detoxification

The gut is a conduit for the elimination of toxins that are produced as by-products of the thousands of biochemical reactions that occur in the liver and the digestive tract. The safe transfer of these potentially noxious substances outside of the body requires the gut microbiota to perform a number of essential duties in keeping our bodies safe from a multitude of toxic waste products that are formed in the gut. Toxic metabolites formed in the liver are excreted in bile acids which undergo transformation by the gut microbiota along with potentially harmful chemicals known as xenobiotics such as hormones, procarcinogens, and medications. Bile acids (or bile salts) are steroid acids that are produced in the liver from cholesterol and secreted in bile and whose main function is to facilitate the metabolism of dietary fat and the absorption of fat-soluble vitamins and cholesterol. They complete an enterohepatic cycle between the gut and liver about eight times per day, with 90–95 % of bile acids being reabsorbed by the intestine and returned to the liver. About 5–10 % of bile acids are biotransformed largely through degradation by intestinal bacteria.

Certain medications such as sulfasalazine are activated by the enzyme azoreductase of enteric bacteria while the vitamin K produced by bacteria can alter the efficacy of blood thinners such as Warfarin [41]. The gut microbiota has the ability to metabolize dietary compounds into metabolically active forms, reduce dietary nitrate to biologically active nitrite, and degrade dietary oxalate reducing kidney stone formation [42]. Furthermore, gut inhabitants can prove invaluable in preventing adverse outcomes following inadvertent environmental exposure to toxic compounds [43].

### Gut Microbiota and the Nervous System

Germfree animals have been found to have underdeveloped nervous systems with a host of derangements ranging from maladaptive stress and pain responses. There is an emerging area of research into the enteric microbiota–gut–nervous system whereby the brain can affect the microbiota which in turn

influences the brain [44]. Mental stress alters motility, compromises gut barrier function, promotes inflammation, and favors the colonization of pathogenic flora. The gut microbiota appears to control the levels of various signaling molecules and neurotransmitters in different areas of the central nervous system and appears to modify behavior and mood [45]. These observations prompted many to hypothesize on the role of the microbiota in the regulation of mood and behavior and their contribution to the pathophysiology of mood disorders [46].

## The Gut Microbiota and Obesity

Eubiosis is when we have a normal microbiota structure that provides protection against infections, educates the immune system, ensures tolerance to foods, and contributes to nutrient digestion and energy harvest. The overpresence of harmful species or underpresence of commensal species in the microbiota is known as dysbiosis. The microflora in the setting of dysbiosis produces dysfunction in the gastrointestinal tract systemically. Moreover abnormal pattern of microbiota has been consistently detected in specific diseases including obesity and its associated conditions.

## Helicobacter pylori *Infection*

*Helicobacter pylori* infection has been shown to be associated with peptic ulcer disease as demonstrated by the Nobel Prize laureate Barry Marshall MD. *H. pylori* chronic infection tones down the production of gastric acid. Interestingly as *H. pylori* had become more aggressively treated, more gastroesophageal reflux may be resulting in a higher prevalence of Barrett's esophagus and adenocarcinoma of the esophagus. *H. pylori* also regulates appetite by influencing the action of the hormone ghrelin [47]. Ghrelin, a peptide hormone secreted by the stomach, is involved in the regulation of food intake and appetite and may account for some of these changes. Gastric expression of ghrelin which is suppressed by *H. pylori* increases following eradication. One study has shown that 92 veterans treated for *H. pylori* with antibiotics gained significant weight when compared to their untreated counterparts [48]. *H. pylori* has virtually disappeared in our children with only 6 % showing evidence of infection from multiple courses of antibiotics. It is no surprise that obesity rates are climbing most in the young. So is *H. pylori* a commensal in disguise? We may have opened up Pandora's box [49].

## *Nonalcoholic Fatty Liver Disease*

Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by fatty infiltration of the liver in individuals who do not drink excessive alcohol. An individual is considered to have NAFLD if more than 5–10 % of the liver's weight is fat. The US prevalence of NAFLD is approximately 25 %—one in every four people has it. The highest risk factors for NAFLD include diabetes, overweight–obesity, the metabolic syndrome, and disordered lipid metabolism—all of these conditions have linkages to bacterial dysbiosis. The pathophysiology of the fatty accumulation in the liver includes insulin resistance, inflammatory proteins (cytokines), and oxidative damage to liver cells with the accumulation of fatty acids inside the cells until they die. There is strong evidence to suggest that gut bacteria-derived endotoxins are involved in the pathogenesis of NAFLD and cause a chronic inflammatory response—nonalcoholic steatohepatitis—which can lead to cirrhosis and liver cancer [50]. Dysbiosis may cause loosening of the tight junctions that maintain gut barrier defense—allowing the bacterial toxins to enter into the liver circulation. The bacterial endotoxin promotes an increase in free

fatty acid uptake and production by the liver and promotes inflammation and insulin resistance [51]. Interestingly, individuals with NAFLD have a higher prevalence of small intestine bacterial overgrowth (SIBO) which improves after antibiotic administration [52, 53]. There is ongoing investigation with regard to the role of the gut microbiota in liver diseases [39].

## *Cardiovascular*

CVD develops from dysbiosis of the oral cavity in the setting of gingivitis and lipid metabolism but also appears to result from gastrointestinal dysbiosis. Gut microbes metabolize dietary phosphatidylcholine (PC), generating trimethylamine (TMA) whose metabolites have been associated with CVD. Furthermore, in atherosclerosis-prone (*Apoe*$^{-/-}$) mice, the phosphatidylcholine metabolites exacerbated disease in a microbiota-dependent fashion [54]. Others have proposed that dietary endotoxemia that occurs with a high-fat diet—from the gut microbiota causing systemic inflammation—may portend towards CVD [40]. Gut microbiota have been shown to lower serum cholesterol and have anti-atherosclerotic properties by altering signaling molecules involved in cholesterol transport [55].

## *Diabetes (Adult Onset-Type 2)*

A number of disorders outside of the alimentary tract have been tied to bacterial dysbiosis. By-products of the gut microbiota have been found to activate the intestine–brain–liver neural axis to regulate glucose homeostasis and improve hyperinsulinemia. The intestinal microbiome has also been studied in the context of insulin resistance in adult patients with type 2 diabetes (T2D). Gut microbiota in human adults with T2D differs from nondiabetic adults. Bacteroides species contain a rich collection of carbohydrate-utilization pathways, and such gut bacteria can easily assimilate dietary carbohydrates. Altered ratios of Bacteroidetes to Firmicutes have been correlated with blood glucose concentration in adults with T2D [56]. Recall that these two phyla represent 90 % of the gut microbiome and scientists are correlating altered ratios with disordered energy metabolism and now insulin resistance. Seepage of bacterial endotoxin through the gut lining into the circulation contributes towards systemic inflammation and insulin resistance. Modulation of the microbiota with antibiotics has been shown to improve glucose tolerance in mice independent of diet intake or adiposity [57].

## *Obesity*

The metabolic syndrome epidemic, associated with obesity and numerous other health problems, is arguably the greatest single health-care challenge in the industrialized world, one now rapidly spreading to encompass less developed nations. Up until the last few decades, obesity has been a rare pathophysiological state. Now however, the number of obese or overweight humans has come to outnumber those suffering from malnutrition. This is an unprecedented state for our species, resulting from a mismatch between our evolutionary biology and our modern environment. The human body is a complex system, made all the more complex through its interactions with the trillions of microorganisms that coat the body surface and densely populate the gut. Recent work has shown that the microbes of the gut may play a role in human metabolism and adiposity. Because they are environmentally acquired, microbes constitute one part of our environment that may contribute to the obese state.

Recent works report that individuals with a low bacterial richness (23 % of the tested Danish population) are characterized by more marked overall adiposity, insulin resistance, dyslipidemia, and inflammation compared with high bacterial richness individuals [58]. Obesity was previously associated with a shift in the representation of the dominant phyla of bacteria in the gut, both in human and animal models. Studies of the effect of excess body fat on the abundances of different bacterial taxa in the gut generally show alterations in the gastrointestinal microbiota and changes during weight loss. Obese and overweight individuals with low bacterial gene richness seem quite refractory to dietary intervention and exhibit persistent inflammation and metabolic disorders [59]. The gastrointestinal microbiota has been shown to impact insulin resistance, inflammation, and adiposity via interactions with epithelial and endocrine cells. The gut microbiota modulates adiposity by changing the expression of host genes that are involved in fat storage and oxidation, gastrointestinal hormone production, and barrier function and in the inflammatory response. Restoration of the gut microbiota to a healthy state may ameliorate the conditions associated with obesity and help maintain a healthy weight.

## Microbiome Composition

Germfree mice are leaner than their conventional counterparts and have a suppressed appetite despite having a higher metabolism. When the luminal contents from the ceca of obese or lean mice were provided to lean germfree recipients, the mice receiving the microbes from the obese donors gained more weight over a 2-week period than recipients of the lean microbes, despite equivalent food intake [60].

Mice that have a deletion of both pairs of genes coding for the appetite-controlling hormone leptin become obese and voracious and are termed “ob/ob mice.” The bacterial communities of ob/ob mice ceca have an altered composition of the two dominant phyla (Bacteroidetes, Firmicutes) when compared to lean genetically normal mice or those possessing only one gene deletion for leptin [61]. A greater representation of Firmicutes and fewer Bacteriodetes characterize the microbiota in ob/ob mice. The Firmicutes-dominant microbiota in obese mice was found to be enriched in genes involved in energy extraction from food relative to that of the lean host’s microbiome.

Microbiota transplantation experiments showed that the accumulation of body fat depends on the type of the gut microbiota, which supports the role of the gut microbiota in the development of obesity. The influence of microorganisms in the development of obesity appears to be transmissible—giving rise to the term “infectobesity” [62, 63]. There have been several studies to date that have attempted to compare the gut microbiota of lean and obese people in order to define an obese microbiota profile. At the phylum level, contradictory results from different groups have made it difficult to ascertain an obesity signature.

Studies in obese humans have attempted to corroborate the gut microbiome data observed in mice. In contrast to studies performed in humans, studies of gut microbial ecology and obesity conducted in animals tend to have less variable outcomes. In a study extending these observations to humans, 12 obese participants were randomly assigned to either carbohydrate-restricted or fat-restricted diets, and on average, the proportion of Bacteroidetes bacteria increased over time for both diets, mirroring reductions in host weight [61].

Several studies reported by members of Dr. Gordon’s lab showed that the gut microbiota differs at the phylum level depending on weight status. In agreement with results from animal studies, his lab demonstrated that human obesity is associated with a low abundance of intestinal Bacteroidetes and high abundance of Firmicutes together with enrichment in carbohydrate and lipid-utilizing genes [61, 64, 65]. This team of investigators compared the fecal microbial communities between adult female monozygotic and dizygotic twin pairs concordant for leanness or obesity, and their mother. The microbiome of the mother and both pairs of twins were comparable to each other having a shared core

microbial community but were significantly different from the controls (unrelated individuals) showing the influence of genetics and perhaps housing on the microbiome. Obesity was found to be associated with reduced bacterial diversity and reduced representation of the Bacteroidetes [64]. Furthermore, the microbiome differed between obese and lean hosts in much the same way it had in the obese mouse model, with obese host microbiomes enriched in gene categories involved in carbohydrate and lipid metabolism. Significant reduction in the Bacteroidetes to Firmicutes phyla ratio and decreased Bacteroides spp. has been reported in obesity which approaches the profile of lean subjects with weight reduction [64].

Kalliomaki et al. have shown that *Bifidobacterium* spp. counts were higher in children who exhibited a normal weight at 7 years than in children becoming overweight, showing that changes in the gut microbiome precede and even predict the development of obesity [66]. In this study, the authors also observed a reduced *Staphylococcus aureus* count in normal-weight children compared to children who became overweight several years later. Along these lines, Santacruz et al. reported that *Bifidobacterium* spp. counts were lower in overweight women [67]. The burden of Firmicutes in the gut microbiota of obese individuals has been shown to be decreased after weight loss from either a reduced carbohydrate diet or after gastric bypass surgery [68, 69]. Variable alterations of the ratio of Bacteroidetes to Firmicutes and other patterns of fecal microbial ecology in relation to body weight in humans have been reported recently by other investigators [66, 68–73]. For many years the overall consensus was that obesity is characterized by an overabundance of Firmicutes, fat-forming bugs, while there is some variation in the findings for the Bacteroidetes phyla. However, other studies have shown that obesity has variations of the Firmicutes phyla and that there are genus/species that may be helpful in fighting obesity. Studies focusing on the genus/species level have consistently revealed that there is too overrepresentation of *Staphylococcus aureus* and deficiency of Bifidobacteria in obesity. Overall, caution should be exercised when stratifying strains of bacterial species with obesity risk. For example, there are discrepancies concerning the link between lactobacilli (LB) and obesity; the type of LB would be important to consider, but there are not enough data to state clearly which one could be "positive" and others "negative."

An increasing number of studies relate imbalances in the composition of the gut microbiota to obesity and its associated diseases. The approaches used to characterize gut microbiota vary widely, which might explain in part why the specific alterations in the microbiota associated with excess body fat, or weight loss, can also vary between studies. To compare studies will require some standardization of approaches or use of a variety of approaches within single studies.

A new way of separating out the microbiome of lean and obese individuals is to analyze and compare their metabolic functions. Greenblum et al. have used a metagenomic systems biology approach to show that lean and obese microbiomes do indeed differ and that these differences are related to the metabolic pathways encoded by the microbiota, with the obese phenotype enriched in pathways likely to interface with the host and additionally reduced in modularity, possibly as a result of reduced diversity [74].

Interestingly, the human obese microbiota can be transferred to mice, in order to explore the potential modulation of host physiology through changes in gut microbiota composition. Cohousing mice with obese twin's microbiota with mice harboring lean co-twin microbiota presents the development of obesity and related metabolic disorders. The improvement correlated with invasion of specific members of Bacteroidetes coming from the lean individual [75].

Dysbiosis of the small intestine has also been linked to obesity and fatty liver disease. Shifts in the microbiota are known to cause increased small intestine permeability, endotoxin translocation from the gut to the liver, and hepatic fat accumulation and injury. Sabate et al. analyzed 137 morbidly obese individuals referred for bariatric surgery and 40 healthy controls for SIBO by glucose-hydrogen breath testing and liver biopsy [76]. These investigators reported that SIBO was more common in obese versus lean participants. Obese subjects testing positive for SIBO had more severe hepatic steatosis than those who were SIBO negative.

Dysbiosis of the alimentary canal has also been linked to obesity. Epidemiological data indicate nearly one-third of Americans have untreated tooth decay, and the vast majority of the population has some form of gum disease. Probiotic species, particularly lactobacilli, have been identified as common residents of the oral cavity and studies indicate they antagonize pathogenic organisms implicated in dental caries and periodontitis. In a study of the oral microbiota, Goodson et al. show differences in the diversity and abundances of salivary bacteria between overweight and healthy weight people. Although preliminary, these studies indicate that obesity may be associated with a dysbiosis of the alimentary canal [77].

## *Mechanisms Linking the Gut Microbiota to Obesity*

### Metabolism

Gut microbes have a role in the host's metabolic homeostasis and energy metabolism is now a well-recognized function of gut microbiota. A key mechanism by which the gut microbiota affects body weight is by increasing energy harvesting from dietary fibers. The intestinal microbiota breaks down indigestible polysaccharides (i.e., fiber) to SCFAs providing 80–200 kcal per day or about 4–10 % of daily energy intake in normal adults [78]. Compared with their germfree counterparts, mice with gut microbiota have an increased capability to harvest energy from the gut. The aforementioned potential role of the gut microbiota and its influence on body size has long been acknowledged in the usage of low-dose antibiotics in farming practices. In fact, similar effects for low-dose antibiotics have been shown in humans in the 1950s [79].

Genetically altered leptin-deficient obese mice (ob/ob) have an increased capacity to harvest energy from luminal nutrients compared with their lean counterparts [62]. Metagenomic analyses of the microbiota performed in obese mice and humans revealed an increased capacity for the degradation (fermentation) of carbohydrates. The fermentation by-products are used as metabolic substrates to extract additional energy and appear to increase nutrient absorption and adipose fat mass development. The concept of changing energy harvesting by the gut microbiota has also been tested in humans. The amount of stool energy in proportion of ingested calories was positively correlated with the abundance of phylum Bacteroidetes and negatively correlated with the abundance of phylum Firmicutes in the feces. Thus fat-forming bugs, Firmicutes, increase the calories we extract from food relative to Bacteroides. An estimate of 150 kcal difference can be achieved with a change of 20 % relative abundance of Firmicutes and corresponding decrease of Bacteroidetes in the stool of lean individuals. Thus, excessive calories taken in the form of SCFAs from microbiota metabolism of fiber may be a contributing factor in the obese state [80].

Manipulation experiments have shown that germfree animals are resistant to diet-induced obesity compared with conventionally raised animals, regardless of caloric intake [81]. The presence of a microbiota increases serum levels of glucose and SCFAs, which can induce triglyceride production in the liver, and is associated with greater adiposity and reduced glucose tolerance. Bäckhed et al. showed that the gut microbiota regulates an important gut-derived regulator of host lipid metabolism, angiopoietin-like protein 4 (Angptl4), also known as FIAF, or fasting-induced adipose factor [81]. Angptl4 regulates fatty acid oxidation in both muscle and adipose tissue. When a normal mouse microbiota is administered to germfree mice, Angptl4 production is suppressed in the intestine, and a greater proportion of triglycerides are deposited in adipose tissue. Furthermore, germfree mice lacking Angptl4 are no longer protected against diet-induced obesity [81]. The relevance of these findings to human health is underscored by population genetic and metabolic studies in humans showing that ANGPTL4 may be an important regulator of lipid metabolism in humans as well [82]. Another mechanism of microbiota-induced obesity could be its influence upon energy expenditure and appetite. Early work showed that

basal metabolic rate, cardiac output, and body temperature of germfree rats were lower than those of their conventional counterparts, indicating that microbiota may affect energy expenditure in animals. Furthermore, germfree mice consume less food than conventional mice highlighting the role of the microbiota in appetite regulation [83].

### Endocrine Regulation

The gut communicates with the brain using endocrine signals to coordinate energy intake and expenditure. Enteroendocrine cells respond to nutrient intake by secreting incretin hormones, including glucagon-like peptides 1 and 2 (GLP-1 and GLP-2). GLP-1 stimulates insulin release from the pancreas, slows gastric emptying, and promotes satiety and weight loss; GLP-2 stimulates intestinal glucose transport and reduces gut permeability [84, 85]. The gut microbiota can regulate enteroendocrine cells and influence the release of gut hormones and gut permeability [86]. In a series of studies, a connection between gut microbes and levels of both GLP-1 and GLP-2. Endogenous GLP-1 production is promoted by dietary nondigestible carbohydrates (oligofructose); the higher GLP-1 secretion could participate in the control of obesity and associated disorders. Nondigestible fibers were found to promote enteroendocrine L-cell differentiation in the proximal colon, leading to a higher endogenous GLP-1 production, suggesting a new mechanism by which dietary fibers may lower food intake and fat mass development [87].

In yet another distinct pathway, gut microbes have been shown to stimulate gut hormones. Dietary fibers are fermented by gut bacteria into SCFAs. The enteroendocrine cells of the gut have the G-protein receptor *Grp41* for SCFAs which signals the production of peptide YY (PYY), resulting in changes in gut transit and extraction of energy from dietary fiber [88]. SCFAs function both as an energy source and as a signaling molecule, and their abundance and type (e.g., butyrate, propionate, acetate) are directly related to the species composition of the microbiota. Germfree animals exhibit dysregulation of their hypothalamic–pituitary–adrenal axis, leading to an exaggerated stress response, impaired cardiac output, altered brain-derived hormones (e.g., norepinephrine and tryptophan), and increased caloric intake to maintain body weight. Germfree mice, which have a naturally low body weight, gain more body fat after colonization with gut microbiota from obese mouse donors compared with lean mouse donors, without increases in food consumption or obvious energy expenditure. Interestingly, comparisons between the distal gut microbiota of obese and lean individuals, as well as genetically obese and lean mice, have revealed differences in the distal gut microbiota composition and their metabolites.

### Host Genetics

Animal studies have shown that the host genome modulates gut microbiota composition. Obesity caused by a leptin mutation in mice (ob/ob) is associated with altered gut microbiota profiles. Ob/ob mice have decreases in Bacteroidetes phyla, in particular *Bifidobacterium* spp. while increasing the Firmicutes phyla [62]. Thus, the microbiome of obese mice is imbalanced, having a higher Firmicutes to Bacteroidetes ratio which is dictated in part by host genetics but can be manipulated by diet. The gut microbiota profile of mice with a leptin receptor mutation (db/db) has recently been published [89]. In accordance to ob/ob mice, db/db mice cecal microbiota was characterized with higher wealth of phylum Firmicutes and lower abundance of phylum Bacteroidetes compared to the lean mice.

### Inflammation and Insulin Resistance

Low-grade metabolic inflammation is recognized as an important component of obesity and metabolic syndrome as evidence to support the role of inflammation in obesity continues to mount. Diet-induced intestinal inflammation has recently been implicated as an early driver of obesity and insulin resistance

[90]. T2D mellitus and obesity are associated with low-grade inflammation and an altered composition of the gut microbiota. Gut bacterial produces factors that appear to act as a triggering factor in the development of obesity, diabetes mellitus, and inflammation induced by a high-fat diet. One of the ways bacteria can impact inflammation and insulin resistance is through the activity of lipopolysaccharide (LPS), an essential component of the cell walls of gram-negative bacteria. Several experiments have indicated that this bacterial product or endotoxin might be LPS, a component of the cell wall of gram-negative bacteria. In addition to insulin resistance, LPS also induces inflammation. Plasma LPS levels are also higher in participants with obesity and/or T2D [91]. Researchers have shown that subcutaneous infusion of LPS can cause weight gain and insulin resistance in mice without altering energy intake [92]. Accordingly, mice lacking toll-like receptor 4 (TLR4), which recognizes LPS, are resistant to diet-induced obesity and insulin resistance [93]. Furthermore, associations between serum levels of LPS and serum levels of insulin and triglycerides were reported in patients with T2D and obesity [94]. Mice that are deficient in toll-like receptor 5 (TLR5), a transmembrane protein that recognizes bacterial flagellin and regulates immunity and inflammation, spontaneously develop obesity and other features of the metabolic syndrome. Transfer of gut microbiota from TLR5-deficient mice to germfree mice induced obesity and insulin resistance in the recipients, providing further support for the role of microbiota in obesity and metabolic disease [95]. One type of inflammatory molecule that appears to be induced by LPS is the serum amyloid A (SAA) proteins, which exhibit increased levels in the serum of obese persons [96].

Diet may produce inflammation by promoting LPS translocation from the gut into the blood stream to induce an inflammatory response that promotes fat accumulation and interferes with the oxidation of fat. A Western diet rich in energy can increase levels of plasma LPS in humans and mice. A high-fat feeding induces changes in the gut microbiota that lead to metabolic endotoxemia and resultant inflammation [97]. Mice fed with a high-fat diet exhibited enhanced level of LPS while obese and diabetic individuals on a high-fat diet have a tendency to have elevated circulating LPS levels. Infusing a low level of LPS into a male rat causes the same degree of weight gain as feeding a Western high-fat diet for 4 weeks [97]. These investigators demonstrated that rats naturally prone to weight gain on a high-fat diet have intestinal inflammation, inflammation alone can cause weight gain in normal rats, and the absence of inflammation protects rats against weight gain from a high-fat diet. A Western-based high-fat diet has been shown to promote a bloom in Firmicutes and decrease in Bifidobacteria levels in the gut microbiota [60, 98]. Short-term antibiotic administration of obese mice with high LPS has been shown to decrease weight and body fat. Modulation of gut microbiota controls metabolic endotoxemia-induced inflammation in part by improvement in gut permeability.

### Intestinal Permeability

The endotoxin elaborated by bacteria upon systemic absorption promoted the release of inflammatory factors that may contribute towards the development of obesity. The low-grade chronic inflammation of obesity is controlled by gut-derived peptides that are influenced by the gut microbiota. Some of the mechanisms that are involved in the development of metabolic endotoxemia from LPS seem to be related to the fat content of the diet. However, a growing amount of evidence indicates that changes in the integrity of the intestinal barrier occur both in the proximal and the distal part of the gut, which can contribute to the entrance of LPS into the systemic circulation [86]. A breach of the tightness between the gut lining cells aka “leaky gut” can allow either the entire bacteria or bacterial components such as LPS enter the circulation.

Augmenting levels of Bifidobacteria in the gut, either directly as an ingested probiotic or indirectly with bifidogenic prebiotics, have been shown to reduce inflammation and improve glucose tolerance [99]. Greater levels of Bifidobacteria have also been associated with reduced gut leakiness, allowing less LPS to translocate to the serum [100]. Thus, a high-fat diet is thought to modulate the composition of the gut bacteria (notably by reducing levels of Bifidobacteria), which increases gut permeability and allows higher LPS plasma levels.

## *The Role of Diet in Altering Microbiome in Obesity*

Diet may alter the composition of the microbiota to facilitate weight gain. In particular, examination of the role of the Western diet-associated cecal microbiota in facilitating weight gain has revealed that ex-germfree mice receiving via fecal transplantation the microbiota from mice fed a Western diet gained significantly more body fat than the mice receiving the normal chow diet-associated gut microbiota [62]. While the host genotype has been proven to affect microbiota, the effect of diet, specifically dietary fat, also plays an important role in determining bacterial composition and promoting LPS translocation and systemic inflammation.

A high-fat-fed animal displays a significant shift in both bacterial and metagenomic profiles as compared to an animal on a normal, chow diet [60]. Western diet-associated cecal microbiota is characterized with a reduction in the relative abundance of Bacteroidetes and an increase in the relative abundance of Firmicutes. The number of bacteria belonging to the phylum Firmicutes increases dramatically following the consumption of a high-fat Western diet and does so within 24 h [101]. Mice fed an obesogenic high-fat Western diet overexpressed genes that drive fat accumulation and sugar processing [60, 102]. Mice fed a high-carbohydrate, high-fat Western diet developed more adipose tissue and exhibited greater glucose intolerance than germfree mice that were fed a standard diet [103, 104]. In contrast, obese mice fed a diet rich in fermentable prebiotic foods can switch the microbiome back to a higher Bacteroidetes to Firmicutes ratio and increase Bacteroides species (see below). Thus the quality of the diet instead of the weight of animals is a stronger modulator to the composition of the gut microbiota. The gut microbiota is involved in multiple elements of energy metabolism, including energy harvest, metabolic rate, and energy storage. Diet impacts the phenotype of the core microbiome and shifts the bacterial balance either towards or away from obesity.

*Key point*. Diet is a primary factor in determining the composition of the gut microbiota and can rebalance the inner flora an obesogenic microbiota.

In summary, the gut microbiota is a central component of the host's phenotype. The host's intrinsic characteristics (i.e., age, gender, genetic background, gut motility, and immune function), diet (nondigestible carbohydrates, fat, prebiotics, probiotics), and antibiotic use influence the composition and metabolic activity of the gut microbiota. Obesity is associated with phylum-level changes in the microbiota, reduced bacterial diversity, and altered representation of bacterial genes and metabolic pathways. Changes in the gut microbiota affect the processes involved in energy storage and influence gene expression in various tissues of the host with regard to fat mass development, glucose tolerance, insulin sensitivity, inflammation, fatty liver, satiety, and the efficiency of energy metabolism. Collectively, the influence of the gut microbiome on these factors contributes to the occurrence of metabolic disorders associated with obesity (Table 7.2).

### Manipulation of the Gut Microbiota to Influence Health

There are numerous studies confirming the health benefits of manipulating the microbiome. The gut microbiome can be manipulated by the consumption of friendly bacteria, fermented foods that are rich in friendly bacteria, and foods that selectively feed the friendly bacteria or by instilling donor fecal bacteria into the gut lumen. The most common methods to manipulate the gut microbiome are through dietary alterations and probiotic administration.

## *Dietary Manipulation of the Microbiome: The Prebiotic Effect*

Diet is a major factor driving the composition and metabolism of the colonic microbiota. The amount, type, and balance of the main dietary macronutrients (carbohydrates, proteins, and fats) have a great

**Table 7.2** Conditions associated with alterations of the gut microbiota (dysbiosis)

| |
|---|
| Autism [105, 106] |
| Allergic disorders [107] |
| Autoimmune disease |
| Bacterial vaginosis |
| Cardiovascular disease |
| Dental caries |
| Dermatological disease |
| Diabetes |
| Gastrointestinal disease |
| Colorectal cancer |
| Gallstones |
| Infectious colitis |
| Diverticulitis |
| Irritable bowel syndrome |
| Inflammatory bowel disease |
| Peptic ulcer disease |
| Liver disease |
| Mood disorders |
| Obesity |
| Rheumatoid arthritis |

impact on the large intestinal microbiota. Prebiotics have been defined as selectively fermented ingredients that allow specific changes, both in the composition and activity in the gastrointestinal microflora that confer benefits upon host well-being and health.

Which foods are loaded with fermentable carbohydrates and provide a prebiotic effect by stimulating the growth of *Bifidobacterium* spp.? The most extensively tested foods in the literature occur naturally in several foods such as leek, asparagus, chicory root, Jerusalem artichoke, yacon, garlic, artichoke, onion, wheat, banana, jicama and oats, as well as soybean. Changes in the microbiota's composition, especially increase in *Bifidobacterium* spp., can be regarded as a marker of intestinal health. Prebiotics have routinely been screened for their ability to selectively promote *Bifidobacterium* spp. Many studies, therefore, have shown increases in *Bifidobacterium* spp. following dietary supplementation with fructans and galacto-oligosaccharides (GOS) [108].

Currently and mostly for historical reasons, the majority of the scientific data (both experimental and human) on prebiotic effects have been obtained using food ingredients/supplements belonging to two chemical groups, namely inulin-type fructans (ITF) and the GOS. Fructooligosaccharides (FOS) can be produced by enzymatic degradation of inulin. A large number of human intervention studies have been performed that have demonstrated that dietary consumption of certain food products can result in statistically significant changes in the composition of the gut microbiota in line with the prebiotic concept. Thus the prebiotic effect is now a well-established scientific fact.

The prebiotic effect has been shown to associate with a beneficial modulation of biomarkers and activities of the immune system. Infants who were fed with cereal supplemented with prebiotics have reduced the risk of gastroenteritis and infections, improved general well-being, and lowered the incidence of allergic symptoms such as atopic eczema [109]. The aforementioned changes in the gut microbiota composition are classically considered as one of the many factors involved in the pathogenesis of either IBD or irritable bowel syndrome. The use of prebiotic food has shown promising beneficial effects including changes in gut microbiota composition and improved clinical outcomes [110]. Often associated with toxic load and/or miscellaneous risk factors, colon cancer is another pathology for which a possible role of gut microbiota composition has been hypothesized [111]. Numerous experimental studies have reported reduction in incidence of tumors and cancers after feeding specific

food products with a prebiotic effect [112]. Some of these studies (including one human trial) have also reported that, in such conditions, gut microbiota composition was modified (especially due to increased concentration of *Bifidobacterium* spp.) [113].

Dietary intake of particular food products with a prebiotic effect has been shown, especially in adolescents but also tentatively in postmenopausal women, to increase calcium and magnesium absorption as well as bone calcium accretion and bone mineral density [114]. Recent data, both from experimental models and from human studies, support the beneficial effects of food products with prebiotic properties on energy homeostasis, satiety regulation, and body weight gain [115, 116]. Carbohydrates showing a prebiotic effect have received special attention in this context, since they have been shown—mostly in experimental animal studies—to regulate food intake and weight gain, as well as metabolic disorders associated with obesity, such as liver steatosis, dyslipidemia, diabetes, and/or even hypertension [117]. Prebiotics improve glucose and lipid homeostasis [118].

Together with data in obese animals and patients, these studies support the hypothesis that gut microbiota composition (especially the number of *Bifidobacterium* spp. *but also of other bacteria such as Faecalibacterium prausnitzii or Akkermansia muciniphila*) may contribute to modulate obesity and T2D [119–121]. Certain fermentable carbohydrates with prebiotic properties can counteract the overexpression of several host targets that are involved in the development of adiposity, metabolic disorders, and inflammation. There are data to support that prebiotic food stuff that select for the growth of *Bifidobacterium* spp. may combat obesity. Dietary fructans, which are present in various fruits and vegetables and added to food products, are used as an energy substrate by bacteria which have been found to decrease appetite, fat mass, hepatic insulin resistance by regulating gut hormones [118]. Fructan administration was able to increase *Bifidobacterium* spp. levels in high-fat diet-fed mice quite selectively with negative correlations of bacterium levels and glucose tolerance, visceral fat mass, fasting insulinemia, plasma LPS level, and inflammatory markers [92].

Changes in the composition of the gut microbiota at childhood may predict the future development of obesity. Overweight mothers give birth to neonates that have a decreased number of *Bifidobacterium* spp. [66]. A lower number of *Bifidobacterium* spp. at birth have been associated with being overweight later in childhood; thus, obesogenic microbiota is an "inheritable" trait [122]. The number of *Bifidobacterium* spp. has been inversely correlated with the development of fat mass, glucose intolerance, and LPS level. *Bifidobacterium* spp. have been found to produce conjugated linolenic acid (CLA) from polyunsaturated fatty acids. CLA in mice has been shown to reduce fat mass and weight and improve diabetes [123].

Eating a high-fat Western diet has been shown to shift the gut microbiota in obese mice towards more efficient carbohydrate fermentation and energy extraction [124]. Thus, eating an unhealthy Western diet creates a double whammy effect—high caloric density meals cause the microbiome to extract unneeded excess energy from food.

What is the clinical evidence to support the potential role for dietary manipulation of the microbiome to treat obesity? The addition of fermentable carbohydrates with prebiotic properties (ITF) into the diet lessens the fat mass development in obese mice or human subjects [125]. Some beneficial effects of fructans on BMI, waist circumference, fat mass, and/or insulin resistance were shown mainly in experimental models of obesity but also in the limited studies in humans [126–131].

A clinical trial of 48 individuals with overweight or obesity was randomized to insulin-like dietary fructan prebiotics or placebo. Those who received the prebiotic had reduced body weight, caloric intake, postprandial glycemia, and insulin [132]. Gut hormones were involved in the favorable results on appetite regulation; ghrelin which stimulates appetite was decreased while PYY which decreases appetite was increased. Gut bacteria-derived compounds can affect liver metabolism and cause local and systemic disease. Obesity and fatty liver are associated with elevated serum level of LPS which is a major component of the gram-negative bacteria. LPS stimulates hepatic and systemic inflammation causing deranged glucose and lipid metabolism in the liver and in adipose tissue. Increased LPS in the enteric cavity leads to gut mucosal barrier damage and metabolic endotoxemia [133].

Importantly, it has been recently demonstrated that obesity and NAFLD are associated with increased gut permeability, dysbiosis, endotoxemia, inflammatory mediators, and insulin resistance [86, 134]. Compelling data obtained in animals and humans provide evidence that changing the gut microbiota by using prebiotics or probiotics has a salutary effect on the development of liver diseases by restoring gut permeability which restricts hepatic endotoxin and inflammation [51]. There is a cannabinoid receptor system inside the gut lining which upon activation increases permeability. In obesity, the endocannabinoid system is activated and prebiotics improve barrier function in obesity in part by blunting its activation [135]. Altogether, these studies strongly suggest a direct link between the gut microbiota, the gut barrier function (leaky gut), and hepatic alterations.

In summary, prebiotics change the composition of the gut microbiota which is associated with restored gut integrity, and plasma LPS levels (metabolic endotoxemia) are lowered. The modulation of the gut microbiota is associated with specific changes in the plasma gut peptide profiles [enhanced GLP-1, GLP-2, and PYY which decrease appetite and reduced ghrelin which stimulates appetite] [116]. Altogether, these effects are associated with a decrease in hunger, body weight, fat mass, T2D, gut permeability, and low-grade inflammation characterizing obesity.

## *Manipulation of the Microbiome: The Probiotic Effect*

The hypothesis of the beneficial effects of ingested bacteria on human health has a long tradition in medicine. First references date back to the Nobel Prize laureate Ilia Ilyitsch Metchnikoff from Georgia, Caucasus, who reported a long life to be associated with the bacteria in yogurts [136, 137]. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. The ability of probiotics to survive and thrive in this complex ecosystem is accomplished by their ability to withstand high concentrations of acids and enzymes as well as eliminate competitive pathogens. The source of probiotic bacteria should be of human origin. Over the last two decades, there has been a growing interest on both basic and clinical science in probiotics. This has resulted in more than 9,000 publications in the biomedical literature, with the majority published since 2008 including articles in the highest-ranking medical and basic scientific journals. Gut microbiota deviations have been associated with enhanced risk of specific diseases; therefore, modulation of an unbalanced indigenous microbiota forms the rationale of probiotic therapy. Some of the beneficial effects of probiotic consumption include improvement of intestinal health by the regulation of microbiota and stimulation and development of the immune system, synthesizing and enhancing the bioavailability of nutrients, reducing symptoms of lactose intolerance, imparting numerous health benefits, and reducing the risk of a number of conditions (Table 7.3).

### Probiotic Foods

We previously discussed how prebiotic foods help the friendly flora proliferate, but there are fermented foods that contain friendly bacteria (Table 7.4).

Kefir is a popular health drink in many European countries that is produced by adding kefir grains to milk and fermented for 24 h. The bacteria in kefir grains *Lactobacillus kefiranofaciens* and *Lactobacillus delbrueckii subspecies bulgaricus* produce what is known as kefiran, a gel-like polysaccharide. In experiments conducted on animals, kefiran was found to exhibit antitumor and anti-inflammatory properties. It also reduced blood pressure, blood glucose, and cholesterol levels in rats. The fermentation of milk by the bacteria and yeasts in kefir starter breaks down lactose in the milk. That's why kefir is suitable for those who are otherwise lactose intolerant. Nondairy kefir is made from sugary water, coconut water, and fruit juice. To distinguish between different types of

**Table 7.3** Health benefits of probiotic bacteria to the host and speculated mechanisms involved

| Health benefits | Proposed mechanisms involved |
|---|---|
| Resistance to enteric pathogens | Antagonism activity |
| | Adjuvant effect increasing antibody production |
| | Systemic immune effect |
| | Colonization resistance |
| | Limiting access of enteric pathogens (pH, bacteriocins/ defensins, antimicrobial peptides, lactic acid production, and toxic oxygen metabolites) |
| Aid in lactose digestion | Bacterial lactase acts on lactose in the small intestine |
| Small bowel bacterial overgrowth | Lactobacilli influence the activity of overgrowth flora, decreasing toxic metabolite production |
| | Normalization of a small bowel microbial community |
| | Antibacterial characteristics |
| Immune system modulation | Strengthening of nonspecific and antigen-specific defense against infection and tumors |
| | Adjuvant effect in antigen-specific immune responses |
| | Regulating/influencing Th1/Th2 cells, production of anti-inflammatory cytokines |
| | Decreased release of toxic N-metabolites |
| Chemoprevention of colon cancer | Antimutagenic activity |
| | Detoxification of carcinogenic metabolites |
| | Alteration in pro-cancerous enzymatic activity of colonic microorganisms |
| | Stimulation of immune function |
| | Influence on bile salt concentration |
| Decreased detoxification/excretion of toxic microbial metabolites | Increased *Bifidobacterium* spp. l cell counts and shift from a preferable protein- to carbohydrate-metabolizing microbial community, less toxic and for putrefactive metabolites, improvements of hepatic encephalopathy after the administration of *Bifidobacterium* spp. and lactulose |
| Allergy | Prevention of antigen translocation into blood stream |
| | Prevent excessive immunologic responses to increased amount of antigen stimulation of the gut |
| Blood lipids, heart disease | Assimilation of cholesterol by bacterial cell |
| | Alteration in the activity of BSH enzyme |
| | Antioxidative effect |
| Antihypertensive effect | Bacterial peptidase action on milk protein results in antihypertensive tripeptides |
| | Cell wall components act as ACE inhibitors |
| Urogenital infections | Adhesion to urinary and vaginal tract cells |
| | Competitive exclusion |
| | Inhibitor production ($H_2O_2$, biosurfactants) |
| Infection caused by *Helicobacter pylori* | Competitive colonization |
| | Inhibition of growth and adhesion to mucosal cells, decrease in gastric *H. pylori* concentration |
| Hepatic encephalopathy | Competitive exclusion or inhibition of urease-producing gut flora |
| Neutralization of dietary carcinogens | Production of butyric acid neutralizes the activity of dietary carcinogens |
| Necrotizing enterocolitis (necrotic inflammation of the distal small intestine) | Decrease in TLRs and signaling molecules and increase in negative regulations |
| | Reduction in the IL-8 response |
| Rotaviral gastroenteritis | Increased IgA response to the virus |

(continued)

**Table 7.3** (continued)

| Health benefits | Proposed mechanisms involved |
|---|---|
| Inflammatory bowel diseases, type 1 diabetes | Enhancement of mucosal barrier function |
| Crohn's disease | Reduction in proinflammatory cytokines including TNFα, reduction in the number of CD4 cells as well as TNFα expression among intraepithelial lymphocytes |
| Caries gingivitis | Reduction in gingivitis by *L. reuteri*, affects on streptococcus mutants, colonization of the teeth surface by lactobacilli |
| | Less carries after the ingestion of living or oral vaccination with heat-killed lactobacilli |
| Enhanced nutrient value | Vitamin and cofactor production |

**Table 7.4** Probiotic foods

| |
|---|
| Kefir |
| Kimchi |
| Kombucha tea |
| Milk products (added probiotics) |
| Microalgae |
| Miso soup |
| Natto |
| Pickles |
| Sauerkraut |
| Soy milk (added probiotics) |
| Tempeh |
| Yogurt |

*NB*: Probiotics can be added to foods that naturally do not contain bacteria such as pasteurized milk, soy milk, and dark chocolate

kefir, dairy kefir is also called milk kefir, while nondairy ones are generally known as water kefir. Interestingly, kefir has been shown to have a number of health benefits: anti-inflammatory, anti-allergy, anticarcinogenic, and low-density lipoprotein (LDL) cholesterol-lowering benefit [138]. Kefir has anti-fat-forming effects that may explain in part the benefit of fermented milk in fighting obesity in one clinical trial [139].

Kimchi is a pickled dish that is created by mixing a main ingredient such as cabbage with a host of other seasonings and ingredients, like hot pepper flakes, radish, carrot, garlic, ginger, onion, salt, and fish sauce. Chinese cabbages are the main ingredient in kimchi, but there are countless other variations that are made with cucumbers, eggplants, leeks, radishes, and other in-season vegetables. The mixture is then left aside to ferment from a few days to a couple of weeks. Kimchi contains the bacterium called *Lactobacillus kimchii* as well as other lactic acid bacteria that are beneficial to our gastrointestinal as well as immune systems. A typical kimchi made with Chinese cabbage, carrot, garlic, ginger, onion, and pepper is also high in vitamins A, C, B1, and B2, beta-carotene, calcium, and iron. Kimchi consumption has been shown to reduce allergies and produces a metabolic lean effect by lowering body weight and improving cardiovascular and inflammatory markers in obese and overweight adults [140].

Sauerkraut is the Western counterpart of kimchi, except that it doesn't contain as much seasonings and ingredients the way kimchi does. It's produced by allowing salted cabbage to ferment on its own without the addition of any starter or vinegar for two weeks or more and is a good source of natural lactic acid bacteria. Miso is produced by fermenting soybean, barley, brown rice, or other grains with a type of fungus known as koji (*Aspergillus oryzae*) in Japan. The fermentation process produces a

paste with a buttery texture. The soy isoflavones contained in miso soup impart a number of health benefits including cardiovascular, bone health, cancer protection, and even obesity; however, the probiotic effects of miso itself are not well studied [141–143].

Kombucha tea (K-tea) has been around for more than 2,000 years and has a rich anecdotal history of preventing and fighting cancer, arthritis, and other degenerative diseases. Kombucha is made from sweetened tea that's been fermented by a symbiotic colony of bacteria and yeast. Brewers rely on what's called a starter a bit of already fermented tea that is passed between makers and referred to reverentially as "the mother." This "mother" will expand and split into smaller patties called "babies," which brewers often give to friends or sell online. Once the mother is added to sweetened tea and allowed to sit in a glass jar unrefrigerated for 7–14 days, a glop known as a symbiotic colony of bacteria and yeast grows over the surface. K-tea has been found to have anti-stress effects and impressive hepatoprotective properties with reversal of carbon tetrachloride-induced liver toxicity [144–146]. K-tea in animal models of diabetes was found to improve blood lipids, glucose control, and reverse liver and kidney damage [147]. Mice consuming K-tea exhibited reduced appetite, food and beverage consumption, and weight [148]. Toxicity has been a concern following the two reports of toxicity in HIV-positive individuals after drinking K-tea [149, 150]. Studies on rats have not shown that kombucha consumption produces toxicity [151].

One of the best probiotic foods is live-cultured yogurt, especially handmade which can contain up to 100 times as many live cultures per serving when compared to store-bought brands. Look for brands made from goat milk that have been infused with extra forms of probiotics like lactobacillus or acidophilus. Goat's milk and cheese are particularly high in probiotics like thermophilus, bifidus, bulgaricus, and acidophilus.

There are several lines of evidence demonstrating that yogurt may prevent obesity. A clinical study of over 120,000 individuals that was reported in the New England Journal of Medicine showed that nonobese healthy individuals who consumed yogurt lost weight [152]. A study of 212 Korean women reported similar findings—lower-weight females consumed yogurt at least one serving daily [153]. Another Korean study demonstrated that consumption of a specially formulated yogurt NY-YP901 improved blood lipids, cardiovascular markers, and induced weight loss in obese individuals with the metabolic syndrome [154]. Elderly individuals who were fed yogurt in attempt to improve constipation were instead only found to lose significant body weight [155]. Consumption of Olibra yogurt was found to decrease body weight and post-meal hunger. The investigators measured that those who consumed yogurt had higher levels of a gut-derived hormone-GLP-2, which suppresses appetite [156]. An isocaloric substitution of yogurt has been shown to preserve lean muscle mass while augmenting fat loss, improving waist circumference, and reducing central adiposity during energy restriction [157].

Tempeh is another probiotic food derived from fermented soybeans. The primary probiotic in tempeh is *Rhizopus oligosporus* which produces a natural antibiotic against enteric pathogens and produces phytase which helps to break down phytate acid which increases the absorption of minerals. Interestingly, fermented soy paste has been shown to reduce visceral fat accumulation [158]. Natto is made from fermented soybeans which contains the bacterial strain *Bacillus subtilis* (used to be known as *Bacillus natto*) which gives its characteristic stringy consistency. Aside from being a probiotic source and containing soy, natto contains the enzyme nattokinase which dissolves dangerous blood clots [159]. Like miso and natto, the protein and other nutrients in soybean become more digestible after it's broken down by bacteria or mold. That's why fermented bean products like tempeh wouldn't case the same symptoms that are associated with eating beans. In addition, since tempeh is not salted, it's suitable for people who are on low-sodium diet.

Soy itself may impart an anti-obesity benefit. Several nutritional intervention studies in animals and humans indicate that consumption of soy protein reduces body weight and fat mass in addition to lowering plasma cholesterol and triglycerides [160]. In animal models of obesity, soy protein ingestion limits or reduces body fat accumulation and improves insulin resistance, the hallmark of human obesity [161]. In obese humans, dietary soy protein also reduces body weight and body fat mass in addition to reducing plasma lipids.

### Probiotic Supplements and Obesity

There is evidence for probiotic supplements reversing obesity. Studies which have evaluated the quantities of *Lactobacillus* spp. belonging to the Firmicutes phylum in obese subjects have shown inconsistent results. Several strains of lactobacilli have been tested as a probiotic approach in experimental models of obesity and in humans. Specific strains of *Lactobacillus plantarum* and *Lactobacillus paracasei* spp. reduce adipocyte cell size and body fat in high-fat diet-fed mice [104, 162]. In individuals with obesity, the administration of different strains of *Lactobacillus* has been shown to decrease fat mass and the risk of T2D mellitus and insulin resistance [163, 164].

Analyses of fecal microbiota pre- and post-manipulation have raised eyebrows about the potential role of probiotics in the treatment of obesity. Roux-en-Y gastric bypass surgery (RYGP) entails the creation of a small gastric pouch from the proximal stomach, and the distal stomach and proximal small intestine are bypassed. RYGP is known to be complicated by SIBO with resultant impaired vitamin B12 absorption, and the stomach chambers formed in RYGP surgery are colonized by bacteria to a greater extent than the normal stomach [68]. Interestingly, the administration of probiotic microbes after the procedure has been shown to improve post RGBY outcomes, accelerate weight loss, and improve SIBO and vitamin B12 availability [165].

Finally, compelling evidence suggests that early gut microbiota modulation with probiotics (i.e., lactobacilli) strongly reduces the BMI in young children by restraining excessive weight gain during the first years of life (from 0 to 10 years of follow-up) [166]. All of these data support an improvement of obesity and related disorders by lactobacilli supplementation.

### Fecal Bacteriotherapy

Fecal bacteriotherapy (FBT) is the transfer of intestinal flora from one individual to another which reestablishes balance to the intestinal flora. The origins of FBT stem back to the fourth-century China when human feces were consumed to treat food poisoning and chronic diarrhea [167]. In Western society the first use of FBT was used in veterinary medicine in the seventeenth century for chronic gastrointestinal infections [168]. The first human study using FBT was for *Clostridium difficile-associated* pseudomembranous colitis in 1958 [169]. *C. difficile* became the most commonly identified cause of nosocomial infectious diarrhea in the United States. During the past decade, there has been an alarming increase in the incidence and severity of this disorder, with associated increases in mortality and economic cost. The preponderance of literature for the use of FBT in humans is for chronic and recurrent *Clostridium difficile* infection whereby the cure rate is greater than 90 % for over 400 reported cases in the medical literature [65]. FBT provides a therapeutic benefit by reintroducing a balanced microbiota via donor feces and resolving the underlying dysbiosis. *Clostridium difficile* colitis is associated with a depletion of the Bacteroidetes phyla which is replete after transplantation. This is the phylum that is felt by gut microbiome experts to fight obesity. Studies have shown that after FBT the recipient's stool closely resembles the donor's microbiome which persists for at least 30 days after FBT and 3 months in rats—the transplanted microbiome is stable for at least one year in the absence of antibiotics. No long-term studies have been performed to date. How does FBT compare to oral administration of probiotics? FBT is felt to have a long-term influence on the reestablishment of the intestinal microbiota in recipients whereas oral administration of probiotic bacteria rapidly diminishes with only 50 % of the original strains present after 3 weeks of administration [170]. Thus, probiotic use needs to be perpetual to reap its benefits whereas FBT generally needs only 1 treatment for *Clostridium difficile* infection. Dysbiosis has been linked to many chronic illnesses (Table 7.2) and consumption of probiotics ameliorates disease by restoring a healthy microbiota, eubiosis (Table 7.3). Thus, the use of FBT to rebalance the gut microbiome and treat conditions is being actively investigated for a number of conditions.

The use of FBT for IBD was first reported in 1989 by a physician who had ulcerative colitis that was nonresponsive to medications—the disease was placed into remission after large volume retention enemas containing donor stool [171]. There are nine reported cases of FBT for IBD in the literature—all using retention enemas and improving symptoms [172]. Eight patients with ulcerative colitis undergoing FBT had complete resolution of their UC symptoms with cessation of their medications within 6 weeks with sustained remission lasting up to 13 years. Dr. Borody has preliminary evidence showing that FBT may be beneficial for other chronic conditions including constipation, chronic fatigue syndrome, multiple sclerosis, myoclonic dystrophy, autism, and Parkinson's disease [173].

Other indications for FBT are IBD, irritable bowel syndrome, and prevention of colorectal carcinoma, to name just a few, but the question at hand is whether FBT can become a tool to treat obesity and metabolic syndrome? Experiments in lean and genetically programmed obese animals have used FBT to manipulate the gut microbiome and alter body weight. Obese mice have an increased capacity to harvest energy compared to lean counterparts—having a higher Firmicutes to Bacteroidetes ratio. Characteristics of the gut microbiota contribute to the host's phenotype. If an altered gut microbiota is transplanted into germfree recipients, the functional characteristics of the donor microbiota can be transferred as well, hence the term infectobesity. FBT of the stools of conventionally raised mice into germfree mice raises their body weight and insulin resistance by 60 % [62]. The leptin-resistant obese (ob/ob) phenotype has been shown to be established in germfree mice after undergoing FBT with the intestinal microbiota from the ob/ob mice [35]. Furthermore, dietary alteration of the microbiome to an obese phenotype is also transmissible to the host. The microbiota from conventionally raised mice who were fed a high-fat Western diet were transplanted into germfree mice. The recipient mice became obese despite being fed with a standard low-fat, low-carbohydrate diet [60].

Is the opposite true? Can one be protected against the development of obesity by transfer of the microbiome from a lean individual? Experiments in diabetic mice are suggestive. Nonobese diabetic (NOD) mutant mice, which are prone to develop type 1 diabetes mellitus, were protected from the disease if a crucial gene for diabetes was ablated, and this protection could be transferred to germfree recipients [174]. A double-blind randomized controlled trial on the use of FBT for diabetes and obesity was conducted in 18 male subjects [175]. Half of the patients received fecal material from lean male donors, and the other half were implanted with their own feces as controls. After transplantation of fecal flora from lean donors, fasting triglyceride levels in patients with the metabolic syndrome were markedly reduced; no effect was observed in the control group re-instilled with their own feces. In addition, peripheral and hepatic insulin sensitivity markedly improved after 6 weeks in the lean donor group. Another study by Vrieze et al. described a clinical trial of fecal transfer from lean to obese individuals resulting in an increase in insulin sensitivity in the recipients [176].

There has been no consensus regarding volume, route of instillation, treatment given before FBT, or screening tests for donors. The most common method until 1989 was retention enema; however, nasogastric tube, self-administered enemas, and colonoscopy are being used with good results. Colonoscopy is the preferred method for FBT by clinicians since it permits seeing of the microbiome throughout the colon and requires only one treatment in many cases. On the other hand, self-administered enemas require frequent administration, have a longer duration of therapy, and are unpleasant to undergo.

The safety of fecal transplantation has never been formally investigated and clinicians have expressed concerns about FBT "opening up a can of worms" [177]. A rigorous screening process for donors is conducted, generally household or family members who are without evidence of gastrointestinal infections, viral hepatitis, HIV1 and HIV2, and syphilis. A systematic review on some 300 patients describes only minor side effects similar to irritable bowel syndrome symptoms. However, a recent review of 77 patients reports that two of the patients who underwent FBT had an improvement in their preexisting allergic sinusitis and arthritis, while four other patients reported a new medical condition after FBT: peripheral neuropathy, Sjogren's disease, idiopathic thrombocytopenic purpura, and rheumatoid arthritis [178, 179].

New knowledge such as the metagenome systems biology described above may pave the way to more targeted, safer approaches to the problem, if the foundation for the obese phenotype lies in reduced diversity. For example, it may be possible to evaluate the gut microbial ecosystem of an obese individual and to supply particular taxa (possessing particular, missing metabolic potential) to "patch up" the dysbiotic microbial community and restore balance to the ecosystem. Although not practically possible at present, knowledge and technology are rapidly advancing to the point where such personalized medicine will become mainstream in the not-too-distant future. At the present time the best approach to rebalancing the microbiome away from dysbiosis is to strategically starve off pathogens then repopulate and cultivate an ecosystem of health.

## Conclusions

We are all covered in trillions of microbes—in fact, they outnumber human cells 10:1. The trillions of bacteria that live on and in us are collectively called the microbiome. Like the rainforest, the healthy human microbiome is a balanced ecosystem. The correct balance of microbes keeps potential pathogens in check and regulates our immune system. Microbes also perform essential functions such as digesting food and synthesizing vitamins. An inner world of life exists in the deepest recesses of our inner being, the gut microbiota. A renaissance of research is uncovering its wide-sweeping influence on health and disease, in particular how the gut microbiota can regulate metabolism and influence body weight.

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# Chapter 8
# Nutritional Assessment in Obese Patients

**Michele Nicolo, James R. Henry, Cara Stewart, Cecelia Pompeii, Joseph I. Boullata, and Charlene Compher**

**Abstract** As the prevalence of obesity has risen, clinicians must evaluate nutritional status across a range of patient obesity levels and in varied clinical settings. Assessment of the nutritional status of obese patients may be challenging but follows the same schema as for undernourished patients. Patients who undergo bariatric surgery are cared for by multiple nutrition professionals at varied times relative to surgery. The early nutritional assessment evaluates the suitability for surgery and needed lifestyle modifications including dietary, nutritional supplement, and physical activity behaviors. If patients have a surgical complication, they may require a short course of parenteral nutrition that will require assessment of nutrient intake requirements. If patients fail to thrive, most typically at later times after malabsorptive surgical procedures, assessment for micronutrient deficiencies may also be indicated.

**Keywords** Obesity • Bariatric surgery • Nutrient deficiency • Nutritional assessment • Gastric bypass • Sleeve gastrectomy • Gastric band

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**Key Points**

- As the prevalence of obesity rises, clinicians must evaluate nutritional status across a range of patient obesity levels and in varied clinical settings.
- Assessment of the nutritional status of obese patients may be challenging but follows the same schema as that for undernourished patients.
- Patients who undergo bariatric surgery are cared for by multiple nutrition professionals at varied times relative to surgery.
- The early nutritional assessment evaluates the suitability for surgery and needed lifestyle modifications including dietary, nutritional supplement, and physical activity behaviors.
- If patients have a surgical complication, they may require a short course of parenteral nutrition that will require assessment of nutrient intake requirements.
- If patients fail to thrive, most typically at later times after malabsorptive surgical procedures, assessment for micronutrient deficiencies may also be indicated.

Assessment of the nutritional status of obese patients is an essential first step in the care process. While most nutritional assessment programs have focused largely on undernourished patients, obese patients also have increased health risks and merit evaluation. The Academy-American Society for Parenteral and Enteral Nutrition (ASPEN) Consensus approach to nutritional assessment may include subjects who are obese [1, 2].

The Academy-ASPEN approach considers an adult's disease-associated inflammatory challenge in the context of their patterns of loss of weight, fat, and muscle mass and their food intake history. Patients who experience an acute medical or surgical illness or injury are likely to have a powerful inflammatory response that will challenge the adequacy of their body muscle mass and fat stores to provide needed nutrients. Many patients also experience chronic medical conditions such as cardiovascular disease, diabetes, arthritis, gastrointestinal, or other conditions for which a low-grade inflammation has been described [1]. The condition of obesity itself may be associated with low-grade inflammation. While these inflammatory conditions cannot be ameliorated with nutritional therapy, they should be considered as a risk to a patient's nutritional status.

The assessment of patients with obesity begins with calculation of the body mass index (BMI) in weight (kg)/height ($m^2$). Several levels of obesity have been described by NHLBI [3] and are used globally to identify obesity:

BMI 30–34.9 (class I obesity).
BMI 35–39.9 (class II obesity).
BMI $\geq$ 40 (severe obesity).

In the general population, the risk of chronic health conditions increases with increasing BMI. Weight loss improves many of these health conditions. On this basis, many obese patients are encouraged to lose weight, a goal that can be quite difficult to achieve.

Weight loss history in subjects with obesity should include whether the loss was intentional or unintentional. If the weight loss was unintentional, some underlying disease or condition may be suspected and may result in loss of muscle mass. The weight loss in obese patients should be calculated as a percentage of their usual body weight and considered in the context of time. By the Academy-ASPEN framework, weight loss of 5 % over 1 month, 7.5 % over 3 months, 10 % over 6 months, or 20 % over 12 months is one criterion for moderate malnutrition though two criteria are required for the diagnosis. Weight loss greater than these amounts over the same time frames is a criterion for severe malnutrition. Loss of weight may be masked by the presence of edema. In the obese population, edema may be difficult to detect and therefore make it problematic to ascertain if weight loss has occurred. The presence of edema on physical exam whether moderate or severe qualifies as a contributing factor for diagnosis of malnutrition.

Given the challenges of assessing weight loss in the obese population, it may be beneficial to measure lean body mass. Loss of muscle mass and fat mass may be challenging to observe by physical

examination in an obese subject without some measurement of body composition. Bioelectrical impedance analysis (BIA), while not commonly available in clinical settings, might provide measures of change in body composition in patients who are seen repeatedly. A second alternative is the calculation of lean body mass (LBM) based on equations validated by both BIA and dual X-ray absorptiometry measures in subjects with BMI 17–70 kg/m$^2$ [4, 5]:

- Men (9,270)(kg)/(6,680 + 216(BMI))
- Women (9,270)(kg)/(8,780 + 244(BMI))

By evaluation of a subject's measured weight history over time, a loss in LBM could also be calculated based on weight (kg) and BMI (kg/m$^2$). The Academy-ASPEN framework considers mild, moderate, or severe loss of muscle mass to be indicative of malnutrition, but no objective measures or percentages are given by contrast to weight loss. Patients who have lost weight may be able to self-report their perception of loss of muscle mass, strength, or physical function. Measurement of muscle strength by use of hand grip dynamometry has been recommended by the Academy-ASPEN framework, but would also require repeated measures in obese subjects to show change.

Change in usual food intake is also a component of the nutritional assessment. Energy intake <75 % of requirements or usual intake for more than 1 week in patients with acute illness or injury or the same reduce intake over 1 month in patients with chronic (but not acute) illness or that level of intake over 3 months in patients with compromised social or environmental circumstances is a component of moderate malnutrition by the Academy-ASPEN framework. When energy intake is ≤50 % of requirements or usual intake over similar time windows, a component for severe malnutrition has been reached.

The Academy-ASPEN framework requires two components from evaluation of weight loss, reduced food intake, loss of fat mass, loss of muscle mass, loss of muscle function, or edema to be attained in order to justify a diagnosis of moderate or severe malnutrition [2]. The assessment of patients with obesity, using this framework, will undoubtedly be refined over time.

## Severe Obesity Treated with Bariatric Surgery

Nutritional assessment of the bariatric surgery patient spans several phases of care. The initial nutritional assessment that is part of the bariatric surgery preoperative evaluations assesses a relatively stable obese patient preparing for an elective weight loss surgery and includes evaluation of education needs. Postoperatively, clinically stable bariatric surgery patients are evaluated in clinical settings for weight loss patterns, diet advancement and educational needs, and symptoms of diet or supplement intolerance. When patients are admitted to the hospital, the nutritional assessment will include evaluation of nutrient deficiencies or therapies. The purpose of this chapter is to highlight the components of and rationale for nutritional evaluation over these varied times.

## Preoperative Nutritional Assessment

According to the National Institutes of Health, candidates for bariatric surgery must have BMI ≥ 40 kg/m$^2$ or ≥35 kg/m$^2$ with an obesity-related comorbidity. Candidates must also have failed prior attempts at diet and exercise; should understand the risks, benefits, lifestyle requirements, and expected outcomes of surgery; and be free from any uncontrolled psychiatric illness or drug or alcohol dependency [6].

A comprehensive evaluation of the weight loss surgery patient involves a multidisciplinary team, including a registered dietitian skilled in bariatric care [6, 7]. The dietitian's role is integral in the

**Table 8.1** Preoperative and postoperative nutritional assessment elements

| Preoperative nutritional assessment | Postoperative nutritional assessment |
|---|---|
| *Anthropometric* | |
| Height | Height |
| Weight | Weight |
| Body mass index (BMI) | BMI |
| Excess body weight (EBW) | |
| *Weight loss history* | |
| Failed weight loss attempts | Percent loss of EBW or preoperative body weight |
| Recent preoperative weight loss attempt (if required by program) | |
| Personal weight loss goals | |
| *Medical history* | |
| Current comorbidities | Changes from baseline comorbidities, medications, supplements |
| Current medications | Intolerances to vitamin/mineral protocol |
| Vitamin/mineral/herbal supplements | Adherence to vitamin/mineral protocol |
| Food allergies/intolerances | |
| *Biochemical* | |
| Micronutrient levels, if available | Micronutrient levels, if available |
| | Albumin level |
| *Dietary intake* | |
| Typical daily intake (weekday/weekend) | Food intolerance (nausea, vomiting, dumping syndrome, pace of eating, separation of solids and liquids) |
| Restaurant meal patterns | Adherence to dietary texture, phase, fluid, protein, protein supplement, and food choice (low vs. high kcal foods) goals |
| Beverage intake | Disordered eating patterns |
| Alcohol intake | Assess lifestyle and educational needs for long-term weight loss maintenance |
| Disordered eating patterns | |
| *Physical activity* | |
| Physical conditions limiting activity | Change in physical activity limitations |
| Current level of activity | Current level of physical activity |
| Types of activity enjoyed in the past | Guidance regarding increased activity |
| *Psychosocial* | |
| Motivation/reasons for seeking surgical intervention | Satisfaction with weight loss outcome |
| Readiness to make behavioral, diet, exercise, and lifestyle change | Readiness for further behavioral change |
| Willingness to comply with program protocol | Factors challenging adherence to diet, activity, vitamin/mineral protocol |
| Support system | |
| Financial constraints | |

Adapted from Table 3 in reference [7]

bariatric surgery process and has been correlated with successful outcomes [8]. Preoperatively, the dietitian provides a comprehensive nutritional assessment, education regarding pre- and postoperative dietary changes, and weight management. A comprehensive nutritional assessment can be done during the initial visit with the bariatric team, with education and weight management sessions scheduled at regular intervals before surgery. Suggested components of the nutritional assessment can be found in Table 8.1.

A nutritional assessment may include the review of a dietary questionnaire that the patient has prepared. Figure 8.1 provides a sample questionnaire designed to help the dietitian shape the preoperative plan of care.

The weight assessment includes weight loss history and expectations of postoperative weight loss. A summary of previous weight loss attempts and their outcomes should be reviewed, as well as the greatest duration of weight loss and weight maintenance [6, 7]. Excess body weight (EBW) is calculated based on the weight at a BMI of 25 kg/m$^2$ for the patient's height and is used to predict expected

**Weight Loss Goals:**

1. If you have weight loss surgery how much weight do you expect to lose? _____lbs
2. Do you have other health or diet goals/expectations? _____

**Weight Loss History:** Please record your most recent weight loss efforts which resulted in a loss of 10 pounds or more.

| Age at time | Year | Initial Weight | Pounds lost | Method used to lose weight | Challenges with this method |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

**Eating Habits:**

3. Who prepares the meals at your home? _____
4. Who does the food shopping? _____
5. How many people in your household?_____
6. How many times each month do you food shop?_____ Where do you usually shop? _____
7. Do you participate in these programs: ___SNAP ___WIC ____Local food pantry_____
8. In the past 12 months, did you ever worry that food will run out before you can go shopping again? Often _____ Sometimes _____ Never _____
9. Are there times during the month that you cannot afford to eat balanced meals? Yes__No___
   If yes, how often? Often _____ Sometimes _____
10. Circle the appliances you have in your kitchen.
    Refrigerator Toaster oven Blender
    Stove/oven Food processor Food scale
    Microwave
11. Do you read food labels? Yes ___ No ___
    If yes, how often do you read them? Always ___ Usually ___Sometimes ___
12. How many time per day do you usually eat
    Fruit _____ *Please list types*_____

**Fig. 8.1** Patient questionnaire (Adapted from Weight Assessment Lifestyle Index, David Sarwer, PhD)

Vegetables _____ *Please list types*_____

13. How many times a week do you eat snack foods (chips, pretzels, or others?)
Never ___1-2 times _____ 3-4 times ____5-6 times _____Daily ____

14. How many times a week do you eat sweets (cake, candy, ice cream, or others?)
Never ___1-2 times _____ 3-4 times ____5-6 times _____Daily ____

15. How many ounces of the following beverages do you drink in a day?
_____skim milk _____low-fat milk _____whole milk _____fruit juice
_____diet soda _____regular soda _____coffee _____tea
_____wine _____beer _____hard liquor _____water

16. How many meals/week you eat out or buy take-out food?_____

17. Are you allergic to any foods? Yes___No_____ If yes, which foods?_____

18. List foods you dislike or do not tolerate:_____

19. Have you been diagnosed with a vitamin or iron deficiency? Yes____ No____
If yes, list deficiency and date_____

20. Are you following a diabetic meal plan? Yes____ No_____

21. Do you limit your salt intake? Yes____ No_____

**Physical Activity:**

22. Do you have any physical problems or injuries that limit your activities of daily living or your ability to exercise Yes____ No____If yes, what physical problems are they? _____
_____

23. Do you exercise regularly? Yes____ No____If yes, what types of exercise? _____
_____How many days each week? _____
How many minutes each day ? _____

Adapted from Weight Assessment Lifestyle Index, David Sarwer, PhD

**Fig. 8.1** (continued)

weight loss after surgery. Patients seeking surgery may have unrealistic weight loss goals that should be addressed preoperatively.

The medical history is pertinent to the nutritional assessment if the patient has medical conditions that may be partially managed through diet, such as diabetes or hypertension. The dietitian should note any medications that may affect nutrient levels or body weight, such as diuretics, corticosteroids, diabetes medications, and psychiatric medications. Use of dietary supplements preoperatively is also important.

Biochemical measures are typically limited at the preoperative assessment. The surgical laboratory values typically include a complete blood count with differential. Consider screening for iron, vitamin $B_{12}$, and vitamin D status [6]. Due to cost constraints, other micronutrient levels are not typically checked [7], even though there is evidence suggesting that micronutrient deficiencies occur prior to surgery. These include vitamin D [9–13], thiamin [11–15], vitamin C [16], and vitamin E [11, 15], as well as iron, zinc [11–13], copper [13], and selenium [12].

Assessment of a patient's dietary intake allows the dietitian to identify opportunities for change and to establish the focus of preoperative nutrition education. Most uncomplicated admissions for bariatric surgery are short (2–4 days), which is why much of the diet education for postoperative use is done prior to admission. The dietitian may briefly address psychosocial issues that may affect success with desired dietary behaviors after surgery, but these factors are typically further identified and explored during the preoperative psychological evaluation, which is required by most insurance carriers, as well as the American Society for Metabolic and Bariatric Surgery (ASMBS) Centers of Excellence and the American College of Surgeons Bariatric Surgery Centers.

## Nutritional Evaluation After Bariatric Surgery

Routine nutritional assessment and teaching by a dietitian in the first year following bariatric surgery is essential for patients to meet nutrition needs and maximize weight loss. During this time, patients are at increased risk for dehydration, protein malnutrition, and micronutrient deficiency due to reduced food intake, reduced hunger, and potential food, fluid, and micronutrient supplement intolerance. Adequate nutrients are required to support tissue healing after surgery and to support the preservation of LBM during extreme weight loss [7]. Also, the foods and beverages consumed after surgery must minimize reflux, too early satiety, and dumping syndrome while maximizing weight loss and ultimately weight maintenance [7]. During the first postoperative year, patients should have nutrition follow-up within the first 2 weeks, then 6 weeks, 3 months, 6 months, 1 year, and then at least annually. Depending on program resources, nutrition intervention may take place in the office during follow-up visits with the surgical team, by individual appointment, or via telephone/webcam conferencing. The elements included in the nutritional assessment are listed in Table 8.1.

The majority of bariatric programs prescribe a specific multiphase diet to follow for the first 6–8 weeks postoperatively. The prescribed diet progression will incorporate varying food textures and phase durations. While there is not an accepted standard multiphase diet plan at present, the ASMBS surveyed 68 member dietitians regarding their diet phase recommendations. Most programs reported clear liquids (95 %), full liquids (94 %), puree (77 %), ground or soft (67 %), and ultimately regular diets with sugar, fat, and/or fiber restrictions (87 %) [7]. Table 8.2 provides a suggested multiphase diet plan for the uncomplicated bariatric patient [6]. Since the sleeve gastrectomy is a relatively new procedure in the United States, a conservative approach is applied regarding diet advancement [17]. However, the surgeon or dietitian may decide to progress the diet sooner based on the individuals needs and tolerances.

Adequate hydration is crucial for all postoperative bariatric patients, especially as they are not able to consume large volumes of fluid at one time. To maintain adequate hydration, fluids should be consumed consistently and slowly throughout the day with a daily fluid goal of ≥48–64 oz. Patients should be reminded of dehydration symptoms, especially during periods of extreme environmental temperature changes and when performing physical activity. Skin turgor evaluation can be used to assess hydration. If patients complain of severe symptoms of dehydration, appear dehydrated, or report persistent nausea and vomiting in the initial weeks and months postoperatively, they should be referred to the surgical team for evaluation.

A thorough assessment of the patient's protein intake is paramount during each interaction with the patient, commonly by assessment of a dietary protein log. Many programs recommend a range of 60–80 g/day protein intake or 1.0–1.5 g/kg ideal body weight (IBW), though data to support these levels are limited [7]. One study in Roux-en-Y gastric bypass (RYGB) patients suggested nutritional adequacy with daily consumption of 1.1 g protein/kg IBW [18]. Due to malabsorption induced by biliopancreatic diversion (BPD), protein intake should be increased to approximately 90–110 g/day [19]. If a patient is meeting the protein goal but reports areas of alopecia or presents with low serum albumin, dietary habits should be examined further in the overall clinical context. Protein malnutrition is usually associated with other symptoms that lead to decreased dietary intake, including anorexia, prolonged vomiting, diarrhea, food intolerance, depression, fear of weight regain, alcohol/drug abuse, low socioeconomic status, or other reasons that might cause a patient to limit protein intake [7].

During the first 6 weeks after surgery, liquid protein supplements are a vital tool for patients to achieve daily protein goals. Therefore, it is important for patients to find a protein supplement with an acceptable protein and sugar content, taste, mouth feel, and one which does not cause gastrointestinal distress. Flavorless protein supplements can be used to enhance the protein content of any food or beverage source. Finally, if patients choose not to use protein supplements, the dietitian should help them create a menu with the means to achieve protein goals.

**Table 8.2** Suggested diet progression in the uncomplicated bariatric patient

| Diet stage[a] | Duration | Sample fluids/food | Other considerations |
|---|---|---|---|
| Stage I—clear liquids | 1–2 days; mainly in the hospital | Broth | 1 oz every 10–15 min or 4–6 oz per hour as tolerated |
| | | Sugar-free gelatin | Noncarbonated |
| | | Reduced sugar or diluted fruit juice | No caffeine |
| | | | No alcohol |
| | | | ≤15 g sugar per serving[b] |
| Stage II—full liquids (400–600 kcal per day) | 10–14 days; start first full day at home from hospital | Reduced sugar yogurt | Begin vitamin protocol; space out vitamins over the course of the day |
| | | Reduced sugar pudding | Consume 4–8 oz per hour or minimum 48–64 oz fluids daily |
| | | Strained soup | Noncarbonated |
| | | Protein supplements | No caffeine |
| | | | No alcohol |
| | | | ≤15 g sugar per serving[b] |
| | | | Consume at least 60–80 g protein daily |
| | | | If lactose intolerance develops, consider lactose-free products and protein supplements |
| | | | Alternating sweet and non-sweet items to prevent taste fatigue |
| Stage III—pure (600–800 kcal per day) | 10–14 days | Scrambled egg | Eat 5–6 small meals per day every 3–4 h (4–6 oz serving size) |
| | | Oatmeal | Consider preparing foods in moist medium (e.g., broth, low-fat gravy, or mayonnaise) |
| | | Cottage or ricotta cheese | Mindful slow eating ~30 min per meal |
| | | Flaked tuna or chicken | Use small plates, bowls, and utensils to prevent overconsumption |
| | | Pureed fruits (reduced sugar applesauce) | Separate fluid from food ~30 min |
| | | Cooked pureed vegetables | Consume minimum 48–64 oz fluids per day. ≤15 g sugar per serving[b], noncarbonated, no caffeine, no alcohol |
| | | Mashed yams/potatoes | Consume at least 60–80 g protein daily |
| | | Pureed chicken or turkey | Continue to mix flavors to prevent taste fatigue |

| | | | |
|---|---|---|---|
| Stage IV—mechanical soft (800–1,000 kcal per day) | 10–14 days | Soft cooked meat and fish textures | Eat 5–6 small meals per day every 3–4 h (6–8 oz serving size) |
| | | Soft fruits and vegetables without tough skins | Continue to preparing foods in moist medium (e.g., broth or low-fat gravy or mayonnaise) should be able to easily cut food with a fork |
| | | | Food preparation: slow cooker, broiled, or baked fish |
| | | | Avoid fried, grilled, or microwave meats |
| | | | Cut food into small pieces (size of an eraser on a pencil) |
| | | | May add crackers |
| | | | Avoid bread, rice, and pasta |
| | | | Mindful slow eating ~30 min per meal |
| | | | Use small plates, bowls, and utensils to prevent overconsumption |
| | | | Separate fluid from food ~30 min |
| | | | Consume minimum 48–64 oz fluids per day. ≤15 g sugar per serving[b], noncarbonated, no caffeine, no alcohol |
| | | | Consume at least 60–80 g protein daily |
| Stage V—regular diet (800–1,000 kcal per day) | ~6 weeks post-op | Healthy solid food diet | Advance to regular texture meats, fruits, and vegetables as tolerated It may take several months before grilled or baked meat textures are tolerated |
| | | | Eat 5–6 small meals per day every 3–4 h (6–8 oz serving size) |
| >6 months post-op (1,200–1,400 kcal per day) | | | Consume minimum 48–64 oz fluids per day. ≤ 15 g sugar per serving[b], noncarbonated, and no alcohol |
| | | | Caffeine can be introduced if daily fluid goals obtained |
| | | | Consume at least 60–80 g protein daily. If daily protein goals are obtained from whole foods, protein supplements should be discontinued. Protein supplements may not provide adequate satiation at this time |
| | | | Mindful slow eating ~30 min per meal |
| | | | Use small plates, bowls, and utensils to prevent overconsumption |
| | | | Separate fluid from food ~30 min |
| Band fill/adjustment[c] | ~6 weeks post-op and possibly every 4–6 weeks until satiety reached | Full liquids × 2–3 days post-fill then advance to stage III × 2–3 days then advance to regular diet as tolerated | When advancing to regular diet, special attention to mindful eating and chewing until in liquid form, since more restriction may increase risk for obstruction above stoma of band if food not thoroughly chewed (consistency of applesauce) |

Adapted from Tables 9 and 10 Mechanick et al. [6]
Adapted from Table 8 Aills et al. [7]
[a]There is no standardization of diet stages, time on each stage, or what types of fluids and foods are recommended
[b]There is no standardization on sugar limitation per serving or amount to which dumping syndrome will occur; therefore, program requirements may vary
[c]For adjustable gastric band procedure

**Table 8.3** Nutritional supplement guidelines by bariatric surgical procedure

| Nutrient | LAGB | LSG | RYGB | BPD |
|---|---|---|---|---|
| *Multivitamin*<br>• High potency vitamin containing 100 % of daily value for at least 2/3 of the nutrients<br>• At least 18 mg iron, 400 μg folate, selenium, and zinc<br>• A chewable or liquid form should be used for at least the first month post-op<br>• Most gummy vitamins do not contain a complete formulation | √ | √ | √√ | √√ |
| *Cobalamin*<br>• 350–500 μg sublingual crystalline form or 1,000 μg injection monthly | | √ | √ | |
| *Calcium citrate w/vitamin D*<br>• Split dosage 500–600 mg<br>• A chewable or liquid form should be used for at least the first month post-op<br>• Be mindful of serving size and pill size<br>• Do not take within 2 h of MVI or iron supplement<br>• Suggest brand that contains magnesium, especially for BPD | 1,500 mg | 1,500–2,000 mg | 1,500–2,000 mg | 1,800–2,400 mg |
| *Iron*<br>• For menstruating women, those at risk of anemia<br>• Dosage recommendation: 50–100 mg elemental iron<br>• Take iron with 250 mg vitamin C to improve iron absorption<br>• Do not take iron and calcium at the same time, separate by at least 2 h | | √ | √ | √ |
| *Fat-soluble vitamins*<br>10,000 IU vitamin A<br>2,000 IU vitamin D<br>300 μg vitamin K | | | | √ |
| Optional B complex | √ | √ | √ | √ |

Adapted from reference [7]
*LAGB* laparoscopic adjustable gastric band, *SG* sleeve gastrectomy, *RYGB* Roux-en-Y gastric bypass, *BPD* biliopancreatic diversion

Vitamin and mineral supplements are required for lifelong prophylaxis after bariatric surgery. Table 8.3 provides a list of the most commonly recommended vitamin and mineral protocols for the adjustable gastric band (AGB), sleeve gastrectomy (SG), RYGB, and BPD [7]. Typically, patients begin taking this protocol when they start the full liquid diet, using chewable or liquid form during the first 6 weeks with the transition to pill form as tolerated thereafter. Other techniques to increase tolerance and adherence with the vitamin protocol include having patients separate their vitamins over the course of the day, setting alarm reminders, use of a pill box, and taking vitamins with food. Complete multivitamin/multi-mineral formulations that provide the RDA, plus a separate calcium citrate product, are advised. Despite good patient adherence, vitamin deficiencies may be identified during laboratory review and dictate further exploration by the bariatric team.

Patients having an SG, RYGB, or BPD can experience an average of 50–70 % loss in EBW (25–35 % preoperative weight) within 12–18 months postoperatively. The most rapid weight loss occurs within the first 3 months postoperatively, an average of 1–1.5 lb daily. The total weight loss depends

on many factors, including higher preoperative weight, age, diet adherence, medications, level of physical activity, and frequency of program follow-up. It is imperative that the dietitian reminds patients of the importance of adherence with postoperative diet principles as a means to develop proper dietary habits to obtain optimal weight loss and to prevent weight regain over the long term. Over the first decade following bariatric surgery, patients can expect to gain back approximately 10 % of their lost weight [20].

Weight loss is more gradual for the restrictive AGB procedure but may continue for several years [21]. AGB patients can expect an average weight loss of 1–2 lb per week provided they are compliant with diet, physical activity, and band adjustment follow-up. It is important to reinforce with AGB patients that it may take a few adjustments before they feel adequate restriction, the ability to eat small amounts of solid food with prolonged satiety, and no symptoms of nausea, vomiting, reflux, or chronic cough. If these latter symptoms are reported, the patient should be referred to the medical team for band management. Because the level of restriction may fluctuate between band adjustments, patients are encouraged to continue to take small portions as patients who eat larger portions or calorically dense liquids experience less weight loss or even weight gain because of their total greater caloric intake. Patients who experience poor tolerance with solid textures should be referred to the medical team for band management as it may be too tight.

During the first postoperative year, short-term weight plateaus are common and can be quite alarming to patients. When compliant patients experience weight plateaus, it is importance to review their weight loss progress and reduction in BMI to reinforce their success. Weight plateaus are a great opportunity for the dietitian to assess the patient's diet for increasing amounts of energy-dense foods and liquids which could increase total daily caloric intake. Evaluation of adequacy of physical activity is also indicated, as bariatric surgery patients may have limited prior experience with exercise, may be limited by chronic joint pain, and prefer less strenuous options.

## Nutritional Evaluation of Bariatric Surgery Patients for Home Parenteral Nutrition

In the months after bariatric surgery, some patients may be referred for a course of home parenteral nutrition (PN). While the frequency of late complications is small, the development of marginal gastric ulcers or strictures may occur in 1–16 % of patients, resulting in nausea and vomiting or bleeding [22]. When patients are inadequately responsive to medical therapy or if a fistula or anastomotic leak occurs, a short course of bowel rest and home PN may be employed. In a case series of 23 patients treated with bowel rest and home PN for anastomotic leak or fistula, the average duration of PN was 6 weeks [23]. Eighty-three percent of these patients transitioned to oral diet, while 9 % transitioned to tube feedings and 4 % needed longer PN therapy.

The nutritional goals for PN provision are usually to continue the planned weight loss while providing adequate protein (as amino acids) and micronutrient requirements. Amino acid intake must be adequate to promote healing of fistulas or leaks [24, 25] and to promote the retention of muscle protein as weight loss occurs. While the most optimal amino acid dose has not been thoroughly evaluated with a large RCT, recommendations for 2 g/kg IBW [24, 25] or 1.2 g/kg actual body weight [23, 26, 27] have been given, based on nitrogen balance studies. The mean amino acid intake provided in the few existing studies is 115–150 g daily [23–27]. Rather than use of IBW, a metric that has not been validated, calculation of LBM as outlined above [5] is recommended for assessment of protein requirements.

Indirect calorimetry measures of energy expenditure can be used to target the energy goal, if available [24, 25, 28]. When indirect calorimetry is not available, the Mifflin-St. Jeor equation has been recommended [29]. The energy goal has been based on 50 % of measured energy expenditure [24,

26], 13–19 kcal/kg/day [25], or a kcal/nitrogen ratio of 75:1 [26, 27]. Patients should not become deficient in essential fatty acids even without intravenous fat as a component of PN, provided they remain in a weight-losing condition, as their stored body fat will contain a proportion of essential fatty acids. Also, provision of high glucose loads may require monitoring of blood glucose levels and insulin coverage in patients with insulin resistance or diabetes. Thus, a conservative regimen that provides balanced but conservative doses of glucose and fat kcal to provide total energy intake (including protein intake of at least 115 g) of 10–14 kcal/kg body weight may be optimal. Daily delivery of amino acids at 1.2 g/kg and 13.6 kcal/kg body weight was associated with maintenance nutritional status and 7 % weight loss in patients with home PN [23]. If the patient does not continue to lose weight with the initial regimen, however, the glucose and fat kcal should be reduced.

The electrolyte mix should be designed based on the patient's clinical condition and organ function. Daily multiple vitamins are needed. If the patient is permitted to take multivitamins orally, then they should continue their usual vitamin supplementation plan during the short course of home PN, rather than risk breaking the habit of taking these important oral vitamin supplements. The trace element mix used for other patients should suffice for the short duration of home PN administration; though bariatric surgery patients may have multiple micronutrient deficiencies (see below) necessitating more individualized vitamin and trace element dosing. Weekly monitoring of electrolytes, complete metabolic panel, and complete blood count is usual practice to enable adjustment of regimen components.

## Nutritional Assessment for Failure to Thrive After Bariatric Surgery

Patients may present months or even years following bariatric surgery with failure to thrive, commonly including micronutrient and/or protein deficiency. Micronutrient deficiencies have been reported for vitamin A, vitamin $B_{12}$, folic acid, vitamin C, vitamin D, iron, and calcium despite compliance with routine multivitamin/mineral regimens [26, 27]. The most commonly reported include vitamin D and vitamin B12 [28, 29, 30]. Nonadherence with recommended regimens may further increase the risk for micronutrient deficiencies. Routine adherence has been reported in one-third of patients whereas approximately 40 % of patients have not complied with recommended micronutrient intake [31, 32].

Postoperative symptoms including prolonged anorexia, nausea, and vomiting increase the risk for micronutrient deficiencies. This includes thiamin deficiency which could present within the first 2–3 months following surgery [33]. Alteration of the gastrointestinal anatomy may create an environment for small bowel bacterial overgrowth which has also been linked to micronutrient deficiencies including thiamin and vitamin $B_{12}$ [34]. Fat malabsorption as a consequence of the altered gastrointestinal tract and a longer limb of exclusion with RYGB may influence fat-soluble vitamin status [35, 36, 37]. Longer sections of exclusion of the proximal small bowel have been suspected as a factor affecting both zinc and copper deficiency [38].

A nutrition-focused history and physical examination will provide valuable data on the postoperative bariatric patient. Physical and laboratory assessments of micronutrient and protein status are imperative when a post-bariatric surgery patient presents with failure to thrive. A comprehensive physical assessment looking for signs or symptoms related to micronutrient deficiency or protein/energy malnutrition should be included as part of the initial nutritional evaluation. Table 8.4 provides potential signs and symptoms of micronutrient deficiencies by system to guide physical assessment. Table 8.5 outlines potential physical findings for each nutrient deficiency. Suggested laboratory parameters are provided in Table 8.6 for initial assessment of micronutrient status in patients whose adherence is poor or unknown or for any post-bariatric surgery patient with a sign or symptom of a micronutrient deficiency.

When post-bariatric patients are hospitalized for failure to thrive, it may be necessary to empirically administer intravenous fluids containing micronutrients after first obtaining blood samples for analysis. A standard dose of the available intravenous multiple vitamin product (contains 13 vitamins)

**Table 8.4** Potential nutrient deficiencies by system

| System | Signs/symptoms | Potential nutrient deficiency |
|---|---|---|
| Skin | Hyperpigmentation | Protein |
| | Hyperkeratinization, xerosis | Vitamin A |
| | Dermatitis | Zinc, vitamin $B_2$ or $B_3$, linoleic acid, α-linolenic acid |
| | Petechial rash or capillary fragility | Vitamin C, vitamin K |
| | Poor wound healing | Protein, vitamin C, zinc, copper |
| | Seborrheic rash | Vitamins $B_2$, $B_3$, $B_6$ |
| | Casal's necklace | Niacin |
| | Edema | Protein, vitamin $B_1$ |
| | Pallor | Iron, vitamin $B_{12}$, folic acid |
| Neurologic | Change in mental status | Vitamin $B_1$, vitamin $B_{12}$, vitamin $B_3$ |
| | Gait abnormalities | Vitamin $B_{12}$, copper |
| | Neuropathy | Vitamin $B_{12}$, copper |
| | Peripheral neuropathy | Vitamins $B_1$, $B_6$, $B_{12}$ |
| Eyes | Night blindness, Bitot's spots | Vitamin A |
| | Optic neuropathy | Copper |
| | Angular palpebritis | Vitamin $B_2$, niacin |
| Mouth | Taste abnormalities | Zinc, B vitamins, folate, iron Vitamins $B_2$, $B_3$, $B_6$ |
| | Angular stomatitis | B vitamins |
| | Beefy red tongue | B vitamins |
| | Glossitis | Vitamins $B_2$ and $B_3$ |
| | Cheilosis | Vitamin C, vitamin K |
| | Bleeding gums | |
| Hair/nails | Alopecia | Protein |
| | Koilonychias (concave nails) | Iron |
| Cardiovascular | High-output heart failure | Vitamin $B_2$ |

**Table 8.5** Potential nutrient deficiencies by findings

| Nutrient | Physical finding | Laboratory assessment |
|---|---|---|
| Vitamin A | Nyctalopia, Bitot's spots, poor wound healing, corneal damage, keratomalacia, perforation, endophthalmitis, night blindness, xerosis and hyperkeratinization of the skin, loss of taste, xerophthalmia | Plasma vitamin A<br>Retinyl palmitate<br>Retinol-binding protein |
| Vitamin D | Hypo- or normocalcemia, possible low phos, high alk phos, high ptn, osteomalacia, rachitic tetany | Serum 25-OH vitamin D |
| Vitamin E | Hyporeflexia, disturbances of gait, decreased proprioception and vibration, ophthalmoplegia, RBC hemolysis, neurologic damage, ceroid deposition in muscle, nyctalopia, muscle weakness, nystagmus | Plasma α-tocopherol<br>β–/γ–τοχοπηερολ |
| Vitamin K | Hemorrhage, easy bruising, bleeding gums, delayed blood clotting, osteoporosis | Prothrombin time |
| Vitamin $B_1$ (thiamin) | Beriberi can affect various organ systems including the heart, gastrointestinal tract, and peripheral and central nervous system. Change in mental status, lower extremity weakness and edema, anorexia, gait ataxia, paresthesias, muscle cramps, irritability, peripheral neuropathy, Wernicke (encephalopathy, ataxic gait, oculomotor dysfunction)-Korsakoff (amnesia or changes in memory, confabulation, impaired learning) syndrome. Irreversible neuromuscular disorders, permanent defects in learning and short-term memory, coma, and death | Whole blood thiamin |

(continued)

**Table 8.5** (continued)

| Nutrient | Physical finding | Laboratory assessment |
|---|---|---|
| Vitamin $B_2$ (riboflavin) | Sore throat, hyperemia and edema of pharyngeal and oral mucosa, cheilosis, angular stomatitis, glossitis, seborrheic dermatitis (face, scrotum), corneal vascularization, photophobia, visual impairment, normochromic and normocytic anemia | Erythrocyte glutathione reductase activity coefficient (preferred)<br>Plasma riboflavin |
| Vitamin $B_3$ (niacin) | Pellagra: 4 Ds (dermatitis, diarrhea, dementia, death); hyperpigmentation on exposed skin sites (neck—Casal's necklace, hands, forearms) | 24-h urine N-1-methyl-nicotinamide (preferred)<br>Plasma niacin |
| Vitamin $B_6$ (pyridoxine) | Seborrheic rash, epithelial changes, atrophic glossitis, neuropathy, abnormal electroencephalogram findings, epileptiform convulsions, depression, confusion, microcytic and hypochromic anemia ($B_6$ required for hemoglobin production), platelet dysfunction, hyperhomocysteinemia | Plasma vitamin $B_6$ |
| Vitamin $B_{12}$ (cyanocobalamin) | Gait abnormalities, pernicious or megaloblastic anemia, pale with slightly icteric skin and eyes, SOB, fatigue, light-headedness or vertigo, tinnitus, palpitations, rapid pulse, angina, symptoms of heart failure, sore tongue with smooth and beefy red appearance, ataxia, changes in reflexes, anorexia, diarrhea, polyneuropathy, paresthesias, permanent neural impairment, extreme delusions, hallucinations, and overt psychosis | Serum vitamin $B_{12}$<br>Serum methylmalonic acid<br>Plasma homocysteine |
| Folate | Megaloblastic or macrocytic anemia, pallor, weakness, diarrhea, cheilosis, and glossitis | RBC folate |
| Biotin | Anorexia, pallor, glossitis, nausea, vomiting, depression, lethargy, muscle pain, and hair loss | Serum biotin |
| Choline | Fatty liver and/or liver damage associated w/PN | Not currently available at HUP |
| Iron | Hypochromic, microcytic anemia, pallor, fatigue, dysphasia, koilonychias, enteropathy, rapid heart rate, palpitations, decreased work performance, impaired learning ability | Serum iron<br>Serum ferritin |
| Vitamin C | Petechial rash, capillary fragility, bleeding gums, impaired wound healing, fatigue, depression | Plasma vitamin C |
| Zinc | Hypogeusia (decreased taste sensation), alterations in sense of smell, poor appetite, poor wound healing, irritability, impaired immune function, diarrhea, hair loss, muscle wasting, dermatitis | Serum/plasma zinc |
| Copper | Pancytopenia (neutropenia, thrombocytopenia, iron-resistant anemia), hypochromic, microcytic anemia, neurologic dysfunction (peripheral neuropathy, myelopathy, spastic gait, ataxia, optic neuropathy, encephalopathy, CNS demyelination, polyradiculoneuropathy, rhombencephalopathy), hypotonia, osteoporosis, separation of epiphyses, fractures of ribs/long bones | Serum copper<br>Serum ceruloplasmin |
| Phosphorus | Rhabdomyolysis, respiratory failure | Serum phosphate |
| Magnesium | Poor reproductive performance, congenital abnormalities in offspring, abnormal bone and cartilage formation, ataxia, growth retardation, defects in carbohydrate, and lipid metabolism | Serum magnesium (total) |
| Selenium | Altered thyroid hormone metabolism, increased plasma glutathione levels, cardiomyopathy, and skeletal muscle weakness | Plasma selenium |
| Calcium | Tetany, osteoporosis, leg cramping, neuromuscular excitability | Ionized calcium |

[a]Interpret with care if obtained during an acute-phase response in the patient

**Table 8.6** Bariatric failure to thrive lab panel

| Micronutrient assays | Other labs | Consider[a] |
|---|---|---|
| Red blood cell folate | Complete blood count | Plasma vitamin A |
| Vitamin B12 | Basic metabolic panel | Retinyl palmitate |
| Methylmalonic acid, serum | Liver evaluation panel | Retinol-binding protein |
| Homocysteine, plasma | Calcium | Plasma α-tocopherol |
| Vitamin C | Phosphate | β-/γ-tocopherol |
| 25-hydroxy vitamin D | Magnesium | Prothrombin time |
| Copper | Vitamins | |
| Ceruloplasmin | | |
| Ferritin | | |
| Iron/transferrin | | |
| Selenium | | |
| Zinc | | |

[a]If signs/symptoms of fat-soluble vitamin deficiency (other than vitamin D)

and the multiple trace element preparation (contains five minerals) has been suggested [39]. Administration of additional thiamin (e.g., 100 mg) should be included if the intravenous fluid contains dextrose to avoid the risk of inducing Wernicke–Korsakoff syndrome [40, 41]. Electrolytes may be added to intravenous fluids as necessary, and additional intravenous folic acid and vitamin $B_{12}$ can be considered if initial presentation suggests possible deficits. Once micronutrient deficiencies have been identified the appropriate route, dose, and duration of repletion must be determined, with most patients likely to tolerate oral repletion. Repletion of specific micronutrients should be provided in addition to maintenance (Table 8.3) micronutrient supplementation. The parenteral route can be considered for repletion if there is concern for significant gastrointestinal malabsorption that will influence the efficacy of enteral supplementation.

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# Chapter 9
# Childhood Obesity: Solutions to a Growing Problem

**Jason P. Schaub**

**Abstract** Common knowledge to healthcare professionals and laymen alike, obesity has reached epidemic proportions in both the adult and juvenile populations. While each constitutes serious implications for health, childhood obesity is of particular significance due to the relatively fragile state of children's physical and psychological development. Intense research in this field has identified numerous causative factors; however, the incidence of childhood obesity continues to rise, further endangering the health of future generations. In the following chapter key risks associated with childhood obesity are discussed, accompanied with an overview of the obesogenic environment contributing to weight gain in America. The interplay between various factors associated with childhood obesity is investigated, augmented by the development of a global childhood obesity correlation model. With a cohesive understanding of the current state of childhood obesity, established recommendations and future directions, centered on weight loss-specific dietary and exercise regimens pertinent to healthcare professionals, are further discussed.

**Keywords** Childhood obesity • Physical education • Health education • School lunch • Health literacy • Obesogenic • Weight loss • Glycemic index • Glycemic load • High-intensity interval training

## Abbreviations

| | |
|---|---|
| AAHPERD | American Alliance for Health Physical Education, Recreation, and Dance |
| BMI | Body mass index |
| CDC | Centers for Disease Control and Prevention |
| CSA | Community supported agriculture |
| CVD | Cardiovascular disease |
| DGA | Dietary guidelines for Americans |
| FIT | Fitness integrated with teaching |
| GI | Glycemic index |
| GL | Glycemic load |

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| | |
|---|---|
| HIIT | High-intensity interval training |
| HTN | Hypertension |
| HHFKA | Healthy Hunger-Free Kids Act |
| IOM | Institute of Medicine |
| NAFLD | Nonalcoholic fatty liver disease |
| NSLP | National School Lunch Program |
| PE | Physical education |
| PEP | Physical Education Program |
| SHPPS | School Health Policies and Programs Study |
| TEE | Total energy expenditure |
| USDA | United States Department of Agriculture |
| YRBS | Youth Risk Behavior Survey |

**Key Points**

- It is common knowledge that obesity has reached epidemic proportions in both the adult and juvenile populations.
- The implications for health of childhood obesity are of particular significance due to the relatively fragile state of children's physical and psychological development.
- Intense research in this field has identified numerous causative factors but childhood obesity continues to rise.
- Discussion of key risks associated with childhood obesity accompanied by an overview of the obesogenic environment contributing to weight gain in America, demonstrates the extent of the problem.
- Investigation of the interplay of various factors associated with childhood obesity augmented by the development of a global childhood obesity correlation model, moves towards a cohesive understanding of the current state of childhood obesity and recommendations and future directions centered on weight loss-specific dietary and exercise regimens pertinent to healthcare professionals.

## Introduction

Over the past decade childhood obesity has been placed in the media spotlight on a near constant basis. Well chronicled, the crisis has garnered national attention from individuals of all walks of life, from professional chefs to the First Lady of the United States [1, 2]. Yet despite widespread acknowledgement, the incidence of childhood obesity in America continues to rise. Numerous state- and community-level programs have been initiated to improve child health at the local level and, while some have been promising as evidenced by fluctuating or plateaued childhood obesity rates in select counties and states, others have been less successful [3–5]. Numerous and diverse, these local initiatives have multiple factors influencing their effectiveness. In light of these complexities, a rigorous investigation into all of these programs is inconsistent with the objectives of this book. Rather, the following chapter focuses on concepts healthcare professionals can readily synthesize into their own practice. First, an overview of the current status of childhood obesity in America is provided, supplemented with the identification of notable associated risk factors. Then, an analysis of the environmental factors influencing childhood obesity is discussed, enabling a thorough understanding of the conditions that have contributed to the current obesity epidemic. Weight loss-specific nutrition and exercise recommendations are also provided, with a focus on assisting healthcare professionals in developing more effective treatment protocols for their patients. Further methods of improving patient health through indirect means are presented to augment dietary behavioral changes at a fundamental level.

## A Focus on Childhood Obesity

The Obesity Society reports that obesity and obesity-related comorbidities contribute to more death, disease, and disability than any other disease in America—accounting for the single greatest proportion of healthcare expenditures in the United States [6]. Although recent reports have suggested that national childhood obesity rates may have plateaued, subclassifying children by age reveals that between 2003 and 2006, the 2–5- and 6–11-year-old age groups experienced a decline in incident rates, while 12–19-year-old incidence continued to rise. Today the incidence of 2–5-year-old obesity continues to decline [7–9]; however, all other age groups are increasing. The Centers for Disease Control and Prevention (CDC) now estimates the current net childhood obesity rate at 17 %, up from 16.4 % between 2007 and 2010 [8–10]. Obese children are at risk for the same gamut of complications as their adult counterparts and, due to their developmental stage in life, are particularly vulnerable to the establishment of poor lifestyle habits associated with physical and mental health complications [11]. Several of these complications are noteworthy due to their impact on total-body wellness, as discussed below.

### *Atherosclerosis*

Heart disease is the single greatest cause of death in the United States and is responsible for nearly 25 % of deaths annually [12]. Although complex in origin, atherosclerosis is widely recognized as one of the key modulators in the development of cardiovascular disease (CVD). Pediatric cardiovascular studies have established that precursors to CVD begin developing at a young age [13], with childhood obesity linked to pro-inflammatory and pro-thrombotic states independent of other risk factors [14]. Additionally, the degree of fibrous plaques, fatty streaks, and raised lesions in coronary vessels is positively correlated to body mass index (BMI), with marked increases when obesity is clustered with other risk factors such as hypertension (HTN), dyslipidemia, and insulin resistance [15, 16]. Atherogenesis is also linked to elevated glycohemoglobin, as found in diabetic and prediabetic states, independent of adiposity [17]. The development of atherosclerosis has been attributed not only to the presence of risk factors but to the maintenance of risk factors over time [16]—of notable importance considering 70–80 % of overweight or obese children are expected to remain overweight their entire lives [9]. The take-home message: Obesity is an independent risk factor for the development of atherosclerosis in children and, when clustered with other commonly associated risk factors, this risk is amplified significantly.

### *Insulin Resistance*

Insulin resistance, characterized by impaired glucose tolerance and hyperinsulinemia, is prerequisite to the development of type-II diabetes and a key modulator in the metabolic syndrome [18]. A devastating disease, type-II diabetes is the number one cause of blindness, kidney failure, and lower limb amputation [19, 20] and is a leading cause of neuropathy, HTN, and CVD [20]. Both insulin resistance and type-II diabetes are strongly associated with visceral adiposity and physical inactivity in children [18, 21, 22], with childhood adiposity strongly predicting the development of insulin resistance in young adulthood [22]. When present in metabolic syndrome, type-II diabetes may be considered a coronary artery disease risk equivalent, placing diabetics at the same risk for heart attack or stroke as nondiabetics who have previously experienced a cardiac event [23].

A state of severe homeostatic imbalance, metabolic syndrome refers to the common clustering of several conditions including dyslipidemia, HTN, hyperglycemia or type-II diabetes, and obesity [18, 24]. Because metabolic syndrome is a constellation of comorbidities whose interrelations are still being elucidated, there are no universally accepted diagnostic criteria. However a 2004 article published by the American Diabetes Association's *Diabetes Care* journal estimated that 32.1 % of obese adolescents exhibit characteristics of metabolic syndrome [24]. The take-home message: Prerequisite to type-II diabetes and metabolic syndrome, insulin resistance is associated with a multitude of risk factors and may seriously jeopardize children's future health.

## *Nonalcoholic Fatty Liver Disease*

Nonalcoholic fatty liver disease (NAFLD) is a leading cause of cirrhosis in the United States [25] and is estimated to be present in approximately 38 % of obese children [26]. Comprising a collection of potentially life-threatening conditions resulting from the accumulation of fatty deposits in hepatocytes, NAFLD is directly associated with the severity of obesity and insulin resistance [27, 28]. As the disease progresses the initially benign fatty deposits induce inflammation, leading to hepatic steatosis with subsequent scarring of the liver [25, 27, 29]. If not treated NAFLD may result in end-stage liver disease necessitating liver transplant. The take-home message: Because the initial stages of NAFLD are reversible with improvements in insulin sensitivity, exercise and weight loss should be induced in children to protect the vital metabolic functions carried out by the liver [27].

## *Psychosocial*

Low self-esteem, low self-concept, negative body image, and depression have all been linked with childhood obesity [30, 31]. Depression is of particular interest due to its bidirectional relation to obesity: Studies have indicated that formerly healthy-weight teens who become obese are more prone to develop depression [32–34], whereas adolescents clinically diagnosed with depression are at a greater risk for obesity [34–36]. Additionally, obese children are at a 2–3 times increased risk of developing depression as adults [33]. Disordered eating, including emotional and binge eating, has also been positively associated with BMI [36, 37].

In addition to self-perspective emotional disorders, weight-related teasing and social stigma can have considerable influence on a child's mental health [38]. Independent of BMI, peer victimization has been positively associated with self-reported depression, anxiety, negative self-image, loneliness, suicidal thoughts, physical inactivity, and other behavioral issues [39, 40]. In a study published by the American Medical Association, 14 % of parents reported that their children were victims of teasing, with obese children four times more likely to experience peer victimization than their nonobese counterparts [41]. The take-home message: Obese children are at a greater risk for an expanse of potentially severe psychological disorders, and as such emotional health should be monitored closely in overweight and obese patients.

As a result of these enhanced risk factors, a generation suffering from chronic diseases at younger ages is being realized, with concomitant earlier and greater death rates in adulthood [30]. Obesity's debilitating effects on health aside; this largely preventable disease further cripples our troubled healthcare system. Healthcare expenditures attributable to obesity have risen dramatically over the past two decades [42, 43]. Estimates indicate that the total direct and indirect cost of obesity treatment in 2008 topped $147 billion [43], up from $78.5 billion in 1998, with future costs projected to rise significantly [44]. A sobering Harvard University study underscores this point, indicating that incidence rates may

not plateau until at least 42 % of the adult population is obese [45]. In light of these findings, and because parental overweight or obesity increases their children's risk of becoming obese to 80 %, it is critical to implement aggressive obesity-reduction protocols on a nationwide scale [46].

## Obesogenic America

Definitive statements on childhood nutrition and activity levels are difficult to make due to large variances present within the population. Factors including organized sport participation, socioeconomic status, personal hobbies, parental occupation, and environmental factors such as neighborhood safety and park accessibility can have considerable influence over diet and physical activity levels. Despite these variables, estimates drawn from epidemiological studies can be used to construct a national perspective on the issues relating to childhood obesity, which in turn can be considered when assessing individual patient lifestyles. Outlined in Fig. 9.1 and expanded upon below are the numerous corollaries contributing to childhood obesity in America today.

A 2010 report from the Kaiser Family Foundation identified that children's media usage has increased 50.4 % since 1999 with an estimated 10 h 45 min of media exposure per day [47]—more time than the average American adult spends at work [48]. Television viewing and computer screen time, sedentary pursuits in and of themselves, have been positively associated with BMI and increased daily energy intake via snacking, with food advertisement exposure linked to even greater snacking [49, 50]. Upwards of 98 % of advertisements targeted towards children are for convenience foods, often those high in sugar or exceeding recommended daily values for saturated fat, total fat, and sodium [50, 51]. Furthermore, such advertisements result in increased preference and child-to-parent purchase requests for advertised foods [52]. Continuing in this vein, National Institutes of Health (NIH) findings indicate that physical activity levels among children drop significantly between ages 9 and 15, with 69 % of adolescents failing to meet activity recommendations during the weekday and 83 % failing during the weekend [53]. In short, the sedentary pursuits that have replaced physical activity augment the development of unhealthy diet and eating behaviors, further contributing towards weight gain.

CDC data estimates that the majority of the US youth fail to consume recommended amounts of fruits, vegetables, and whole grains, with 40 % of daily calories coming from only six sources: soda, fruit drinks, dairy and grain desserts, pizza, and whole milk. In some instances youth drink more than twice as much regular soda per day than milk [54]. Likewise in the adult population, the United States Department of Agriculture (USDA) reports that from the 1970s to 2000, per capita grain and sugar consumption increased significantly, 45 % and 39 %, respectively [55]. Such findings indicate both children and adults are consuming increasingly greater proportions of refined carbohydrates in their diet. Another agent linked to adiposity is the significant increase in portion sizes of snack and convenience foods, fast foods, and restaurant entrées, with increased portion sizes in all foods associated with increased caloric consumption [9, 56–60]. Not only has the composition of food changed dramatically, but the amount eaten has increased significantly as well.

### *A Focus on School Health Environments*

When promoted regularly, research indicates that physical education (PE) is effective at improving health knowledge, cognitive function, academic performance, and risk factors for chronic diseases in school children [44, 61–65]. Notwithstanding widespread support from parents for increased physical activity in schools [44, 66], there has been a significant decline in the number of students enrolled in PE classes since the 1970s [67]. The 2007 CDC School Health Policies and Programs Study (SHPPS)

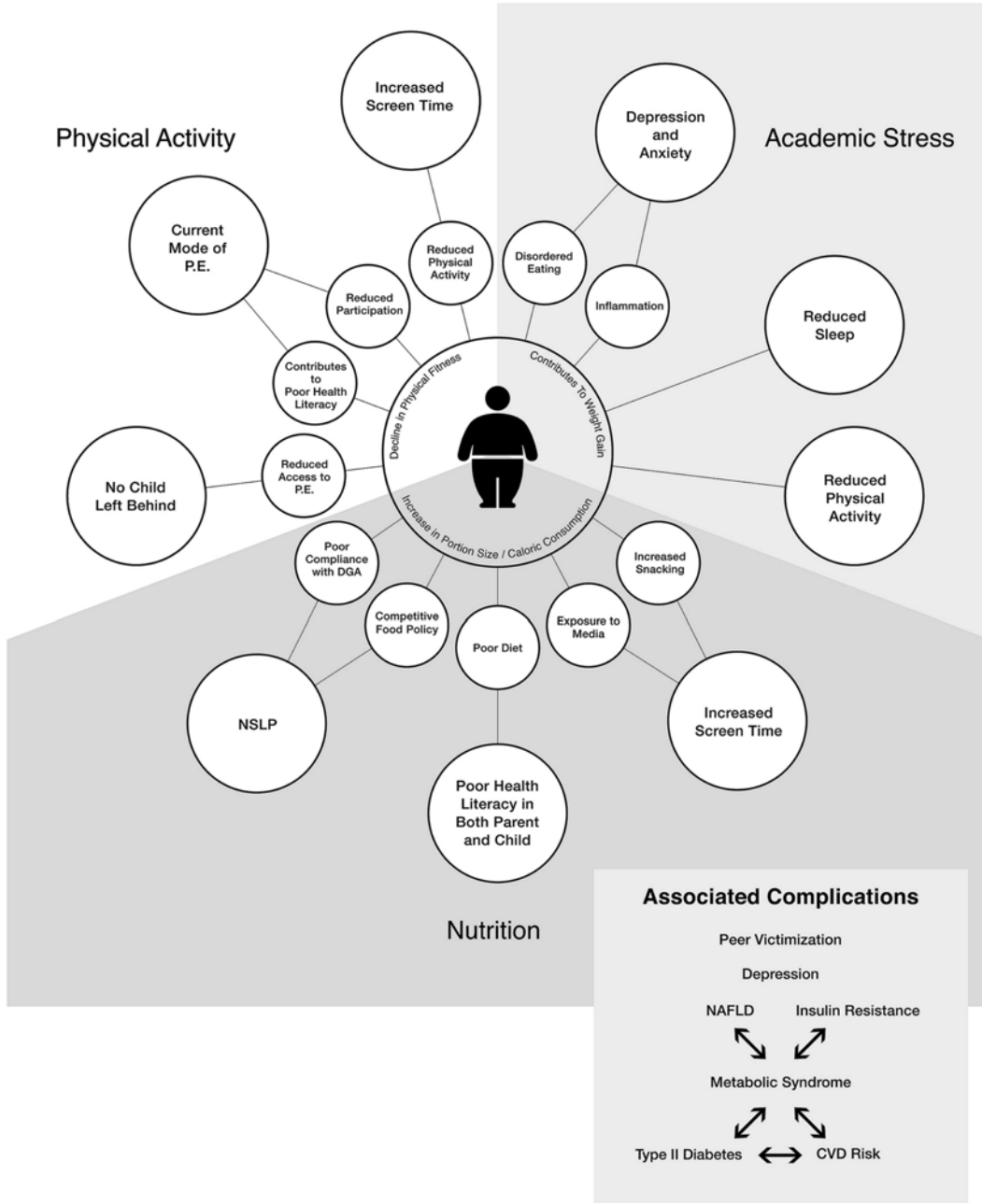


**Fig. 9.1** Childhood obesity correlation model

identified that only 3.8 % of elementary, 7.9 % of middle, and 2.1 % of high schools provide full-term daily physical education [68]. Furthermore, the 2011 CDC Youth Risk Behavior Survey (YRBS) identified that 69 % of the US high school students did not attend daily PE classes while in school, with 48 % not attending PE in an average week [69]. Additional results from the YRBS determined that there has been no significant change in net weekly or daily PE class attendance since 1995, indicating little progress on increasing physical activity or education has occurred [70]. The implications of reduced physical activity on health are deleterious, with declines in cardiorespiratory fitness in

childhood associated with increased obesity and insulin resistance later in life [71]. Judith Young, vice president for programs of the American Alliance for Health, Physical Education, Recreation, and Dance (AAHPERD), cites both monetary and time constraints for reduced PE in schools resulting from an increased emphasis on standards-based academic curriculums [72, 73].

Of considerable influence over school budget appropriations is the Elementary and Secondary Education Act. Commonly known as the No Child Left Behind Act, the measure identifies core and additional academic subjects of national interest, neither of which includes physical education. According to the National Association for Sport and Physical Education, this exclusion marginalizes PE's importance and "lowers the value of PE to school policy makers," providing rationale for school boards to minimize appropriations to physical education, further hindering efforts at combating the obesity epidemic [74]. Fortunately, despite Department of Education proposals for cutbacks, funding for the only Federal support for physical education, the Carol M. White Physical Education Program (PEP) grants, has thus far remained intact [74–77]. However, while PEP grants are an effective means of bolstering PE programs in select schools, with just 77 grants awarded in 2011 [78], only small fractions of American schools may benefit.

To compound the problem, what is taught as PE does not adequately address the health education needs of students in twenty-first-century America. Physical education has a long history rooted in the practice of health education and preventive medicine [61]. However the current mode of PE, with its overwhelming focus on sports, is strictly an advent of the twentieth century [79]. The AAHPERD identifies the four primary components of PE programs as health-related fitness, motor skills and movement forms, character development, and preparation for sport participation [80]. Given the current status of childhood obesity, a continued focus on sport activity rather than health promotion and obesity prevention fails to utilize current PE programs' time and financial allocations to their fullest potential. In addition to a deficit of nutrition and health education, CDC SHPPS data indicates that of schools requiring PE, 68.1 % taught dodge ball or bombardment, with over half of elementary schools teaching king-of-the-hill, steal-the-flag, or other elimination games [81]. Research indicates that competitive sports emphasizing particular skills are associated with students' perceived confidence in the sport, particularly in boys. This can lead to students abstaining from such activities to avoid being subject to social stigma, which in turn has been shown to predict physical activity and fitness outcomes both in childhood and later in life [82, 83].

Acknowledging these shortcomings, US Representative Ron Kind and Senator Tom Harkin have cosponsored H.R. 1057, the Fitness Integrated with Teaching (FIT) Kids Act which seeks to modify the No Child Left Behind Act. In addition to promoting weekly PE in elementary and high schools, the revisions would require schools to incorporate physical education "grades" into student report cards featuring comparisons to CDC national standards. Other provisions include assistance to incorporate healthy learning practices into the classroom, with additional funding for research and development [84, 85]. Supported by the American Heart Association, the FIT Kids Act is considered an "essential tool" in reversing the decline of PE and physical activity levels in youth [86]. While H.R. 1057 failed to be enacted, the bill was reintroduced as H.R. 2178 in 2013. However, according to *Govtrack.us*, an Internet-based tool that monitors the activities of the United States Congress, as of early 2014 the bill has an estimated 4 % chance of being implemented [87].

Heavily influenced by the National School Lunch Program (NSLP), the campus nutrition environment is a key modulator of student diet during the school day. Established at the end of WWII to address undernutrition in America's youth for national security purposes through the provisioning of low cost or free meals, the NSLP now operates in more than 101,000 schools across the country, nearly 95 % of all schools in the United States [61, 88–92]. Implemented by the USDA, the NSLP stipulates that meals must conform to USDA-Dietary Guidelines for Americans (DGA) which includes standards for fat, saturated fat, protein, iron, calcium, calories, and vitamins A and C [91]. However, reports have determined that on average, meals provided by schools have exceeded limits on fat, saturated fat, calories, and sodium, with fruit and vegetable intake below recommended values [93–96]. To meet mandated federal contributions to the program, the NSLP allows for schools to contract with private vendors who operate a la carte stands, vending machines, and other venues to

sell *competitive foods*, or foods sold outside of the NSLP. Largely unrestricted at the national level, these vendors are free to sell soda, sports drinks, salty and calorically dense snacks, and baked goods to students campus-wide [88, 97]. One must consider the message sent to students when schools fail to educate on health and nutrition while concurrently providing chips, cookies, pizza, and soda on a daily basis—from this standpoint it is not hard to conjecture how childhood obesity has spiraled out of control.

Academic-related stress and subsequent alterations in eating behavior demand attention from healthcare providers. School-related stress has increased steadily over the past several decades with students today facing ever-greater workloads and competition between peers for college acceptance [98–101]. The high school age group is of particular importance due to the fact that, while other age groups have experienced recent albeit temporary declines in obesity, high school obesity rates continue to rise annually [8]. A major source of academic stress for students competing for college acceptance is the rise in popularity of accelerated placement courses, the availability and enrollment in which has increased significantly in recent years [99, 100, 102]. More rigorous than traditional classes and in some cases considered equivalent to introductory college classes, these courses allow students a perceived academic advantage among their peers. However, due to their apparently detrimental effects on social and physical health, the ultimate utility of these classes has come into question [99–101]. An American Academy of Pediatrics study reports that the increased academic stress placed on students is harmful in the long term and linked to increased depression, anxiety, and perfectionism in college [103], while additional reports on stress estimate that upwards of 15.8 % of students are at risk for suicide [98, 104, 105].

The degree of time devotion required for high school students to excel in such advanced courses can limit their ability to engage in other activities, such as extracurricular sports and recreational hobbies [101, 106–108]. This may result in an increase in physical inactivity and stress-induced eating behaviors, a known risk factor for overeating [109]. Stress and anxiety, associated with increased serum markers for systemic inflammation, are also known to elicit food cravings for sweet, salty, or calorie-dense foods [110, 111]. Vending machines, a la carte stands, and to a lesser extent the realities of what has typically been served in NSLP meals cater directly to these cravings. Sleep duration, a correlate of stress, is also critically important to developing bodies. Numerous studies have associated reduced sleep duration and late time-to-sleep with increased BMI [112–116], as well as other factors including reduced quality of life, poor diet and exercise, and ineffective stress management in teens [114].

## 2012: Initiation of the Healthy, Hunger-Free Kids Act

Fiscal year 2012 represented a landmark year for school nutrition with the implementation of the Healthy, Hunger-Free Kids Act (HHFKA) of 2010, the first major revision to the NSLP in over 15 years [117]. Introduced by former Arkansas Senator Blanche Lincoln, the final rule updates nutrition standards of the NSLP in alignment with the current DGA, as set forth by the Institute of Medicine (IOM) of the National Academies [118, 119], with increased program enforcement. Other notable updates to the NSLP include [119]:

- Offer fruit daily at breakfast and lunch
- Offer vegetables daily at lunch
- Ensure 50 % of grains offered are whole grain rich
- Offer only fat-free and low-fat milk
- Offer meals that are calorie specific per age group
- Reduce sodium content over a 10-year period
- Eliminate trans fat food products

- Require students to select a fruit or vegetable
- Increased program monitoring

In addition to NSLP meal modifications, the HHFKA is poised to implement first-ever national nutrition standards for competitive foods sold in vending machines, a la carte stands, and other campus venues [120]. Currently under further development and consideration by the IOM, an interim Final Rule released June 2013 by the USDA goes into effect for the 2014–15 school year [121]. Considered a monumental step towards reforming campus nutrition environments, the changes slated to occur include strict standards on fat, sodium, sugar, calories, and whole-grain content of foods, potentially improving student diet considerably [121]. However, without proper nutrition education, a raised concern is that student demand for unhealthy snack foods may remain with the potential for after-school purchases at nearby convenience stores to rise. Convenience stores have been positively associated with BMI and are established sources of unhealthy snack foods and food advertisements [122, 123]. A similar argument can be made for NSLP meals; while positive change is on the horizon, whether or not it will be sufficient is unknown and, without an understanding and appreciation for healthy foods, the success of the program may be jeopardized, evidenced by reports of cafeteria boycotts following the programs' initiation [124]. Regardless, the implementation of the HHFKA is long overdue and will likely mark an important step towards reversing the childhood obesity epidemic.

## Solutions to a Growing Problem

Solutions to the childhood obesity epidemic can vary as widely as its causes; there is no silver bullet that can solve such a complex issue. Rather, a combination of actions will be required to reverse the rising trend in childhood obesity. Below, the factors most relevant to healthcare providers are discussed, emphasizing the potential of specific dietary and exercise recommendations for weight loss in children.

### *Nutrition*

Obesity results from metabolic imbalance where a greater proportion of ingested food is directed towards anabolic processes, namely increased adipose tissue storage. Although total caloric intake is indicative of the maximum weight loss or weight gain possible, it appears that dietary composition can have considerable influence over variations in the metabolic response to food. Glycemic index (GI) and glycemic load (GL), both measures of the resulting blood glucose flux in response to carbohydrates, have been shown to significantly influence adiposity in both healthy-weight and obese patients. Although the mechanism of action has yet to be fully elucidated, results from dietary interventions suggest that glycemic index and load are intimately linked with adiposity.

In overweight or obese patients, low GI/GL diets have been associated with significantly increased weight loss compared to traditional low-fat diets [125–128]. Combination high-protein and low glycemic index diets have also been shown to be protective against obesity in healthy-weight children [129] and are associated with greater weight loss in adults [128]. Additionally, low GI/GL diets have resulted in significantly greater weight loss ad libitum versus traditional diets, suggesting that low glycemic diets may be both more effective and easier to comply with than traditional diet methods [125, 127, 128]. This effect has been attributed to the increased satiating effect observed with low GI/GL diets, possibly aiding in portion control and net calorie consumption [130, 131].

Weight regain has been identified as a serious issue for dieters, with only 1 of 6 overweight or obese individuals reporting to have maintained at least 10 % of weight loss following 1 year [132]. A 2012 study published in the Journal of the American Medical Association investigated the

effects of three diets on weight regain: low fat, very-low carbohydrate, and low glycemic index. It was determined that the low GI diet was associated with significantly greater total physiologic energy expenditure (TEE) and improvements in metabolic syndrome factors as compared to the low-fat diet, attenuating weight regain. While the very-low carbohydrate diet produced an even greater beneficial effect in TEE, it was also associated with significantly elevated C-reactive protein and cortisol levels, indicating a risk for insulin resistance and CVD [133]. The protective effect against weight regain has been noted in other reports, both with and without significant differences in energy expenditure over traditional diets [131, 134].

Numerous positive effects of low GI/GL diets on disease risk measures have been observed. Of considerable importance with respect to obesity are marked improvements in insulin sensitivity [125, 131, 135, 136], postprandial hyperinsulinemia [136, 137], and metabolic syndrome factors [131, 137, 138]. Insulin resistance, discussed above, is a key target for therapy due to its central effects on metabolism, while hyperinsulinemia is associated with the early stages of type-II diabetes, preceding pancreatic beta-cell destruction. Moreover, low GI/GL diets enable the inclusion of a wide variety of fruits, vegetables, dairy, and healthy meat products [139, 140]. The overall composition of these diets complies with traditional macro- and micronutrient standards, can be rich in phytonutrients, and has been associated with better overall nutrient intake in children as compared to traditional diets [141]. Stemming from epidemiological studies identifying that children are consuming the majority of their daily calories from sugar and refined carbohydrates, it can be inferred that children are also consuming relatively high GI/GL diets. In light of the numerous improvements in metabolic risk factors, weight loss, diet compliance, and nutrient intake among children, without any observable detrimental side effects, diets low in glycemic load should be considered as a primary course of action when seeking to improve patient weight status. There is currently no data available regarding the glycemic load of NSLP meals.

## *Exercise*

While physical activity of any nature is beneficial in burning calories acutely, exercises resulting in increased basal energy expenditure can aid the body in utilizing additional calories throughout the day, promoting sustained weight loss. When compared to traditional moderate-intensity long-duration cardio-type exercise, high-intensity short-duration interval training (HIIT) exercises are associated with significantly greater body fat reduction [142–145], increases in lean body mass [142, 146], equivalent or improved insulin sensitivity [143–145, 147], and increased vital lung capacity [142, 143, 145, 148]. Lung capacity is of particular interest as it has been identified as one of the strongest predictors of mortality, independent of age, sex, or smoking history [149–151]. HIIT has also been shown to achieve equivalent improvements in training-adapted muscle oxidative capacity and arterial distensibility as observed with traditional exercises [147]. By nature HIIT exercises are relatively short in duration, capable of being incorporated into a variety of childhood activities with greater ease than long-duration exercises. With numerous advantages over traditional cardio-training, short-duration high-intensity exercises should be considered foremost when developing childhood activity plans.

## *Knowledge Is Power*

While modifications to diet and exercise are widely acknowledged as necessary steps towards achieving weight loss, of equal importance is understanding the factors influencing the adoption of these changes into patients' daily lives. Paramount to health promotion and disease prevention is assessing patients' health literacy [152]. Low parent health literacy is associated with poorer health outcomes

in children, while children's health literacy has been directly associated with BMI [153–155]. Considered by former Surgeon General Richard Carmona to be one of the largest contributors towards overweight and obesity in America, the US Department of Health and Human Services estimates that only 12 % of adults have proficient health literacy [152].

Given the widespread lack of nutrition and health education in schools, combined with broad variances of knowledge base within the adult population, it is likely that many patients lack a thorough understanding of how diet contributes to physiologic dysfunction. Intense media advertising for both processed convenience foods and fad-type weight loss diets adds to confusion, further complicating the matter [156–158]. Teaching patients the significance of nutrition and exercise on health may empower them to commit to real, significant changes in eating and exercise behaviors [159]. However, the realities of medical practice today may prohibit the time necessary to sufficiently coach individuals and families on health. As such it may be prudent for practitioners to compile a catalogue of recommended readings and health education resources to make available to patients. Rather than simply being prescribed a regimen, with a greater understanding of health established families will be more adept at translating nutrition and exercise recommendations into their personal lifestyles.

## *Food Relationships and a Novel Pathway to Improve Dietary Behavior*

Food is complex, more than simple calories on a plate; food can represent an individual's cultural beliefs, inclinations and predispositions, and ultimately, their health. Such deep-rooted associations are not easily changed; however, experiences that improve an individual's relationship with food may hold promise towards effecting positive dietary change. The Center for Mindful Eating, a nonprofit multidisciplinary forum for health professionals, has identified key components towards improving eating behaviors. These include recognizing mindless eating hunger cues such as emotional and social pressures, placing an increased value on high quality food, and developing an appreciation of the sensual and nourishing aspect of the eating experience [160]. While there are numerous methods towards increasing the mindfulness of one's eating, a method of potentially family-wide influence is involvement in the current sustainable agriculture movement.

Common practice in years past but largely absent in today's curriculum is educating children on farm ecology. Understanding where food comes from, how it is produced, and humans' role in the ecological cycle may be an effective means of improving a child's relationship with food while concurrently instilling health-promoting dietary choices. The popularity of organic and sustainably grown meat and produce has risen significantly in the past two decades for a variety of reasons, including health concerns over pesticide usage in conventionally grown foods, to disdain for the environmental, social, and economic impact of modern "super-farms" [161, 162]. As such, these "green consumers" tend to place higher value on natural, whole-food products [163]. Stemming from the greater concept of environmental stewardship, sustainable agriculture constitutes a steadily growing subgenre of farmers and consumers, garnering attention as a novel avenue to influence healthier diet choices in overweight and obese populations.

One such method being utilized at a local level in programs across the country is Community Supported Agriculture (CSA) cooperatives. CSAs enable direct consumer to farmer interaction, where families purchase food shares upfront at the beginning of the growing season and then receive regularly timed food packages throughout the year [164]. CSAs are also known to host field days, enabling members an opportunity to meet growers and participate in harvests, gaining further insight into farm operations [164]. In addition to produce, CSAs may also be involved in animal husbandry, offering organic or naturally raised egg, poultry, and meat products [164–166]. Overall, community-supported agriculture affords consumers the ability to develop a deeper understanding of the origins of their food

while in turn supporting a diet rich in fresh fruits and vegetables. Such programs are now being implemented in underprivileged areas as well, providing increased fruit and vegetable accessibility at affordable costs to populations in need [167, 168].

## Conclusion

The continued childhood obesity epidemic poses a significant threat to the future health of America. While the causes for weight gain are numerous, the development of a childhood obesity correlation model aids in visualizing how these factors interrelate while identifying possible avenues for intervention. Through an understanding of the obesogenic environmental factors influencing weight gain, more effective patient treatment protocols can be developed, with the characteristics of public health advocacy initiatives to improve America's health environment more readily conceptualized.

In American schools, the initiation of the HHFKA represents progress towards improving campus nutrition environments; however, substantial work remains for increasing the physical activity levels and health education of students. Largely attributed to the No Child Left Behind Act, the current lack of regularly administered PE, compounded by its overwhelming focus on sport, is not conducive to reversing the incidence of childhood obesity. Alternatively, promoting health-based physical education as a nationally recognized academic subject offers the potential to effect significant change, positively influencing health across the entire student population.

Pertinent to healthcare professionals, actions that can be implemented immediately include direct dietary and physical activity regimens. Paramount of these includes reducing children's sedentary pursuits that are associated with poor dietary behaviors, with a focus on increasing the variety of foods consumed to deter excessive consumption of soda, fruit drinks, desserts, pizza, and whole milk. Diets of low glycemic load are associated with greater weight loss, numerous improvements in disease risk factors, increased compliance, improved nutrient intake, and attenuated weight regain as compared with traditional low-fat diets. Likewise, with respect to traditional long-duration moderate-intensity cardio-type exercises, short-duration high-intensity exercises result in greater reductions of adipose tissue stores, increased lean muscle mass, improvements in metabolic risk factors, and increased lung capacity. With the relative flexibility of low GL diets, coupled with the short, spontaneous nature of HIIT exercises, both of these approaches can be readily assimilated into the lifestyle of patients seeking health promotion.

A common theme underlying both childhood and adult obesity is poor health literacy. Given the current lack of health education in schools, coupled with low health literacy in the adult population, it can be argued that the childhood obesity crisis is largely a product of our collective health knowledge. To reverse the rising trend of obesity in America, marked improvements in health literacy must be achieved at a population-wide scale. In the absence of health education at school, it would seem prudent for medical practitioners and allied health professionals to bolster patient knowledge through the provisioning of educational resources to improve health literacy, thus augmenting the effectiveness of treatment plans. Continuing in this vein, instilling an awareness and appreciation for food through the development of mindful eating behaviors may promote the establishment of long-term healthy lifestyles in both children and their parents.

Such circumstances harken back to elements of the Great Depression when, despite attempts made under the Hoover administration, economic conditions across the country continued to deteriorate. In conversation with U.S. Secretary of Labor Frances Perkins, President Franklin D. Roosevelt stated candidly, "One thing is sure. We have to do something. We have to do the best we know how at the moment… If it doesn't turn out right, we can modify it as we go along" [169]. Correspondingly, the childhood obesity crisis merits a similar approach—new actions must be taken now to propel our nation towards a brighter future, as despite our best intentions, efforts heretofore *have not turned out right*.

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# Part II
# Morbidity and Mortality of Obesity

# Chapter 10
# Nonalcoholic Fatty Liver Disease

**Melissa Palmer**

**Abstract** Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide. With the current obesity epidemic, its prevalence is increasing among both adults and children at an alarming rate. NAFLD occurs in individuals who do not drink excessive alcohol, yet have hepatic histology that mimics alcoholic liver disease. NAFLD is often associated with type 2 diabetes mellitus, central obesity, dyslipemia, and/or hypertension—conditions which comprise the metabolic syndrome. The spectrum of NAFLD ranges from simple steatosis, which is typically nonprogressive, to nonalcoholic steatohepatitis (NASH), which may progress to cirrhosis and its complications. Patients are usually asymptomatic, and histologic evaluation via liver biopsy is the gold standard for both diagnosing NAFLD and differentiating between simple steatosis and NASH. Patients with simple steatosis typically have a benign, nonprogressive disease course, while people with NASH have a progressive disease course, with an estimated 20 % advancing to cirrhosis. While clinical trials of numerous medications have been performed, there are currently no pharmacological agents approved for treatment. Management includes lifestyle modification comprising weight reduction, nutritional alterations, and exercise, in addition to aggressive treatment of other components of the metabolic syndrome.

**Keywords** Nonalcoholic fatty liver disease • NAFLD • Steatosis • Nonalcoholic steatohepatitis • NASH • Obesity • Insulin resistance • Cirrhosis • Metabolic syndrome • NAFLD Activity Score (NAS)

## Abbreviations

| | |
|---|---|
| AASLD | American Association for the Study of Liver Disease |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BMI | Body mass index |
| CK | Cytokeratin |

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| | |
|---|---|
| DM | Diabetes mellitus |
| GGT | Gamma-glutamyl transferase |
| GI | Glycemic index |
| HCC | Hepatocellular carcinoma |
| HDL | High-density lipoproteins |
| HDL-C | High-density lipoprotein cholesterol |
| HFCS | High-fructose corn syrup |
| HTN | Hypertension |
| IHTG | Intrahepatic triglyceride content |
| MOA | Mechanism of action |
| MRI | Magnetic resonance imaging |
| MUFAs | Monounsaturated fatty acids |
| NAFLD | Nonalcoholic fatty liver disease |
| NAS | NAFLD Activity Score |
| NASH | Nonalcoholic steatohepatitis |
| NHANES III | Third National Health and Nutrition Examination Survey |
| *PNPLA3* | Patatin-like phospholipase 3 gene |
| SFAs | Saturated fatty acids |
| SNP | Single-nucleotide polymorphism |
| US | United States |
| VLDL | Very-low-density lipoproteins |

**Key Points**

- Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide, and with the current obesity epidemic, its prevalence is increasing among both adults and children at an alarming rate.
- NAFLD occurs in individuals who do not drink excessive alcohol, yet have hepatic histology that mimics alcoholic liver disease.
- NAFLD is often associated with type 2 diabetes mellitus, central obesity, dyslipemia, and/or hypertension, conditions which comprise the metabolic syndrome.
- The spectrum of NAFLD ranges from simple steatosis, which is typically nonprogressive, to nonalcoholic steatohepatitis (NASH), which may progress to cirrhosis and its complications.
- Patients are usually asymptomatic, and histologic evaluation via liver biopsy is the gold standard for both diagnosing NAFLD and differentiating between simple steatosis and NASH.
- Patients with simple steatosis typically have a benign, nonprogressive disease course, while people with NASH have a progressive disease course, with an estimated 20 % advancing to cirrhosis.
- There are currently no pharmacological agents approved for treatment; management includes lifestyle modification comprising weight reduction, nutritional alterations, and exercise, in addition to aggressive treatment of other components of the metabolic syndrome.

## Definition

Nonalcoholic fatty liver disease (NAFLD) is a clinical condition occurring in individuals who do not drink excessive alcohol (>20 g/day), yet have hepatic histology that mimics alcoholic liver disease. NAFLD is characterized by intrahepatic triglyceride (IHTG) content of greater than 5.6 %

**Table 10.1** Diagnostic criteria for metabolic syndrome [78]

| Measure any 3 of the 5 criteria constitute a diagnosis of metabolic syndrome | Categorical cut points |
|---|---|
| Elevated waist circumference | ≥102 cm (>40 in.) in males |
| | ≥88 cm (>35 in.) in females |
| Elevated triglycerides | ≥150 mg/dL (1.7 mmol/L) or on drug treatment for elevated triglyceride |
| Reduced high-density lipoprotein cholesterol (HDL-C) | <40 mg/dL (0.9 mmol/L) in males |
| | <50 mg/dL (1.1 mmol/L) in females or on drug treatment for reduced HDL-C |
| Elevated blood pressure | ≥130 mmHg systolic blood pressure or |
| | ≥85 mmHg diastolic blood pressure or on drug treatment for hypertension is an alternate indicator |
| Elevated fasting glucose | ≥100 mg/dL or on drug treatment for elevated glucose |

*HDL-C* high-density lipoprotein cholesterol

of liver volume [102] consisting primarily of macrovesicular steatosis on histology. Other causes of macrovesicular steatosis should be excluded when making a diagnosis of NAFLD and include the following:

- Alcohol consumption
- Hepatitis C genotype 3
- Wilson's disease
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Medications such as tamoxifen, corticosteroids, amiodarone, and methotrexate
- Abetalipoproteinemia

The spectrum of NAFLD ranges from simple steatosis, which is typically nonprogressive, to nonalcoholic steatohepatitis (NASH), which may progress to cirrhosis and its complications [15]. NAFLD is often associated with type 2 diabetes mellitus (DM) [8, 117], central or visceral obesity [180], dyslipemia [18, 193], and hypertension (HTN) [54].

Together these conditions comprise the metabolic syndrome, and NAFLD is considered the hepatic component of this syndrome [81, 125, 143]. Specific criteria for the diagnosis of metabolic syndrome can be found in Table 10.1 [78, 79]. In addition, NAFLD has also been linked to cardiovascular disease, obstructive sleep apnea, colonic adenomas, pancreatic steatosis, hypothyroidism, and polycystic ovarian syndrome [109, 112, 201].

## Epidemiology

NAFLD is the most common liver disease worldwide [41, 153, 201]. With the current obesity epidemic, its prevalence is increasing among both adults and children at an alarming rate. In the United States, it is estimated that up to 35 % of people have NAFLD, although rates vary depending upon the population studied and the diagnostic criteria utilized [31, 201, 210]. The prevalence of NAFLD increases with rising body mass index (BMI) [168].

NASH is estimated to occur in between 3 % [201] and over 12 % [210] of Americans. Over 90 % of morbidly obese people undergoing bariatric surgery have been found with the spectrum of NAFLD [77, 122, 128, 147]. Autopsy studies in adults have revealed hepatic steatosis in 36 % of lean and 72 %

of obese adults and NASH with severe fibrosis in 14 % of markedly obese adults [204]. Autopsy studies in children reveal NAFLD in approximately 10 % with NASH occurring in approximately one quarter of these cases [164, 175].

## Risk Factors for NAFLD/NASH

There are numerous factors that have been associated with an increased likelihood for NAFLD and for progression to advanced stages of disease. While originally felt to be a female-predominant disease, NAFLD has now been found to occur more frequently among males [201], with a prevalence of 31 % in men and 16 % in women [19, 35, 42, 210]. Among different ethnic backgrounds, prevalence is highest in Hispanics and lowest in African Americans [19, 31, 98, 203, 210]. Individuals over 60 years old with NAFLD have been found to have an increased likelihood of advanced disease as well as overall liver-related deaths [6, 73, 86, 148]. However, Hui and colleagues postulated that this might be a reflection of disease duration as opposed to advancing age [92].

Up to 18 % of patients with NAFLD/NASH have been found to have a first-degree relative with the disease [174, 184, 211]. NAFLD patients have also been found to have more family members with cirrhosis compared with patients without NAFLD [2]. NAFLD has been found to occur more frequently in siblings of overweight children with NAFLD when compared to siblings of overweight children without NAFLD [174]. The single-nucleotide polymorphism (SNP) rs738409 in the patatin-like phospholipase 3 gene (*PNPLA3*) has been discovered to correlate with an increased likelihood of NAFLD/NASH [90, 114]. While these studies suggest that NAFLD and NASH are inherited, there is currently insufficient evidence to recommend screening family members for this disease [40].

Individuals with an increased likelihood of metabolic conditions have an increased prevalence of NAFLD/NASH [12, 13]. For example, approximately half of patients with dyslipemia also have NAFLD [18], and up to 76 % of people with type 2 DM also have NAFLD [110, 157, 189, 210]. Type 2 DM and a family history of type 2 DM are both strongly associated with an increased severity of fibrosis in NASH patients [2, 117]. While high BMI, central obesity, and a family history of obesity are all risk factors for NAFLD and advanced fibrosis [118], approximately 30 % of obese individuals have normal IHTG content and are not at risk for developing NAFLD or other metabolic abnormalities [30, 209]. Thus, it appears that a high content of IHTG in obese individuals is a sensitive marker for the development of NAFLD.

There are data to suggest that hepatitis C genotype 3, hypothyroidism, hypopituitarism, hypogonadism, sleep apnea, and polycystic ovary syndrome are important risk factors for NAFLD, independent of obesity [40]. The following is a list of risk factors for NAFLD/NASH:

- Male gender
- Older age (>60 years old)
- Hispanic race
- Family history
- Patatin-like phospholipase 3 gene (*PNPLA3*)
- Components of the metabolic syndrome
- FH diabetes
- FH obesity
- High content of IHTG in obese individuals
- Hepatitis C genotype 3
- Hypothyroidism
- Hypopituitarism
- Hypogonadism
- Sleep apnea
- Polycystic ovary syndrome

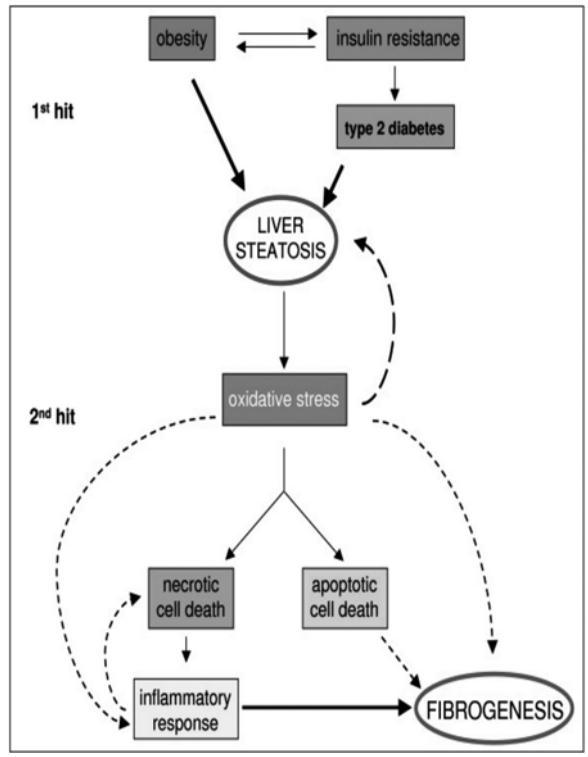


**Fig. 10.1** The two hit theory of NAFLD progression. The first hit is a metabolic one controlled by IR. NAFLD is associated with both liver and adipose tissue IR, as well as decreased insulin sensitivity of the entire body (Day 1998). This can cause (1) a significant decrease in glucose disposal and a lack of suppression of hepatic glucose production, (2) a defect of disposal of free fatty acids (FFAs) at the adipocyte level and skeletal muscle that, in turn, (3) will allow a high circulating levels of FFAs and hypertriglyceridemia coming from subcutaneous and visceral fat, which will lead to a constant excess delivery of FFAs to the liver. This eventually leads to steatosis (Angulo 2002; Marchesini 2005; Tilg 2000). Reprinted with permission From "Redox mechanisms in hepatic chronic wound healing and fibrogenesis" Erica Novo and Maurizio Parola. Copyright © 2008 Novo et al; licensee BioMed Central Ltd

## Mechanism of Action

The mechanism by which NAFLD leads to NASH is typically attributed to the "two-hit" hypothesis [194] (Fig. 10.1). The "first hit" involves fat deposition in hepatocytes under the influence of insulin resistance (IR) which leads to lipid peroxidation from dysfunctional mitochondria. Free radicals from fatty acids stimulate cytokine production which increases oxidative stress. The "second hit" involves inflammation and upregulation of stellate cells partially due to increased levels of tumor necrosis factor-alpha. This step is believed to lead to progression of disease to fibrosis and cirrhosis. An example of this second hit is a diet that predominantly consists of cholesterol and saturated fats.

## Diagnosis

There are no signs or symptoms distinctive to NAFLD/NASH. In fact, patients are usually asymptomatic. If symptoms do occur, they are nonspecific, such as fatigue. Diagnosis of NAFLD is typically made in a variety of ways such as during an evaluation of abnormal liver-related blood tests found during a routine checkup; as a result of rejection from a life insurance exam due to

elevated liver-related blood tests (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevated levels); the detection of hepatomegaly on a physical exam; or the discovery of fatty infiltration and/or hepatomegaly on an imaging study performed during the evaluation of an unrelated disorder.

## *Laboratory Tests*

When elevated, ALT and AST are typically 1–3 times the upper limit of normal [44, 84]. However, some studies have noted that the spectrum of NAFLD may occur despite normal aminotransferase levels in between 60 and 70 % of patients [71, 131]. The degree of AST and ALT elevations do not correlate with the extent of histologic inflammation and damage [71]. Elevated gamma-glutamyl transferase (GGT) may be a surrogate marker for fibrosis severity and increased mortality [82, 168, 187]. A study of over 600 NAFLD patients found an inverse correlation between indirect hyperbilirubinemia and the degree of inflammation and fibrosis found on liver histology [89]. This suggests that indirect bilirubin may delay or inhibit NASH progression.

In patients without gout, elevated uric acid levels have been found to correlate with increased severity of NASH [111, 156]. Iron overload occurring in NAFLD/NASH is believed to be due to IR-associated hepatic iron overload syndrome [129, 132]. Elevated ferritin >1.5 times the upper limit of normal has been shown to correlate with the extent of scarring and may be an indicator of advanced fibrosis in NASH patients [75, 104, 142].

## *Imaging Studies*

The diagnosis of NAFLD is often considered when an imaging study such as an ultrasound, computed tomography, or magnetic resonance imaging (MRI), performed for an unrelated medical problem, reveals steatosis. The utility of noninvasive modalities is decreased in morbidly obese patients and when less than 30 % steatosis is present [136, 150, 154]. It should be kept in mind that although the diagnostic accuracy of imaging studies is improving, differentiation between simple steatosis and NASH, in addition to determining the presence and degree of inflammation and fibrosis, is inadequate and presently cannot substitute for a histologic diagnosis.

## *Histology*

Histologic evaluation via liver biopsy continues to be the gold standard for both diagnosing NAFLD and differentiating between simple steatosis and NASH. It is the only modality that accurately displays mild to moderate disease, ballooning degeneration, extent of fibrosis, and severity of necroinflammatory activity. A standard histologic scoring system known as the NAFLD Activity Score (NAS) is based on the fact that the diagnosis of NASH relies on a spectrum of characteristics instead of one individual feature [32, 102]. The components of NAS include steatosis (score of 0–3), lobular inflammation (score of 0–3), and hepatocyte ballooning (score of 0–2). The sum of these three components represents the NAS score. A score greater than 5 is consistent with a diagnosis of NASH. Fibrosis is evaluated separately from NAS and is divided into four stages with cirrhosis being stage 4.

### *Noninvasive Biomarkers and Composite Scoring Systems*

The development of noninvasive biomarkers or a scoring system capable of accurately diagnosing and assessing the severity of NASH is highly anticipated as either of these modalities could potentially reduce or eliminate the need for an invasive liver biopsy. Numerous scoring systems have been proposed that comprise a composite of variables. To date, while some scoring systems have been found to be useful in detecting advanced stages of NASH, most are less useful and often inaccurate in detecting intermediate degrees of fibrosis [14, 139, 210].

Various serum/plasma biomarkers are also being researched [7]. The biomarkers most extensively investigated are cytokeratin (CK) 18, specifically CK 18 M30, which detects apoptosis and CK 18 M65 which detects necrosis [70, 206, 207]. Current society guidelines do not recommend routine use of any biomarker until further research is conducted [40].

## Natural History

Patients with simple steatosis typically have a benign, nonprogressive, or slowly progressive disease course [149, 190, 213]. In contrast, people with NASH have a progressive disease course, with an estimated 20 % advancing to cirrhosis [51, 216]. Sequential comparative histologic studies have revealed that between 23 and 53 % of NASH patients progressed by at least one stage within a follow-up period ranging approximately 3–6 years [67, 85, 92, 179, 213].

Individuals with NAFLD have a higher death rate compared with healthy matched controls, the most common cause of mortality being cardiovascular disease. In patients with NASH, liver disease-related complications are the third most common cause of death [6, 17, 48, 49, 56, 59, 86, 148, 161]. After a follow-up period of 18.5 years, 18 % of NASH patients had liver-related deaths [161]. A study of children with NAFLD followed for up to 20 years demonstrated that their long-term survival was significantly diminished and their likelihood of death or liver transplantation was almost 14-fold increased when compared with the general population of the same age and gender [69].

Components of the metabolic syndrome such as IR, type 2 DM, obesity, and dyslipemias are known risk factors for the progression of NASH to cirrhosis and for the progression of cirrhosis to its complications [34, 58, 191]. Patients with type 2 DM represent a subgroup particularly at high risk for increased liver-related morbidity and mortality, as well as all-cause mortality [6, 215].

The increasing incidence of NASH in the United States is felt to be an important contributing factor to the rise in the numbers of hepatocellular carcinoma (HCC) [17, 61]. Of note, patients with NASH-induced cirrhosis have a lower incidence of HCC when compared to the incidence of HCC in HCV-induced cirrhosis.

## Treatment of NAFLD/NASH

Management of NAFLD/NASH includes lifestyle modification comprising weight reduction, nutritional alterations, and exercise, in addition to aggressive treatment of other components of the metabolic syndrome if present. Goals include normalization of AST/ALT and GGTP, reduction in steatosis as assessed by imaging studies or histology, and improvement in or stabilization of fibrosis. While clinical trials of numerous medications have been performed, there are no pharmacological agents as yet approved for the treatment of NAFLD/NASH. Table 10.2 provides a summary of agents, both nutritional and pharmacologic, that have undergone investigation for the treatment of NASH.

**Table 10.2** Agents evaluated in clinical trials for NAFLD/NASH

| Agent | Comment |
|---|---|
| **1. Dietary supplementation with variations in long-chain omega-3 polyunsaturated fatty acids (PUFAs)** | |
| Logic—patients with NASH consume less PUFAs and more saturated fats than patients without NASH. PUFAs have been shown to be beneficial to patients with other components of the metabolic syndrome such as hypertension and hypertriglyceridemia. PUFAs also decrease lipid peroxidation and ameliorate hepatic steatosis in animal models of NAFLD | |
| Ethyl eicosapentaenoic acid (E-EPA) | Approved in Japan for hypertriglyceridemia |
| Lovaza | Reduces hepatic production of triglycerides |
| Docosahexaenoic acid | An omega-3 fatty acid |
| Omega-3 fish oil supplements | May reduce steatosis by increasing beta-oxidation, retarding free radical formation, decreasing inflammation, and downregulating de novo lipogenesis |
| **2. Nutritional supplements** | |
| Logic—used for their purported antioxidant, hypoinsulinemic, or hepatoprotective properties | |
| Protandim | Five botanical extracts: Bacopa monnieri extract, milk thistle extract, ashwagandha powder, green tea, and turmeric extract |
| Siliphos | Silybin-phospholipid complex—herb that possesses antioxidant, hypoinsulinemic, and hepatoprotective properties |
| Betaine (Cystadine) and S-adenosyl methionine (SAM-e) | Betaine, a trimethylated compound of the amino acid glycine, is a precursor of S-adenosyl methionine—a purported hepatoprotective agent |
| Vitamin $D_3$ | See text |
| Vitamin E | The only agent recommended for NASH |
| Cysteamine | Used in the body to form the essential biochemical coenzyme A |
| Hoodia gordonii | A shrub with appetite suppressant activity associated with specific steroid glycosides |
| L-Carnitine | Acts an essential cofactor for the *beta*-oxidation of fatty acids by facilitating the transport of long-chain fatty acids across the mitochondrial membrane as acyl-carnitine esters |
| Resveratrol | A natural phenol and phytoalexin produced by several plants when under attack by pathogens such as bacteria or fungi |
| L-Alanine | Alterations in the alanine cycle that increase ALT levels are linked to the development of type II DM |
| Diamel | A dietary supplement made from natural ingredients with purported capabilities of increasing the peripheral sensitivity to insulin |
| Hepaguard (Phyllanthus urinaria) | A purported hepatoprotective herb |
| Femarelle (DT56a) | A selective estrogen receptor modulator (SERM) for the treatment of menopause and bone health. Contains purported hepatoprotective agents DT56a (a tofu extract) and flaxseed powder |
| **3. Metabolic syndrome agents** | |
| Logic—works on the various components of the metabolic syndrome with NASH being the liver component | |
| *Hypoglycemic agents* | |
| Pioglitazone (Actos) | Major side effect limiting usefulness is significant weight gain |
| Exenatide (Byetta) | SQ glucagon-like peptide-1 receptor agonist (incretin mimetic) |
| Metformin (Glucophage) | An oral antidiabetic drug in the biguanide class |
| Sitagliptin (Januvia) | An oral antidiabetic drug |
| *Dyslipemic agents* | |
| Obeticholic acid | A farnesoid X receptor (FXR) ligand bile acid that changes the body's lipid metabolism |
| TROI 19622(Olesoxime) | A cholesterol-like molecule |
| Aramchol | Inhibits the liver enzyme stearoyl coenzyme A desaturase (SCD). Found to reduce fatty acid synthesis while increasing fatty acid oxidation |

(continued)

**Table 10.2** (continued)

| Agent | Comment |
|---|---|
| Colesevelam (Welchol) | An oral bile acid sequestrant used to reduce LDL and to improve glycemic control in type 2 DM |
| Atorvastatin (Lipitor) | A competitive inhibitor of HMG-CoA reductase |
| *Antihypertensive agents* | |
| Losartan (Cozaar) | An antihypertensive angiotensin-II type 1 receptor blocker with possible anti-stellate cell properties |
| Polypill | An agent able to prevent cardiovascular events, containing atorvastatin (Lipitor) and valsartan (Diovan) |
| **4. Miscellaneous agents** | |
| Rifaximin | A nonabsorbable antibiotic which decreases hepatic inflammation by reducing gut flora |
| Orlistat (Xenical) | A reversible lipase inhibitor that prevents absorption of 30 % dietary triglycerides |
| Pentoxifylline (Trental) | A xanthine derivative that has anti TNF-alpha properties |
| Genfit 505 | Triggers peroxisome proliferator-activated receptors (PPAR nuclear receptors) |
| GS-6624 | Monoclonal antibody against lysyl oxidase-like 2 (LOXL2) |
| Probiotics | May reduce liver fat and AST level in NASH patients [212] |
| CP-945,598 | A potent and selective cannabinoid-1 (CB1) receptor antagonist currently being developed for obesity |
| Glucomannan | A water-soluble polysaccharide that is considered a dietary fiber |
| Bovine colostrum | Found to alleviate chronic inflammation, liver injury, and insulin resistance in mice |
| Metreleptin (recombinant leptin) | An adipocyte-derived antiobesity hormone that in rodents prevents "lipotoxicity" by limiting triglyceride accumulation |
| *Continuous positive airway pressure* (CPAP) | Intermittent hypoxia may influence blood pressure, lipid levels, and insulin resistance |
| Muromonab-CD3 (OKT3) | A monoclonal antibody targeted at the CD3 receptor, a membrane protein on the surface of T cells |

## Nutritional Interventions for Patients with NAFLD/NASH

Many nutritional interventions have been studies for patients with NAFLD/NASH with varying success.

## Weight Reduction

In overweight people with NAFLD, weight loss of at least 3–10 % results in improvement of liver-related blood tests, IR, and hepatic histology. The degree of improvement has been found to be proportional to the extent of weight reduction [99, 151, 172, 173, 186, 188, 192]. This poses a dilemma for the estimated 3 % of the population who have NAFLD but are not overweight. Thus, the dietary patterns of people with NAFLD regardless of their BMI have been evaluated. Patients with NAFLD have been found to consume a higher percentage of saturated fatty acids [139] and overall calories [37] compared with their healthy counterparts without NAFLD. Visceral fat has been shown to correlate with the development of NAFLD [47] and has been found to be a risk factor for hepatic steatosis independent of BMI or total adipose tissue [64, 65, 115, 154]. While there is no standardized weight reduction regimen for patients with NAFLD, rapid weight loss, fad diets, and starvation techniques can lead to worsening of NAFLD and should be discouraged.

## Specific Dietary Restrictions

### *Fat Restriction*

*Saturated Fatty Acids* (*SFAs*). In animals, consumption of SFAs leads to endoplasmic reticulum stress, steatosis, and liver injury [113]. In patients with NASH the amount of SFA intake has been shown to correlate with the degree of visceral fat deposition—a known risk factor for NAFLD/NASH. Patients with NASH have been found to consume more SFAs (i.e., butter, fatty red meat, poultry skin) compared with patients without NASH. Diets consisting of greater than 10 % SFA can promote IR [39, 139]. However, restriction of SFA to <7 % of total calories does not provide further health benefits in patients with IR [76]. As such, it is reasonable for patients with NASH to adhere to a diet consisting of between 7 and 10 % SFAs.

*Monounsaturated Fatty Acids* (*MUFAs*). Diets high in MUFAs (i.e., olive oil, nuts, and avocados) have been shown to benefit individuals with type 2 DM by lowering triglycerides and very-low-density lipoproteins (VLDL), without reducing high-density lipoproteins (HDL) [106, 165]. While further study is needed, MUFAs may be beneficial to patients with NAFLD.

*Omega-3 Fatty Acids*. Omega-3 fatty acids (i.e., herring, salmon, sardines, and swordfish) have been found to have numerous properties that can result in a reduction steatosis such as increasing beta-oxidation, retarding free radical formation, decreasing inflammation, and downregulating de novo lipogenesis [11]. Alpha-linolenic acid, docosahexaenoic acid, and eicosapentaenoic acid are examples of omega-3 fatty acids found in fish oils. Improvements in transaminase (ALT and AST) elevations and reduction in steatosis found on imaging modalities have been demonstrated in studies evaluating the effects of diets containing 1–2 g fish oil/day versus diets devoid of fish oil [36, 181]. Others found similar declines in ALT elevations and reductions or normalization of steatosis on repeat imaging studies performed after patients consumed differing doses omega-3 fatty acid-supplemented diets [46, 87, 218]. In summary, consuming omega-3 fatty acids may be beneficial to NAFLD/NASH patients.

### *Carbohydrate Restriction*

NAFLD patients experience similar amounts of weight loss on a fat-restricted or a carbohydrate-restricted diet. However, compared to a low-fat diet, greater reductions in ALT levels occur when NAFLD patients consume a low-carbohydrate diet [169].

#### Fructose

NAFLD patients have been found to drink 80 % more high-fructose corn syrup (HFCS) sweetened soft drinks compared to people without NAFLD [5]. In fact, the intake of HFCS, a combination of glucose and fructose, has risen over time and parallels both the obesity and NAFLD epidemics [29]. High-fructose consumption may cause an increased deposition of lipids in the liver, worsening of IR, and hypertriglyceridemia [108]. The dyslipemic effect of consuming a fructose-sweetened beverage with meals was exacerbated in children with NAFLD compared with matched controls without NAFLD [95]. NAFLD patients consuming high-fructose-containing diets have more fibrosis compared to NAFLD patients consuming lower fructose diets [4]. Visceral obesity is an accepted risk factor for NAFLD [40]. A cross-sectional study of 791 non-Hispanic adults found that those drinking fructose-sweetened beverages had a higher ratio of visceral to subcutaneous adipose tissue compared

**Table 10.3** Glycemic index of common foods

| Category | GI range | Food examples |
|---|---|---|
| Low | <55 | Most vegetables, most sweet fruits, beans, seeds |
| Medium | 56–69 | Sweet potato, raisins, table sugar, pumpernickel bread |
| High | >70 | White rice, pretzels, white bread, soft drinks |

with those drinking non-fructose-containing beverages [145]. From these findings it can be concluded that excessive dietary fructose consumption is likely a key factor to the development of NAFLD and NASH [152]. A prospective controlled trial with histologic end points is ongoing that will possibly define the quantity of dietary fructose that is safe for consumption for NAFLD patients. Until the results of this trial are published, it is reasonable to recommend that patients with NAFLD refrain from or at least minimize dietary fructose intake, especially in the form of HFCS, which is an ingredient in most soft drinks in the United States.

### Glycemic Index

Patients with IR who consume diets consisting of excessive high-glycemic index (GI) foods (Table 10.3) have been found to have livers with extensive steatosis [198]. In contrast, diets consisting primarily of low-GI foods have been found to be beneficial to those with obesity, type 2 DM, and cardiovascular disease [21, 28]. In a group of older patients who consumed a low-saturated fat/low-GI diet, liver fat content quantified by MR spectroscopy decreased, insulin sensitivity improved, and total cholesterol and LDL cholesterol decreased compared with those who consumed a high-saturated fat/high-GI diet, independent of weight change [195].

*Summary of Fat and Carbohydrate Recommendation*. Additional studies assessing liver histology are needed to establish the optimal percentages of type of fat and carbohydrates to include in the diet decrease the likelihood of developing NAFLD/NASH and to retard or prevent disease progression. However, it appears reasonable for patients with NAFLD/NASH to maintain a low SFA intake between 7 and 10 % of total daily energy, substituting MUFAs or omega-3 fatty acids for SFAs, and to eliminate fructose, HFCS, and high-glycemic index foods as a source of calories.

## Other Dietary Considerations

There are many other dietary alterations that should be addressed in patients with NAFLD/NASH.

### *Coffee*

Coffee consumption has been associated with improvements in hyperglycemia, steatosis and a reduced likelihood of developing type 2 DM [26, 162]. Diabetic mice fed with coffee had less steatosis and improved insulin sensitivity compared to diabetic mice not fed with coffee [214]. NAFLD patients who drank more than three cups of espresso per day were less likely to have steatosis on ultrasound compared with those who drank fewer coffee-containing beverages per day [38]. Anty and colleagues demonstrated the protective effect of regular coffee, but not espresso, in NASH patients during an evaluation of 161 obese women for bariatric surgery. Findings found that women who drank regular

coffee had less fibrosis than women who drank espresso coffee [16]. It has been suggested that the protective effect of coffee may be related to a reduction of inflammatory cytokine expression [214]. Excessive coffee intake may lead to osteoporosis. This is important to remember, since patients with NASH have often been found to have a lower bone mineral density compared with patients without NASH [159]. Thus, prior to recommending increased coffee consumption to those with NAFLD/NASH, each patient should be evaluated on a case-by-case basis.

### *Alcohol*

The hepatotoxic properties of alcohol are well documented. In patients with NAFLD alcohol consumption can accelerate disease progression and hasten HCC development in those with cirrhosis [60]. However, some studies have demonstrated that individuals consuming moderate amounts of alcohol (1–2 drinks/day in women and 2–3 drinks/day in men) have less fibrosis and steatohepatitis compared with nondrinkers [55]. An analysis of the population-based Third National Health and Nutrition Examination Survey (NHANES III) participants identified 0.4 % of modest wine drinkers with suspected NAFLD versus 3.2 % of nondrinkers with suspected NAFLD. Moderate red wine intake has the potential to decrease IR, reduce hyperlipidemia, and diminish the risk for cardiovascular disease [25, 80]. Animal studies have demonstrated that resveratrol, a polyphenol antioxidant found in the skin of red grapes and a constituent of red wine, decreases steatosis in rats fed with a high-calorie diet [23]. These findings suggest that similar to the cardioprotective effect of wine in patients with coronary artery disease, wine may have hepatoprotective properties in those with or at increased risk for NAFLD/NASH [56]. However, the NHANES III study also revealed that there was a greater incidence of liver injury in those with higher BMIs compared with those with lower BMIs even in the individuals who drank alcohol minimally [167]. Until the results of additional prospective studies are obtained evaluating the effect of alcohol on NAFLD, it is advisable for patients with or at risk for NAFLD to refrain from or at least minimize all alcohol consumption.

## Antioxidant Supplements

Supplements with antioxidant capabilities may reduce free radical formation. Since oxidative stress is one of the proposed Mechanism of Action (MOA) in the pathogenesis of NASH, antioxidant supplementation has been an area targeted for therapy. However, for most supplements in this category, with the exception of vitamin E, conflicting outcomes have been reported, and further trials are needed before definitive recommendations can be made.

### *Vitamin E*

Vitamin E has been the antioxidant most thoroughly studied in NASH patients. Two hundred and forty-seven nondiabetic NASH patients who were supplemented with 800 IU/day of vitamin E improved their liver-related blood tests and histologic hepatic steatosis and lobular inflammation more often than patients who took a placebo or the thiazolidinedione hypoglycemic pioglitazone [171]. Reduction of fibrosis occurred in adult NASH patients after taking a combination of vitamin E and vitamin C daily for 6 months [85]. Vitamin E and C combination supplementation was also found to be as effective as ursodeoxycholic acid for reducing elevated aminotransferase levels [62].

Since vitamin C enhances iron absorption, iron status should be assessed prior to implementing this combination regimen. Based on this data, AASLD guidelines on NAFLD/NASH recommend that nondiabetic biopsy-proven NASH patients begin supplementation with 800 IU/day of vitamin E [40].

## *Betaine*

Betaine, a trimethylated compound of the amino acid glycine, is a precursor of S-adenosyl methionine—a purported hepatoprotective agent. Betaine functions as a methyl group donor to homocysteine to form methionine which lowers homocysteine levels. NASH has been associated with elevated levels of homocysteine [170], which has been linked with diminished methyl group availability. Some studies have demonstrated that betaine supplementation (Cystadane 20 g/day) may reduce elevated transaminase levels, may decrease hepatomegaly, and may reduce steatosis, necroinflammatory grade, and fibrosis stage, in patients with NASH [1, 130, 137]. However, Abdelmalek and colleagues more recently concluded that betaine at a dose of 20 g/day was not beneficial when used as the sole treatment for NASH, but may protect against worsening steatosis [3]. Thus, betaine may prove to be beneficial as an adjunct to NAFLD therapy.

## *Vitamin D*

Patients with NAFLD have been found to have lower vitamin D levels than patients without NAFLD [20, 144]. An inverse correlation has been noted between the extent of steatohepatitis and fibrosis and the severity of 25-hydroxyvitamin D deficiency [189]. An association between vitamin D deficiency, IR, and NAFLD has been found in overweight children [123]. Small animal studies have confirmed that vitamin D deficiency worsens NAFLD [166]. Continued study needs to be conducted assessing the effect of vitamin D supplementation on NASH; however, since results from NHANES III determined that between 75 and 90 % of U S adults are vitamin D deficient, evaluation of vitamin D status in all patients with NAFLD with supplementation as appropriate is recommended.

## *Pharmacologic Agents*

Numerous pharmacologic agents have been studied or are currently undergoing clinical trial assessment for patients with NAFLD/NASH.

### Diabetic and Insulin-Sensitizing Agents

Many agents used in patients with DM have also been studied in NAFLD/NASH patients due to purported similar MOAs.

#### Thiazolidinediones

Pioglitazone is the best evaluated agent in this class of drugs and among all classes of drugs studied to date. Multiple trials have been performed on varying populations—either with or without type 2 DM or IR, at varying dosages of pioglitazone (30–45 mg/day), for varying lengths of time 12–24 months,

and with varying control groups (placebo, vitamin E) [10, 24, 171]. Overall, results have shown that pioglitazone treatment was advantageous for NAFLD/NASH patients, as it generally reduced aminotransferase elevations, steatosis, ballooning, and necroinflammation. In most studies NAS improved and a trend toward decreased fibrosis was seen. Weight gain was a consistent side effect in these trials. It also should be noted that patients with type 2 DM treated with pioglitazone have been noted to have an increased risk of congestive heart failure and bone loss [138]. Finally, the effects of pioglitazone are not durable upon treatment discontinuation; thus, long-term therapy may be required [120]. AASLD guidelines on NASH have recommended that while pioglitazone may be used to treat NASH, it should be used with caution as the long-term efficacy and safety in this patient population has not as yet been determined [40].

Metformin

When NASH patients were treated with metformin, aminotransferase elevations reduced in many, but not all, clinical trials [33, 57, 88, 93, 119, 124, 140, 141, 146, 176, 196]. However, overall improvements on liver histology have not been seen, and thus, its use in the treatment of NAFLD/NASH cannot be recommended. However, in contrast to the weight gain seen with pioglitazone, metformin promotes weight loss in many NAFLD/NASH patients.

### Orlistat

Orlistat, a reversible lipase inhibitor, prevents absorption of 30 % dietary triglycerides. In patients with NASH, orlistat decreased ALT elevations [217], but failed to cause weight loss, improve IR, or improve liver histology [83]. After orlistat was FDA approved, cases of severe hepatotoxicity were reported [133]. Thus, patients with NAFLD/NASH should avoid taking orlistat.

### Other Agents

Numerous other agents such as ursodeoxycholic acid, angiotensin-receptor blockers, and various lipid-lowering agents, including fibrates and statins, have been evaluated in NAFLD/NASH patients (Table 10.2). While the results of some of these medications appear promising, most failed to demonstrate significant improvements in biochemical, radiographic, and/or histologic parameters. Thus, until additional more beneficial results are obtained, none of these agents can be recommended for the treatment of NAFLD/NASH.

## Exercise

Individuals who are more active and physically fit are less likely to have NAFLD [27, 99, 155, 199]. Aerobic exercise has been shown to regulate steatosis via effects on hepatic mitochondrial biogenesis resulting in enhanced lipid oxidation [202]. While goals should be set to lose approximately 3–10 % body weight [96], numerous studies have demonstrated the benefits of exercise on NAFLD/NASH even in the absence of weight loss. This is consistent with the finding from studies showing that exercise improves insulin sensitivity, retards progression to type 2 DM, reduces fatty acid availability, and improves lipid profiles without weight reduction in metabolic conditions other than NAFLD [103, 107, 177]. While Suzuki and colleagues showed that physical activity combined with a weight loss diet reduced ALT elevations in NAFLD patients, St. George and colleagues demonstrated that independent

of weight loss, adherence to a consistent exercise regimen improved ALT elevations in NAFLD patients when compared with those not adhering to regular exercise [182, 186]. Similarly, in obese individuals, aerobic exercise can diminish IHTG even when weight loss is not achieved [97] or percent body fat is not reduced [185]. Histologic improvements have resulted in NAFLD patients who increased their physical activity [91], especially when ≥7 % weight reduction was achieved [158]. Even short-term exercise, such as walking on a treadmill for 1 h/day at <85 % of maximal heart rate for 1 week, has been shown to decrease serum markers of hepatocyte apoptosis (CK-18 M30) in obese NAFLD patients [68]. Thus, an exercise regimen should be incorporated into the lifestyle of all patients with or at risk for NAFLD/NASH NAFLD, as long as there are no medical contraindications.

## Phlebotomy

Patients with NASH often have elevated iron indices. Thus, iron reduction therapy has been evaluated as a treatment modality. It has been demonstrated that when NASH patients lose weight on a low-calorie diet, elevated ferritin levels normalize [66]. Phlebotomy has been shown to improve IR and reduce elevated transaminase levels in both patients with type 2 DM and NASH [9, 63, 197]. The prevalence of the gene mutation associated with hemochromatosis—C282Y—has been evaluated in NAFLD patients. While some studies noted worsening fibrosis scores in C282Y-positive NAFLD patients, other studies found no relationship. Currently, iron reduction therapy is not recommended.

## Bariatric Surgery

Over 200,000 bariatric surgeries are performed each year for the treatment of morbid obesity. This operation has been shown to be the most successful approach for promoting long-term weight loss and for controlling obesity-related comorbidities, including NAFLD/NASH. Bariatric procedures can be divided into three categories—malabsorptive, restrictive, and combination (Table 10.4). A detailed description of these procedures is provided elsewhere in this book. Bariatric surgery has been shown to improve or even reverse NAFLD in most instances [52, 72, 105, 127, 135, 178]. When progression of fibrosis and/or steatohepatitis did occur postoperatively, it was found to be associated with higher BMI, NAS, steatosis, ballooning, inflammation, fibrosis, and IR at baseline [126]. In addition, patients who lost large amounts of weight rapidly—within the first 6–12 months of surgery—also had a worsening of liver disease. It has been suggested that increased lipolysis with hepatic deposition of excessive long-chain fatty acids from visceral adipose tissue may account for this aggressive progression [200]. A summary of published data on the effects of weight loss due to bariatric surgery on hepatic histology in patients with NAFLD is provided in Table 10.5.

**Table 10.4** Types of bariatric surgeries

| |
|---|
| *A. Malabsorptive procedures* |
| 1. Jejunoileal bypass |
| 2. Duodenal switch |
| *B. Restrictive procedures* |
| 1. Vertical banded gastroplasty |
| 2. Laparoscopic adjustable gastric banding (LAGB) |
| *C. Combination approaches* |
| 1. Roux-en-Y gastric bypass (RYGB) |
| 2. Sleeve gastrectomy |

**Table 10.5** Weight loss or BMI change and histologic outcomes in NASH patients after bariatric surgery

| Study | Year | *N* | Study design | Preop BMI (kg/m$^2$) | Weight loss (kg) or BMI change (kg/m$^2$) | Second biopsy months | Outcome histology on second liver biopsy | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Steatosis | Inflammation | Fibrosis |
| *RYGB* | | | | | | | | | |
| Silverman et al. [178] | 1995 | 91 | RC | Not Rep | 36.4 kg WL | 18.4 | Improved | Lobular less<br>Portal more | Improved |
| Clark et al. [43] | 2005 | 16 | PC | 51.1 | 18.2 BC | 10.2 | Improved | Improved | Improved |
| Mattar[a] et al. [127] | 2005 | 70 | PC | 56 | 17 BC | 15 | Improved | Improved | Improved |
| Mottin et al. [135] | 2005 | 90 | RC | 46.7 | 81.4 % WL | 12 | Improved | Not rep | Not rep |
| Klein et al. [101] | 2006 | 7 | PC | 58 | 17 BC | 12 | Improved | No change | No change |
| Barker et al. [22] | 2006 | 19 | PC | 47 | 18 BC | 21.4 | Improved | Improved | Improved<br>Worse 10.5 % |
| Csendes et al. [45] | 2006 | 16 | PC | 44.3 | 15.7 BC | 17.5 | Improved | Improved | Improved<br>Worse 6.7 % |
| De Almeida et al. [50] | 2006 | 16 | PC | 53.4 | 22 BC | 23.5 | Improved | Improved | Improved |
| Furuya et al. [74] | 2007 | 18 | PC | 51 | 20 BC | 24 | Improved | Improved | Improved |
| Liu et al. [116] | 2007 | 39 | RC | 47.7 | 18.2 BC | 18 | Improved | Improved | Improved |
| Weiner[b] [208] | 2010 | 116 | RC | 55.2 | 24.7 BC | 18.6 | Improved | Improved | Improved |
| Moretto et al. [134] | 2011 | 78 | RC | 45.4 | 16.1 BC | Not rep | Not rep | Not rep | Improved<br>New 11.6 % |
| *AGB* | | | | | | | | | |
| Dixon et al. [53] | 2006 | 60 | PC | 45.9 | 11.9 BC | 29.5 | Improved | Improved | Improved |
| Mathurin[c] et al. [126] | 2009 | 381 | PC | 50 | 12.3 BC | 60 | Improved | No change | Worsened |
| *BPD/DS* | | | | | | | | | |
| Kral et al. [105] | 2004 | 104 | PC | 47 | 16 BC | 41 | Improved | Improved<br>New 11.6 % | Improved 26.8 %<br>Worse 40.4 % |
| Keshishian et al. [100] | 2005 | 78 | RC | 50.5 | Not rep | Jun-36 | Improved | Improved | Not rep |
| *VBG* | | | | | | | | | |
| Ranløv and Hardt [163] | 1990 | 8 | PC | Not rep | Not rep | 12 | Improved | Improved | No fibrosis |
| Luyckx et al. [121] | 1998 | 69 | RC | 23.9 | 32 WL | 27 | Improved | Worse | Not rep |
| Stratopoulos et al. [183] | 2005 | 216 | PC | 52.8 | 66 % WL | 18 | Improved | Improved | Improved 47 %<br>Worse 12 % |
| Jaskiewicz et al. [94] | 2006 | 10 | PC | 46.7 | 35 WL | 8 | Improved | Improved | Not rep |

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*Rep* reported, *PC* prospective cohort study, *RC* retrospective cohort study, *BMI* body mass index, *WL* weight loss, *BC* BMI Change, *Preop* preoperative, *RYGB* Roux-en-Y gastric bypass, *AGB* adjustable gastric banding, *BPD/DS* biliopancreatic diversion/duodenal switch, *VBG* vertical banded gastroplasty

[a]RYGB: 58.6 %; sleeve gastrectomy: 31.1 %; AGB 8.6 %

[b]RYGB: 55.7 %; AGB: 31.1 %; BPD-DS: 13.1 % 32.9 %

[c]RYGB: 21 %; AGB: 56.2 %; biliointestinal bypass: 22.8 %

While weight loss is the primary factor leading to decreased steatosis and fibrosis seen in NAFLD/NASH patients after bariatric surgery, additional factors affecting carbohydrate and lipid metabolism also play an integral role in histologic improvements [160]. Finally, it is important to underscore that the presence of NASH does not increase the likelihood of complications after bariatric surgery [205].

## Conclusion

As a large part of the population has adopted a sedentary lifestyle and unhealthy dietary habits, the prevalence of obesity and IR have escalated. As such, NAFLD has become the most common cause of chronic liver disease worldwide. As almost all people who have, or are at risk for, NAFLD/NASH are overweight, an integrative approach to weight reduction provides the best overall management strategy for this disease.

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# Chapter 11
# Obesity and Cancer

**Mary Marian and Cynthia A. Thomson**

**Abstract** Obesity is a global epidemic and a wealth of evidence suggests that obesity in addition to sedentary lifestyle and diet are modifiable risk factors associated with cancer. Several cancers including breast (in postmenopausal women), cervical, colon, endometrial, esophageal, gallbladder, multiple myeloma, non-Hodgkin's lymphoma, rectal, renal, thyroid cancer, and even pancreatic cancer have been associated with obesity. A variety of biological mechanisms involving the adipocyte has been implicated in tumorigenesis. Moreover, poorer outcomes in terms of worsened disease survival have been reported for obese patients. A number of small, randomized, controlled trials to promote weight loss in cancer survivors have been undertaken and suggest modest results in relation to weight control. This chapter will review the potential mechanisms linking obesity and cancer together with a summary of the available studies of weight control in cancer survivors. Guidelines for cancer survivors regarding diet and physical activity for risk reduction and weight control also will be discussed.

**Keywords** Obesity and cancer • Adipokines and cancer • Weight control and cancer • Obesity and cancer survivors

### Key Points

- Obesity is a global epidemic and a wealth of evidence suggests that obesity in addition to sedentary lifestyle and diet are modifiable risk factors associated with cancers including breast (in postmenopausal women), cervical, colon, endometrial, esophageal, gallbladder, multiple myeloma, non-Hodgkin's lymphoma, rectal, renal, thyroid cancer, and even pancreatic cancer.
- A variety of biological mechanisms involving the adipocyte has been implicated in tumorigenesis.
- Poorer outcomes in terms of worsened disease survival have been reported for obese patients.
- A number of small, randomized, controlled trials to promote weight loss in cancer survivors have suggested modest results in relation to weight control.
- Potential mechanisms linking obesity and cancer are explored and guidelines for cancer survivors regarding diet and physical activity for risk reduction and weight control are discussed.

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## Introduction

The incidence of new cancers in the United States is approximately 1.2 million cases per year, accounting for 22.9 % of deaths in the United States annually [1]. When deaths are aggregated by age, cancer has surpassed heart disease as the leading cause of death for individuals under the age of 85 years [1]. Prostate cancer is the most commonly diagnosed cancer in men followed by cancer of the lung and bronchus, colon, and rectum [1]. For women, breast, lung, and bronchus, followed by colon and rectal cancers are the most common [1]. Annually, approximately 600,000 Americans are expected to die from cancer, accounting for just over 1,500 deaths per day [1]. Cancers of the lung and bronchus, prostate, and colon and rectum in men and cancers of the lung and bronchus, breast, and colon and rectum in women continue to be the most common fatal cancers. These four cancers account for one-half of the total cancer deaths among men and women.

## Cancer Risk Associated with Obesity

A wealth of evidence suggests that obesity, sedentary lifestyle, and diet are modifiable risk factors associated with cancer. In fact, a thorough review of the literature by the World Cancer Research Fund and the American Institute for Cancer Research [2] concluded that excess body fat is a significant risk factor for several cancers including breast (in postmenopausal women), cervical, colon, endometrial, esophageal, gallbladder, multiple myeloma, non-Hodgkin's lymphoma, rectal, renal, and thyroid cancer [2] and even pancreatic cancer [3]. Obesity may also increase the risk for aggressive forms of prostate cancer [2] and has been associated with most forms of leukemia in adults [4]. Obesity is a global epidemic, and according to the National Cancer Institute if the current trends in obesity continue an additional 500,000 new cancer cases will be diagnosed by 2030 due to obesity [5]. An additional concern is the number of overweight and obese adolescents; what is currently unknown is how this will influence their cancer incidence as they age. Importantly, the combined risk of overweight/obesity, which now affects over 65 % of the population, and the advancing age of the population suggests that the incidence of cancer will increase markedly over the next several decades [6].

The American Cancer Society reports that one-third of cancer-related deaths annually are related to lifestyle habits including an imbalance in energetics related to diet and physical activity thereby leading to excess body fat and obesity [2]. Guidelines for cancer prevention published by a variety of organizations typically emphasize the importance of consuming a healthy diet, maintaining a healthy weight, and obtaining regular physical activity. These recommendations are consistent with those suggested for risk reduction for not only cancer but also other chronic diseases such as heart disease, hypertension, and diabetes [7]. In fact, Kushi et al. reported that risk for cancer is estimated to be reduced by an estimated 30 % in individuals who adhere to the American Cancer Society recommendations for weight control, physical activity, and alcohol intake [8], and even greater reductions can be expected if these behaviors are combined with an avoidance of tobacco. This chapter, in addition to describing the association between obesity and cancer incidence, will review several proposed mechanisms by which obesity may contribute to cancer promotion and describe the current state of the evidence for obesity modulation in people previously treated for cancer.

## Mechanisms by Which Adiposity Alters Cancer Risk

While the precise mechanisms of how obesity promotes cancer growth and progression are unknown, a multitude of interrelated mechanisms are thought to contribute that revolves around the production of obesity-related hormones and alterations in insulin pathways leading to a state of chronic subclinical inflammation.

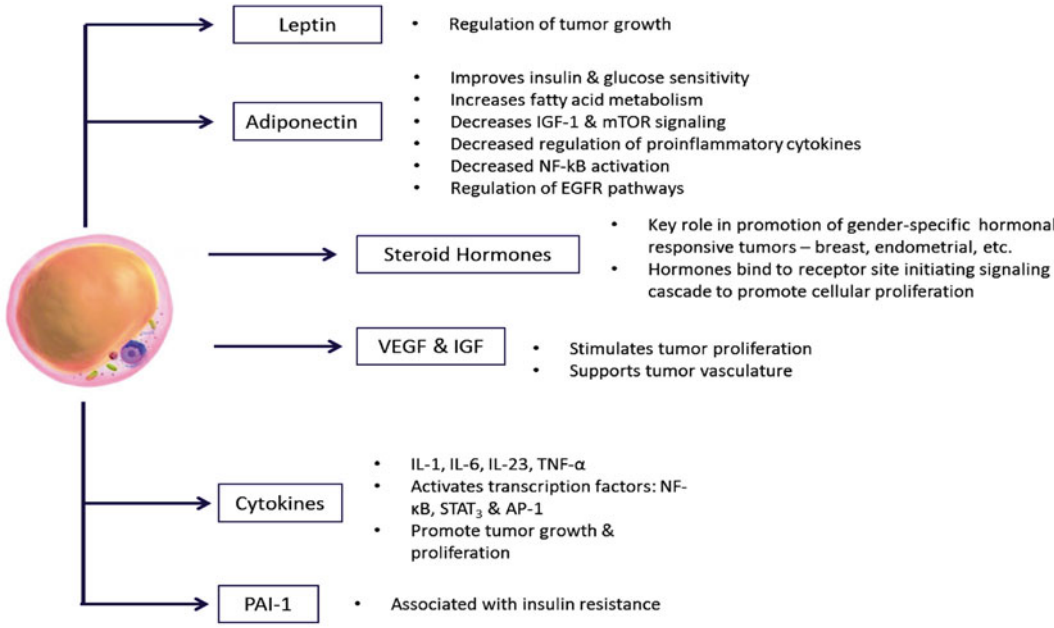


**Fig. 11.1** Substrates secreted by adipocytes that may promote tumorigenesis. *VEGF* vascular endothelial growth factor, *IGF* insulin-like growth factor-1, *IL-1* interleukin-1, *IL-6* interleukin-6, *IL-23* interleukin-23, *TNF-α* tumor necrosis factor-alpha, *NF-κB* nuclear factor-kappa B, *$STAT_3$* signal transducer and activator transcription 3, *AP-1* activator protein-1, *PAI-1* plasminogen activator inhibitor-1

A number of substrates including sex steroid hormones, cytokines, adipokines, growth factors, and insulin have been noted to influence cellular reactions and affect cell signaling in such ways leading to dysregulation and neoplasia. Energy balance has also been implicated in playing a role through its affects on insulin pathways, the genome leading to cellular dysfunction, as well as influencing transcription factors through activation of pro-inflammatory pathways [9]. Inhibitions of apoptosis and angiogenesis are additional avenues that are likely involved (see Fig. 11.1).

## Inflammation

Animal studies have helped shed light on understanding the complex interactions between adipocytes and the body. Adipocytes are commonly described as an active endocrine organ with significant systemic effects that may exert endocrine, paracrine, and/or autocrine functions. Inflammatory macrophages and leukocytes that infiltrate the adipocyte secrete pro-inflammatory cytokines including leptin, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) leading to a state of chronic inflammation and laying the foundation for the development of chronic diseases and cancers.

## Insulin Resistance

Obesity is associated with a state of insulin resistance, hyperglycemia, and hyperinsulinemia and ultimately, the diagnosis of type 2 diabetes. Hyperinsulinemia and type 2 diabetes have been convincingly linked with an increased risk for several cancers including breast, colon, endometrial, kidney, and pancreatic cancers [9, 10]. Moreover, insulin pathways are affected by energy intake

with some evidence showing that higher circulating insulin levels in nondiabetic patients can increase mortality in patients with a history of breast and colon cancer [11, 12] in Denmark. This may be secondary to signal transduction following insulin receptor binding in extracellular signal-regulated kinase (ERK) and phosphatidylinositol-3 kinase (PI3-k) pathways [11]. Insulin is believed to promote carcinogenesis through indirect effects by exerting mitogenic effects via increased levels of Insulin-like growth factor 1 (IGF-1) [11]. Increased levels of pro-inflammatory cytokines, namely TNF-α and IL-6, have been implicated in promoting insulin resistance through downregulation of insulin receptors and glucose transporters; others have reported that insulin receptors may be overexpressed reflecting the complexity of assessing this issue [9].

IGF-1 is a hormone produced primarily in the liver that plays a key role in cellular and tissue growth and development. Circulating levels of IGF-1 levels are regulated via IGF-1 binding proteins; insulin also plays a role in controlling circulating IGF-1 levels as it can reduce the level of IGF-1-binding proteins resulting in higher circulating levels of IGF-1 [9]. Once IGF-1 binds to its receptor site, a host of downstream signaling events through a number of pathways, including the ERK and PI3K pathways, are initiated that influence transcription and gene expression that influence carcinogenesis [9].

Plasminogen activator inhibitor-1 (PAI-1) is another substrate produced by the adipocytes that may also be involved in obesity-related cancers as elevated levels are associated with insulin resistance [13]. Through the disruption of the extracellular matrix, PAI-1 facilitates cell migration and angiogenesis resulting in tumor invasion and metastasis [13]. Additionally, PAI-1 production by tumor cells may promote tumor growth through interaction with insulin signaling pathways.

## Growth Factors

Secretion of additional growth factors by adipocyte may also be involved. Hepatocyte growth factor and vascular endothelial growth factor (VEGF) have the ability to stimulate tumor growth through enhancing tumor cell proliferation and tumor vasculature [14]. This appears to be perpetuated with obesity due to the presence of insulin resistance as well as increased levels of IGF-1, a metabolic abnormality commonly seen in obesity, are associated with physiological alterations including decreased expression of IGF-1 antagonists such as binding proteins IFBP-1 and IFBP-2—this in turn leads to increased insulin receptor and IGF-R signaling that results in up-regulated mitogenic, pro-angiogenic, and antiapoptotic signaling cascades which are critical for tumor development and progression [9].

## Leptin and Adiponectin

Leptin has also been identified as a possible pro-tumorigenic factor. Under normal circumstances, leptin functions as a hormone that regulates intake through its impact on hypothalamic pathways in the brain which results in reductions in appetite. How things change in the obese state where the adipocytes overproduce leptin with the brain no longer responding to leptin signaling—a state known as "leptin resistance" [15].

Exposures including estrogens, insulin, glucocorticoids, and TNF-α promote the synthesis of leptin. Subsequently, leptin modulates other physiologic functions including immunity, cytokine production, angiogenesis, and tumorigenesis [9]. Elevated leptin levels have been identified in both obese

individuals and individuals with some types of cancers including breast, prostate, and colon [16]. Leptin also influences pro-inflammatory pathways through the increased production of the interleukin cytokines IL-6 and IL-1β in addition to TNF-α. In turn NFκB is activated thereby affecting a host of downstream signaling cascade events. Once leptin binds to the receptor site, signaling cascades are activated regulating pathways such as PI3K (phosphatidylinositol 3-kinase)/AKT/mTOR and MAPK (mitogen-activated protein kinase) that are involved in regulating tumorigenesis [17]. Increased expression of leptin receptors on tumor cells has also been noted [17]. However, leptin comprises at least four splicing isoforms that possess different biological functions thereby making it difficult to determine the precise role of leptin in carcinogenesis.

Adiponectin is a peptide hormone produced by the adipocyte that plays an important role in counteracting the metabolic profile associated with obesity by improving insulin and glucose sensitivity, increasing fatty acid metabolism, decreased levels of IGF-1 and mTOR signaling along with a reduction in the production of pro-inflammatory mediators thereby decreasing the risk for carcinogenesis [18]. However, as body fat increases, adiponectin levels decrease which likely contributes to the chronic subclinical inflammatory state.

Cellular proliferation appears to be regulated by adiponectin through an AMP-activated protein kinase pathway. Adiponectin provides anti-inflammatory benefits through the downregulation of pro-inflammatory cytokine production and inhibition of NFkB receptor activation [18]. Animal models demonstrate a role for adiponectin in promoting apoptosis and inhibition of tumor angiogenesis reducing cell proliferation [18].

## Sex Steroid Hormones

Various steroid sex hormones are produced by adipocytes and have been implicated in the development of gender-specific cancers through the excessive production of estrogens and androgens. In postmenopausal women, adipocytes serve as the primary storage site for aromatase and 17 β-hydroxysteroid dehydrogenases, enzymes which are responsible for synthesis of estradiol and estrone as well as testosterone [19].

Plasma estrogen and androgen levels have been shown to increase breast cancer risk in obese postmenopausal women. In a study by Key et al., the risk for breast cancer doubled for women in the highest quartile versus lowest quartiles for both circulating levels of free estradiol and testosterone [20]. The binding of estrogen to the estrogen receptor facilitates a cascade of signaling events resulting in cellular proliferation and expression of antiapoptotic pathways. The risk for breast cancer related to body mass index (BMI) has been linked to elevated plasma levels of estradiol. Indeed, suppression of androgen conversion to estrogens is a targeted therapy for women with estrogen receptor positive breast cancers.

## The Role of Adipose Stromal Cells

The adipocyte may contribute to tumorigenesis in a number of other ways in addition to secreting the procarcinogenic substrates discussed above. Adipocytes also comprise adipose stromal cells (ASC) that have potent pro-angiogenic properties that may support the cancer cells' needs for angiogenesis needed for tumor progression. ASC-associated substrates have also been noted to influence cell-signaling pathways that can suppress apoptosis and silence T-cell-mediated immunity [21]. Elevated levels of

ASC have been measured in obese cancer patients reflecting a potential role for ASC in cancer progression. Animal models have illustrated a migratory pattern for ASC with the tumor recruiting ASC to become a component of the tumor's microenvironment [21]. Subsequently, ASC functions contribute to tumor progression by promoting cellular proliferation and supporting angiogenesis.

As the fat content in the adipocyte increases, the fat cells become more inflamed, oxygen deprived, and fibrotic. A relative state of hypoxia develops as oxygen diffusion within the cell becomes limited due to the size of the cell and lack of adequate vascular support [22]. As the hypoxic state develops, adiponectin levels decrease while leptin levels increase. Levels of IL-6 and hypoxia-inducible factor 1alpha (HIF1alpha) are also elevated. HIF1alpha is a transcription factor inducing expression of VEGF in tumors—this has been associated with poorer outcomes for cancer patients [23]. Additionally, oxidative stress increases as a result of chronic inflammation resulting in an elevation in cancer risk. Levels of reactive oxygen species (ROS), free radicals, and peroxides increase causing damage to lipids and protein as well as DNA [24]. Activation of NFκB by the ROS further contributes to a pro-inflammatory environment. Macrophages recruited to the site infiltrate the cell contributing further to an inflammatory state by producing more inflammatory substrates. Interestingly, the adipocyte can also trans-differentiate into a macrophage further promoting an inflammatory state [24].

In summary, the link between obesity and cancer is complex involving a variety of mechanisms and substrates that are influenced by energetics, fat cell metabolism, and a chronic state of subclinical inflammation. A number of interacting pathways are involved and represent various avenues that can be targeted for risk reduction.

## Obesity and Prognosis After Cancer

Obesity has also been associated with prognosis after cancer. The risk may be attributable to the excess adiposity at the time of diagnosis, may be further influenced by the effects of treatment on body composition, and finally may influence not only cancer-related mortality but also all-cause mortality as well as post-diagnosis obesity-associated comorbidities.

## Effects of Cancer Treatment on Adiposity

Cancer therapies including surgery, radiation, chemotherapy, and hormone modulation all have potential detrimental effects on adiposity. For example, surgical interventions, particularly those involving the oral cavity and/or gastrointestinal system (e.g., colorectal cancer, pancreatic cancer, gallbladder, and gastric cancers), can result in significant reductions in nutrient intake, unintentional weight loss, and reductions in lean mass. Inactivity after surgery can result in greater loss of lean mass leading to an undesirable shift in fat-free to fat mass that may promote metabolic dysregulation. Importantly, the surgical complication rate may also be elevated in obese individuals leading to prolonged disability or limited activity as has been shown in relation to fistula development after surgery for pancreatic cancer [25], although this was not shown in a recent study of ovarian cancer tumor debulking [26]. Radiation is associated with fatigue that may further exacerbate loss of lean mass related to insufficient physical activity, particularly strength training. Chemotherapy can markedly reduce intake leading to nutrient depletion with a propensity to mobilize not only fat but muscle stores to meet energy needs. In select patients prescribed with antihormone medications, these effects may be further exacerbated by the loss in estrogen and androgens associated with preservation of lean mass.

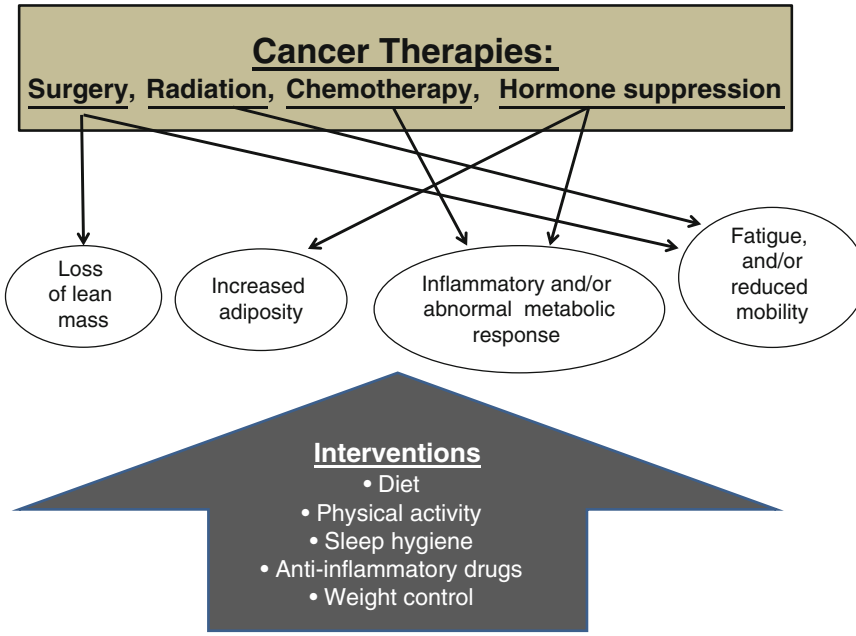


**Fig. 11.2** Anti-neoplastic therapies are associated with a variety of adverse consequences. Bed rest following surgical interventions can promote the loss of lean body mass. Surgery, radiation, and chemotherapy promote fatigue resulting in decreased mobility that often promotes lean body mass loss and reduced quality of life. Chemotherapy and hormone suppression interventions promote a proinflammatory environment and alterations in metabolic pathways that result in adverse changes in body composition. A multi-modal approach that includes medical nutrition therapy and possibly pharmacologic agents should be employed to attenuate these adverse effects

Beyond the direct treatment-related effects on body composition, several indirect consequences of therapy can also promote either an undesirable increase in adipose or a shift toward greater fat to fat-free body mass. These include such factors as fatigue, disrupted sleep that results in reduced sleep-related energy expenditure, stress/anxiety and/or depression that can promote elevated cortisol leading to appetite stimulation, and reduced energy expenditure with loss of lean mass. The overall result of these direct and indirect consequences of therapy and diagnosis is a predisposition toward weight gain and concomitant rise in adipose tissue mass (Fig. 11.2).

## Association Studies Linking Obesity to Cancer Prognosis

While early detection and treatment advances for cancer have increased the number of cancer survivors to over 14 million [27], poorer outcomes in terms of worsened disease survival have been reported for obese patients, particularly those diagnosed with breast, prostate, and colon cancer [28, 29] (IOM Report). The majority of the epidemiological research has evolved from well-established cohort trials that while not specifically designed to evaluate the role of obesity in cancer prognosis, most are sufficiently robust in the available data to accomplish this goal. Most of the available evidence is specific to breast cancer recurrence, progression, or cancer-specific and/or total mortality after diagnosis and treatment for breast cancer. Importantly when evaluating the data regarding BMI and cancer prognosis, it is relevant to consider time of measurement with some studies evaluating pre-diagnosis BMI, others the change in BMI during treatment and still others assessing post-therapy BMI in relation to recurrence and/or cancer progression risk.

## Obesity and Mortality After Cancer

BMI may be a prognostic indicator for cancer. Much of the current evidence suggests that excess body weight at the time of diagnosis may reduce overall survival and that this association is not a result of insufficient chemotherapy dosing has had been postulated in earlier reports. As an example, a review of breast cancer prognosis and mortality reported by Protani et al. supported a statistically significant and clinically relevant increase in all-cause as well as cancer-specific mortality for obese women with breast cancer as compared to non-obese women with breast cancer—HR (95 % CI): 1.33 (1.21–1.47) and 1.33 (1.19–1.50), respectively [28]. More recently a systematic review suggested that higher pre-diagnosis BMI increased risk of disease-specific mortality in premenopausal breast cancer patients [30]. BMI prior to diagnosis has not been convincingly linked to colorectal cancer mortality, although evidence is limited and one prospective cohort did show a significant association [31], and for post-menopausal women association studies suggest a twofold greater risk of colorectal cancer mortality in obese women [32]. Higher body fat and central adiposity as assessed by waist circumference and/or waist-to-hip ratio also has been shown to be associated with an increase in disease-specific mortality [33]. Similarly, pre-diagnosis BMI has been associated with prostate cancer-specific mortality [34, 35], a relationship that is not explained by lengthened screening interval and/or chemotherapeutic dose. Obesity at time of diagnosis has also been shown to reduce survival in older individuals diagnosed with pancreatic cancer [36]. Of note, for endometrial cancer, a cancer with incidence in obese women, BMI has not been shown influence prognosis possibly related to the reduced aggressiveness of tumors diagnosed in obese women [37]. Similarly, pre-diagnosis BMI has not generally been associated with prognosis for ovarian [38] and colon [39] cancers. The epidemiological studies evaluating the relationship between adiposity and cancer survival have relied almost exclusively on either BMI or waist circumference as surrogates for adiposity. A recent evaluation using preoperative CT scans to quantify visceral (abdominal) adiposity in 219 patients undergoing bowel resection for colorectal cancer showed no difference in survival by BMI category, but for stage II cancer, those with greater visceral obesity demonstrated an almost threefold decrease in disease-free survival [40]. Similarly, body composition, rather than BMI, was also associated with Gleason scores in men with prostate cancer [41].

## Obesity and Recurrent or New Primary Cancer Events

Evidence linking pre-diagnosis obesity to recurrence of cancer is limited. A review by Parekh in 2012 suggested that in the three studies evaluating recurrence after breast cancer, two found an association and one did not [30]. In the largest single study of breast cancer survivors, Kroenke et al. showed a significant increase in recurrent disease with any increase in BMI above 0.5 kg/m$^2$ [42]. Obesity has also been associated with more advanced pathology and nodal involvement in males with colorectal cancer [43] suggesting a greater likelihood of recurrent disease. To date, few studies have ample statistical power to evaluate the associations between obesity and disease prognosis according to tumor subtype, although most clinicians and researchers support the hypothesis that obesity may have differential associations with prognosis after cancer depending on the tumor molecular characteristics. These associations should be evaluated through pooled study analyses in the future.

Obesity posttreatment has been studied more widely particularly in relation to cancer-specific and overall mortality. Poorer survival outcomes have been suggested for obese prostate cancer survivors [44] as well as those treated for colorectal [30], ovarian cancer [38]. Importantly, the data are not always consistent, particularly when those with more advanced disease are included in the analysis as with disease progression unintentional weight loss is a common clinical manifestation of disease.

## Obesity and Comorbidity in Cancer Survivors

Obesity also may have an adverse impact on long-term treatment side effects as obesity has been noted to exacerbate lymphedema in breast cancer survivors [45], and weight-lifting intervention has been associated with reduced severity of lymphedema over time [45]. Additionally, many of the chemotherapeutic agents used to treat cancer can have adverse side effects that are further aggravated in the presence of obesity. For example, taxol-inclusive chemotherapeutic regimes place patients at risk for neuropathy. Rates seem to be elevated in those with obesity. Further, obesity in the setting of neuropathy leads to significant limitations in physical function thus further exacerbating the risk for weight gain. Cancer survivors may also be at heightened risk for metabolic perturbations as was the finding of a small study of overweight breast cancer survivors. Specifically the investigators identified a 53 % incidence of undiagnosed metabolic syndrome in overweight/obese breast cancer survivors [46]. With a primary focus on cancer therapies, these comorbidities may go unrecognized and could contribute to overall survival. In a study by Patterson et al., type 2 diabetes, a comorbidity that was not uncommon, was shown to increase mortality in breast cancer survivors by over twofold [47]. Further, a recent study of cancer patients showed that T2DM also was common in patients diagnosed with pancreatic, liver, bladder, and prostate as well as female lung cancer [48]. Co-diagnosis was further associated with higher mortality in females.

## Intervention Trials Targeting Weight Loss in Survivors

Given the general adverse outcomes associated with obesity after cancer efforts to provide weight control have been undertaken an evaluated in the scientific literature although on a fairly limited basis. The randomized, controlled trials to promote weight loss in cancer survivors that have been undertaken suggest modest results in relation to weight control. Table 11.1 summarizes the available studies of weight control in cancer survivors. Of note most are relatively small in number and several are of short duration. Overall the data suggest the cancer survivors can and will make significant changes in diet and/or activity to promote weight control in the posttreatment setting. Studies that have attempted to promote weight control during therapy have proven to be more challenging in relation to recruitment and have had less success in inducing significant weight change [49]. Interventions have been delivered in clinics, using commercial programs and also using home-based approaches. Most have targeted overweight or obese breast cancer survivors and suggest targeted behavioral approaches that integrate behavior change in relation to diet and strength training are likely to be the most effective [50].

## Guidelines for Cancer Survivors

The American Cancer Society has published guidelines for diet and physical activity for cancer survivors [6]. These guidelines promote an eating pattern consistent with primary cancer prevention and place an emphasis on the role of weight control albeit a leading modifiable risk factor for reduced morbidity and mortality after cancer. While gaps remain as to the specific lifestyle behaviors and the adoption of these behaviors may modify cancer mortality, overall mortality, and even comorbid conditions after cancer, the following recommendations are the best practice for promoting health in this vulnerable segment of the population:

- Achieve and maintain a healthy body weight
- Limit energy-dense foods and beverages

**Table 11.1** Summary of obesity-related intervention trials in cancer survivors

| Study | Target population | Sample size | Duration | Intervention | Outcome |
|---|---|---|---|---|---|
| *Breast cancer* | | | | | |
| Campbell [51] | Overweight or obese breast cancer survivors | 14 | 24 weeks | Single arm, pre-, post-, group-based intervention of the diabetes prevention program | Mean weight loss of 3.8 kg at 24 weeks; 4.6 kg at 36 weeks |
| Demark-Wahnefried [52] | Breast cancer receiving chemotherapy | 9 Active; 36 controls | 6 months | Clinic-based exercise program | +2.2 kg weight gain controls versus −2.0 kg in intervention; +1.8 % body fat versus −1.3 % in intervention |
| Demark-Wahnefried [53] | Newly diagnosed premenopausal breast cancer survivors | 90 | 6 months | Calcium rich diet versus exercise versus exercise plus low fat, plant-based diet | No difference in weight change or adiposity except extremity adiposity greater in combination arm |
| Djuric [54] | Obese women diagnosed with breast cancer | 48 | 12 months | One-on-one counseling or without weight watchers program participation in a 2×2 factorial design | Control—increased 0.85 kg; counseling alone decreased 8.0 kg; weight watchers alone −2.6 kg; counseling with weight watchers decreased 9.4 kg |
| Djuric [55] | African American breast cancer survivors | 31; 24 completers | 18 months | Weight loss counseling versus weight loss with spirituality | No significant change in body weight |
| Goodwin [56] | New diagnoses of locoregional breast cancer; BMI 20–35 kg/m$^2$ and on standard adjuvant therapies | 61 | 12 months | Psychological supportive-expressive group weight loss intervention—goals, energy restriction, and physical activity | Exercise strongest predictor of weight loss; weight maintenance in normal weight women; weight loss in obese (−6.3 kg) |
| Irwin [57, 58] | Postmenopausal breast cancer survivors | 75 | 6 months | Exercise—150 min/week of moderate-intensity versus usual behavior | Significant reduction I percentage body; increase lean body mass |
| Pakiz [59] | Overweight breast cancer survivors | 68; 44 active; 24 controls | 16 weeks | Cognitive behavioral therapy for weight loss; physical activity and energy restriction | Weight loss of −5.76 kg in intervention versus +0.2 kg in controls; modest improvements in inflammatory biomarkers |
| Sedlacek [60] | Overweight and obese postmenopausal breast cancer survivors | 370 | 6 months | Low fat/high carbohydrate versus low carbohydrate high-fat diet | Pending |

| | | | | | |
|---|---|---|---|---|---|
| Thomson [46] | Overweight and obese breast cancer survivors on hormone-modulating medications | 40 | 6 months | Low fat versus low carbohydrate energy-restricted diet delivered by dietitian counseling | Significant weight loss with both diets, average 6.1 kg; marked improvements in most metabolic biomarkers |
| *Breast and prostate and/or colorectal combined* | | | | | |
| Ligibel [61] | Active After Cancer Trial (AACT); sedentary breast and colorectal cancer survivors | 121 | 16 weeks | Telephone-based diet and activity counseling; ten calls | Physical activity increased by 54.5 min/week versus 14.6 min/week; improved 6-min walk and physical function |
| Christy [62] | Fresh start<br>Breast and prostate cancer survivors | 543 | 10 months | Sequentially tailored mailed print materials for diet and exercise behavior change versus publically available materials | Both arms decreased saturated fat and increased fruit and vegetables and improved diet quality score although tailored materials group had higher overall diet quality scores and lower saturated fat at year 2 follow-up |
| Demark-Wahnefried [63] | Long term, sedentary, overweight/obese, US or UK, breast, colorectal, and prostate cancer survivors | 641 | 12 months | Mailed print information on diet and exercise and telephone counseling | Improvements in diet quality score, physical activity; slight reduction in BMI (−0.56 kg/m$^2$); less loss of physical performance |
| Ligibel [61] | Active After Cancer Trial (AACT); sedentary breast and colorectal cancer survivors | 121 | 16 weeks | Telephone-based diet and activity counseling; ten calls | Physical activity increased by 54.5 min/week versus 14.6 min/week; improved 6-min walk and physical function |
| Morey [64] | Older, overweight, long-term breast, colorectal, and prostate cancer survivors | 641 | 12 months | Weight loss diet—high vegetable, 10 % fat, strength training versus wait-list control | Weight loss of 2.06 kg in intervention versus 0.92 kg in control |

(continued)

**Table 11.1** (continued)

| Study | Target population | Sample size | Duration | Intervention | Outcome |
|---|---|---|---|---|---|
| *Endometrial cancer* | | | | | |
| Von Gruenigen [65] | Overweight/obese early stage endometrial cancer: the SUCCEED study | 75 | 12 months | Diet and exercise; ten weekly counseling sessions followed by six biweekly sessions | Intervention reduced weight by 3.5 kg versus 1.4 kg weight gain in control |
| *Prostate cancer* | | | | | |
| Parson [66] | Prostate cancer survivors | 43 | 6 months | Telephone-based diet counseling | Increase in vegetable intake; no change in body weight |
| *Colorectal cancer* | | | | | |
| Campbell [67] | Colorectal cancer survivors | 266 | 9 months | Tailored print with telephone-based motivational interviewing counseling versus usual behavior | Significant increase in fruit and vegetables in intervention group; no change in physical activity or body weight |
| Bourke [68] | Colorectal cancer survivors; 6–24 months post-primary treatment | 18 | 12 weeks | Combined supervised and independent exercise and diet versus standard care | >90 % Adherence rate to=intervention; reduced fatigue, increased functional capacity, and reduced waist circumference with intervention assignment |

- Increase physical activity to promote weight control; engage in regular physical activity (150 min/week; strength training twice/weekly)
- Achieve a dietary pattern high in vegetables, fruits, and whole grains

Additional well-designed intervention trials are needed to more clearly elucidate the dietary pattern, activity plan (including type, dose, and intensity), and associated health habits (sleep, stress reduction, etc.) most associated with improved survival for cancer survivors.

## Conclusion/Summary

The majority of Americans, including cancer survivors, are either overweight or obese. Excess energy intake and sedentary lifestyle lead to excess body weight—these are important modifiable risk factors for cancer prevention and risk reduction for recurrent. The Institute of Medicine consensus report, "From Cancer Patient to Cancer Survivor: Lost in Translation," outlines guidelines for quality cancer survivorship including the recommendation that an individualize cancer survivorship plan be designed for all survivors providing suggestions for how to have a healthy lifestyle, achieve a healthy body weight, and how to be physically active on a regular basis following completion of treatment [69]. Research reflects that cancer survivors are interested in and motivated to improve lifestyle habits that promote a healthy lifestyle and weight control. However, further research is needed from large, well-designed trials to address current gaps in knowledge such as "what is the role of obesity in recurrence and/or development of new primary cancers?"; "what are the associations between obesity and disease prognosis according to tumor subtype?"; and "what strategies can be used to promote control weight control during treatment?" Further data regarding optimal dietary patterns, activity levels (including type, dose, and intensity), and associated health habits (sleep, stress reduction, etc.) relative to body weight will improve care and outcomes for cancer survivors.

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# Chapter 12
# Diabesity: The Causes of Our Modern Plague

**Mark Hyman**

**Abstract** Diabesity (the spectrum from mild insulin resistance to end-stage diabetes) now affects over one billion people worldwide. From 1983 to 2008 there has been a sevenfold increase in diabetes worldwide, its most extreme form. Metabolic syndrome and its consequences including cardiovascular disease, cancer, and dementia are emerging as the major driver of most chronic diseases of aging. Up to 50 % of diabetics and nearly all prediabetic are undiagnosed. Current strategies of pharmacologic intervention have proven ineffective or harmful. Emerging research clarifies underlying causes of this pandemic of insulin resistance including our refined, nutrient-poor, high-glycemic load diet, sedentary lifestyle, and chronic stress. Novel etiologic factors including environmental toxins, food sensitivities, hormonal dysregulation, gut microbiology, latent infections, nutrient deficiencies, and abnormal gene expression provide important diagnostic considerations and avenues for therapeutic intervention. A whole systems approach based on functional medicine provides a methodology for a comprehensive approach to this life-threatening and economically crippling modern disease.

**Keywords** Insulin resistance • Diabetes • Obesity • Inflammation • Prediabetes • Functional medicine • Heart disease • Cancer • Dementia

### Key Points

- Diabesity (the spectrum from mild insulin resistance to end-stage diabetes) now affects over one billion people worldwide.
- From 1983 to 2008 there has been a sevenfold increase in diabetes worldwide, its most extreme form.
- Metabolic syndrome and its consequences, including cardiovascular disease, cancer, and dementia, are emerging as the major driver of most chronic diseases of aging.
- Up to 50 % of diabetics and nearly all prediabetic are undiagnosed and current strategies of pharmacologic intervention have proven ineffective or harmful.
- Emerging research clarifies underlying causes of this pandemic of insulin resistance including our refined, nutrient-poor, high-glycemic load diet, sedentary lifestyle, and chronic stress.
- Novel etiologic factors including environmental toxins, food sensitivities, hormonal dysregulation, gut microbiology, latent infections, nutrient deficiencies, and abnormal gene expression provide important diagnostic considerations and avenues for therapeutic intervention.

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- A whole systems approach based on functional medicine provides a methodology for a comprehensive approach to this life-threatening and economically crippling modern disease.

## Epidemiology

The global prevalence of overweight and obesity of one billion people now exceeds that of malnutrition. In 1980 there were no states with obesity rates over 15 %. In 2008 there were no states with obesity rates under 15 %, and all except Colorado have obesity rates over 20 % [1]. Recent NHANES data show that nearly three quarters of Americans are now overweight [2]. Childhood obesity has increased three- to fourfold since the 1960s [3]. Diabetes prevalence has risen sevenfold from 1983 to 2008. Obesity also places a large economic burden on our society. The direct and indirect annual costs of obesity in America are $113 billion and $174 billion for diabetes. Over the past 10 years, these two conditions cost a total of $3 trillion. The problem is expanding globally. In China 92 million have diabetes, 60 % of which are undiagnosed and 148 million have metabolic syndrome, 100 % of which are undiagnosed [4].

Overweight and obesity are, for the majority, markers of a single unifying metabolic dysfunction—insulin resistance. Rather than discrete risk stratification based on ideal body weight, overweight (BMI < 25), obesity (BMI > 30), or diabetes (fasting glucose <126), it is more useful to consider the metabolic dysfunction as a continuum of dysfunction from optimal insulin sensitivity to end-stage diabetes. Risk increases progressively with increasing BMI, even below the overweight level of 25. This spectrum has been referred to as "diabesity" and is a more useful clinical concept focusing on mechanism rather than phenotype for obesity.

## Mortality and Morbidity

Obesity will take 9 years off the life of the average person [5], and obesity in adolescents creates the same risk of premature death as heavy smoking [6]. Diabesity along the entire continuum of metabolic dysfunction is the main driver of cardiovascular disease [7], diabetes, dementia [8], cancer [9], and most chronic disease mortality [10] and our decreasing life expectancy. A recent 40-year prospective study of 4,857 Pima Indian children found that the most important predictor of premature death was insulin resistance, neither hypertension nor hyperlipidemia. Those in the highest quartile of glucose intolerance had a 73 % increased death rate compared to those in the lowest quartile [11].

## Risk Factors or Causes: Changing the Focus of Clinical Intervention

Focus has been on pharmacologic or bariatric surgical approaches to correct downstream risk factors to address to this epidemic and its chronic disease sequelae (heart disease and diabetes) at great cost and little or no benefit. The recent ACCORD [12] and NAVIGATOR trials documented that aggressive pharmacologic intervention for lipids [13], glucose [14], and blood pressure [15] did not decrease cardiac or overall mortality and in some cases increased adverse cardiac events and mortality. Surgical approaches of cardiac bypass [16] or angioplasty [17] fared no better. However despite a rich evidence base [18], little attention has been placed on the lifestyle, biological, social, and policy drivers of obesity and overweight.

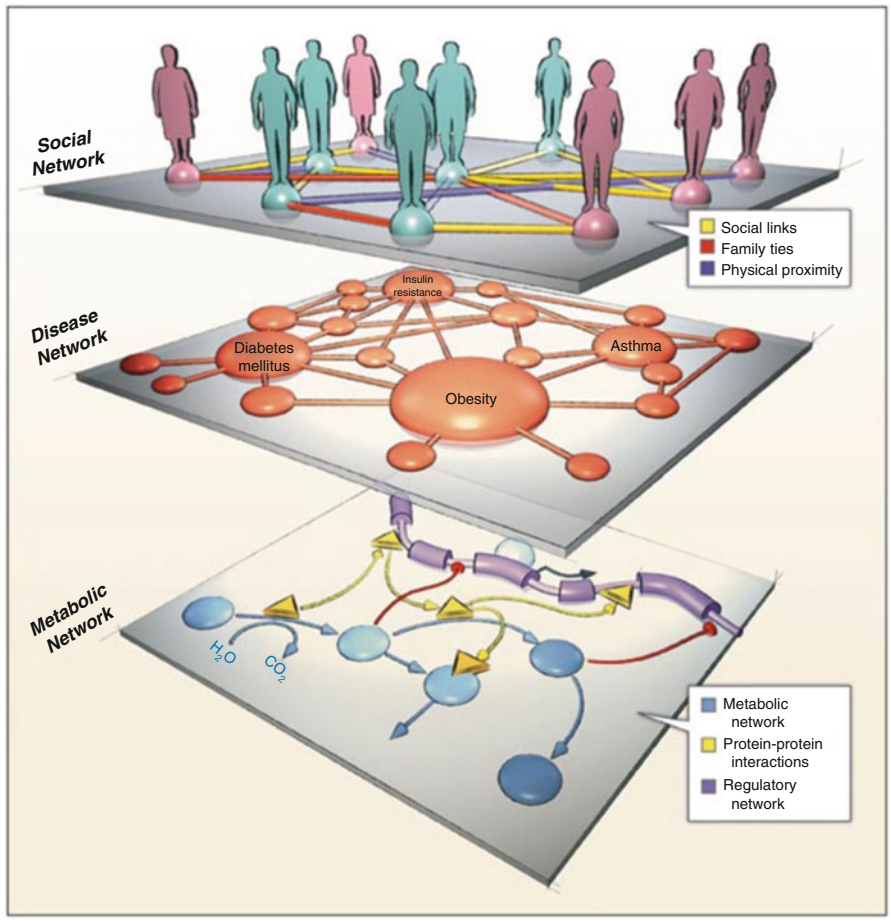
Network or systems medicine provides a new framework for addressing the causes, rather than the risk factors of this epidemic. Functional medicine [19] is a system-based approach model of integrative medicine that addresses the underlying causes of disease and engages both patient and practitioner in a therapeutic partnership [20]. The dynamic interaction of the social, business and policy systems, lifestyle, and environmental toxins drives our expanding phenotype.

Chronic disease and obesity are the results of complex network of biological disturbances driving systemic neuroendocrine-immune dysregulation induced by the effects of diet, levels of stress, our social environment, physical activity, and exposure to environmental toxins affecting gene expression. Isolating one risk factor or even separately treating multiple risk factors will fail until it is done in the context of addressing the upstream drivers of disease. Distinguishing between risk factors and causes is necessary for effective primary prevention and treatment of chronic disease [21].

Treatment must focus on the **system not the symptom**. Obesity and its chronic disease consequences, commonly referred to as "risk factors," dyslipidemia, hyperglycemia, and hypertension, are only downstream symptoms of upstream biological causes. They are the smoke, not the fire. Unless medicine refocuses on treating the system rather than symptoms (risk factors) through a comprehensive clinical and social systems approach that addresses diet, exercise, stress management, and treatment of environmental toxic exposures, medicine will fail to stem the impending tsunami of obesity and chronic disease.

Whole systems approaches of lifestyle interventions reduce the incidence of cardiovascular disease [22] and diabetes by over 90 % [23]. These studies are part of a large evidence base documenting how lifestyle intervention is often more effective in reducing cardiovascular disease, hypertension, heart failure, stroke, cancer, diabetes, and deaths from all causes than almost any other medical intervention [18].

Despite the difficulty of behavior change and lifestyle and environmental treatment, it is the only proven model for preventing chronic disease. Risk factor treatment must be replaced with elimination of the drivers, triggers, and causes of chronic disease based on the network model of disease and obesity. Metabolic disease and social networks predict disease and outcomes more effectively than risk factors [24].



For example, the risk of obesity if a sibling is overweight is 40 %, if a friend is overweight, 171 % [25]. If a friend of a friend is overweight the risk of obesity is 20 %. Newer tools supporting behavior change with regular feedback metrics and social networks have proven successful and should be widely adopted in policy and medical practice [26].

## Etiology and Pathophysiology

### *Social Etiologies*

Structural violence [27] has driven the obesity epidemic through an obesogenic environment. Policies and practices in agriculture, transportation, education, advertising, technology, health care, environment, and the food industry promote obesity. These policies and practices have created limited access to whole fresh foods, but unlimited access to calorie-dense, nutrient-poor foods consumed mostly outside the home or made in a plant, rather than grown on a plant. The built environment and adoption of technology limits physical activity. Hours of television watched are second only to consumption of liquid sugar calories as a risk factor for obesity [28]. Environmental toxins also promote obesity [29]. *Obesogens* are implicated in the 73 % increase in obesity in 6-month-old infants since 1980 [30]. Growing awareness of the obesogenic environment is driving changes in social, media, business, and government policies including limiting sweetened beverages in schools, science rather than industry-based nutrition guidelines from the UDSA [31], and Michelle Obama's *Let's Move* campaign [32].

### *Biological Etiologies*

Emerging evidence points to obesity as more than simply genetics or a thermodynamic problem of calories in/calories out or eating less and exercising more. Contributing etiologies include poor quality food, nutritional deficiencies, hormonal dysfunction, inflammation, food allergens, chronic infections, gut-derived endotoxins, altered gut barrier integrity, environmental toxins, oxidative stress, defects in energy metabolism and mitochondrial function, and chronic stress. These factors all interact in a dynamic network of dysfunction that leads to insulin resistance and obesity better described as diabesity.

Systematic focus on diagnosing and treatment of each and all of the underlying causative factors in the network of metabolic dysfunction will result in more successful clinical outcomes and improved gene expression.

### *Nutritional Factors: Sugar, Fiber, Micronutrients, Macronutrients*

*Nutrigenomics*, the effect of macronutrients, micronutrient, phytonutrients, and glycemic load on gene expression, provides an important lens in understanding the impact of nutrition on obesity and insulin resistance [33, 34].

The single biggest contributor to obesity is the increased consumption of refined sugar and carbohydrates. Our Paleolithic ancestors ate 22 teaspoons of sugar per year [35]. Sugar consumption

increased from 10 lb in 1800 to 150–180 lb per person per year. In the last 30 years, the sugar calories we consume from high-fructose corn syrup have increased from 0 to 66 %, mostly in the form of liquid calories from soft drinks and other sweetened beverages. Liquid calories increase obesity more than calories from solid food [36].

Glycemic load and nutrient density is also controlled by fiber content of food. Our Paleolithic fiber consumption decreased from 100 g a day to less than 8 g per day [37]. Lack of fiber promotes heart disease, diabetes, obesity, cancer, and many other chronic diseases [38]. Consumption of 50 g of fiber per day lowers hemoglobin A1c as effectively as diabetic medication [39].

Obesity is often associated with malnutrition. Obese children are increasingly diagnosed with scurvy, B vitamin deficiencies, and rickets. Nutrient-poor, calorie-dense diets promote a society of overfed and undernourished citizens. A number of nutrients are particularly important in the prevention and treatment of diabesity, including vitamin D [40], chromium [41, 42], magnesium [43], zinc [44], biotin [45], omega-3 fats [46], and antioxidants such as alpha lipoic acid [47, 48]. These nutrients regulate glucose metabolism and insulin sensitivity [33, 49]. Supplementing with nutrients is necessary because modern food-growing and food-processing practices have greatly diminished the quality of our diet [50].

Shifting from a nutrient-poor diet to a nutrient-dense diet that is abundant in plant foods such as fresh, whole fruits, vegetables, nuts, seeds, beans, and whole grains improves the function of hundreds of genes that control insulin function and obesity. An optimal diet to prevent and treat diabesity includes healthy fats such as olive oil, nuts, avocados, and omega-3 fats, along with modest amounts of lean animal protein. This is commonly known as a Mediterranean diet [51, 52].

## Hormonal Dysregulation: Insulin, Thyroid, Adrenal, and Sex Hormones

Obesity results from and drives neurohormonal immune dysregulation [53]. Impairment in insulin sensitivity, thyroid metabolism, adrenal function, and sex hormones and neuroendocrine appetite regulation are common features in diabesity.

Undiagnosed thyroid disease worsens insulin resistance [54], and insulin resistance worsens thyroid function [55]. Chronic stress drives chronically elevated cortisol which promotes insulin resistance, central adiposity, dyslipidemia, depression, and even dementia [56]. Elevated cortisol also promotes muscle loss, interferes with thyroid and growth hormones, and negatively impacts sleep, all of which lead to problems with weight gain. Sleep deprivation or impaired sleep, in turn, increases appetite and increases sugar and refined carbohydrate cravings. In a study of healthy young men deprived of just 2 h of sleep, their blood levels of *ghrelin* (the hunger hormone) increased and *PYY* (the brake on appetite) decreased [57].

Diabesity also drives sex hormone dysregulation. Insulin resistance underlies infertility [58] and polycystic ovarian syndrome [59]. In men, insulin resistance results in androgen deficiency and impaired sexual function [60].

## Inflammation: Refined Sugars and Food Sensitivities

Silent inflammation is a final common pathway in most chronic diseases, including heart disease, cancer, Alzheimer's, and diabesity [61]. Elevated C-reactive confers a 1,700 % increased risk of developing diabetes [62]. Inflammation from any source (allergen, infection, toxin, diet, stress) promotes obesity and obesity drives further inflammation. Anti-inflammatory medications do not address the most important question, "What is causing the inflammation and how do we treat it most effectively?"

Sugar, refined carbohydrates, artificial sweeteners, food allergies and sensitivities, chronic infections, environmental and metabolic toxins, stress, and a sedentary lifestyle all promote inflammation. Each of these underlying causes of inflammation has to be addressed if diabesity is to be treated effectively.

## *Dietary Sugars, Refined Flours, and Artificial Sweeteners*

Dietary sugars and refined flours are the single biggest triggers of inflammation driving hyperinsulinemia leading to a biochemical cascade that alters gene expression promoting inflammation [63] and downward spiral into further inflammation and insulin resistance. Lack of fiber and too many inflammatory omega-6 fats (soybean and corn oil) and not enough anti-inflammatory omega-3 fats (fish oil, flax seeds) also contribute to the development of systemic inflammation.

## *Special Note: Artificial Sweeteners*

Artificial sweeteners promote obesity through increasing hunger, food consumption, and reductions in body temperature and thermogenesis.

In a recent study, rats were fed yogurt sweetened with either sugar or artificial sweetener for 14 days. The rats that consumed the artificially sweetened yogurt increased their total food consumption, but not total calories, and yet body fat and weight increased, while body temperature and *thermogenesis* decreased [64].

## *Food Sensitivities and Allergies*

Delayed or type 3 IgG food sensitivities or allergens also may play a role in the development of insulin resistance and diabesity through promotion of systemic low-grade inflammation. In a study that compared obese children to normal-weight children, the obese children had threefold higher levels of C-reactive protein and a two-and-a-half-fold higher level of IgG antibodies for the 277 different foods tested [65]. In addition, these obese children had increased carotid intimal thickness.

## *Special Note: Gluten, Inflammation, and Obesity*

Another growing problem is gluten intolerance or celiac disease, which triggers systemic inflammation and has been linked to autoimmune diseases, mood disorders, cancer, and cardiovascular mortality. In a recent study comparing blood samples taken from a cohort of 10,000 people 50 years ago to a modern cohort of 10,000, researchers found a 400 % increase in celiac disease based on antibody testing (tissue transglutaminase) [66].

In a 30-year study of over 30,000 people, hidden gluten sensitivity, even without biopsy proven celiac, was shown to increase risk of death by 35–75 %, mostly from cardiovascular and cancer mortality, both known to be driven by inflammation [67].

Damage to the gastrointestinal tract and impaired intestinal permeability from overuse of antibiotics, NSAIDs, and proton pump inhibitors and H2 blockers, combined with our low-fiber, high-sugar diet, combined with genetic alternations in gliadin proteins [68], leads to the development of celiac disease and gluten intolerance or sensitivity and the resultant inflammation.

### *Other Factors Driving Chronic Inflammation: Infections, Toxins, Stress, Sedentary Lifestyle, Nutrient Deficiencies*

Chronic infections can also trigger inflammation and cause persistent weight gain. New studies show that chronic infections, such as adenovirus, may be linked to obesity and insulin resistance [69]. The increasing load of persistent organic pollutants (like PCBs and pesticides) and heavy metals (such as arsenic, mercury, and lead) has been linked to both diabetes [70] and insulin resistance [71], in part through increased cytokine production. Chronic stress is yet another cause of chronic inflammation [72]. Lack of regular exercise promotes low-grade inflammation while regular exercise reduces inflammation [73].

Low-level nutrient and antioxidant deficiencies promote inflammation. Taking a multivitamin and mineral supplement is as effective for lowering inflammation as is statin medication, at less expense with fewer side effects [74].

## Digestive Dysfunction

Metabolic dysfunction and insulin resistance has recently been linked to disturbances in intestinal ecology or the *microbiome* [75]. Shifts from our Paleolithic diet to a highly processed, high-sugar, high-fat, low-fiber diet has dramatically altered gut microflora.

When the microflora is altered, the homeodynamic balance shifts from *symbiosis*—a mutually beneficial relationship to *dysbiosis*—a harmful interaction between microflora and host. These altered flora create *metabolic endotoxemia* through an increase bacterial endotoxins or *lipopolysaccharides* (LPS) binding to lymphocytes releasing *tumor necrosis factor alpha* (*TNF-α*) which blocks *the PPAR* (*peroxisome proliferator-activated receptor*) *family* of nuclear receptors that control inflammation, insulin sensitivity, and mitochondrial function. This triggers a cascade of inflammation, insulin resistance, and weight gain [76]. Improving diet quality and normalizing gut flora with probiotics can reduce the burden of systemic inflammation.

## Toxic Burden and Impaired Detoxification

Environmental toxins interfere with glucose and lipid metabolism and cause insulin resistance [70]. In 2006, scientists at Harvard School of Public Health found that rates of obesity in infants less than 6 months old have risen 73 % since 1980. The Environmental Working Group study found the average newborn has 287 chemicals in the umbilical cord blood, 217 of which are neurotoxic [77].

Bisphenol A, a petrochemical that lines water bottles and canned food containers, increases a person's risk of diabetes, heart disease, and abnormal liver function [78]. Data from the government's National Health and Nutrition Examination Survey 1999–2002 found a very striking correlation between blood levels of six common persistent organic pollutants (petrochemical toxins) and diabetes [79]. Those people who had the highest levels of pollutants in their blood had a dramatically higher risk of diabetes. Studies of Air Force veterans of the Vietnam War found that those who had been exposed to Agent Orange (dioxin) had a much higher risk of diabetes [80].

Environmental toxins alter normal thermodynamics making weight regulation simply a matter of calories in/calories out obsolete. New evidence shows that weight gain can occur in the absence of excess calorie intake. Rats given toxic chemicals gained weight and increased their fat storage *without* increased caloric intake or decreased exercise. In 6 months, these rats were 20 % heavier and had 36 % more body fat than rats unexposed to those chemicals [81]. A large population study published in *Environmental*

*Health* found higher levels of organochlorine pesticides in diabetics [82]. Heavy metals such as mercury, lead, and arsenic also cause diabesity. Arsenic exposure increases the risk of diabetes [71].

Toxins promote obesity through multiple well-documented mechanisms [29]. Toxins are PPARs (*peroxisome proliferator-activated receptors*) antagonists, receptors which regulate insulin sensitivity, inflammation, and mitochondrial energetics [83]. Using new techniques of genetic and metabolic analysis, scientists have shown how toxins cause increases in glucose, cholesterol, and fatty liver [84].

This opens a whole new area of potential treatment for diabetes and obesity. A comprehensive detoxification program for petrochemical and heavy metal toxins can be an effective addition to the treatment of diabesity.

## Mitochondrial and Redox Dysfunction

Obesity and diabetes is linked to defects in mitochondrial function [85] and oxidative stress [86]. Even then otherwise healthy first-degree relatives of diabetics have mitochondria that are 50 % less active than those of people without a family history of diabetes [87].

Impaired mitochondrial function and oxidative stress results from calorie-rich, high-sugar, nutrient- and antioxidant-poor foods. Toxins, infections, and any inflammatory trigger further damage mitochondria through increasing *oxidative stress,* which alters gene expression that drives insulin resistance.

A plant-based, low-glycemic-load, phytonutrients-rich, nutrient-dense diet enhances mitochondrial function and reduces oxidative stress. *HIT or high-intensity interval training* also significantly improves mitochondrial function and leads to enhanced weight loss and improved cellular metabolism [88].

Newer treatments are also being developed to address mitochondrial dysfunction, including one based on *resveratrol*, the antioxidant compound in red grapes.

Resveratrol affects mitochondrial health through its impact on a master class of genes called *sirtuins* that regulate insulin sensitivity and mitochondrial function and helps reverse diabetes and increase longevity [89].

Calorie restriction also helps improve mitochondrial function [90]. However modifying lifestyle, engaging in interval training and exercise, eating a nutrient-dense diet, and using dietary supplements appropriately can enhance mitochondrial function and reduce oxidative stress [91].

## Psychosocial/Spiritual Imbalances

Stress promotes central obesity [92], insulin resistance, and diabetes through elevations of cortisol, insulin, and *cytokines*. Mice bred to be obese and diabetic had improved metabolic function and lost weight through adrenalectomy, not an optimum strategy for weight loss [93]. However stress management including relaxation therapies, meditation, breathing exercises, yoga [94], group support, biofeedback, massage, exercise, saunas, dancing, and laughing reduces the stress response and helps normalize adrenal function and neuroendocrine signaling. Depression and diabetes are linked [95] and may be interactive. A comprehensive psycho-spiritual approach to obesity is necessary.

Obesity and diabesity is a complex, multifactorial, multigene disorder embedded within a complex psychosocial–cultural fabric. Systematic attention, review and treatment of each factor, and fundamental clinical imbalance are essential to address the modern plague of diabesity.

The causes of diabesity are not the same for every person. For some diabesity may be simply a result of poor diet. For others it may be due to environmental toxins, chronic inflammation, digestive imbalances, chronic stress, or even food sensitivities. This is why we must take a comprehensive approach to understanding, diagnosing, and treating these fundamental clinical imbalances that drive diabetes, insulin resistance, and most chronic diseases.

## Functional Medicine Approach to Diabesity: Case Studies

Obesity (diabesity) is a complex, multifactorial, multigene disorder with dynamic web-like physiological imbalances affecting gene expression and phenotype. A systemic approach directed at removing the impediments to optimal function (diet, toxins, allergens, infections, stress) and providing the "ingredients" for optimal health (whole foods, micronutrients, light, air, water, movement, rhythm, sleep, connection, community, meaning, and purpose) based on the model of functional medicine [96] provides a roadmap for diagnosis and treatment of the underlying clinical imbalances at the root of obesity and chronic disease. The functional clinical imbalances are influenced by the environment including diet and nutritional status on core functional systems—hormonal/metabolic, immune/inflammatory, digestive, detoxification, mitochondrial energetics and redox status, structural, and psycho-spiritual.

These diagnostic and treatment principles are illustrated in the following cases.

### *Case 1: Inflammation, Obesity, and Diabetes*

SR is a 67-year-old woman with a 10-year history of type 2 diabetes. Her weight was 233 lb with a BMI of 36 and waist-to-hip ratio 0.91. Her past medical history was significant for hypertension, angina, reflux, rheumatoid arthritis and lupus, hypothyroidism, chronic allergies and sinusitis, and depression. Her medications included metformin, benazepril, fluoxetine, pravastatin, bioidentical hormone replacement, cetirizine, lansoprazole, levothyroxine, naproxen, a multivitamin glucosamine, and calcium with D. She is a widow who lives alone and is estranged from her family. She is a recovering alcoholic with a history of childhood sexual abuse. Her diet consisted predominately of refined carbohydrates including bread, pasta, muffins, and ice cream. She does no exercise. Her medical symptom questionnaire (MSQ) was 86.

Functional diagnostic assessment revealed hyperinsulinemia of 23 (nL <5), glucose of 140 mg/dL, and HbA1c of 6.8. Her high-sensitivity C-reactive protein was elevated at 10.6 (nL <1) and her sedimentation rate was 20. Her antinuclear antibodies were 1:80 speckled pattern. On a statin her total cholesterol was 198 mg/dL, LDL-C 119 mg/dL, HDL-C 54 mg/dL, and triglycerides 199 mg/dL. She had a fatty liver with an elevated gamma glutamyl transferase (GGT) of 40. Organic acid analysis revealed impaired fatty acid and carbohydrate metabolism and mitochondrial dysfunction as well as impaired detoxification and dysbiosis with small intestinal bacterial overgrowth (SIBO).

Treatment consisted of low-glycemic load, high-fiber, phytonutrient-rich, allergen elimination (gluten and diary), whole foods plant-based diet and moderate exercise of 30 min of walking daily. Digestive imbalances were treatment by stopping NSAID, proton pump inhibitor, herbal antimicrobials, probiotics, glutamine, and an anti-inflammatory rice-based medical food for treating dysbiosis. Oral estrogen was changed to vaginal to reduce fat deposition and inflammation. Antidepressant was changed from fluoxetine to bupropion to improve appetite control. In addition to her multivitamin, she treated with coenzyme Q10 and alpha lipoic acid (antioxidants and mitochondrial cofactors) as well as B complex and milk thistle for fatty liver and enhanced detoxification. After 2 years of treatment, she lost 45 lb. Her medical symptoms score (MSQ) reduced from 86 to 6. Her C-reactive protein reduced from 10.6 to 2.8, total cholesterol from 198 to 171, triglycerides from 199 to 88, and HDL-C increased from 57 to 65. Her insulin reduced from 23 to 11, fasting glucose from 140 to 103, hemoglobin A1c from 6.8 to 5.7, and GGT from 40 to 17. Organic acids showed normalization of fat and carbohydrate metabolism and citric acid cycle normalized as did the markers of impaired detoxification and dysbiosis.

## *Case 2: Treatment Resistant Obesity and Diabetes*

J.L was a 59-year-old African American female college dean with obesity and diabetes. She had a history of hypertension, obstructive sleep apnea, and hyperlipidemia. She presented with severe fatigue, unable to drive, watch television, exercise, or cook for herself. Her BMI was 35 at 190 lb. Despite maximal intensive medical therapy, she remained hypertensive with a blood pressure of 160/104 and was about to start insulin therapy and retire because she could no longer fulfill her work obligations. Her hemoglobin A1c was 10.1.

She was on atorvastatin, metformin, glyburide metoprolol, aspirin, lotrel (amlodipine and benazepril), and a multivitamin. She was single, a nonsmoker, exercised irregularly, and ate prepared and microwavable foods and sweets at night.

Her laboratory evaluation revealed urine 3+ glucose, fasting glucose 312, and hemoglobin A1c 10.1. Her 25 OH vitamin D was 17 ng/mL (normal 45–100). She had elevated liver function tests with an ALT of 56. Urine microalbumin was negative. On a statin her total cholesterol was 186 mg/dL, HDL 54 mg/dL, LDL 122 mg/dL, and TG 101 mg/dL.

However on nuclear magnetic resonance spectroscopy, she had predominately small LDL (1,320/1,608) and HDL particles. Her cardio C-reactive protein was 0.7, homocysteine 6.4, fibrinogen 311, and her Lp(a) was elevated at 423 (normal <30). She had elevated lipid peroxides of 2.2 nmol/mL (nL <1.5).

Her organic acids revealed an elevated lactate and beta-hydroxybutyrate indicating impaired carbohydrate metabolism, abnormal Krebs cycle metabolites, and coenzyme Q10 and B vitamin deficiencies.

A functional assessment suggested **hormonal imbalances** with uncontrolled type 2 diabetes, hypertension, hyperlipidemia with small LDL and HDL particles, and obstructive sleep apnea. Fatty liver or NASH indicated **impaired detoxification. Mitochondrial and redox imbalances** were indicated by abnormal carbohydrate and Krebs cycle metabolites and elevated lipid peroxides. Nutritional evaluation revealed severe vitamin D deficiency.

Addressing the underlying causes of her metabolic dysfunction focused on diet, exercise, and nutritional supplementation. Dietary recommendations emphasized protein in the morning and with each meal, only WHOLE grains; no flour or sugar; 50 g of fiber; an increase in omega-3 fats intake; a reduction of red meat; smaller, more frequent meals; and no processed food, junk food, trans fats, juices, or sodas or high-fructose corn syrup.

The oral hypoglycemic (glyburide) and beta-blocker were eliminated because they increase hyperinsulinemia and weight gain. To improve particle size, atorvastatin was reduced and high-dose niacin was added. She exercised 30 min daily with interval training three times a week.

Nutritional supplementation focused on addressing the underlying clinical imbalances. She was treated with a whole soy protein shake with plant sterols, glucomannan (konjac root), a multivitamin with extra biotin, chromium, alpha lipoic acid, omega-3 fatty acids, protein kinase modulators (from acacia), and cinnamon. She was also treated with vitamin D3 5,000 U daily and a mitochondrial support supplement including coenzyme Q10, *n*-acetylcysteine, acetyl-L-carnitine, creatine, magnesium malate, phosphatidylcholine, and sodium succinate.

After 1 year her BMI reduced from 35 to 31 with a 20-lb weight loss and resolution of sleep apnea. Her energy increased and she was able to resume a full workload and travel schedule. Her blood pressure reduced from 160/104 to 127/79 mmHg, her hemaglobinA1c from 10.1 to 5.9, her fasting glucose reduced from 321 to 111 mg/dL, and her LDL from 122 to 71 mg/dL (small particles from 1,320 to 615) and her vitamin D increased from 17 to 62 ng/dL.

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# Chapter 13
# Cardiovascular Complications of Obesity

**M. Dominique Ashen and Roger S. Blumenthal**

**Abstract** Obesity is a costly public health epidemic which contributes to increased morbidity and mortality from cardiovascular disease (CVD) and diabetes mellitus (DM). Insulin resistance (IR), the crucial underlying link between obesity and CVD, is associated with adipose tissue dysfunction. IR drives unopposed upregulation of proinflammatory and prothrombic factors resulting in systemic inflammation, oxidative stress, and a prothrombic environment. Among the resultant effects are hypertension, atherogenic dyslipidemia, and impaired glycemic control, which are all risk factors for CVD. Inflammation and oxidative stress also underlie vascular endothelial dysfunction and a favorable milieu for the promotion of atherosclerosis. Through understanding the mechanisms by which IR links obesity to CVD, health professionals can educate their patients about ways to maintain weight loss and prevent weight gain and, thus, slow the obesity epidemic and reduce CVD morbidity and mortality.

**Keywords** Obesity • Cardiovascular disease • Insulin resistance

*Key Points*

- Obesity is a costly public health epidemic which contributes to increased morbidity and mortality from cardiovascular disease (CVD) and diabetes mellitus (DM).
- Insulin resistance (IR), the crucial underlying link between obesity and CVD, is associated with adipose tissue dysfunction.
- IR drives unopposed upregulation of proinflammatory and prothrombic factors resulting in systemic inflammation, oxidative stress, and a prothrombic environment, that contributes to hypertension, atherogenic dyslipidemia, and impaired glycemic control, all risk factors for CVD.
- Inflammation and oxidative stress also underlie vascular endothelial dysfunction and a favorable milieu for the process of atherosclerosis.
- Through understanding the mechanisms by which IR links obesity to CVD, health professionals can educate their patients about ways to maintain weight loss and prevent weight gain and, thus, slow the obesity epidemic and reduce CVD morbidity and mortality.

Obesity is a costly public health epidemic. Recent data from 2009 to 2010 indicate that one in three US adults (36 %) are obese (body mass index, BMI $\geq$ 30 kg/m$^2$) [1]. Among women, 42 % of those 60 years of age and older are obese compared with 32 % aged 20–39, with no significant difference in

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obesity prevalence by age among men [1]. When viewed nationally, 12 US states in 2011 had a prevalence of obesity ≥30 %, with no state having a prevalence <20 % [2]. This is significantly different from 1990 when obesity prevalence of the "thinnest" states was <10 % and that of the "fattest" was between 10 and 14 %. From an economic standpoint, the obesity epidemic is costing this country $150 billion a year, which is nearly 10 % of all health-care spending [3]. If this trend continues, the total health care costs attributable to obesity could be greater than $860 billion by 2030 [4].

What is driving the obesity epidemic? A combination of factors, including genetic, metabolic, hormonal, behavioral, environmental, cultural, and socioeconomic, is certainly involved. Changes in the American lifestyle over the last 30 years have contributed to this discussion [5]. Caloric intake has increased through increased portion sizes and consumption of calorie-rich and processed foods. We are eating out more and eating more frequently during the day. Our activity level at school, work, and home has decreased with more than 55 % of waking hours spent sitting, often using some form of twenty-first century technology. We are exercising less, driving more, and live in communities that are built in ways that make it difficult or potentially unsafe to be physically active.

We are increasing the risk of death from cardiovascular disease (CVD) and diabetes mellitus (DM) by eating more, sitting more, and getting fatter. Not only does obesity increase the age-adjusted relative risk for CVD in men and women (by 46 % and 64 %, respectively), it is also an independent risk factor for ischemic stroke in all race/ethnic groups [6–9]. In addition, the increasing prevalence of obesity is driving an increased incidence of type 2 diabetes mellitus (DM), a risk equivalent for CVD, with BMI ≥35 being the most powerful predictor of DM in women [10, 11]. This obesity-driven morbidity results in significantly increased mortality from CVD and DM [12].

## Insulin Resistance: The Link Between Obesity and CVD

"Lifestyle-induced obesity" [13] is manifest as increased abdominal obesity. The INTERHEART study, which looked at cardiovascular (CV) risk factors in nearly 30,000 people in 52 countries from all over the world, demonstrated that together abnormal lipids, hypertension, diabetes, abdominal obesity, psychosocial, and lifestyle factors accounted for the vast majority of the risk for myocardial infarction (MI) worldwide in both sexes and at all ages [14]. Not all studies, however, conclude that abdominal obesity is an independent predictor of CVD. The Third National Health and Nutrition Examination Survey suggests that abdominal obesity estimated from waist circumference was not an independent predictor of MI [15]. In addition, the Emerging Risk Factors Collaboration concluded that abdominal obesity, estimated from BMI, waist circumference, or waist-to-hip ratio (singly or in combination), did not improve CVD risk prediction in developed countries [16]. Several other studies, however, conclude that markers of abdominal obesity (waist circumference and waist-to-hip ratio) are independently associated with CVD risk [17, 18].

How is obesity linked to CVD? Reaven [19] has postulated that the link between obesity and coronary heart disease (CHD) is related to the fact that obese individuals have an increased likelihood of being insulin resistant (IR) and displaying those abnormalities associated with syndrome X, including glucose intolerance, increased plasma triglycerides (TGs), decreased high-density lipoprotein cholesterol (HDL-C), and elevated blood pressure. Figure 13.1 [19] is a schematic diagram of the link between insulin resistance and CHD. Reaven argues that a smaller proportion of IR individuals develop type 2 DM (T2DM), with CHD as the major cause of morbidity and mortality (left), while a larger proportion are at increased risk for presenting with components of syndrome X and increased risk for CHD (right).

IR is associated with adipose tissue dysfunction, which has been well described by Eckel et al. [20]. A major contributor to the development of IR in obesity is an overabundance of circulating free fatty acids (FFA) derived from lipolysis of expanded stores of adipose tissue triglycerides (especially

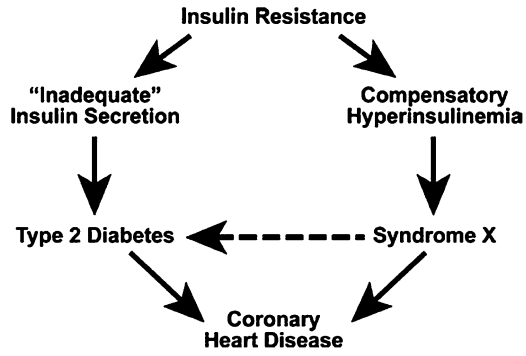


**Fig. 13.1** Schematic description of the link between insulin resistance and coronary heart disease (CHD) via either type 2 diabetes mellitus or syndrome X. The majority of insulin-resistant individuals never develop type 2 diabetes mellitus, but the dotted line indicates that the degree of compensatory hyperinsulinemia in some portion of individuals with syndrome X will decline and is no longer able to prevent the appearance of frank hyperglycemia. Reproduced from Arteriosclerosis, Thrombosis, and Vascular Biology, August 2012, Vol. 32, Pages 1754–1759 with permission of ATVB

from the visceral depot) as well as triglyceride-rich lipoproteins in tissues (Fig. 13.2a) [20]. Insulin is important in anti-lipolysis, as it blocks hormone-sensitive lipases in adipocytes. However, as IR develops there is increased lipolysis of stored triglycerides resulting in increased levels of circulating FFA. Superimposed on this excess of FFA in IR is the release of proinflammatory adipokines, including interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), resistin, and C-reactive protein (CRP), and prothrombic factors, including fibrinogen and plasminogen activator inhibitor-1 (PAI-1), from dysfunctional adipocytes (Fig. 13.2b) [20].

Adiponectin, abundantly produced by adipose tissue, stimulates endothelial nitric oxide synthase (eNOS, which is important in controlling vascular tone, inflammation, and smooth muscle cell proliferation) and confers protection against oxidative stress. With the development of IR, adiponectin is suppressed by proinflammatory adipokines.

Taken together, the unopposed upregulation of proinflammatory adipokines and prothrombic factors and the suppression of adiponectin in IR contribute to systemic inflammation, oxidative stress, and a prothrombic environment. Among the resultant effects are hypertension (HTN), atherogenic dyslipidemia, hyperinsulinemia, reduced partitioning of glucose to glycogen, and increased circulating glucose.

## Impact of Obesity on CVD Risk Factors: HTN, Atherogenic Dyslipidemia, and DM

HTN, which increases the risk of stroke, CHD, and peripheral arterial disease, is common in obese individuals and is correlated with degree of obesity. There are multiple mechanisms that link obesity to HTN [21]. Leptin, an adipose tissue-derived hormone, functions to suppress appetite in the hypothalamus. Leptin levels rise with the development of adiposity. Unfortunately, many obese individuals are resistant to the action of leptin (either through deficiencies in leptin, leptin receptors, or genes controlling hypothalamic feedback) to suppress appetite despite elevation in serum leptin levels [22]. Leptin has been linked to HTN through (1) upregulating renal Na, K-ATPase activity and enhancing renal sodium reabsorption, (2) activating the renin-angiotensin-aldosterone axis (RAAS; components of which are produced by adipose tissue, increased in the circulation and involved in renal sodium

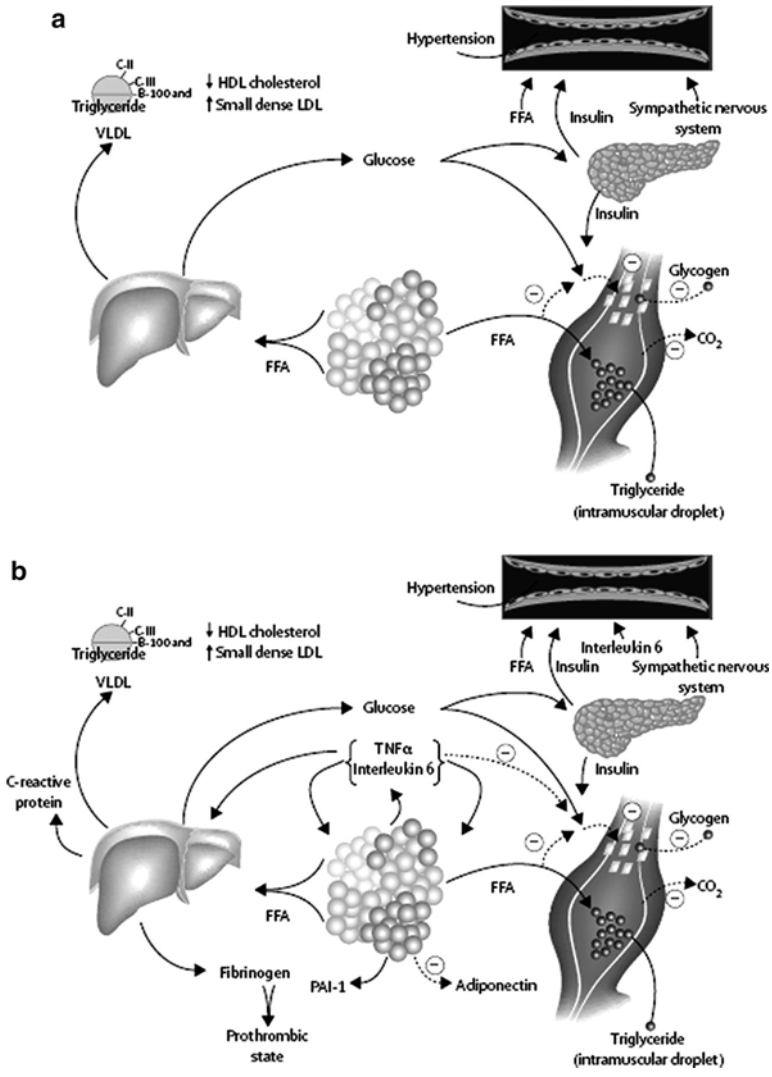


**Fig. 13.2** (**a**, **b**). Pathophysiology of the metabolic syndrome (insulin resistance). (**a**): free fatty acids (FFA) are released in abundance from an expanded adipose tissue mass. In the liver, FFA produce an increased production of glucose, triglycerides, and secretion of very low-density lipoproteins (VLDL). Associated lipid/lipoprotein abnormalities include reductions in high-density lipoprotein (HDL) cholesterol and an increased density of low-density lipoproteins (LDL). FFA also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation in triglyceride (TG). Increases in circulating glucose and to some extent FFA increase pancreatic insulin secretion resulting in hyperinsulinemia. Hyperinsulinemia may result in enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity and contribute to the hypertension as might increased levels of circulating FFA. (**b**) Superimposed and contributory to the insulin resistance produced by excessive FFA is the paracrine and endocrine effect of the proinflammatory state. Produced by a variety of cells in adipose tissue including adipocytes and monocyte-derived macrophages, the enhanced secretion of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) among others results in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating FFA. IL-6 and other cytokines also are increased in the circulation and may enhance hepatic glucose production, the production of VLDL by the liver and insulin resistance in muscle. Cytokines and FFA also increase the production of fibrinogen and plasminogen activator inhibitor-1 (PAI-1) by the liver that complements the overproduction of PAI-1 by adipose tissue. This results in a prothrombic state. Reductions in the production of the anti-inflammatory and insulin sensitizing cytokine adiponectin are also associated with the metabolic syndrome and may contribute to the pathophysiology of the syndrome. *PAI1* plasminogen activator inhibitor-1. Reproduced from The Lancet, April 2005, Vol. 365, Pages 1415–1428 with permission of The Lancet

reabsorption, vascular hypertrophy, and peripheral vasoconstriction), and (3) acting with proinflammatory adipokines to induce vascular oxidative stress and arterial HTN [23, 24]. IR and hyperinsulinemia may induce HTN through chronic stimulation of both sympathetic and vascular tone along with antinatriuretic effects [25, 26]. Decreased production of adiponectin (hypoadiponectinemia) has been related to vasomotor dysfunction (impaired vasoreactivity and endothelium-dependent vasodilation), elevated peripheral vascular resistance, and HTN [26–29].

Abdominal obesity is associated with atherogenic dyslipidemia, defined as low HDL-C and elevated triglycerides, remnant lipoproteins, and small dense low density lipoprotein cholesterol (LDL-C) which, in turn, has been shown to increase the risk of CVD. A crucial underlying mechanism of atherogenic dyslipidemia is IR which, as indicated above, is associated with adipose tissue dysfunction. Tonstad and Despres have suggested that genetically predisposed subjects unable to expand subcutaneous fat stores in a positive-energy state end up storing energy in visceral fat stores, including the liver, skeletal muscle, heart, and the kidney [30]. The impaired triglyceride storage and oxidation of visceral fat stores results in increased lipolysis and transport of nonesterified fatty acids to the liver via the portal system. This, in turn, stimulates hepatic synthesis of triglycerides, apolipoprotein B 100 (ApoB 100), and very low-density lipoprotein (VLDL), observed as elevated plasma concentrations of triglycerides, ApoB, VLDL triglycerides, and VLDL-Apo-B, as well as altered adipokine and adiponectin secretion contributing to a proinflammatory milieu (Fig. 13.3) [30].

Increased cholesterol ester transfer protein (CETP), also associated with obesity in part due to enlarged adipose tissue stores, drives the exchange of triglycerides for cholesterol esters between VLDL and large LDL-C and HDL-C molecules. This results in the production of small dense LDL-C, HDL-C, and remnant molecules contributing to levels of circulating markers that define a proatherogenic milieu (Fig. 13.4) [30]. Both small, dense LDL particles and low HDL-C are closely associated with IR and, because of their contribution to the process of atherosclerosis, are closely linked to CVD [30–33].

T2DM is a risk equivalent for CVD. The incidence of T2DM has paralleled the obesity epidemic and is among the many serious health conditions associated with obesity [34]. In obese individuals, increased systemic inflammation marked by increased levels of adipokines is associated with development of IR and prediabetes [35–38], defined as impaired fasting glucose (IFG; 100–125 mg/dL) or impaired glucose tolerance (IGT, 140–199 mg/dL) or HbA1C of 5.7–6.4 %. Prediabetes has been identified as an early indicator for risk of T2DM, CVD, and microvascular consequences (retinopathy, glomerular disease, and neuropathy). Individuals with both IFG and at least two other components of syndrome X (abdominal obesity, increased plasma triglycerides, decreased HDL-C, and elevated blood pressure) will progress to T2DM at roughly 20 times the rate of those without either condition [39].

## Inflammation and Oxidative Stress: Effect on the Vasculature

In obesity, the dysfunction of adipose tissue (especially visceral) is strongly related to enhanced systemic inflammation and oxidative stress. Dorresteijn describes the “vicious cycle” within dysfunctional adipose tissue of unopposed upregulation of proinflammatory adipokines from adipocytes (IL-6, TNF-alpha, resistin) with the attraction and accumulation of macrophages which, in turn, produce proinflammatory cytokines [26]. TNF-alpha and resistin from adipocytes induce expression of intracellular adhesion molecule-1 (ICAM-1), macrophage chemoattractant protein-1 (MCP-1), and colony-stimulating factor-1 (CSF-1) which enhance expression of monocyte adhesion molecules to the vascular endothelium, facilitate monocyte diapedesis through the vascular wall, and stimulate monocyte differentiation into macrophages within the adipose tissue, respectively.

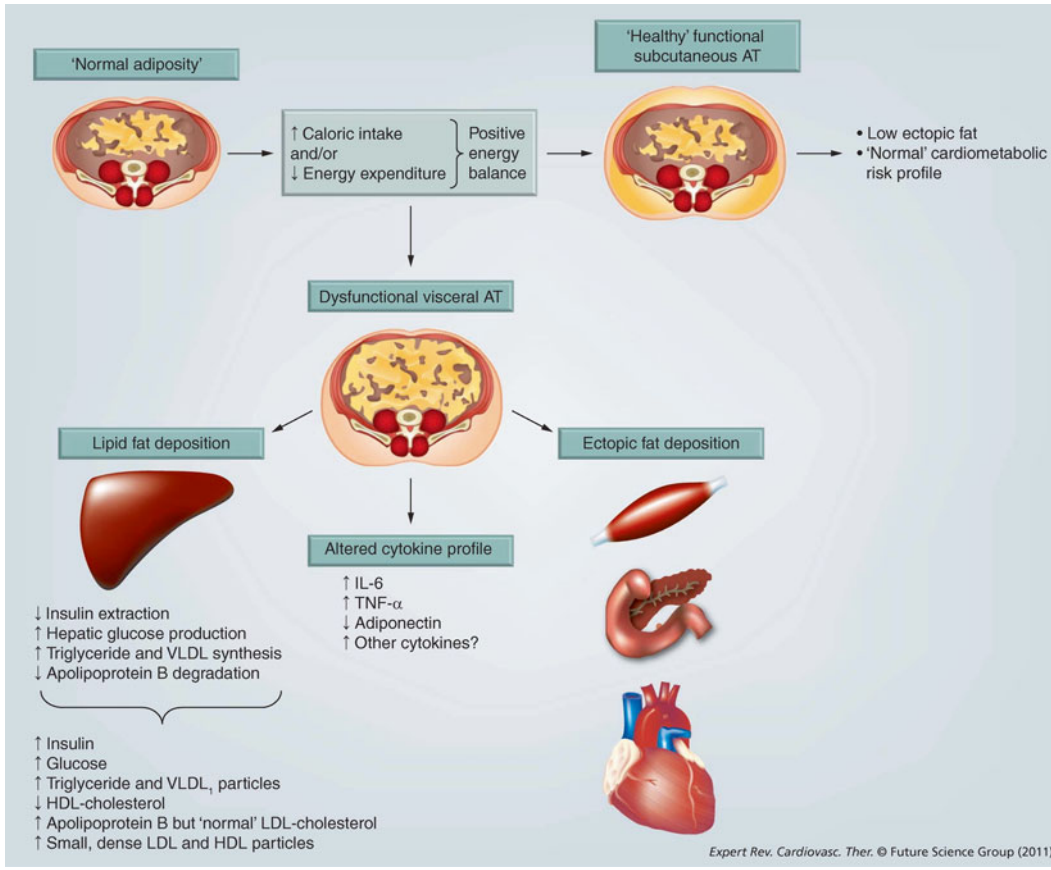


**Fig. 13.3** Potential key mechanisms involved in the relationship between visceral adiposity and atherogenic dyslipidemia. Under the "pressure" of a positive-energy balance, if the subcutaneous adipose tissue expands and acts properly as a buffering tissue in storing the excess energy, such subcutaneous fat deposition will spare the body against the deleterious consequences of ectopic fat deposition, and a normal cardiometabolic risk profile will be observed. However, among genetically predisposed subjects, the relative inability of subcutaneous adipose tissue to properly expand will lead to an overspill of energy that will be stored in the visceral fat depot as well as in other undesired sites such as the liver, heart, skeletal muscle, and the kidney, and a substantially altered cardiometabolic risk profile will be measured. Under this model, excess visceral adipose tissue accumulation is a marker of dysfunctional subcutaneous adipose tissue. However, the hypertrophied visceral fat depot could also influence the cardiometabolic risk profile via an increased flux of nonesterified fatty acids toward the liver and via an altered cytokine profile secretion. *AT* adipose tissue. Reproduced from Expert Review cardiovascular Therapy, August 2011, Vol. 9, No. 8, Pages 1069–1080 with permission of Expert Reviews

FFA, increased in IR obesity, augment adipose tissue macrophage production of TNF-alpha, IL-6, and ROS which subsequently induce transcription of mediators that further attract and accumulate adipose tissue macrophages. With adequate levels of the anti-inflammatory adiponectin, there is stimulation of endothelial eNOS, suppression of macrophage produced TNF-alpha, and suppression of TNF-alpha induced expression of adipokines conferring protection against oxidative stress. However, the suppression of adiponectin in IR enhances oxidative stress which, in turn, further suppresses adiponectin secretion and adipocyte fatty acid storage contributing to this "vicious cycle" [40–43].

Inflammation (mediated by proinflammatory cytokines) and oxidative stress (mediated by ROS) underlie vascular endothelial dysfunction and a favorable milieu for the process of atherosclerosis. Roos et al. diagram the pathophysiologic pathway from obesity to atherosclerosis (Fig. 13.5) [44].

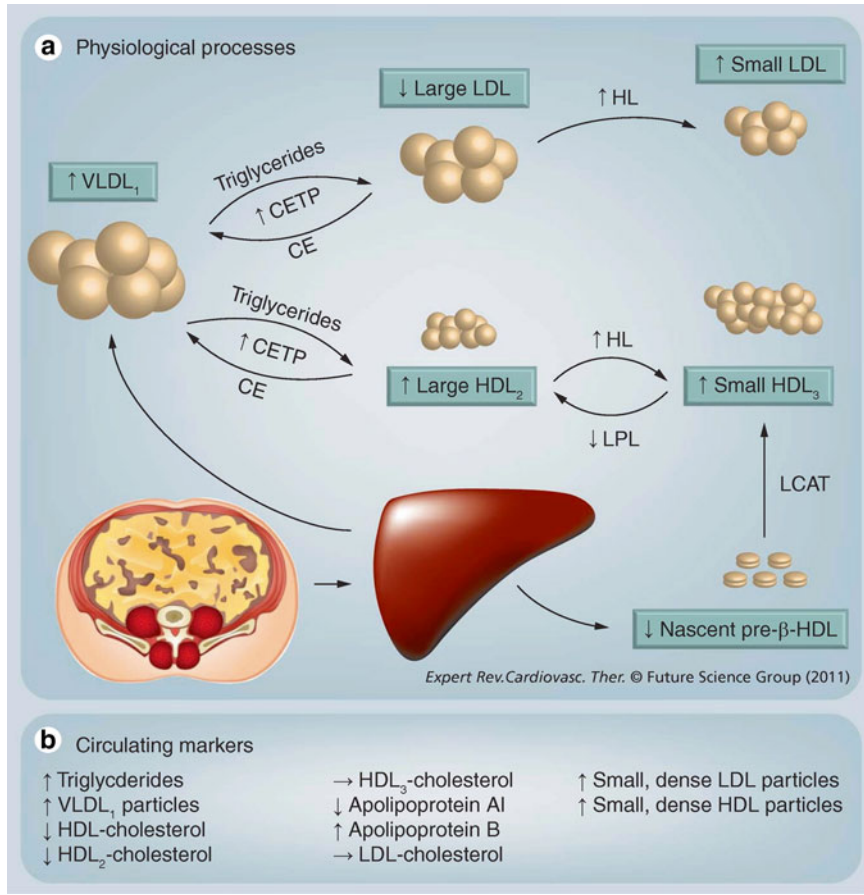


**Fig. 13.4** Consequences of the hypertriglyceridemic state associated with visceral obesity and excess liver fat. (**a**) The overproduction of large very LDL particles will promote the bidirectional exchange of triglyceride molecules for cholesterol esters, leading to the triglyceride enrichment of LDL and HDL particles. Such triglyceride-enriched lipoproteins will become good substrates for the enzyme hepatic lipase, leading to the formation of cholesteryl ester-depleted and smaller LDL and HDL particles. Plasma HDL2 cholesterol levels will also be reduced due to a reduced lipoprotein lipase activity. (B) Clinically, such processes will be reflected by the altered levels of circulating markers. *CE* cholesterol ester, *CETP* cholesteryl ester transfer protein, *HL* hepatic lipase, *LCAT* lecithin–cholesterol acyltransferase, and *LPL* lipoprotein lipase. Reproduced from Expert Review cardiovascular Therapy, August 2011, Vol. 9, No. 8, Pages 1069–1080 with permission of Expert Reviews

Increased adipose tissue mass in obesity results in dysfunctional adipose tissue secretion: increased release of FFA and proinflammatory adipokines and reduction in release of the anti-inflammatory adiponectin. The overabundance of circulating FFA derived from lipolysis of expanded stores of adipose tissue triglycerides and triglyceride-rich lipoproteins in tissues contributes to IR in the liver, skeletal muscle, and vasculature. IR increases vascular ROS which target LDL resulting in the production of oxidized LDL. Oxidized LDL (1) leads to the formation of foam cells which are inflammatory cells in the early stage of atherosclerosis; (2) reduces the transcription rate of eNOS resulting in reduction in nitric oxide (NO) synthesis, a potent vasodilator, thus, decreasing vasodilation in response to stimuli such as acetylcholine and mechanical stress; and (3) induces expression of ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells facilitating attraction and migration of monocytes into the subendothelial space. Vascular ROS also increases platelet reactivity via release of mediators facilitating coagulation [45–48].

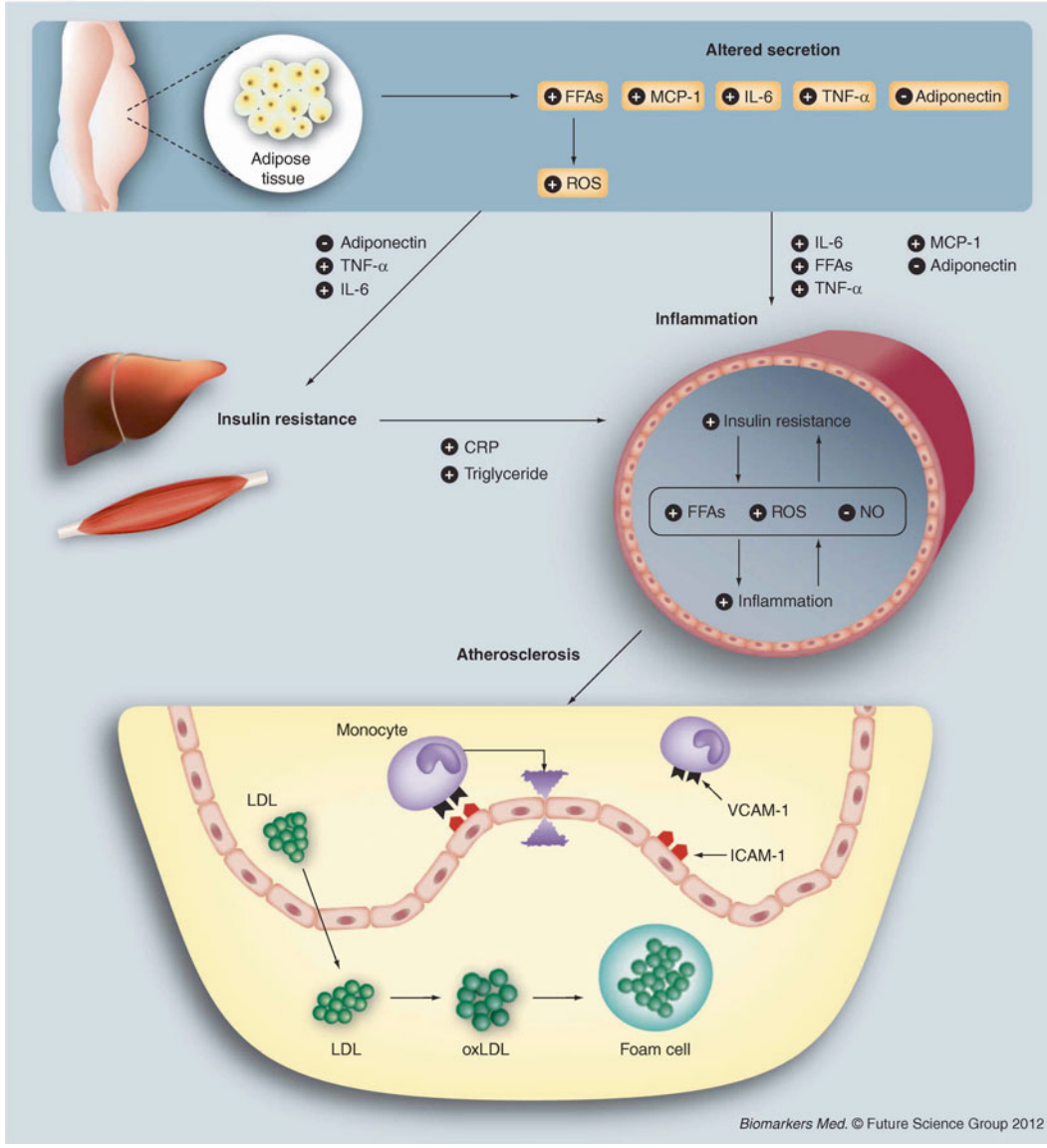


**Fig. 13.5** The pathophysiologic pathway from obesity to atherosclerosis. Increased adipose tissue mass has an altered secretion, including an increased release of proinflammatory adipokines, cytokines, and FFAs, whereas the release of anti-inflammatory adiponectin is reduced. This causes an increased insulin resistance in the liver and skeletal muscle. Circulating FFAs raise the insulin resistance in the vasculature and increase ROS, which in turn lowers NO bioavailability. This increases both insulin resistance and inflammation. The loss of insulin signaling reduces its anti-inflammatory actions and further contributes to inflammation. Endothelial cells express ICAM-1 and VCAM-1 in response to inflammatory mediators, which attract immune cells to the subendothelial space. The penetration of LDL and its oxidative modification in the intima of the arterial wall induces local inflammation and the formation of foam cells. Foam cells secrete proinflammatory mediators and express toll-like receptors that act as pattern-recognition molecules, which, upon binding an antigen, can activate T cells and intracellular NF-κB. + increase, − decrease, *CRP* C-reactive protein, *FFA* free fatty acid, *LDL* low-density lipoprotein, *NO* nitric oxide, *oxLDL* oxidatively modified LDL, *ROS* reactive oxygen species. Reproduced from Biomarkers in Medicine, February 2012, Vol. 6, No. 1, Pages 35–52 with permission of Future Medicine Ltd

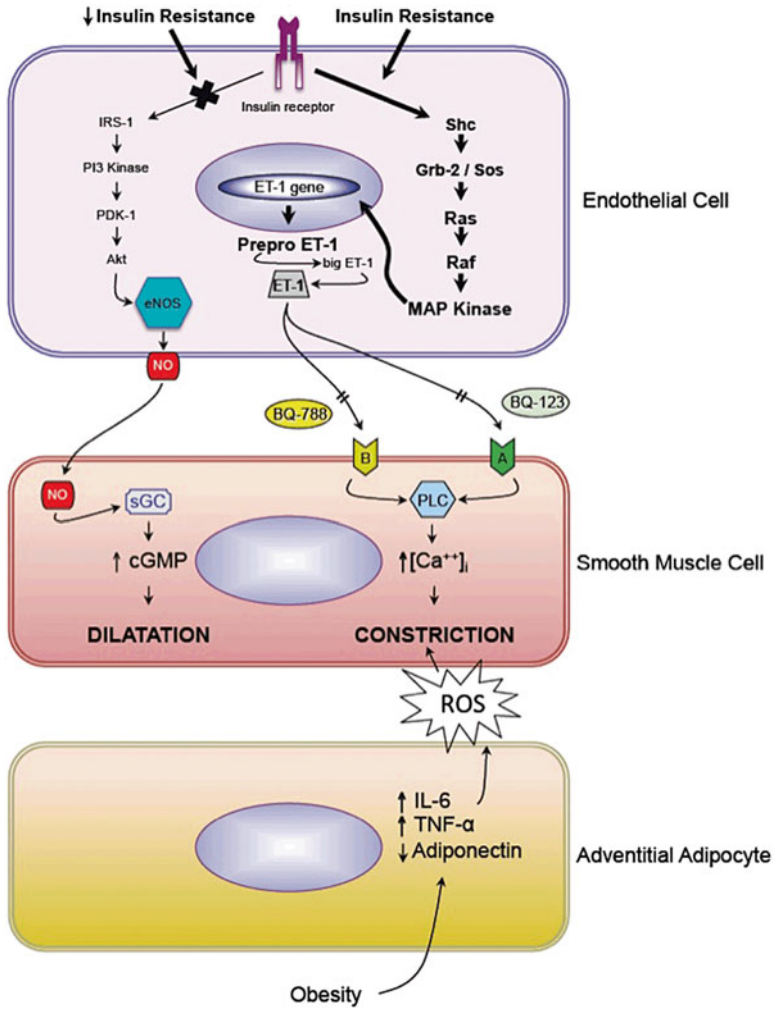


**Fig. 13.6** Interactions among endothelial, smooth muscle, and adventitial cells in the physiological regulation of vasoactive function. In conditions of insulin resistance, the physiological balance between vasoconstrictor and vasodilator pathways in endothelial cells is shifted toward a predominant vasoconstriction, due to the prevalent activation of the endothelin system. In addition, the impairment of adipocyte function and the production of inflammatory cytokines within the perivascular adipose tissue lead to increase ROS production and oxidative stress which, in turn, increases smooth muscle cell contractility. Reproduced from British Journal of Pharmacology, August 2012, Vol. 165, No. 3, Pages 561–573 with permission of BJP

Vascular dysfunction in obesity, however, may be far more complex. Campia et al. [49] suggest that vascular dysfunction in obesity may not be limited to the endothelium but may also involve smooth muscle cells and adventitial adipocytes. They indicate that besides the deficit of NO leading to impaired vasodilation in vessels under conditions of obesity-induced IR, there may also be enhanced bioactivity of endothelin-1 (ET-1), a potent vasoconstrictor produced by the endothelium. This would suggest a shift from normal NO-mediated vasodilation toward enhanced ET-1-mediated vasoconstriction. In addition, impaired adipocyte function of the adventitia in obesity-induced IR could lead to the production of proinflammatory cytokines and ROS that, in turn, increase medial smooth muscle contractility (Fig. 13.6) [49]. In addition, a recent review by Rajwani et al. [50] suggests that altered functional properties of a number of cell types (endothelial cells, macrophages, endothelial progenitor cells,

vascular smooth muscle cells, and fibroblasts) in the environment of IR are relevant to atherosclerosis. However, while there is evidence for a pro-atherogenic influence of IR on some cell types (particularly endothelial cells) there is antiatherogenic influence on others (specifically macrophages).

## Strategies to Maintain Insulin Sensitivity and Prevent CVD

There is a clear association between obesity and CVD, with IR as the crucial underlying link. IR not only affects risk factors for CVD (HTN, atherogenic dyslipidemia, and T2DM) but also results in inflammation and oxidative stress underlying vascular dysfunction favoring the production of atherosclerosis.

Specific guidelines for diet and exercise have been recently updated by the American Heart Association (AHA) and American College of Cardiology (ACC) [51]. They recommend strategies for heart-healthy eating including the DASH diet and the USDA's Choose My Plate, reduction in saturated and trans fats, reduction in sodium intake to 1,500 mg/day, and nutrition therapy. Adults are encouraged to engage in aerobic physical activity 3–4 times per week for an average of 40 min per session. In addition, The Obesity Society (TOS) has worked with the AHA and ACC to develop updated guidelines for management of overweight and obese adults with recommendations for reduced calorie intake and comprehensive lifestyle intervention involving physical activity and behavior modification for sustained weight loss [52]. Weight loss through lifestyle interventions has been shown to reduce IR [53] as well as (1) reduce blood pressure, (2) reduce triglycerides and LDL-C, increase HDL-C, and (3) improve or prevent IFG, IGT, and conversion to T2DM [54–56].

In order to prevent the development of CVD and subsequent events, such as MI and stroke, the focus must not only be to work with obese patients to lose excess weight (regain insulin sensitivity) but to prevent the development of obesity in those of normal weight (preserve insulin sensitivity). To effectively enhance weight loss and prevent weight gain, it is important to understand energy balance, clearly reviewed by Cornier et al. [57]. Energy intake matches energy expenditure in homeostatic energy balance. Energy intake reflects food and beverage intake while energy expenditure reflects the combination of basal metabolic rate (BMR, 55–70 %), energy expended in physical activity (20–40 %), and thermogenesis (5–10 %) [58].

With weight loss, there is a decrease in energy expended and an increased desire to eat. The decrease in energy expended results from reduction in the resting BMR (as a result of loss of lean body mass), reduction in the non-resting energy expenditure, and improved skeletal muscle work efficiency [59–61]. There is also preference for oxidation of carbohydrates and storage of fat [62–64] resulting in the tendency to return to the previous energy-replete state. The increased energy consumption results from complex signaling, including adipose-derived leptin and gut-related peptides, such as ghrelin, protein YY, and glucagon-like peptide-1, which enhance hunger, reduce satiety, and increase food intake [65–68].

Cornier et al. [57] suggest that the reduction in energy expenditure and increased energy intake with weight loss essentially "defends" the overweight or obese state and makes it difficult to maintain weight loss. They indicate that increased physical activity with exercise (particularly with addition of resistance training) [69] is critical for maintaining weight loss and may more than compensate for the decrease in energy expenditure by increasing lean body mass and BMR in the setting of calorie restriction. However, while reduction in energy intake (through calorie restriction) in the absence of physical activity can produce weight loss, it is difficult to maintain over the long term.

Overall, maintenance of weight loss, in the setting of compensatory mechanisms that "defend" the obese state, requires substantial and permanent behavior change which may be difficult to maintain. This could be accomplished by the reduction in caloric intake of 200–300 kcal/day (equivalent to a candy bar or soft drink) or increasing ones pedometer reading by 4,000–6,000 steps per day. By comparison, there would be minimal compensation and thus smaller behavior changes required to prevent weight gain, with either increased energy expenditure through physical exercise or decreased caloric intake of 100 kcal/day [70].

In either maintaining weight loss or preventing weight gain through diet and exercise, behavior change is essential. The National Heart, Lung, and Blood Institute developed a guide to behavior change [71] that includes the following:

- Set the right goals: Develop goals that focus on diet and exercise changes that lead to long-term weight change. Effective goals are specific, attainable, and forgiving.
- Nothing succeeds like success: Using a series of short-term goals that get closer to the ultimate goal (shaping). These consecutive short-term goals continue forward movement toward the overall goal and keep the effort invigorated.
- Success (but not with food): Use of rewards to encourage attainment of behavioral goals. Using numerous small rewards to meet smaller goals is generally more effective. Rewards must be desirable, timely, and contingent on meeting the goal.
- Balance your checkbook: Self-monitoring (tracking) to record behavior (calorie intake, exercise sessions) and outcomes (weight). Success can be monitored and provide encouragement.
- Avoid a chain reaction: Use stimulus (cue) control to learn social or environmental cues that encourage undesired behaviors or prevent beneficial behaviors and then change the cues.
- Get the fullness message: Slow the rate of eating to allow satiety signals to develop by the end of the meal. Use smaller plates, eat a lot of vegetables to fill you up, and set an eating schedule to avoid skipping or delaying meals followed by overeating.

When target behaviors fail to achieve weight loss, pharmacotherapy may be considered. While there are several drugs approved in the United States to treat patients with obesity, only one (Orlistat) is approved for long-term use [72]. Bariatric surgery is also a promising treatment in severely obese patients (BMI > 40 kg/m$^2$) or those with a BMI > 35 kg/m$^2$ with serious obesity-related comorbidities [53, 73]. Studies have demonstrated that bariatric surgery can improve blood pressure and cholesterol and resolve or improve T2DM [74, 75].

Understanding (1) the mechanisms by which IR links obesity to CVD, (2) the importance of weight loss (through lifestyle modifications) in reducing CVD risk factors, and (3) the way in which energy balance can be used to maintain weight loss and prevent weight gain provides health professionals with the tools needed to slow the obesity epidemic and resultant progression to CVD. Obesity represents not just fat storage but a metabolically active tissue that, if unmanaged, results in severe health consequences, including heart attack, stroke, and T2DM. Obese patients want health professionals to address their weight issues and may be more responsive to advice on lifestyle modifications to lose weight if advice comes from health professionals [76–78].

Barriers to the topic of weight loss exist in many obese patients as most have "tried everything" with little or no result. To get beyond these barriers health professionals need to individualize their treatment and provide a comprehensive approach to weight loss through access to specialist such as weight loss clinics, registered dieticians, and behavior counseling. Health professionals also need to remove the barriers they have to successful identification and management of high-risk obese patients. Talking to patients about their lifestyle and the risk that obesity contributes to CVD is worthwhile in that it lets the patient know that a healthy lifestyle is important and opens the door to a productive discussion about ways to modify habits to aid in weight loss as well as prevent weight gain [57].

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# Chapter 14
# Metabolic Support of the Obese Intensive Care Unit Patient

**Sanit Wichansawakun, Dong Wook Kim, Lorraine S. Young, and Caroline M. Apovian**

**Abstract** As the prevalence of obesity has increased, the number of obese patients admitted to ICUs has also increased. Nutritional assessment and support is a key element in the proper management of critically ill obese patients. Estimating caloric requirements of critically ill obese patients with predictive equations is challenging, as most of these equations were developed for the nonobese population. Currently, indirect calorimetry remains the gold standard for estimating energy requirements. Hypocaloric feeding is recommended for most critically ill obese patients. It is intended to reduce nonprotein calorie infusions while maximizing protein sparing. The caloric goal should not exceed 60–70 % of energy requirements, with a daily intake of at least 2.0–2.5 g/kg ideal body weight of protein required. This hypocaloric feeding regimen will prevent complications of overfeeding, such as hyperglycemia and fluid retention, while preserving lean body mass and promoting steady controlled weight loss. Further investigations are needed for clinical use of pharmaconutrients in critically ill obese patients, though some experimental studies have shown positive results. Those listed above may be considered in the nutritional treatment of critically ill obese patients.

**Keywords** Obesity • Critical illness • Nutrition support • Hypocaloric feeding

### Key Points

- As the prevalence of obesity has increased, the number of obese patients admitted to ICUs has also increased.
- Nutritional assessment and support is a key element in the proper management of critically ill obese patients.
- Estimating caloric requirements of critically ill obese patients with predictive equations is challenging, as most of these equations were developed for the nonobese population.

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- Indirect calorimetry is the current gold standard for estimating energy requirements.
- Hypocaloric feeding, which is intended to reduce nonprotein calorie infusions while maximizing protein sparing, is recommended for most critically ill obese patients.
- The hypocaloric feeding regimen will prevent complications of overfeeding, such as hyperglycemia and fluid retention, while preserving lean body mass and promoting steady controlled weight loss.
- Further investigations are needed for clinical use of pharmaconutrients in critically ill obese patients, though some experimental studies have shown positive results.

## Introduction

Obesity is a multifactorial chronic disease that develops from the interaction of genetic, metabolic, physiologic, and environmental factors [1]. The National Heart, Lung, and Blood Institute defines overweight as a body mass index (BMI) of 25–29.9 kg/m$^2$ and obesity as a BMI of >30 kg/m$^2$. Obesity has become a global epidemic problem for the health care system. During the past 20 years, the prevalence of obesity has increased rapidly in the United States from 13 to 32 % and is expected to increase to 41 % by 2015 [2–5].

## Impact of Obesity in the Critically Ill Patient

In the United States, more than one third of patients in the intensive care unit (ICU) are obese and 7 % of patients are morbidly obese [6]. This presents a challenging situation for the ICU team to care for these patients because obesity is associated with multiple comorbidities, in addition to inducing physiologic complications such as hyperglycemia, hyperlipidemia, impaired hepatic function, and increased risk of thromboembolic disease. Many of these complications are the result of a preexisting inflammatory state caused by obesity [7, 8] (Table 14.1).

Despite these inherent physiologic complications of obesity, its reported effects on outcomes such as morbidity and mortality in the ICU are inconsistent. Several observational studies have shown that obesity has a protective effect in critical illness and is associated with improved outcomes. This

**Table 14.1** Medical comorbidities of the obese critically ill patient [10]

| System involvement | Comorbid conditions resulting from obesity | Consequent conditions |
|---|---|---|
| Cardiovascular system | Hypertension | Congestive heart failure |
| | Left ventricular hypertrophy | |
| | Reduced left ventricular contractility and ejection fraction | |
| Respiratory system | Increased abdominal pressure | Aspiration pneumonia |
| | Hypoventilation | High airway resistance |
| | Obstructive sleep apnea | Difficulty in weaning from ventilator |
| Gastrointestinal system | Nonalcoholic fatty liver disease | Liver failure |
| Endocrine system | Insulin resistance (hyperglycemia) | Increased risk of infection |
| | Dyslipidemia (hypertriglyceridemia) | Acute pancreatitis |
| Hematologic system | Hypercoagulable state | Deep vein thrombosis |
| | | Pulmonary embolism |
| Immunologic system | Decrease in immune function | Pressure sores and skinfold infections resulting from poor wound healing |

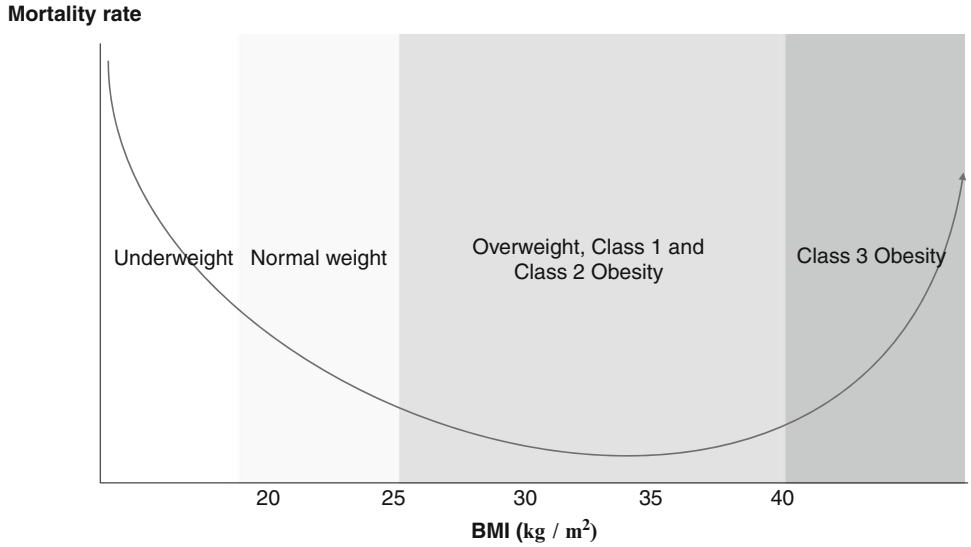


**Fig. 14.1** Association of BMI and mortality rate in the intensive care unit [6, 9, 11]

phenomenon has been coined the "obesity paradox" [8]. However, a cohort study conducted in 28 medical centers in Canada, the United States, and Saudi Arabia between 1996 and 2008 showed no significant decrease in mortality rates in obese ICU patients after adjusting for baseline characteristics [9]. Moreover, a recent prospective study showed a higher mortality in obese patients (average BMI 34 kg/m$^2$) with predominant abdominal fat distribution and concluded that high sagittal abdominal diameter is an independent risk factor for increased mortality in the ICU [10]. Class III obesity (BMI >40 kg/m$^2$) is in particular associated with prolonged mechanical ventilation in ICU patients [11]. The curve representing the overall effect of obesity on mortality over a wide range of BMIs is U-shaped with even a mortality benefit for class I and II obesity: patients with a BMI >40 kg/m$^2$ have an increased risk for mortality [6] (Fig. 14.1).

The physical aspects of severe obesity are also challenging for the medical staff because they frequently require the use of specialized equipment, such as larger beds, lifts, and longer instruments. Moreover, routine procedures for providing appropriate care to obese patients become more technically difficult, for example, obtaining vascular access, performing a tracheostomy, and interpreting radiologic studies.

## Carbohydrate, Fatty Acid, and Protein Metabolism in the Critically Ill Obese Patient

Critical illness, regardless of cause, increases the metabolic rate and promotes catabolism because of the inflammatory response to stress, leading to the release of cytokines and counterregulatory hormones. Critical illness can affect all components of nutritional homeostasis, both macro- and micronutrients. Moreover, obesity is associated with low-grade inflammation of white adipose tissue resulting from chronic activation of the innate immune system, which can subsequently lead to insulin resistance. This likely lowers the threshold at which these mechanisms become overwhelmed or exaggerated during critical illness [8, 12–15].

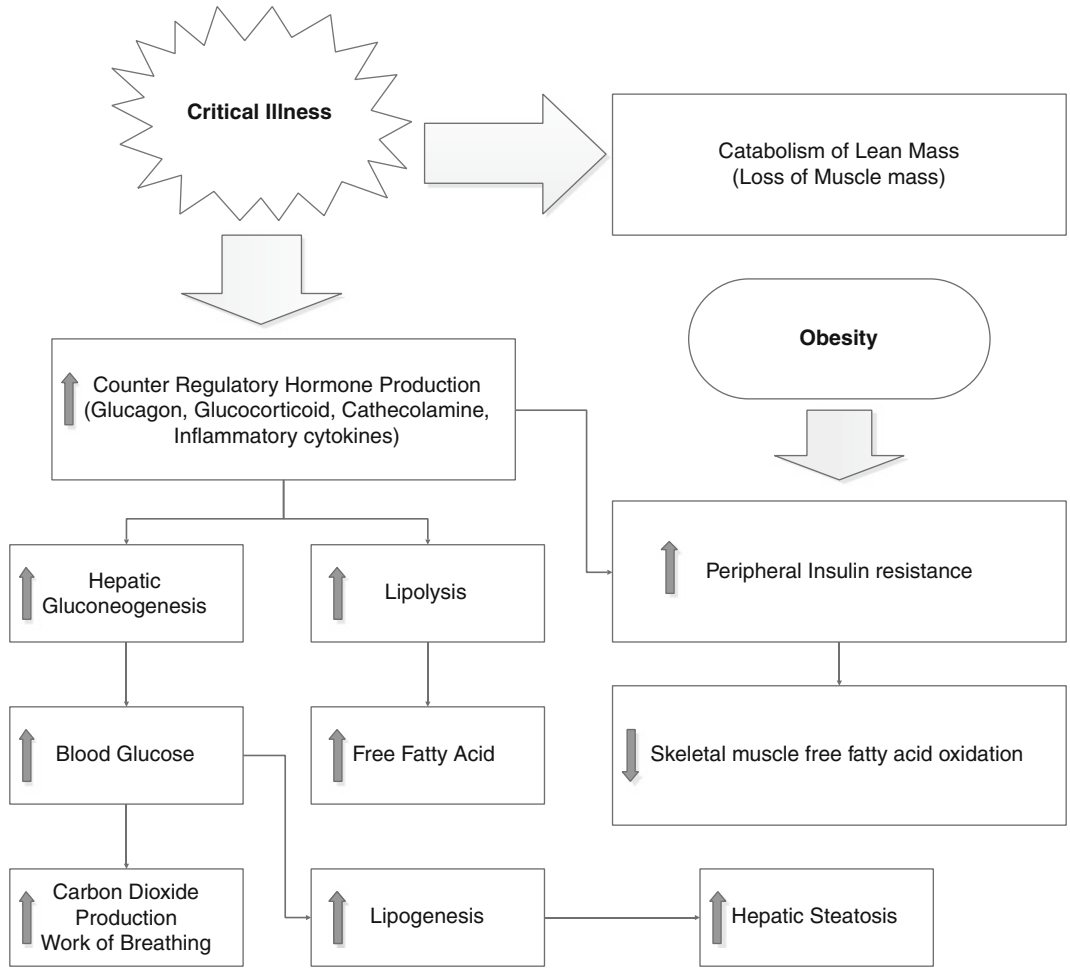


**Fig. 14.2** Alterations in carbohydrate metabolism, fatty acid oxidation, and protein utilization in the obese critically ill patient

During critical illness, counterregulatory hormones such as glucagon, glucocorticoids, catecholamines, and inflammatory cytokines are upregulated and secreted leading to accelerated hepatic gluconeogenesis, lipolysis, and peripheral insulin resistance that results in hyperglycemia. Hyperglycemia during critical illness is associated with poorer outcomes [15] because it can lead to an increase in lipogenesis, hepatic steatosis, and $CO_2$ production, thus increasing the work of breathing and duration of mechanical ventilation [8, 15].

An accumulation of lipid intermediates (e.g., diacylglycerol, ceramides, and fatty acyl-CoAs) in non-adipose tissue can cause cellular dysfunction, leading to organ dysfunction. This phenomenon has been called lipotoxicity [6]. Adipose tissue is subject to lipotoxicity with manifestations of adipokine dysregulation [6, 16]. An increased blood level of free fatty acid (FFA) in obese persons usually signifies insulin resistance, causing impaired skeletal muscle FFA oxidation and reduced suppression of plasma FFA by insulin [8]. Critically ill obese patients are ineffective at using FFA and triglyceride-rich adipose stores, preferentially using the energy from the catabolism of lean tissue and resulting in losses of skeletal muscle. Altered fuel metabolism in obesity predisposes patients to a greater loss of lean body mass and nutritional stress, which can lead to sarcopenic obesity [6] (Fig. 14.2). Therefore, proper nutritional assessment and nutrition support are important elements in managing critically ill obese patients.

## Nutritional Assessment in the Critically Ill Obese Patient

Historically, obese patients were thought to be at lower risk for the adverse nutritional effects of acute illness because of their increased energy reserves stored in adipose tissue, but recent data has revealed that acute illness in obese patients can predispose them to malnutrition and this can be a consequence of critical illness [7, 17]. Nutrition assessment is one of the most important steps in determining an appropriate feeding plan. History taking and a physical examination of obese ICU patients allows care providers not only to evaluate the energy requirements, nutritional risk factors, and comorbidities of these patients, but it also allows them to determine the best approach to nutrition support. In addition to the medical history, a patient's weight loss history and diet history should be obtained from the patient, medical records, family, or caregivers. Calorie counts should be obtained by the nursing or dietary staff in the critically ill obese patient if eating or tallied on tube feeds or parenteral nutrition. Height and weight are essential nutritional parameters and are used for nutritional calculations. The systematic physical examination including general appearance, skin, hair, nail, mucous membranes, respiratory system, cardiovascular system, endocrine system, nervous system, and musculoskeletal system is required for the identification of single or multiple micro- or macronutritional deficiencies in the critically ill obese patient.

## Assessment of Energy Requirements

The assessment of the energy and protein requirements of the obese patient is fraught with controversy as there is no clear consensus about the most precise method to use for the calculating protein and energy needs. Because the relationship between lean body mass and body weight is not linear, obese patients usually have proportionately more fat mass than muscle mass compared to a lean patient. In order to compensate for this, an adjustment is made to estimate lean muscle mass for obese patients. If the actual body weight of an obese patient is used, the estimated energy requirements could be above the true requirements, and if the ideal body weight (IBW) is used, the estimated energy requirements could be underestimated. Therefore, an adjusted body weight (ABW) is used for obese patients [18–20]:

$$ABW = 0.25\left(Actual\ weight - Ideal\ weight\right) + \ Ideal\ weight$$

Determining the basal metabolic rate (BMR) is also a challenge in obese critically ill patients. Even though indirect calorimetry is considered the gold standard for determining metabolic rate, this test cannot always be done because it requires trained personnel and is costly. This test also cannot be used in patients who have air leaks, who need a high fraction of inspired oxygen, or who are uncooperative. Numerous equations have been generated to estimate BMR, but none have yet been validated in this setting. A recent review showed that the Penn State 2003, Swinamer, and Ireton-Jones 1992 equations may be useful in critically ill nonobese patients, whereas the Ireton-Jones 1992 and Penn State 1998 equations are more accurate for an obese cohort [21]. The strength of these equations is moderated because of limited and sometimes inconsistent data. The Penn State equation (using the Harris–Benedict equation (HBE) from ABW) and the HBE with actual body weight and a stress factor (1.1) have the strongest support for use in the obese ICU patient [8, 22]. The Penn state equation is suggested for use in ventilator-dependent obese patients, and the HBE is suitable for use in spontaneously breathing patients [8]. Recently, the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN) recommended a simple method for predicting energy expenditure in critically ill obese patients, which is based on kilocalories per kilogram [8, 20] (Table 14.2). Those some equations have been used with ABW but that there is no clear accurate prediction of energy requirements in the critically ill obese is an ongoing area of research.

**Table 14.2** Predictive equations validated in critically ill obese patients [20, 21]

| Predictive equation | Calculation |
|---|---|
| Harris–Benedict equation (HBE)[a] | Men: kcal/d = 66.5 + (13.8*ABW*) + (5*H*) − (6.8*A*)<br>Women: kcal/d = 655.1 + (9.6*ABW*) + (1.8*H*) − (4.7*A*) |
| Ireton-Jones | kcal/d = 1,784 + (5*W*) − (11*A*) + (244 (if men)), + (239 (if trauma)) + (804 (if burn)) |
| Penn State (using HBE)[a] | kcal/d = 0.85(HBE) + 175($T_{max}$) + 33($V_e$) − 6,344 |
| SCCM/ASPEN applied to hypocaloric feeding situation | kcal/d = (11 − 14)*W* |

*A* age, *H* height (cm), *ABW* adjusted body weight, *W* actual body weight (kg), $T_{max}$ maximum temperature in a 24 h period, $V_e$ minute ventilation

[a]These equations have been used with adjusted body weight, but there is no clear accurate prediction of energy requirements in the critically ill obese. This is an ongoing area of research

## Nutritional Management in the Critically Ill Obese Patient

For critically ill obese patients, high-protein hypocaloric feeding is the recommended approach to maintain nitrogen balance and lean body mass while promoting use of adipose tissue as a fuel. Multiple studies have demonstrated improved metabolic control and improved outcomes in the ICU with this approach, including lower insulin requirements, decreased ICU stay, decreased number of days receiving antibiotics, improved wound healing, better closure of fistulas, and a trend toward reduced duration of mechanical ventilation [7]. Historically, the high-protein hypocaloric feedings approach originated from the early use of the protein sparing modified fast for the treatment of obesity in inpatient and outpatient settings, starting in the early 1970s. This approach contrasts with permissive underfeeding, which is also applied to lean critically ill patients. Permissive underfeeding reduces all macro- and micronutritional delivery, which leads to the provision of less energy, protein, carbohydrates, and other nutrients. On the other hand, hypocaloric feeding reduces the delivery of nonprotein calories, which decreases total energy delivery without a reduction in protein and other micronutrients. Therefore, lean body mass loss is minimized while allowing greater loss of fat mass. However, this should not be the primary objective of nutrition support during critical illness. The main rationale for the administration of hypocaloric feeding is to prevent the metabolic consequences of overfeeding, such as hypercapnea, fluid retention, and hypertriglyceridemia. High-protein hypocaloric feeding also can markedly improve insulin sensitivity and glycemic control [8, 23].

The recent "Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically ill Patient" from the SCCM and ASPEN recommends using high-protein and hypocaloric feeding for all classes of obesity in which the BMI is >30 kg/m$^2$ (Grade D) [7]. The goal for caloric intake in an enteral nutrition (EN) regimen should be to not exceed 60–70 % of energy requirements, a number that can be determined by simple weight-based equations: 11–14 kcal/kg ABW/d or 22–25 kcal/kg IBW/d [5, 7, 18]. This recommendation is also appropriate for use with a parental nutrition regimen. The ideal enteral formulation should contain a nonprotein calories to nitrogen ratio of <40–50:1 [6]. The calories from glucose should be provided at a minimum of 125 g/d but may be as much as 250 g/d in a patient needing to heal large wounds or having significant inflammation [6]. The recommended caloric density should be no greater than 1 kcal/mL [6].

As nitrogen balance is a function of both nitrogen (protein) and caloric intake, this can be achieved by altering either factor. Appropriate protein delivery can promote protein synthesis and preserve lean body mass. High-protein hypocaloric feeding is based on the theory that nitrogen balance increases rapidly until caloric intake approaches 50–60 % of total energy intake; thus, a positive nitrogen balance can be achieved with a high-protein hypocaloric intake [18]. In class I and II obesity (BMI 30–40 kg/m$^2$), protein should be estimated at 2.0 g/kg IBW/d and in class III obesity (BMI>40 kg/m$^2$) at 2.5 g/kg IBW/d [5, 7, 18]. These amounts can be adjusted, if necessary, on the basis of nitrogen balance

measurements taken while monitoring patients when feeding. Even in malnourished or depleted patients, a positive nitrogen balance can be achieved with a hypocaloric intake (relative to energy expenditure) by increasing protein intake. Contraindications to high-protein hypocaloric feeding are progressive renal failure, hepatic encephalopathy, other reasons for ketosis, or a severe immunocompromised state [8].

Enteral feeding is usually the preferred method for critically ill obese patients who have the ability to tolerate feeding through the gut. EN should be started early but after full resuscitation in order to avoid bowel ischemia [6, 7]. Early EN in the critically ill patient is expected to maintain gut integrity and help prevent further increases in intestinal permeability and possible modulation of systemic immunity [6]. Most standard and specialized feeding formulas will not satisfy 100 % of protein requirements using a hypocaloric approach. There are newer "bariatric" or "immune-enhancing" formulas available that have a higher protein-to-calorie ratio. A useful option is to add protein modules to the standard formulas if these specialized formulas are not available. Approximately 60–80 % of the energy requirements should be provided through feeding formulas and the remainder should be fulfilled by extra protein substrates.

The formulas for obese critically ill hospitalized patients should limit the amount of fructose along with high carbohydrate and saturated fat. A fructose and high-carbohydrate diet can lead to an increase in serum triglyceride concentration, resulting from hepatic insulin resistance in the obese critically ill patient. Saturated fat has been shown to increase gut permeability and contribute to inflammation. Medium chain triglyceride oil may be less inflammatory. Total fat should be no more than 15–20 %. Whey protein may be preferred as the protein source in these patients because it can promote satiety and increase the levels of glucagon-like peptide-1 and leucine [12, 24].

Obese patients are more likely to have increased abdominal pressure and delayed gastric emptying because of their predisposition to clinical diabetes and its associated enteric neuropathy, which increases the risks of gastroesophageal reflux and aspiration. For these reasons, post-pyloric feedings and the use of prokinetics may be necessary to reduce these risks [7, 25]. Placement of a percutaneous endoscopic gastrostomy tube may be relatively contraindicated in morbidly obese patients because it is associated with increased complication rates, including postprocedure ileus, and wound infections [7].

## Monitoring in the Critically Ill Obese Patient

Serial indirect calorimetry may be helpful for assessing calorie requirements that may need to be adjusted because of a change in the patient's condition. The confirmation of adequate protein intake can be determined from nitrogen balance with 24-h collections of urinary urea nitrogen. Because of excess protein load in high-protein hypocaloric feeding, blood urea nitrogen and creatinine levels should be measured and a daily physical assessment made for asterixis [6]. Records of intake/output should be monitored to assure delivery of the nutrition regimen. As hyperglycemia can increase morbidity and mortality, serum glucose should be controlled to keep glucose levels at <180 mg/dL (10 mmol/L) [6, 7, 15]. Serum triglyceride, cholesterol, and liver enzyme levels should also be followed in these patients.

## Pharmaconutrients

Oxidative stress may play an important role in both the chronic complications associated with obesity, such as diabetes mellitus, and the poor outcomes associated with critically ill obese patients. Some amino acids, fatty acids, and trace elements may have beneficial pharmacological action and immunomodulation during critical illness in terms of offering protection against oxidative and electrophilic

**Table 14.3** Pharmaconutrients that may be beneficial in the obese critically ill patient [6, 11, 24]

| Pharmaconutrient[a] | Benefit/role in obese patient | Recommended dose |
|---|---|---|
| Omega-3 fatty acids | • Increase in insulin release by activation of peroxisome proliferator-activated receptor (PPAR)-γ and PPAR-α<br>• Decrease in an inflammation by blocking macrophage migration into white adipose tissues and decrease an inflammatory cytokines<br>• Increase in adiponectin levels | 1,860 mg/d of eicosapentaenoic acid and 1,500 mg/d of docosahexaenoic |
| L-Arginine | • Provides vasodilation and increased perfusion of organs through nitric oxide synthase (NOS) pathways<br>• Reduces the effect of asymmetric dimethyl arginine, which is a competitive NOS antagonist<br>• Increase in hepatic blood flow and promotes wound healing<br>*Note*: Arginine can be converted to nitric oxide contributing to hemodynamic instability. Therefore arginine should be used cautiously in critically ill patients and be avoided in patients with severe sepsis | 12.5–25 g of arginine per day per 1,000 kcal of formula |
| Magnesium | • Prevents destruction of tight junctions in the gut epithelial cells<br>• Positive effects on bifidobacteria in the lumen gut | 400 mg magnesium oxide per day |
| Zinc | • Improvement of tight junctions between gut epithelial cells<br>• Antioxidant | 50 mg/d |
| Leucine | • Increases AMP-activated protein kinase<br>• Promotes weight loss while maintaining muscle mass | 6–8 g/d |
| α-Lipoic acid (ALA) | • Increases insulin sensitivity<br>• Reduces inflammation<br>• Promotes energy expenditure and weight loss<br>• Antioxidant | 600 mg/d |

[a]Recommended dosages have not been determined for many of the pharmaconutrients in the critically ill obese patient

toxicity, promoting the anti-inflammatory process, and acting as cofactors for nutrient use in the mitochondria. For example, altered metabolic demand during critically ill conditions results in a change in the requirements for conditionally essential amino acids. However, human data have shown that these effects are limited, especially in the obese population, and therefore more studies need to be performed before promoting the standard use of these nutrients [6, 12, 24]. Recent studies have illustrated that some agents, including magnesium, L-arginine, zinc, leucine, fish oil, whey, betaine, L-carnitine, α-lipoic acid, and *S*-adenosylmethionine, help reduce low-grade systemic inflammatory response syndrome, help improve insulin sensitivity and promote hepatic function [6, 12] (Table 14.3). More research is needed in these areas.

## Summary

As the prevalence of obesity has increased, the number of obese patients admitted to ICUs has also increased. Nutritional assessment and support is a key element in the proper management of critically ill obese patients. Estimating caloric requirements of critically ill obese patients with predictive equations is challenging, as most of these equations were developed for the nonobese population. Currently, indirect calorimetry remains the gold standard for estimating energy requirements.

Hypocaloric feeding is recommended for most critically ill obese patients. It is intended to reduce nonprotein calorie infusions while maximizing protein sparing. The caloric goal should not exceed 60–70 % of energy requirements, with a daily intake of at least 2.0–2.5 g/kg (IBW) of protein required. This hypocaloric feeding regimen will prevent complications of overfeeding, such as hyperglycemia and fluid retention, while preserving lean body mass and promoting steady controlled weight loss. Further investigations are needed for clinical use of pharmaconutrients in critically ill obese patients, though some experimental studies have shown positive results. Those listed above may be considered in the nutritional treatment of critically ill obese patients.

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# Chapter 15
# Obesity and Its Impact Upon Quality of Life

**John Roger Andersen, Tor-Ivar Karlsen, and Ronette L. Kolotkin**

**Abstract** Obesity may have a negative effect on quality of life (QOL) and is an important outcome in the treatment of obesity. In this chapter we discuss the concept of QOL; the measurement of QOL; the mechanisms by which obesity may influence the physical, social, mental, and sexual aspects of QOL; and the effects of weight loss interventions on QOL. Finally, we discuss how health professionals may use QOL measures to improve the quality of clinical practice.

**Keywords** Quality of life • Health-related quality of life • Health status • Patient-reported outcomes • Physical functioning • Mental functioning • Social functioning • Sexual functioning

**Key Points**

- Obesity may have a negative effect on quality of life (QOL) and is an important outcome in the treatment of obesity.
- There are three types of QOL measures: disease-specific measures, generic measures, and overall QOL.
- Obesity may influence quality of life by impacting physical, social, mental, and sexual function.
- Measuring QOL in clinical situations can be broadly useful in working with obese individuals both in measuring clinical outcomes and serving as a motivator for change.

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- Obesity may have a particularly negative effect on physical functioning, but studies suggest that obese individuals who maintain a high level of physical activity seem to be especially resilient to the consequences of obesity.
- One of the greatest social challenges faced by many obese persons is the stigma associated with being obese.
- A large number of studies have found significant associations between obesity and impaired sexual QOL.
- While many obese individuals have good mental health, a number of studies have shown significant associations between obesity and impaired mental quality of life.
- The risk for having reduced QOL is generally smallest in obese individuals not seeking any help for their obesity, intermediate in obese individuals seeking nonsurgical help, and highest in those seeking obesity surgery.
- Individuals with extreme obesity may have an increased risk of being unemployed which is associated with impaired QOL.
- Data suggests that if clinicians take obese patients seriously, patients feel less stigma of obesity, as measured with the obesity problem scale.
- If weight loss is maintained over time and side effects of treatment are tolerable, improvements in QOL are the norm.

## What Is Quality of Life?

One of the earliest references to "a good life" appeared in the Nicomachean Ethic, when Aristotle (384–322BC) spoke about "eudemonia," often translated as "happiness" or "flourishing" [1]. Today we are more likely to describe "a good life" as one in which there is a high quality of life (QOL). It has been argued that defining QOL in a way that is relevant to everyone is indeed a very complex and perhaps impossible task because what matters in life varies from person to person [2]. However, a World Health Organization work group has identified the following elements of QOL cross-culturally: physical health, mental health, social relationships, environment, as well as overall QOL [3].

To distinguish between the general concept of "a good life" and the quantification of QOL in clinical and health research, the term health-related quality of life (HRQL) is frequently used. The most common understanding of HRQL is that it is a multidimensional measurement of the individual's perception of the impact of an illness and its treatment [4, 5]. HRQL captures, at a minimum, physical, psychological, and social functioning. Despite the distinction between HRQL and QOL, the two are often used interchangeably in the literature [6]. In this chapter we shall use the inclusionary term *QOL*, as obesity may have profound effects on almost every aspect of life [7, 8].

## Why Measure Quality of Life?

Measuring QOL in clinical situations can be broadly useful in working with obese individuals both in measuring clinical outcomes and serving as a motivator for change [7–9]. First, assessing QOL allows us to quantify many of the benefits of treatment that go beyond weight loss and resolution of comorbidities. Since the majority of obese individuals, especially those with severe obesity, are unable to maintain a substantial weight loss over time unless they have obesity surgery [10–12], a demonstrated improvement in QOL gives these individuals a way to realize benefits from their lifestyle change efforts even in the absence of a large weight loss. Second, results from QOL measures may indicate the need for supportive interventions [7, 8]. For example, if a person undergoing weight loss treatment is experiencing undisclosed personal problems, QOL assessment may bring these problems out into

the open to be dealt with in the context of treatment. Conversely, if these problems remain private, the patient may find it difficult to perceive improvements in QOL and thus may have difficulty adhering to treatment. Third, QOL measures are strong prognostic indicators that contain unique information beyond traditional clinical variables [4, 5]. Poor QOL affects long-term prognoses in terms of medical problems and survival in a range of populations, even after adjustment for known confounders [13, 14]. Thus QOL measures based on the patient's subjective judgments seem to tap essential predictive information from a source that is not accessible to the clinician or researcher in any other way. Fourth, because interventions may possibly cause harm or risk, it is important to evaluate all the outcomes of a treatment in terms of its influence on QOL [4, 5]. For example, obesity surgery gained widespread acceptance in part because the pioneers included a solid battery of QOL measures in their studies and demonstrated long-term improvements in QOL after surgery [15]. Fifth, the degree of impairment of QOL is often a major source of motivation for seeking help for obesity [7, 8, 16]. Thus, QOL assessments may help clinicians to tailor a treatment that delivers positive outcomes matched to the particular needs of the individual. Finally, measuring QOL is useful in decision-making and health policy [8]. Ideally, we should recommend obesity treatments that have a high probability of maximizing QOL in addition to improving clinical health measures.

## Measuring Quality of Life

There are three types of QOL measures: disease-specific measures, generic measures, and overall QOL. A complete battery of QOL measures should not only include these three types of measures but also cover physical, psychological, and social domains [4, 5].

### *Disease-Specific Measures*

Disease-specific measures contain questions that reflect the characteristics and challenges that are most relevant for a specific disease or condition. Such measures should be very sensitive for change in clinical trials and relate closely to common concerns of the target population [4, 5]. Thus, obesity-specific QOL measures are very important when assessing QOL in the obese. There are several such questionnaires for obesity [17, 18]. Examples of well-designed weight-specific QOL measures are the Impact on Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire [19], the Obesity and Weight Loss Quality of Life Questionnaire (OWLQOL), and Weight-Related Symptom Measure (WRSM) [20, 21], as well as the IWQOL-Kids for adolescents [22]. An important distinguishing feature of these questionnaires is that questions contain phrases such as "because of my weight" or "due to my weight," thus allowing the direct assessment of the impact of weight on QOL.

### *Generic Measures*

Generic measures assess the broad aspects of health and are designed to provide a generalized assessment of QOL in the general population [4, 5]. The main advantage of generic measures is that they allow for comparisons between obese individuals, other disease groups, and the general population. The main drawback with generic measures is that it is not possible to determine if respondents attribute their QOL to their specific disease (e.g., obesity) or to other factors (e.g., age, a comorbid condition such as diabetes). There are many generic instruments, but the most commonly used in

obesity research is the Medical Outcomes Study Short-Form-36 (SF-36), which assesses physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning, and mental health [23]. Generic instruments are also available for children/adolescents [24, 25].

### *Overall Quality of Life*

Overall assessment of QOL can be described as an individual's overall satisfaction with life or sense of well-being. Simply asking the obese individual how she/he rates overall well-being (e.g., on a scale of 0–100) is an easy and convenient way to determine overall QOL. There are also several life satisfaction measures, such as the Quality of Life Inventory [26] and Diener's Satisfaction with Life Scale [27].

Overall QOL is clearly very important at an individual level and is a predictor of mortality independent of other QOL measures and objective health variables across a range of populations [13]. Overall QOL may also provide valuable information about how individuals are coping with and/or adapting to living with a chronic condition, such as obesity [4].

## Obesity and Quality of Life Challenges

Before we take a look at specific problems that are common to individuals with obesity, it is important to acknowledge that the consequences of obesity differ from person to person. It is possible for an obese person to be successful and happy and live a good life [28]. However, each individual has a personal threshold in which obesity harms his/her health or QOL. Thus, one person might feel that her QOL is substantially reduced with a BMI of 30 while another might feel the same with a BMI of 40. The explanation for this between-person variability is complex, combining several factors like genetic, psychological, social, and environmental variables [7, 8].

Some data suggest that QOL is more impaired in obese women compared to obese men and in white obese individuals compared to black obese individuals [29]. Some studies suggest that obese individuals who maintain a high level of physical activity seem to be especially resilient to the consequences of obesity [30]. Findings also suggest that if obesity is associated with physical impairments, the risk of impairments in other domains of QOL increases strongly [31]. The number and severity of comorbidities also influences QOL negatively [32, 33]. In particular binge eating disorder (BED), depression, and musculoskeletal pain seem to have a negative effect on QOL [34, 35]. The risk for having reduced QOL is generally smallest in obese individuals not seeking any help for their obesity, intermediate in obese individuals seeking nonsurgical help, and highest in those seeking obesity surgery [29].

## Physical Challenges

Obesity may have a particularly negative effect on physical functioning [7, 8], with a significant association occurring between increasing BMI and impaired physical functioning [29]. In those who are overweight or moderately obese, only mild reductions of physical functioning may occur. Walking capacity, an important form of physical functioning, may be especially affected by obesity. Using time to exhaustion while walking on a treadmill, data in both men and women have shown that the prevalence of low cardiorespiratory fitness (which is also an indicator of high risk for mortality)

increases about 5% points per unit increase of BMI above 25 kg/m$^2$ [30]. In healthy-weight individuals (BMI 18.5–25 kg/m$^2$) about 8 % have low cardiorespiratory fitness, while in those with a BMI > 40 kg/m$^2$, low cardiorespiratory fitness is the norm. Common physical problems related to obesity include the following: low energy and vitality, difficulty walking long distances, trouble bending down, difficulty getting up from chairs, and inability to climb stairs. In the end such limitations may become so severe that basic self-care (dressing, washing oneself, etc.) becomes difficult, especially for those with a BMI > 40 kg/m$^2$. This can be especially troublesome when obesity is associated with sweating and skin problems [36]. Obesity is also a risk factor for musculoskeletal pain, which may impair physical functioning and well-being in general [37]. Obesity is also associated with sleep apnea which reduces the quality of sleep [38]. These physical problems can lead to reduced vitality with impaired ability to fill social roles in daily life such as participating in paid work, parenting, housework, and hobbies [7, 8].

The mechanisms behind the effects of obesity on physical QOL are quite straightforward. Obesity intensifies the power of gravity and influences physical functioning by increasing the strain on the musculoskeletal and cardiovascular system. Obesity is also associated with increased pressure on organs due to fat mass, making breathing difficult and decreasing the flexibility of body movements [38]. Finally, metabolic effects of obesity may also have a degenerative effect leading to musculoskeletal pain [37].

Individuals often resort to poor coping strategies for dealing with their impaired physical functioning, such as reducing activities that require physical effort and increasing activities that may further exacerbate weight gain. Over time, reduced physical functioning may lead to social isolation due to the challenges of everyday life. More productive strategies include seeking professional help to induce weight loss, ameliorate physical problems (e.g., pain), and break the cycle of inactivity and isolation.

## Social Challenges

One of the greatest social challenges faced by many obese persons is the stigma associated with being obese [39, 40].

Prejudice and stigma against obese individuals begins early in life. In 1967 J. Robert Staffieri reported anti-fat attitudes among 90 boys aged 6–10 years old [39]. The children were to apply 39 different words to three silhouettes (thin, normal, and overweight). The overweight silhouette was characterized as “cheats,” “lies,” “argues,” “lazy,” “sloppy,” “mean,” “dirty,” “ugly,” and “stupid” by the children. Later studies have produced similar results [40, 41]. Even studies of health personnel show anti-fat attitudes [42–44]. Such anti-fat attitudes among health personnel can make obese individuals reluctant to seek medical assistance for their condition. One Swedish population-based study found that obese individuals were twice as likely to report healthcare discrimination as healthy-weight individuals [45]. Other studies have also reported stigma and bias toward obese individuals by healthcare providers [46–48]. In a qualitative study of obese persons’ experience of bias [49], one of the responses exemplifies this stigma:

> The last time I went to [the family doctor] with a problem, he said, “You just need to learn to push yourself away from the table.” It later turned out that not only was I going through menopause, but my thyroid was barely working (63-year-old female).

One effect of stigma and prejudice is that obese individuals as a group have more problems in job settings than normal-weight individuals [50]. A study published in 2011 confirmed earlier studies showing that managers were less likely to invite an obese applicant for a job interview [51]. Another study examined whether obese persons reported discrimination to a greater extent than their normal-weight peers. For both men and women, obesity was associated with perceived workplace discrimination [45].

Examination of the sociological literature may provide some insight into the theoretical causes of stigmatization. The ancient Greeks used the term stigma for the scarring or burn marks on slaves, criminals, or traitors to symbolize their societal status. Today, the term is used in a similar but more subtle way. The Canadian sociologist Erving Goffman's theoretical framework on stigma [52] and social interaction [53] explains the phenomenon of stigma as the categorization of an individual into a discrediting social identity. The external categorization of the individual, according to Goffman, is internalized as the individual eventually accepts his or her stigma, even though it is discrediting. In obesity, this internalization of (external) stigma may lead to an acceptance of having an undesirable body appearance and its implied character defects. This may in turn lead to the poor social interaction and impaired social QOL that many obese individuals report.

It is important for practitioners to be aware of the existence of obesity stigma and to send a clear message to their patients or clients: your weight problem does not define who you are as a person.

## Mental Health Challenges

While many obese individuals have good mental health, a number of studies have shown significant associations between obesity and impaired mental QOL. This impairment encompasses both a wide range of psychiatric diagnoses and minor disturbances. In a nationally representative sample of the US residents ($n = 9{,}125$, 26 % BMI > 30 kg/m$^2$), obesity was associated with an approximately 25 % increase in mood and anxiety disorders but an approximately 25 % decrease in substance use disorders [54]. The prevalence of eating disorders is generally high in the obese population, especially binge eating disorder (BED) and bulimia nervosa (BN). The WHO World Mental Health Surveys on the prevalence of BED and BN estimated an odds ratio (95 % CFI) of BED to 10.2 (5.8–18.1) and of 8.3 (3.3–21.1) of BN in persons with a BMI > 40.

It has been hypothesized [55] that mood disorders, especially depression, are potentiated in the extremely obese due to greater prejudice, discrimination, and stigma. In one US study in a nationally representative sample [56], the BMI–depression relationship varied by gender. There were no significant associations between BMI and depression among men, while women with the highest BMIs were 38 % more likely to score in the depressed range than women with lower BMIs. A second US population study [57] found that obese women were 37 % more likely than normal-weight women to have experienced major depression in the past year. Obese women also reported more suicidal ideation and were more likely to have made a suicide attempt in the past year.

In sum, such studies show that obese individuals, in particular individuals with extreme obesity and women, are at risk of developing psychological distress, especially eating disturbances and depression, even though this distress does not necessarily rise to the level of a formal psychiatric diagnosis. Little is known about the mechanisms behind these associations. There is common agreement that obesity is a multifactorial disorder with both genetic and environmental components. As described in the previous section, being obese is stigmatizing and the social pressure to conform to norms of thinness may be internalized as high levels of psychological distress. Following Eunkyung Park [58] in her discussion of this relation, gender may function as a moderator by exerting more sociocultural pressure on women than men to conform to an idealized physique, leading to mood and depressive disorders. Finally, it is also clear that the physical problems associated with obesity can be a sole cause of mental distress [31].

The clinician should be aware of the stigmatizing effect of obesity and its potential effect on psychological distress—especially in women. This should be addressed and empathic counseling should be applied in addition to pharmacological treatment and/or referral to nurses, psychologists, and other healthcare providers who specialize in issues related to obesity and psychological functioning.

## Sexual Challenges

The World Health Organization defines sexual health as a state of physical, mental, and social well-being in relation to sexuality. Good sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination, and violence [59]. QOL is a multidimensional concept and sexuality crosses many of these QOL dimensions. It is obvious that sexuality is dependent on mental and physical capability, physical functioning, and functional status, which all contribute to desire, arousal, and pleasure. Sexuality is at the same time highly dependent upon emotional well-being and degree of intimacy within the relationship [60], and impaired sexual functioning is generally associated with impaired QOL [61]. A large number of studies have found significant associations between obesity and impaired sexual QOL, though most such studies have been conducted with men, leaving the association between obesity and sexual QOL in women somewhat inconclusive [62]. Understanding the relationship between sexuality and obesity requires the consideration of several factors: the endocrine effect of obesity, the impact of comorbidities, the psychosocial impact [63], and the physical limitations.

The endocrine effects of obesity on the reproductive hormones affect both men and women. In men, the most prominent is late-onset hypogonadism (LOH) caused by low testosterone and sex hormone binding globulin (SHBG) levels and subsequently increased levels of estradiol [64]. LOH is characterized by impaired libido, erectile dysfunction, and impaired QOL [65]. In women obesity is associated with hyperandrogenism and ovulatory dysfunction [64], increasing the risk of polycystic ovary syndrome with masculinization and impaired sexual satisfaction and QOL as dominating consequences [62].

A series of studies on sexual functioning have been conducted in individuals with obesity-related comorbid conditions including urinary incontinence, polycystic ovary syndrome, obstructive sleep apnea, BED, metabolic syndrome, diabetes, and prostate cancer. In most of these studies, there was an association between obesity and impairment in sexual functioning [62].

Many obese individuals experience poor body image, especially when they compare themselves to societal norms that emphasize thinness. Obesity may reduce the individuals' attractiveness in the eyes of others but also in their own eyes. Consequently, there may be sociological explanations of impaired sexual functioning in obese individuals.

The impact of obesity on sexual functioning is not only a hormonal and sociological matter. For the extremely obese, finding coital positions may be difficult and sexual activity may be unpleasant, painful, or even impossible.

The clinician should address the topic of sexuality with his or her patients as sexual health is an important aspect of the patient's total health and QOL. Asking open-ended questions about the patient's QOL allows an opportunity for the patient to reveal sexual concerns. The clinician should be aware that obese women, especially those with visual symptoms of PCOS (hirsutism and masculinization) may feel a loss of a sexual identity [66]. Obese men who report symptoms of impaired sexual functioning should be tested for hypogonadism and, if positive results are obtained, receive testosterone supplements. Referral to psychologists, counseling therapists, or sexologists may help many patients to achieve a better sexual QOL.

## Work-Related Challenges

Individuals with extreme obesity may have an increased risk of being unemployed which is associated with impaired QOL [67, 68]. A systematic review showed a J-shaped relationship between BMI and the risk for a disability pension [69]. Thus, obesity may have economic consequences both on an

individual level and for families—increasing the total burden of life problems in addition to other problems associated with obesity.

Reduced work participation can be directly related to the effect obesity has on health. However, as mentioned earlier in this chapter, obesity stigma could affect wages, promotion, termination, and, ultimately, participation in paid work [70].

Some individuals may eventually end up with disability pension at a relatively young age. For some this may on one hand be a relief, but on the other hand not being able to work may have negative effects on QOL [67, 68]. Because work-related concerns are an important aspect of QOL, the clinician should stress this in his/her consultation with patients. Being too liberal with sick leave may in fact have negative consequences.

## Treatment and Quality of Life

If weight loss is maintained over time and side effects of treatment are tolerable, improvements in QOL are the norm. The amount of weight loss needed to improve QOL is about 5–10 % of total body weight [71], but this may depend on the initial severity of obesity. It has been demonstrated that in individuals with severe obesity, more weight loss is better, and the largest improvement in QOL is often seen in those who have lost >30 % of their initial weight [15].

Prospective studies have suggested that QOL is greatly improved after obesity surgery. However, after 4–5 years, small decreases in QOL are typically seen, often corresponding to some weight regain. After that QOL tends to stabilize and remain well above baseline in most patients [15, 72]. This being said, it is important to pay attention to the 20–30 % of patients who do not experience the full benefits of the obesity surgery [73]. In the long term, inadequate weight loss is often the core reason for not establishing an appropriate QOL, but also side effects and a large amount of excess skin may play a role. Again, the multidimensionality of the QOL concept also opens possibilities for other factors, i.e., social, psychological, and sexual, as barriers to QOL improvements. Accordingly, the clinician should also be aware of a small subgroup of patients who apparently seem to be very successful in terms of weight loss but who struggle to adjust to their "new life." Huge life changes can be stressful, even when they are wanted. Some patients struggle to be the person they see in the mirror. Difficulty adjusting can also manifest itself in relation to other people who suddenly behave differently than before and in relation to adopting new skills such as changes in eating or exercise behavior. These challenges must be addressed properly to maintain a good QOL [74].

Lifestyle intervention programs often lead to improvements in QOL as well, but to a lesser degree than usually seen after obesity surgery, as weight loss typically is smaller [75]. However, for many obese patients, surgery is not a viable option. Maximizing the effects of lifestyle programs on QOL improvements is important, and such programs may offer acceptable results given a long-term follow-up [76], as prevention of weight gain may also be an effective way of preventing QOL reduction [77]. Obesity has genetic, biological, psychological, social, as well as environmental components. Western society has been described as obesogenic in that there is little need for physical activity along with easy access to inexpensive, energy-dense foods [78]. These components working in combination may explain why only approximately 20 % of obese patients achieve a lasting >10 % reduction of their body weight by nonsurgical methods [11]. It is not known whether adopting a healthier lifestyle (physical activity, healthy diet, stress management, etc.), but with little or no weight loss, is effective for improving QOL in the long term. However, prevention of further weight gain in obese individuals may be a highly effective way of preventing worsening of QOL [77].

## Through Thick and Thin

Whether the clinician *really cares* is something patients are quite sensitive to, and it may have a profound effect on patient motivation and adherence to treatment [79]. We argue that being genuinely interested in the patient's QOL is one of the main components of the successful care and treatment of obesity. Good clinicians do this regularly without thinking much about it, but in our opinion it can often be done more systematically. In its most simplistic form, QOL can be assessed in a clinical setting by beginning with general open-ended questions such as "How do you feel about your life these days?" and "How do you feel about the quality of your life right now?" (Overall QOL) and include follow-up questions about relevant physical, social, sexual, and mental aspects of life.

Even if the patient does not lose any weight, data suggest that if clinicians take obese patients seriously, patients feel less stigma of obesity, as measured with the obesity problem scale [15]. Thus, to help patients to accept that they do not need to lose even 1 k to be worthwhile, people deserving of love, respect, and self-esteem may have an important resilient effect [80]. This, we believe, is the foundation of obesity treatment.

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# Part III
# Therapy of Obesity

# Chapter 16
# Behavioral and Psychological Approaches to Weight Management

**Robin A. Frutchey and Robert A. Carels**

**Abstract** Since the 1970s, behavioral weight loss approaches have been the preferred treatment for mild to moderate obesity. Patients are taught how to modify eating and exercise behaviors to meet treatment goals. Cognitive elements, such as avoidance of dichotomous thinking, reduction of negative self-talk, and improvement in coping strategies, are also emphasized. Most behavioral weight loss programs achieve a 7–10 % weight loss in 6 months. Losses of this magnitude are often sufficient to prevent or ameliorate obesity-related health concerns; however, long-term maintenance remains a significant challenge. Studies indicate that weight maintenance is associated with the continued application of behavioral modification techniques (Sarwer et al., Curr Opin Endocrinol Diabetes Obes 16(5):347–352, 2009). Initial assessment should screen for behavioral and psychological factors influencing weight control, such as eating frequency, diet quality, portion size, and activity level. Triggers, which cause the patient to eat when not hungry or to overeat, should be assessed and patients taught to avoid or manage them. Likewise, barriers to behavior change should be identified and addressed. Finally, patients should be screened for mood and/or eating disorders. Stepped-care approaches, provisions for increased patient-provider contact, and use of motivational interviewing or acceptance and commitment therapy (ACT) techniques may help improve the efficacy of behavioral interventions (Sarwer et al., Curr Opin Endocrinol Diabetes Obes 16(5):347–352, 2009; Armstrong et al., Obes Rev 12(9):709–723, 2011).

**Keywords** Behavioral • Psychological • Cognitive-behavioral • Cognitive • Weight management • Lifestyle intervention • Self-monitoring • Stepped care • Motivational interviewing • Maintenance

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**Key Points**

- Since the 1970s, behavioral weight loss approaches have been the preferred treatment for mild to moderate obesity.
- Cognitive elements, such as avoidance of dichotomous thinking, reduction of negative self-talk, and improvement in coping strategies, are also emphasized.
- Most behavioral weight loss programs achieve a 7–10 % weight loss in 6 months, which are often sufficient to prevent or ameliorate obesity-related health concerns; however, long-term maintenance remains a significant challenge.
- Studies indicate that weight maintenance is associated with the continued application of behavioral modification techniques.
- Initial assessment should screen for behavioral and psychological factors influencing weight control, such as eating frequency, diet quality, portion size, and activity level.
- Triggers that cause the patient to eat when not hungry or to overeat should be assessed and patients taught to avoid or manage them, and barriers to behavior change should be identified and addressed.
- Patients should be screened for mood and/or eating disorders.
- Stepped-care (SC) approaches, provisions for increased patient-provider contact, and use of motivational interviewing (MI) or acceptance and commitment therapy (ACT) techniques may help improve the efficacy of behavioral interventions.

## Introduction

In the USA, obesity-related health conditions contribute more than $147 billion to annual health care costs [1]. Nearly two-thirds of adults are overweight (BMI ≥ 25 kg/m$^2$) and one-third are obese (BMI ≥ 30 kg/m$^2$) [2]. Many of the chronic and life-threatening health conditions associated with obesity (e.g., diabetes) are increasingly prevalent and potentially reversible in response to weight loss [2–4].

Weight loss in the 5–10 % of total body weight range can greatly improve obesity-related morbidities. A review of short- and long-term studies evaluating the efficacy of weight loss in ameliorating disorders associated with obesity revealed that weight loss can reduce or, in some cases, reverse obesity-related disorders, such as type II diabetes, osteoarthritis pain, dyslipidemia, and blood pressure [5]. Recent large-scale clinical trials have also documented significant health benefits associated with weight loss [4, 6]. The Diabetes Prevention Program was a large multicenter clinical research investigation examining whether modest weight loss through dietary changes and increased physical activity could prevent or delay the onset of type II diabetes among participants at risk for diabetes. Participants in the weight loss intervention group reduced their risk of developing diabetes by 58 %, significantly outperforming participants taking metformin, who reduced their risk of developing diabetes by 31 % [4]. In another significant weight loss multicenter clinical research investigation entitled Look AHEAD, over 5,000 patients with type II diabetes were randomized to either an intensive lifestyle intervention or a diabetes support and education control group. The primary objective of Look AHEAD is to examine the long-term effects of an intensive lifestyle intervention program on cardiovascular outcomes (e.g., heart attack, stroke) over a planned follow-up period of up to 13.5 years. At 4 years, the intensive lifestyle intervention participants maintained greater improvements than diabetes support and education participants in weight, fitness, hemoglobin A(1c) levels, systolic blood pressure, and high-density lipoprotein cholesterol levels [6]. Finally, behavioral weight loss program participants report improvement in depression, anxiety, and body dissatisfaction following treatment [7, 8].

Since the 1970s, behavioral approaches have been the preferred treatment for mild to moderate obesity [9]. While behavioral programs vary, there is often consistency in their delivery and content. For example, it is common for behavioral programs to be delivered in small, weekly closed groups. These groups typically last between 3 months and a year with the most common length about 6 months.

Individual sessions last between 60 and 90 min and consist of a combination of didactics, individual activities, and out-of-class assignments.

Behavioral weight loss programs aim to teach participants how to modify their eating and exercise behaviors to meet the participants' weight loss treatment goals. This is usually accomplished by having patients generate (or by providing patients with) realistic weight loss goals, teaching patients to monitor their eating and exercise behaviors, and helping patients to understand the antecedents and consequences of their eating and exercise behaviors. Consistent with many behavioral-based therapies in the 1970s and 1980s, these programs evolved to emphasize cognitive elements, such as avoidance of dichotomous thinking, reduction of negative self-talk, and improvement in coping strategies, with the increased recognition that cognitive factors are key factors in treatment success [10].

Most behavioral weight loss programs achieve a 7–10 % weight loss in 6 months (e.g., [4]). However, weight regain is a problem with virtually any weight loss intervention, and behavioral programs are not immune [11]. Following behavioral weight loss, weight regain can sometimes approach one-third to one-half of the lost weight during the first 12 months, followed by gradual regain over 5 years [12]. With the inclusion of posttreatment contact or relapse prevention programs, posttreatment weight regain can be improved [13]. Data from the National Weight Control Registry (NWCR), the largest prospective investigation of long-term successful weight loss maintenance, indicate that weight maintenance is associated with the continued application of behavioral modification techniques [14].

Psychological approaches assess and treat disordered eating behavior and comorbid psychological conditions such as depression and anxiety. A recent comprehensive review affirmed the connection between obesity and depression, with evidence of a reciprocal link [15]. People who are obese may be more prone to depression because they experience themselves in poor health and are dissatisfied by their appearance, while people who are depressed may be more apt to become obese because of physiological (hormonal, immune) changes that occur in depression and because self-care is often compromised as a consequence of the condition [15]. Other studies have found connections between obesity and anxiety, post-traumatic stress disorder, bipolar disorder, and schizophrenia [16, 17]. Untreated, mood disorders tend to hinder weight management [18]; however, the integrated treatment of both psychological problems and obesity can improve both conditions [19].

Thus, initial assessment should screen for both behavioral and psychological factors influencing weight. The behavioral assessment should include questions about eating frequency, diet quality, portion size, and physical activity. The assessment should also examine antecedents or triggers which cause the patient to eat when not hungry or to overeat. Triggers might be environmental (e.g., tempting food in the home), mental (e.g., thoughts about food), emotional (e.g., eating for comfort, eating for reward), social (e.g., dining out, alcohol consumption), habitual (e.g., eating at a certain time), or physiological (e.g., poor sleep, hormones). Psychological assessment should screen for eating disorders, including bulimia nervosa, anorexia nervosa, and binge eating disorder. Additionally, the assessment should rule out depression, anxiety, post-traumatic stress disorder, attention deficit disorder, and other relevant psychological conditions. Wadden's Weight and Lifestyle Inventory (WALI) provides an efficient way to assess these variables before beginning treatment [20].

## Treatment

### *Psychological*

Should assessment reveal an underlying eating disorder such as bulimia or anorexia nervosa, it is imperative that the patient receive treatment for the condition before entering a behavioral weight loss program. Binge eating disorder and other psychological conditions, such as depression or anxiety, may be treated either before or concurrent with lifestyle intervention for weight loss. While

behavioral weight loss programs appear to benefit individuals with mild to moderate binge eating disorder, some individuals may require additional treatment before they can enter into such a program. Cognitive-behavioral treatment of eating disorders, depression, and anxiety is often effective [21–24]. Additionally, patients may benefit from psychotropic medication and/or referral to specialized mental health services. Some psychotropic medications (e.g., amitriptyline) may exacerbate weight problems, whereas others (e.g., bupropion) are more likely to be weight neutral or associated with weight loss [25].

## *Dietary Prescriptions*

Participants in behavioral weight loss programs are often given calorie, and sometimes fat gram, goals designed to produce modest and healthy weekly weight loss (1–2 lb per week). To achieve a 1–2 lb weight loss through calorie reduction, a participant is often given a calorie intake prescription based on a variety of factors, such as their current weight and level of activity. Most behavioral programs are guided by the estimate that 3,500 cal is equivalent to 1 lb of body fat. Therefore, an individual who wants to lose 1–2 lb each week would strive to create a weekly caloric deficit of 3,500–7,000 cal each week (500–1,000 cal a day deficit). Several methods can be used to determine an appropriate daily calorie goal that takes into consideration the participant's daily caloric expenditure and results in a meaningful caloric deficit. For example, one basic method is to assume that the individual consumes 12 kcal/lb to maintain their body weight. For example, a 250-lb person would be estimated to burn 3,000 cal per day (250 lb × 12 kcal/lb = 3,000 cal). If the 250-lb person wanted to lose two pounds (approximately 7,000 cal), he/she would aim to decrease their daily caloric intake by 1,000 cal (i.e., they would consume 2,000 cal a day rather than 3,000 cal a day). Alternative strategies include having participants wear devices capable of assessing daily caloric intake (e.g., pedometers, accelerometers) to provide an estimate of caloric expenditure. The caloric expenditure estimates can be used to derive meaningful caloric intake goals designed to achieve a specific caloric deficit. Other programs estimate resting metabolic rate using formulas, such as Harris-Benedict and Mifflin-St Jeor, and then add additional calories for physical activity expenditure. In the absence of formulas and accelerometers, participants can be encouraged to adhere to a calorie goal of 1,000 kcal/day for participants who weigh less than 200 lb and 1,800 kcal/day for participants who weigh more than 200 lb.

Traditional behavioral treatment (BT) programs commonly sought to achieve a specific level of caloric restriction. Advice on the macronutrient composition of the diet typically reflected published dietary standards (55–60 % cal from carbohydrates; 10–15 % cal from protein; 20–30 % cal from fat) [26], with early attention devoted to limiting dietary fat. Early emphasis on limiting dietary fat was driven by the fact that fat is more energy dense (1 g = 9 kcal) than protein and carbohydrates (1 g = 4 kcal), linked to cardiovascular disease, and overrepresented in the American diet (approximately 40 % of their calories from dietary fat) [26]. However, in the last several decades, the notion that "all calories are created equal" has been replaced with much greater concern for the macronutrient content of the diet. For example, some diets emphasize limiting carbohydrates rather than fat (Atkins diet [27]), others emphasize limiting fat rather than carbohydrates (Ornish Diet [28]), and others emphasize increasing protein [29]. In addition, recommendations to increase in the consumption of whole grains and decrease levels of added sugars have become commonplace [30]. Despite renewed interest in the macronutrient content of diets, the results from several studies indicate that no one approach to diet is clearly superior to any other [31]. What appears to be most important is adherence to whatever prescribed diet an individual is following, with greater adherence predicting greater weight loss.

## *Exercise Prescriptions*

Given that creating a negative energy balance is essential to losing weight, behavioral programs focus on both reducing energy intake and enhancing energy expenditure. Beyond enhancing weight loss and weight maintenance, regular exercise is associated with numerous physical and psychological health benefits unrelated to weight loss [32]. The CDC recommends that American adults engage in 150 min of moderate to intense physical activity each week with higher levels potentially needed to maintain weight loss [33]. It is very common for behavioral weight loss participants to be encouraged to engage in regular physical activity that they enjoy for 60–90 min a day most days of the week. These programs typically recommend increasing both lifestyle and structured exercise. For example, participants are encouraged to look for small opportunities throughout their waking hours to increase lifestyle physical activity (e.g., taking the stairs, parking further away). Regarding structured exercise, weight loss programs commonly recommend aerobic activities, particularly walking.

It is important to note that increasing exercise alone without attention to calorie restriction has been shown to produce only modest weight losses of 1–2 kg [34]. Similarly, the benefits of adding exercise to a diet program are likely to yield only modest benefits [36]. However, in the end, sustaining long-term weight loss appears to benefit from attention to both diet and exercise, compared to diet or exercise alone [34]. Research also indicates that higher exercise goals are superior to lower exercise goals in encouraging better long-term weight control [35] and that short bouts of exercise lead to better exercise adherence and are equally effective as long bouts of exercise in promoting weight loss without compromising cardiorespiratory fitness [36, 37].

## *Self-Monitoring*

Weight loss is achieved by taking in fewer calories than one expends. To achieve this goal, a foundational skill taught in behavioral programs is self-monitoring. The most common type of self-monitoring is to track progress toward calorie goals. However, some behavioral weight loss programs ask participants to track progress toward physical activity goals, and if the participant has been provided with a pedometer or accelerometer that estimates caloric expenditure, the participant is asked to report caloric expenditure and to compute their daily caloric deficit or excess. In addition, self-weighing is increasingly considered by many as an essential part of self-monitoring. Self-weighing allows participants to assess the effectiveness of their current weight loss strategies and to make corrective action if necessary. Regular self-weighing is associated with lower BMI and greater weight loss [38, 39]. Furthermore, some behavioral programs encourage participants to record thoughts and feelings during eating, exercise, dietary lapses, etc., in order to evaluate their eating behaviors to discover important antecedents to overeating or sedentary behaviors. Participants are commonly instructed to complete diaries immediately following eating and exercise to improve accuracy. The availability of smart phone, tablet, and Internet technologies provides innovative and convenient ways for participants to self-monitor both diet and exercise.

The benefits of regular self-monitoring have been well documented. In the NWCR, which include individuals who have successfully maintained a weight loss of at least 30 lb for at least 1 year, 75 % of subjects report weighing themselves more than once per week and 50 % count calories [40]. Another study that compared successful weight losers and maintainers with those unsuccessful at weight loss found that individuals who are successful plan meals more days of the week (35.9 % successful vs. 24.9 % unsuccessful), track calories (17.7 % vs. 8.8 %), track fat (16.4 % vs. 6.6 %), measure portions (15.9 % vs. 6.7 %), and weigh themselves daily (20.3 % vs. 11.0 %) [41]. Despite these benefits, the frequency of self-monitoring behaviors commonly decreases over time in weight

loss programs and is related to diminished weight loss or weight regain. For example, a study that examined predictors of weight regain 1 year following treatment found that those who gained weight decreased the frequency of self-monitoring compared to those that maintained their weight loss [42]. Therefore, efforts toward minimizing the decline in these behaviors and increasing adherence to self-monitoring may be important in achieving long-term weight loss.

## *Additional Behavioral Treatment Techniques*

*Stimulus control*. Stimulus control techniques are an effective tool for modifying eating and physical activity environments to encourage weight loss. Evidence for the impact of the food and physical activity environment on eating and sedentary behaviors is well documented [43–59]. Eating cues in the environment are numerous, ever-present, and often outside of an individual's conscious awareness [45, 47]. Food-related salience, variety, serving utensils, abundance, and convenience can dramatically influence consumption [49]. In fact, individuals are often forced to make in excess of 200 daily food-related decisions [46]. Helping an individual to modify their personal food and exercise environment in a manner that minimizes unhealthy food-related decisions and maximizes healthy food-related decisions can greatly aid weight loss.

*Goal Setting*. Research clearly demonstrates that goals can favorably enhance performance [60], including weight loss outcomes [61]. Whether the goal is a target weight loss goal or a daily calorie or exercise goal, goal setting is a common component in behavioral weight loss treatment. Larger goals can often be broken down into smaller more manageable goals which are easier to implement and monitor. Likewise, behavioral shaping procedures utilize differential reinforcement of successive approximations to bring about desired responses. For example, a participant is initially praised for switching from whole milk to 2 %; later, praise is delivered for switching from 2 % to skim milk.

*Cognitive Techniques*. Behavioral-based therapies have evolved over time to emphasize cognitive elements with the increased recognition that cognitive factors are key factors in weight loss treatment success. For example, participants may be taught to stop dichotomous thinking (e.g., I blew my diet; I'm off the program), to ban perfectionist attitudes and imperatives (e.g., I will *never* eat more than 1,200 cal a day), and to be aware of attitude traps (e.g., my life will be perfect when I lose weight; I can't wait for the program to end so I can get back to normal eating) [62]. Mindfulness-based (e.g., acceptance) and control-based (e.g., distraction and delay) techniques may be taught as a means of helping participants manage cravings or thoughts about food [63]. In addition, problem-solving techniques are often taught to patients to help them to break down more difficult or larger barriers to successful behavioral change [64].

*Social Support*. Social support has been recognized as a potentially important factor in successful weight loss. An early meta-analytic evaluation of weight loss programs that formally involved partners in treatment indicated that couple programs were superior to subject-alone programs at posttreatment and brief follow-up [65]. Support from friends and coworkers can also encourage weight loss. For example, Wing and Jeffrey [66] recruited 166 participants for a 4-month treatment to one of the four conditions (recruited alone and standard behavioral therapy; recruited alone and SBT plus social support; recruited with friends and SBT; recruited with friends and SBT plus social support). Results indicated that the social support condition with four people that signed up together or the condition where members that were recruited alone were assigned to teams were superior to the conditions that did not emphasize social support. Finally, Gorin [67] showed that not only do participants in weight loss programs lose weight, but their spouses do as well demonstrating a "ripple effect" for health benefits within a family.

*Contingencies*. One contingency management technique used to enhance motivation is incentives (usually money). A recent review evaluated studies conducted over the past 30 years that used financial incentives to promote weight loss [68]. Empirical research strongly supports the ideas that providing financial incentives for losing weight motivates people to engage in behaviors that produce weight loss, particularly when participants are required to provide a deposit (e.g., $150) that they can potentially earn back.

*Habit Formation and Disruption*. A number of health behaviors are independently predicted by the degree to which a behavior is habitually performed, even after controlling for important variables, such as the intention to perform the behavior [69]. Habits are behavioral tendencies to repeat well-practiced acts in response to stable environmental cues [69]. Therefore, as behaviors become habitual, the likelihood of regularly performing them increases. Once habits are developed, an individual can forgo a laborious, rational, contemplative decision in favor of a quick, automatic, and effortless habitual response to engage in healthy behavior [70]. A recent weight loss treatment program that taught environmental modification, health habit formation, and unhealthy habit disruption demonstrated superior weight loss maintenance when compared to a more traditional weight loss program [71].

*Self-Care*. Behavioral interventions targeting self-care focus on improving sleep hygiene, time management, and stress management. Sleep and stress are closely and reciprocally linked. In addition, both sleep and stress appear to affect weight. One recent study, involving a 6-month behavioral weight loss intervention, found that lower baseline stress levels and longer sleep duration predicted greater weight loss over the course of the intervention [72].

Time management techniques (e.g., planning, prioritization, scheduling) involve improving self-regulation and can help reduce stress and make time for health-promoting activities, such as meal preparation and physical activity.

Both emotional stress (e.g., interpersonal conflict, job-related concerns) and physiological stress (e.g., insomnia, illness, injury) often result in weight gain and/or make it difficult for overweight individuals to make the lifestyle changes necessary for weight loss/management. Indeed, researchers have consistently found an association between stress and obesity [73]. There is evidence that stress-mediated hormonal changes (i.e., cortisol, ghrelin) may impact appetite, cravings, and metabolism [74]. Stress is also linked to potentially adverse effects on eating patterns (e.g., skipping meals, binging) and food preference [75]. Stress management interventions include training in cognitive restructuring techniques, mindfulness/acceptance techniques, relaxation training, assertiveness training, and problem solving.

A recent pilot randomized controlled trial examined the effects of a stress management-augmented lifestyle intervention for weight management, compared to a lifestyle intervention alone in overweight/obese African American women. The results suggested that the addition of stress management components to a behavioral weight control intervention may be beneficial for overweight/obese AA women with moderate to high stress levels [76].

*Relapse Prevention*. Given the high rates of dietary relapse following weight loss, researchers have attempted to provide relapse prevention training to improve long-term weight loss maintenance. Based on models, such as Marlatt and Gordon's relapse prevention model [77], weight loss researchers have attempted to help participants to identify situations with high risk for a dietary lapse and to teach coping skills to successfully cope with the relapse crisis. While some studies show that providing participants with training in relapse prevention is beneficial [78], a more recent clinical trial comparing two extended therapy programs (relapse prevention training, problem-solving therapy) for weight management with standard behavioral treatment (BT) without additional therapy contacts failed to show improved long-term outcomes with the extended therapies [79].

### *Treatment Advances*

*Motivational Interviewing*. Emerging research suggests that motivational interviewing (MI), a patient-centered directive approach to counseling for behavior change, can be a beneficial adjunct to standard multicomponent behavioral intervention. The goal of this empathic and collaborative form of counseling is to strengthen patient autonomy, improve self-efficacy, and increase readiness to change by helping patients identify and strengthen personally relevant reasons for change [80]. MI also seeks to help patients better understand and resolve ambivalence about change, often via identification of barriers to change and problem solving. MI techniques were first developed and tested in the context of substance abuse [81] but have since been adapted for use with a number of health-related behaviors. A recent meta-analysis of 11 studies examining the effect of MI on weight management found that MI was associated with a greater reduction in BMI and body weight, as compared to controls. The conclusion was that MI appears to enhance weight loss in overweight and obese patients [82].

*Mindfulness/ACT*. Mindfulness and ACT have received increased attention as promising techniques to improve long-term weight loss outcomes. Mindfulness-based interventions, which encourage non-judgmental acceptance of experience, are gaining increasing empirical support in the area of eating disorders [83]. Similarly, ACT which uses acceptance and mindfulness strategies together with commitment and behavior change strategies has also shown promise. Two small pilot treatment outcome studies suggest that ACT approaches are feasible to implement and well accepted by participants and may contribute to improved long-term weight loss maintenance [84, 85].

*Stepped-Care Approaches*. Given the scope of the obesity epidemic, the chronic nature of the condition, and the cost of professional care for obesity-related diseases, many researchers suggest that cost-effective, time-efficient, and minimally intrusive treatments are greatly needed [86]. Applying a stepped-care (SC) approach to the treatment of obesity represents one effort to efficiently allocate treatment resources. In a SC approach to treatment, patients are transitioned (stepped-up) to more intensive treatment when they are unable to meet treatment goals with less intensive treatment [87, 88]. SC approaches have been developed for a variety of conditions, including weight management [88–94]. While stepped-care approaches are generally successful in aiding weight loss [93, 94] they have, at times, produced mixed findings [95, 96]. For example, in the largest weight loss, stepped-care, randomized clinical trial to date (i.e., Step-Up Study), a standard behavioral weight loss intervention was compared to a stepped-care weight loss intervention. Even though the stepped-care intervention was more cost-effective, weight loss outcomes favored the standard behavioral weight loss intervention [95].

## Conclusion

Comprehensive psychological and behavioral treatment for obesity is generally effective in bringing about and maintaining modest, yet clinically significant losses of approximately 10 % of pre-intervention weight. Losses of this magnitude are sufficient to prevent or ameliorate obesity-related health concerns, such as hypertension, hyperlipidemia, and/or type II diabetes. However, long-term maintenance remains a significant challenge. Stepped-care approaches, provisions for increased patient-provider contact (either through in-person visits or telephone, text, or email communication), and use of motivational interviewing or ACT techniques may help improve the efficacy of behavioral interventions [14, 82].

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# Chapter 17
# Physical Activity for Obesity

**Jill M. Maples and Joseph A. Houmard**

**Abstract** The use of exercise training, either aerobic- or resistance-oriented, is a common intervention for inducing weight loss as well as positively manipulating the cardio metabolic risk factors prevalent with obesity. However, it is important to realize that aerobic exercise training alone does not induce substantial weight loss unless coupled with energy restriction via dietary manipulation. Resistance training can also increase daily energy expenditure, increase muscle mass, and reduce fat mass although changes in overall body mass may also be minimal. However, although exercise alone does not appear to contribute substantially to weight loss, any type of exercise appears to be a critical component of maintaining a lowered body mass after weight loss. The current state of knowledge indicates that weight loss/weight maintenance programs should incorporate both exercise and dietary interventions for optimal results and any degree of exercise is preferred over a sedentary lifestyle.

**Keywords** Aerobic exercise • Cardiovascular risk factors • Diabetes • Diet • Obesity • Resistance training • Weight loss

### Key Points

- The use of exercise training, either aerobic- or resistance-oriented, is a common intervention for inducing weight loss as well as positively manipulating the cardio metabolic risk factors prevalent with obesity.
- It is important to realize that aerobic exercise training alone does not induce substantial weight loss unless coupled with energy restriction via dietary manipulation.
- Resistance training can also increase daily energy expenditure, increase muscle mass, and reduce fat mass although changes in overall body mass may also be minimal.

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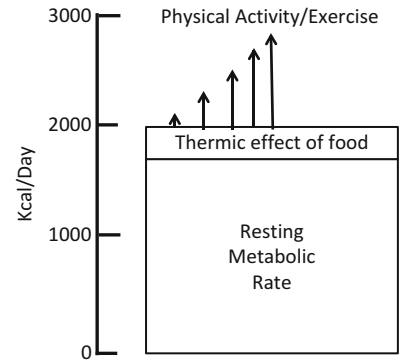


**Fig. 17.1** Components of energy expenditure indicating that physical activity/exercise can increase energy expenditure in proportion to exercise volume and intensity. (Adapted from Donnelly et al. [6])

- Although exercise alone does not appear to contribute substantially to weight loss, any type of exercise appears to be a critical component of maintaining a lowered body mass after weight loss.
- The current state of knowledge indicates that weight loss/weight maintenance programs should incorporate both exercise and dietary interventions for optimal results and any degree of exercise is preferred over a sedentary lifestyle.

## Introduction

Obesity is the result of energy intake exceeding energy expenditure and an ensuing accumulation of fat mass. To induce weight loss and reverse obesity, energy expenditure must exceed energy intake. Perhaps the most common clinical treatment to induce negative energy balance is restricting energy intake by dieting. This intervention, however, has a high rate of weight recidivism with at least 50 % of individuals regaining the initial loss in body mass [8]. The primary components of the energy expenditure side of the equation are resting metabolic rate, the thermic effect of food, and physical activity; of these, it is the energy expended upon physical activity that is under conscious control and can be manipulated by lifestyle interventions (Fig. 17.1). The intent of this chapter is to examine the role of structured exercise training programs in inducing weight loss in obese individuals.

## Aerobic Exercise Training

In this section the term "aerobic" exercise training will be used to encompass endurance-oriented exercise modalities such as walking, running, elliptical trainers, swimming, or cycling. The majority of research examining the relationship between weight loss and exercise training has utilized aerobic-oriented exercise for several reasons including (1) the ability to quantify energy expenditure during these exercise modes via indirect calorimetry, (2) the ability to utilize regression equations to provide global recommendations such as heart rate ranges to approximate exercise intensities and caloric expenditure when formulating exercise prescriptions, and (3) the ability of aerobic training modalities such as walking to be implemented widely in the general population due to low incidence of injury as well as a minimal requirement for equipment and/or clothing to perform the exercise. Many of the studies examining the relationship between aerobic exercise and weight loss have been summarized in comprehensive reviews such as the Physical Activity Guidelines for Americans (US Department of Health and Human Services 2008) and the American College of Sports Medicine (ACSM) Appropriate Physical Activity Intervention Strategies for Weight Loss and the Prevention of Weight Regain for Adults [5].

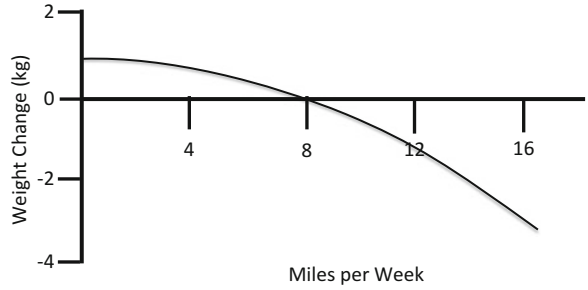


**Fig. 17.2** Relationship between the amount of exercise per week (walking/jogging) and the body weight change. Performing an equivalent of 8 miles/wk would promote weight maintenance while a sedentary lifestyle results in progressive weight gain. (Adapted from Slentz et al. [30])

The following information will attempt to provide information that is relevant for the clinician in terms of utilizing aerobic exercise for inducing weight loss and subsequently promoting weight maintenance.

One strategy for inducing negative energy balance would be to keep energy intake (diet) constant and increase energy expenditure by aerobic exercise. Findings from studies which did not prescribe changes in diet but increased the level of physical activity are summarized in the Physical Activity Guidelines [37]. The data indicate that physical activity performed at an intensity approximating brisk walking (moderate-to-vigorous intensity) for ~150 min/wk produced a fairly minimal loss in body mass (1–3 %). In support of a small effect on body mass with this exercise dosage, the ACSM Position Stand [5] addressing physical activity strategies for weight loss concluded that incorporating less than 150 min of moderate-intensity aerobic activity per week had a negligible effect on body mass when dietary intake was not altered. Suggestive of a dose–response relationship, exercise encompassing 150 or more minutes per week produced weight loss of 2–3 kg whereas performance of 225–420 min/wk resulted in 5–7.5 kg of weight loss when there were no adjustments to dietary intake [5].

Other data are also indicative of a dose–response relationship between the exercise volume and the magnitude of weight loss. The Studies of Targeted Risk Reduction Interventions through Defined Exercise (STRRIDE) examined the effects of different amounts and intensities of 8 months of exercise training without dietary alteration on body composition as well as other factors linked with metabolic disease risk [30]. The subjects examined were middle-aged, overweight-to-obese individuals with insulin resistance and dyslipidemia who were randomized to (1) a control group which remained sedentary, (2) a low-amount/moderate-intensity exercise group which walked (~50 % $VO_2$peak) an equivalent of 12 miles/wk or ~170 min/wk of exercise, (3) a low-amount/vigorous-intensity exercise group which jogged (~75 % $VO_2$peak) 12 miles/wk or ~114 min/wk of exercise, and (4) a high-amount/vigorous-intensity exercise group which jogged (~75 % $VO_2$peak) 20 miles/wk for ~167 min/wk of activity. This design permitted a comparison between groups 2 and 3 to determine the effect of exercise intensity and groups 3 and 4 to determine whether there was a dose–response effect. Additionally, comparison of groups 2 and 4 versus group 3 permitted determination of the impact of exercise duration (min/wk).

In the STRRIDE study one of the more intriguing findings involved the “control” group; rather than remain in a relatively steady state as anticipated, the sedentary lifestyle of the control group resulted in a gain of ~1 kg after only 6 months (Fig. 17.2). This increment corresponded to a weight gain of ~2 % of body mass per year indicating that an inactive lifestyle leads to positive energy balance and gradual weight gain which subsequently places sedentary individuals at an increased risk for negative health consequences and obesity. In agreement, this relatively small gain in body mass induced physiological changes in a manner indicative of increased risk for cardiometabolic disease and reduced cardiorespiratory fitness (Table 17.1). In contrast, with exercise training there was modest weight loss ranging from means of ~1 kg (low-amount groups or ~12 miles/wk of moderate- to

**Table 17.1** Effects of a physically inactive lifestyle on variables linked with disease and cardiorespiratory fitness

| | | |
|---|---|---|
| ↑ Body mass | ↑ Central adiposity | ↑ LDL particle number |
| ↑ Waist girth | ↑ Fasting insulin | ↑Small dense LDL |
| ↑ Waist/hip ratio | ↓ Insulin sensitivity | ↓ HDL size |
| ↑ Visceral fat amount | ↓ Fitness | ↑ LDL cholesterol |

Results summarized from Slentz et al. [29]

vigorous-intensity exercise, 114–170 min/wk) to ~3 kg (high-amount group or ~20 miles/wk of vigorous-intensity exercise, 167 min/wk). When extrapolating these data, the investigators could predict that the equivalent of ~8 miles/wk of walking/jogging was needed for weight maintenance (Fig. 17.2). As the majority of the US population are highly sedentary and do not approach this minimum, it is easy to deduce how physical inactivity contributes to the high prevalence of overweight/obesity. Thus, in relation to body mass, the STRRIDE data are supportive of recommendations from a consensus statement from ACSM and the Centers for Disease Control and Prevention that a minimum of 30 min/day of moderate-intensity physical activity should be performed on most, if not all, days of the week for the maintenance of health and weight loss [25]. Correspondingly, additional amounts of physical activity likely result in additional weight loss in a dose–response manner (Fig. 17.2). The STRRIDE data is somewhat in conflict with the recommendations of the Institute of Medicine recommendation that 60 min of moderate-intensity physical activity per day is needed to prevent weight gain [16].

The modest weight loss evident with exercise training is often less than what would be predicted based upon the energy expenditure of the exercise itself. To address this issue, Thomas et al. [33] systematically reviewed 15 studies that measured exercise-induced changes in body composition. When calculating energy balance, it was found that the majority of the exercise studies induced a negative energy balance of <500 kcal/day, whereas a 500 kcal/d or greater deficit is the magnitude of energy imbalance utilized in caloric restriction studies which induce weight loss. There was no evidence indicating a reduction in resting metabolic rate in obese individuals with exercise training. The authors [33] concluded that the small magnitude of weight loss observed with aerobic exercise training alone is primarily due to low doses of exercise and thus low energy expenditure along with a reciprocal increase in energy intake. An increase in energy intake with exercise training is a common observation which unfortunately compromises the degree of weight loss. Therefore clinicians should keep in mind that the provided exercise prescription must be substantial enough to produce appropriate negative energy balance if weight loss is desired and that the amount of energy expenditure on exercise is frequently overestimated. Additionally, clinicians should be aware that patients may tend to increase energy intake in response to aerobic exercise training.

While the effects of aerobic-oriented exercise training with no dietary alterations on weight loss are minimal, the ability of this intervention to positively manipulate risk factors for the cardio metabolic disease prevalent with obesity is of little doubt. As indicated in the Surgeon General's landmark summary on Physical Activity and Health [36], significant health benefits can be obtained by including as little as 30 min of brisk walking on most, if not all, days of the week. More specifically, this level of activity reduces the risk of coronary heart disease, hypertension, colon cancer, and type 2 diabetes. Similarly, relatively modest increases in exercise volume which lead to a small amount of weight loss (3–4 kg over 1 year) virtually prevented the progression from impaired glucose tolerance to type 2 diabetes in obese individuals [22, 35]. A variety of other health benefits have been summarized elsewhere [6, 19]. Briefly, aerobic exercise elicits a 30–50 % reduction in the risk of developing hypertension and on average a 7/6 mmHg (systolic/diastolic) reduction in hypertensive individuals and a 3/2 (systolic/diastolic) reduction in normotensive individuals [6]. These reductions in blood pressure are a product of both the chronic effects of exercise training and the acute effects from the

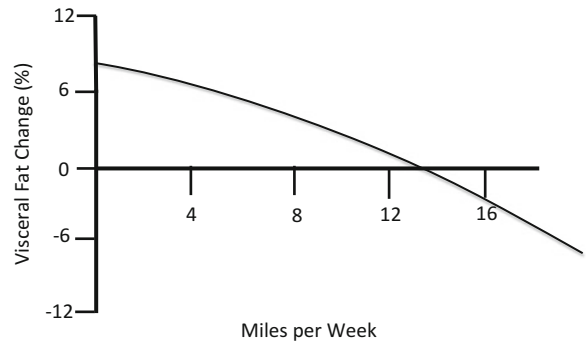


**Fig. 17.3** Relationship between the amount of exercise per week and the change in visceral adipose tissue mass. Performing an equivalent of approximately 12 miles/wk would promote maintenance of visceral fat mass while a sedentary lifestyle results in progressive visceral fat mass gain. (Adapted from Slentz et al. [30])

last exercise bout which persist up to 22 h after training has ceased. Aerobic training also has a small but important effect on plasma lipoproteins by increasing HDL content (+5 %) and reducing LDL and triglyceride concentration (−4–5 %) [6].

Another experimental strategy to determine the effects of exercise alone independent of weight loss is to utilize relatively acute, vigorous-intensity aerobic exercise training protocols (i.e., 60 min of exercise per day over 7–10 consecutive days) as weight loss is minimal as energy utilized by the exercise can be easily replaced by additional energy intake. Using this acute aerobic training model, insulin action has been demonstrated to improve without weight loss in insulin-resistant populations such as the severely obese (BMI >40 kg/m$^2$) [12] and obese, middle- to older-aged men [2]. In men with type 2 diabetes or impaired glucose tolerance, 7 days of vigorous aerobic exercise significantly improved glucose tolerance to the extent that mean values indicated a resolution of the diabetes [27]. Together, these findings indicate the efficacy of exercise alone, without weight loss, for treating many of the risk factors prevalent with the obese condition.

The volume of visceral adipose tissue (VAT) is more highly related to risk factors such as plasma triglycerides and insulin action than total body fat mass [30]. In the STRRIDE study, the inactive control group significantly increased VAT content; in contrast, there was no change in visceral adiposity in the low-volume exercise training groups (avg. of 114 or 170 min/wk) and a significant and sizeable decrease in VAT with high-volume/vigorous-intensity aerobic training (167 min/wk of jogging). These and other data (for a review, see [30]) indicate that there is also a dose–response relationship between VAT change and exercise volume. As VAT is more so related to disease risk and is malleable with exercise, it may be prudent for the clinician/patient to monitor anthropometric variables indicative of VAT such as waist girth or sagittal diameter in addition to body mass. However, it is important to note that VAT gain appears to be conducive with a sedentary lifestyle and that a higher weekly exercise volume (approximately 12 miles/wk) (Fig. 17.3) is needed to maintain/not accumulate VAT [30].

Whereas exercise alone does not regularly induce substantial weight loss, the combination of exercise and dietary restriction is effective in reducing body mass in overweight and obese adults [19]. A review by Curioni and Lourenco [4] concluded that the combination of exercise and dietary restriction resulted in a weight loss 20 % greater than dietary restriction alone. For example, Goodpaster et al. [9] reported that weight loss after 6 months of an energy-restricted diet was 8.2 kg which improved by 25 % to 10.9 kg when exercise was included. The additional weight loss was physiologically relevant as both the hepatic fat content and the degree of VAT (waist circumference) were reduced. Therefore, the combination of aerobic exercise training and dietary restriction should be considered when treating obesity.

If the desired magnitude of weight loss is reached with the use of either diet or exercise, it then becomes important to design a treatment which results in energy balance in order to achieve long-term weight maintenance. When considering aerobic exercise in the treatment of the obese state, perhaps the most effective use of this intervention is in maintaining long-term weight loss. For example, the 2009 ACSM Position Paper [5] concluded that more than 250 min of exercise per week was an

important factor contributing to the maintenance of lost weight. In 2002 the US Institute of Medicine [16] recommended that individuals should accumulate 60 min/day (420 min/wk) of moderate-intensity exercise for weight maintenance. In 2003 the International Association for the Study of Obesity recommended that 60–90 min of moderate-intensity exercise (420–630 min/wk) be performed to prevent weight regain in obese individuals that had lost weight [28]. These recommendations indicate that the amount of energy expended through exercise needed to maintain body mass is extensive and requires a substantial time commitment which may be unachievable for many individuals. Thus, it seems logical to also implement a dietary plan which ensures energy intake at a level to maintain weight; also, it may be effective to break up the exercise pattern into 10–15 min bouts during the course of the day with the goal of achieving 60 min/day. Indeed, when compared to continuous exercise sessions, intermittent exercise appears to result in similar weight loss or weight maintenance [6].

The National Weight Control Registry (NWCR) is a database of the characteristics of individuals that have lost 30 lbs and maintained this weight loss for greater than 1 year. In support of the concept that weight maintenance requires a substantial commitment to exercise is the observation that individuals in the registry are extremely physically active [21]. For example, individuals in the NWCR report expending approximately 2,800 kcal/wk on exercise, which is equivalent to walking/jogging 28 miles/wk. Thus, losing and maintaining weight loss appears to require an active lifestyle to ensure success.

Aerobic exercise contributes to increasing energy demand by several mechanisms. In typical individuals, energy expenditure during the exercise bout can reach levels 8–10 times greater than resting metabolic rate; highly trained endurance athletes attain exercise intensities which result in energy use up to 15 times greater than resting metabolic rate [6]. The commonly used prescription of 30 min/day of moderate-intensity aerobic exercise would result in an energy consumption of approximately 150 kcal (sedentary individual walking) or up to 400 kcal (jogging/running at 7.5 min per mile pace) [6]. An intense and prolonged exercise bout can also increase energy expenditure for 1–3 h after the exercise bout; however, there is no conclusive data indicating that this is a major factor which increases total daily energy expenditure. The ability of aerobic exercise training to increase resting metabolic rate is controversial with some studies indicating an increase while others indicate no change [6].

As indicated by the information provided in this chapter, aerobic exercise should be considered when treating the obese condition. However, aerobic-oriented endurance training does provide some risks that can be minimized with proper considerations. As cardiovascular disease is at an increased prevalence in obese individuals, adequate prescreening should be performed as indicated in accepted guidelines [34]. For example, a medical examination and graded exercise stress test should be performed in individuals who are symptomatic or have known cardiac, pulmonary, or metabolic disease prior to initiating an exercise program. However, this degree of prescreening is not needed if an individual is asymptomatic and has one or less cardiovascular disease risk factors. Generally, exercise participants should follow the guideline that inactive men over 40 years of age and women over age 50 and individuals at high risk for cardiovascular disease should consult their physician before initiating unaccustomed exercise training. As cardiovascular fitness is frequently compromised in obese individuals, the exercise prescription should be ramped from low-intensity exercise for a relatively short duration to more moderate- or vigorous-intensity exercise for a longer duration over weeks and months in an attempt to enhance adherence, minimize musculoskeletal injury, and make the exercise more tolerable. The likelihood of musculoskeletal injury due to solely participation in an exercise program is relatively low and decreases with weight loss [19].

While aerobic exercise is obviously an effective and practical treatment for obesity, long-term adherence is low. One of the challenges to the clinician and the health care society is to design and implement behavioral strategies that promote the performance of regular exercise. Overcoming barriers such as a lack of motivation and lack of time appears to be critical for promoting exercise adherence [20]. Thus, in an attempt to implement an effective exercise program, clinicians should first assess potential barriers and attempt to provide realistic methods for overcoming such barriers.

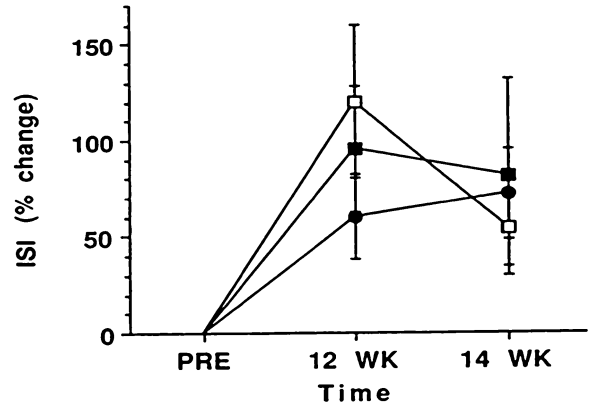


**Fig. 17.4** The effect of regularly performed exercise training (4 days/wk, 45 min/day for 3 months) (pre to 12 week) followed by a 2-week period of either (1) (*open square*) training cessation; (2) (*filled square*) 50 % reduction in training volume (2 day/wk, 45 min/day); (3) (*filled circle*) maintained training on insulin sensitivity (ISI, insulin sensitivity index derived from an intravenous glucose tolerance test). Insulin sensitivity significantly increased with the 12 weeks of training in all groups and declined significantly after 2 weeks of training cessation. (Adapted from Houmard et al. [14])

Promoting the ability of the individual to complete tasks and reach goals (self-efficacy) in the exercise program also appears to be one of the best predictors of adherence to an exercise/weight loss program as well as engaging with others which provide a positive influence and encouragement [19]. Initially breaking up the exercise sessions into intermittent bouts performed at several times during the day may also aid in adherence as the obese individual develops exercise tolerance [6]. One of the key elements of successful weight loss is self-monitoring via record keeping in an exercise and/or food intake diary. The diary should then be shared with a health care professional to insure that behaviors follow recommended guidelines.

An additional method for inducing long-term adherence to aerobic exercise may involve inserting periodic periods of active rest which can maintain the health benefits/weight loss accrued from training yet allow a brief respite from the mental and physical burden of a consistent exercise prescription. For example, our laboratory examined the effects of a 12-day, 50 % reduction in training volume (from 45 min/4 day/wk to 2 day/wk) compared to 2 weeks of no training and sustained training (45 min/day for 4 day/wk) on insulin action in middle-aged, overweight-to-obese individuals that had been exercise training for the previous 12 weeks [14]. The total cessation of training resulted in the return of insulin action to sedentary, pre-training values while the additional 2 weeks of regular training provided no additional benefit to that evident after 12 weeks (Fig. 17.4). The novel finding of this study [14] was that insulin action was also maintained at trained levels after 2 weeks of a 50 % reduction in training volume (Fig. 17.4). Such findings indicate that training volume can be reduced for relatively short periods of time (i.e. 2 weeks) without negative consequences on an important index of health risk, insulin sensitivity. Such findings suggest that exercisers should consider reducing training volume for acute periods of time to deal with mental fatigue, minor injuries, sickness, adverse weather conditions, travel/vacations, and so forth.

While structured exercise programs are an important component of weight loss and the maintenance of weight loss, other more nonstructured physical activity can also contribute to increasing daily energy demand. For example, physical activities such as taking the stairs rather than an elevator or parking farther away from the desired destination can increase daily caloric expenditure. It has been estimated that walking approximately 2,000 steps is the equivalent to walking 1 mile and that the addition of 3,000–4,000 steps (1.5–2 miles) per day in normal sedentary individuals would result in the attainment of the suitable level of 30 min of physical activity per day [19]. Monitoring step count is also relatively simple and inexpensive with pedometers and increasing daily physical activity

via these means provides quickly attainable and positive feedback. Studies have shown that increasing step count by 2,100 steps per day can decrease BMI but by a very small amount (0.38 kg/m$^2$) [5]. Thus, an effective strategy for weight loss/maintenance would be to combine lifestyle changes such as increasing steps taken per day with more structured exercise and appropriate alterations in dietary intake.

## Resistance Training

Most research concerning the role of physical activity and exercise in the treatment of obesity has focused on aerobic activity. Relative to aerobic activity of the same duration, resistance training is associated with lower energy expenditure. In theory, resistance training could be an effective weight loss treatment as it increases lean muscle mass which could in turn elicit an overall increase in daily energy expenditure. Because the development of obesity is associated with energy imbalance increasing energy expenditure, in particular resting energy expenditure which accounts for the largest portion of total daily energy expenditure (Fig. 17.1), could be beneficial for fat loss [39, 42]. However, there are mixed findings concerning the role of resistance training in increasing resting energy expenditure and whether or not this increase in metabolic activity corresponds with weight loss.

Several studies have reported that resistance training increases resting metabolic rate [10, 11, 23, 32], while others have found no increase in resting energy expenditure as a result of strength training [1, 3, 15, 38]. For example, a study by Broeder et al. [1] found that 12 weeks of resistance training had no increase in the average resting metabolic rate among almost 50 young and middle-aged men. In contrast, a study by Lemmer et al. [23] found that 24 weeks of strength training increased resting metabolic rate by 7 %. However, there appear to be gender differences in the metabolic responses to strength training. The significant increase in resting metabolic rate observed by Lemmer et al. [23] seemed to be driven mostly by the male participants. In fact, when the increase in resting metabolic rate was corrected for fat-free mass, the significant increase in resting metabolic rate in response to strength training among women was no longer significant, which is consistent with other findings [3, 15].

The majority of reports describing the effect that resistance training has on fat mass indicate that resistance training does indeed reduce total fat mass and improve body composition [3, 13]. However these improvements typically are not associated with overall weight loss and, in some instances, resistance training causes an increase in total body mass [41]. Improvements in body composition seen with resistance training are due to increases in lean mass and decreases in fat mass. Of particular importance is the tendency for resistance training to reduce visceral fat, which is highly associated with metabolic disease [30] and is an independent predictor of several adverse health effects including elevated blood pressure, heart disease, and insulin resistance [17].

Despite a lack of evidence indicating that resistance training is linked with weight loss, recent guidelines on physical activity and exercise for the treatment of obesity have suggested that the inclusion of resistance training could be beneficial [18, 40]. For example, there is substantial evidence indicating that resistance training can positively affect risk factors evident with obesity [32, 39, 40]. Based on such findings, the American Heart Association states resistance training should be used as a complement to aerobic exercise for reducing the risk for cardiovascular disease [40]. Several studies indicate that resistance training can result in a more favorable metabolic profile, including increasing insulin sensitivity [24, 31] and HDL while lowering total cholesterol and triglycerides [7, 26], especially in older adults.

In summary, resistance training does not appear to be effective for inducing weight loss. Resistance training has been shown to positively influence body composition by decreasing fat mass and increasing lean mass and is associated with an increase in resting energy expenditure in men.

Despite the lack of evidence indicating resistance training is an effective tool to lose total body weight, there is substantial evidence that resistance training has numerous health benefits and reduces the risk of obesity-related comorbidities.

## Summary

Obesity is a condition where fat mass accumulates due to positive energy balance. To reduce fat mass, negative energy balance must be induced, which can be accomplished by increasing energy expenditure through exercise. However, the volume of exercise which induces or maintains weight loss is substantial and typically exceeds recommendations made for maintaining health. Thus, any weight loss/weight maintenance program should incorporate both exercise and dietary interventions for optimal results. However, it is important to acknowledge that both aerobic- and resistance-oriented exercise training consistently reduce the risk for cardiovascular and metabolic disease evident with obesity despite minimal weight loss. Thus, incorporation of exercise into the treatment plan for obesity is recommended and any degree of exercise is preferred over a sedentary lifestyle.

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# Chapter 18
# Pharmacotherapy for Obesity

**Giuseppe Derosa and Pamela Maffioli**

**Abstract** The current recommendations for the treatment of obese people include increased physical activity and reduced calories intake; when the behavioral approach is not sufficient, a pharmacologic treatment is recommended. In the past years, a number of medications have been approved for the treatment of obesity, but many of them have been withdrawn from the market because of their adverse effects. Actually only orlistat is available for use in Europe, because amphetamines, rimonabant, and sibutramine licenses have been withdrawn due to lack of efficacy leading to an unfavorable benefit/risk ratio linked to amphetamines; psychiatric disorders, especially depression, linked to rimonabant; and an increased risk of nonfatal myocardial infarction or stroke linked to sibutramine.

Recently FDA approved two new drugs for the treatment of obesity: the first one was lorcaserin and the second one was phentermine/topiramate extended-release combination. Both these newly approved drugs seem promising and safe also in type 2 diabetic patients; however, long-term studies are ongoing to evaluate their cardiovascular safety.

**Keywords** Amphetamines • Exenatide • Lorcaserin • Obesity • Orlistat • Phentermine and topiramate extended-release

### Key Points

- The current recommendations for the treatment of obese people include increased physical activity and reduced calories intake; when the behavioral approach is not sufficient, a pharmacologic treatment is recommended.
- Though not a first line of treatment, if a person has failed other dietary attempts and is deemed medically appropriate, appetite-suppressing or fat-blocking prescription medications may be used to facilitate weight loss.
- In the past years, a number of medications have been approved for the treatment of obesity, but many of them have been withdrawn from the market because of their adverse effects.
- At the time of this writing, there are 4 FDA-approved medications: orlistat (Xenical), phentermine, lorcaserin (Belviq), and the combination of phentermine and topiramate (Qsymia).
- Only orlistat is available for use in Europe, because amphetamines, rimonabant, and sibutramine licenses have been withdrawn due to lack of efficacy leading to an unfavorable benefit/risk ratio

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linked to amphetamines; psychiatric disorders, especially depression, linked to rimonabant; and an increased risk of nonfatal myocardial infarction or stroke linked to sibutramine.
- Recently the FDA approved two new drugs for the treatment of obesity, lorcaserin and the extended-release combination phentermine/topiramate, both of which seem promising and safe in type 2 diabetic patients as well; however, studies are ongoing to evaluate their cardiovascular safety.

## Introduction

Obesity, defined as a body mass index (BMI) of $\geq$30 kg/m$^2$, has reached epidemic proportions worldwide, with an estimated 97 million adults in the United States overweight or obese [1]. Based on 2005 World Health Organization estimates, approximately 1.6 billion adults are overweight and at least 400 million are obese, and the obesity rate is predicted to increase by 75 % to 700 million by 2015. Obesity substantially raises the risk of morbidity from dyslipidemia [2], type 2 diabetes mellitus [3], fatty liver [4], coronary heart disease and stroke [5], hypertension, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and endometrial, breast, prostate, and colon cancers [6]. The current recommendations for the treatment of overweight and obese people include increased physical activity and reduced calorie intake [7, 8]. When the behavioral approach is not sufficient to get the optimal target of weight and metabolic control, a pharmacologic treatment is needed [9].

Usually weight loss medications are recommended for patients with a BMI $\geq$ 30 kg/m$^2$, as well as for those with a BMI $\geq$ 27 kg/m$^2$ and a weight-related comorbidity [10].

## History of Antiobesity Drugs

Between the 1930s and the present, more than a half dozen drugs were widely prescribed to obese patients, then later removed from the market due to the serious adverse events. The first attempt to develop an antiobesity drug can be dated to the 1800 s, when, based on its effectiveness for hypothyroidism, thyroid hormone became a popular treatment for obesity in euthyroid people. It had a modest effect, but produced the symptoms of hyperthyroidism as a side effect, such as palpitations and difficulty sleeping. Dinitrophenol was introduced in 1933; this worked by uncoupling the biological process of oxidative phosphorylation in mitochondria, causing them to produce heat instead of ATP. The most significant side effect was a sensation of warmth, frequently with sweating. Overdose, although rare, led to a rise in body temperature and, ultimately, fatal hyperthermia. By the end of 1938, dinitrophenol had fallen out of use, because the Food and Drugs Administration (FDA) became empowered to put pressure on manufacturers, who voluntarily withdrew it from the market [1]. Amphetamines became popular for weight loss during the late 1930s as a short-term treatment of obesity ($\leq$12 weeks). They worked primarily by suppressing appetite and had other beneficial effects such as increased alertness. Unfortunately amphetamines elevate cardiac output and blood pressure making it dangerous for use by patients with a history of heart disease or hypertension. Moreover, tolerance was developed rapidly; therefore, periods of extended use required increasing amounts of the drug in order to achieve the same effect. Abuse of amphetamines can result in a stimulant psychosis that can present as a number of psychotic disorders. For all these reasons, and the adding risk of serious adverse events, such as pulmonary hypertension, amphetamines were withdrawn from the European market in 1979, while they were maintained in America. In 1967/1968, a number of deaths attributed to diet pills triggered a senate investigation and the gradual implementation of greater restrictions on the market. This culminated with the FDA banning the use of amphetamines in diet pills [11]. Meanwhile, phentermine was approved by FDA in 1959; phentermine is an amphetamine analog stimulant approved for short-term use because of the lack of long-term clinical trials; this drug acts as sympathomimetic agents. Lately fenfluramine became available in 1973. Dexfenfluramine was developed in

the mid-1990s as an alternative to fenfluramine with less side effects and received regulatory approval in 1996. These drugs bind to the serotonin reuptake pump, causing inhibition of serotonin uptake and release of serotonin. The increased levels of serotonin lead to greater serotonin receptor activation which in turn leads to enhancement of serotoninergic transmission in the centers of feeding behavior located in the hypothalamus. This suppresses the appetite for carbohydrates. These drugs were no more popular than other drugs until a researcher reported that the association of phentermine with fenfluramine or dexfenfluramine caused a 10 % weight loss which was maintained for more than 2 years [11]. An association of the two drugs was created and rapidly became the most commonly prescribed diet medication; however, this coincided with mounting evidence that the combination could cause valvular heart disease in up to 30 % of those who had taken it, leading to withdrawal of fenfluramine and dexfenfluramine from the market in September 1997, while the FDA did not ask manufacturers to remove phentermine from the market; phentermine is still available by itself in most countries [12]. In 1997 sibutramine (5, 10, 15 mg) was approved by FDA for the management of obesity, including weight loss and maintenance of weight loss, in conjunction with a reduced calorie diet, and have been authorized in the European Union (EU) since 1999.

Sibutramine hydrochloride monohydrate is a norepinephrine and serotonin reuptake inhibitor. Sibutramine is rapidly metabolized by the hepatic cytochrome P450 system generating two pharmacologic active metabolites which affect both food intake and energy expenditure [13]. Since sibutramine's FDA approval in 1997, caution has been recommended in using it in patients with poorly controlled hypertension or a history of coronary artery disease, stroke, or arrhythmia because of an increase in systolic (SBP) and diastolic blood pressure (DBP) and pulse caused by the drug. For this reason, first in Europe in August 2010 [14], and then in the United States and Canadian markets in October 2010, sibutramine was withdrawn due to cardiovascular concerns [15] after the data from the Sibutramine Cardiovascular Outcomes Trial (SCOUT) were published [16]. These data showed a 16 % rise in the risk of nonfatal myocardial infarction or stroke in people taking sibutramine.

After sibutramine, rimonabant had been approved for the treatment of obesity in Europe in 2006; it did not receive approval in the United States or Canada due to safety concerns. Rimonabant is a cannabinoid receptor antagonist that acts by blocking a specific type of receptor called cannabinoid type 1 (CB1) receptors that are found in the nervous system and are part of the system that the body uses to control food intake. By blocking the receptors, rimonabant can help patients to reduce food intake and to lose weight [17]. Despite its positive effects on body weight, the European Medicines Agency in October 2008 recommended the suspension of the sale of rimonabant as the risks seem to be greater than the benefits due to an approximate doubling of the risk of psychiatric disorders [12, 18]. Actually the only antiobesity medication currently approved by the EMEA in Europe for long-term use is orlistat, while in the United States other than orlistat also phentermine is available, in addition to the recently approved lorcaserin and phentermine/topiramate extended-release association. In fact, although in Europe phentermine license was withdrawn in 1999, in America phentermine is an approved antiobesity agent indicated as an adjunct to appropriate nutrition and physical exercise for short-term (up to 12 weeks) treatment of obesity.

## Available Antiobesity Drugs (Table 18.1)

### *Phentermine*

Phentermine was first approved by the US FDA in 1959 [19], and to its generic status, phentermine is the most commonly prescribed prescription appetite suppressant [20].

Phentermine is an amphetamine analog stimulant approved for short-term use because of the lack of long-term clinical trials. This drug acts as sympathomimetic agent; the mechanism of action includes an increase in central nervous system dopamine and norepinephrine (both catecholamines)

**Table 18.1** Available antiobesity drugs

| Drug | Dosage | Mechanism of action | Adverse reactions |
|---|---|---|---|
| Phentermine | 15 mg once a day, titrated to 30 mg once a day if needed | It acts as amphetamine analog stimulant | Increase of blood pressure and heart rate |
| Orlistat | 120 mg after each main meal | It acts as antagonist of the action of gastrointestinal lipase in the gastrointestinal tract | Hypoglycemia, headache, upper respiratory infection, oily spotting from the rectum, abdominal pain or discomfort, flatus with discharge, fecal urgency, fatty or oily stools, flatulence, liquid stools, oily evacuation, and increased defecation |
| Exenatide[a] | 5 μg twice a day for the first month than 10 μg twice a day<br>Exenatide LAR 2 mg once a week | It binds to GLP-1 receptor | Gastrointestinal adverse events |
| Liraglutide[a] | 0.6 mg once a day as starting dose, with the possibility to up-titrate until 1.2 or 1.8 mg once a day if necessary | It binds to GLP-1 receptor | Gastrointestinal adverse events |
| Lorcaserin | 10 mg twice a day | It is a selective serotonin 2C receptor agonist | Headache, dizziness, fatigue, nausea, dry mouth, constipation, hypoglycemia, headache, back pain, cough, and fatigue |
| Phentermine and topiramate extended-release | 7.5 mg of phentermine and 46 mg of topiramate extended-release up-titrated until 15 mg of phentermine and 92 mg of topiramate extended-release for selected patients | Phentermine acts as amphetamine analog stimulant, topiramate blocks the action potentials elicited repetitively by a sustained depolarization of the neurons in a time-dependent manner | Paresthesia of hands and feet, dizziness, altered taste sensation, insomnia, constipation, and dry mouth |

[a]This drug was born as antidiabetic agent, and it gives a weight reduction in diabetic patients

and serotonin (an indolamine) activity, resulting in appetite suppression. As stimulants, it also increases blood pressure and heart rate. Moreover, different clinical trials in humans suggest sympathomimetic agents increase energy expenditure [21, 22].

Phentermine resin formulations allow for a slower gastrointestinal release after ingestion. Administration of phentermine resin often begins with a 15-mg dose and is titrated to 30 mg per day if needed. In the 1970s, phentermine hydrochloride (HCl) was developed, with doses ranging from 8 to 37.5 mg, which is generally equivalent to 6.4–30 mg of phentermine resin. The phentermine HCl salt easily dissociates in the gastrointestinal tract, resulting in immediate release of phentermine drug; phentermine HCl is absorbed from the gastrointestinal tract approximately three times faster than phentermine resin [23]. Theoretically, immediate-release phentermine HCl has a more intense appetite-suppressant effect compared with phentermine resin but for a shorter duration of time.

Phentermine is contraindicated in patients with pulmonary artery hypertension, severe arterial hypertension, current or past medical history of cardiovascular or cerebrovascular disease, or

psychiatric disorders including anorexia and depression; it is also contraindicated in patients with propensity towards drug abuse or known alcoholism. Combination drug therapy with any other centrally acting anorectic agent is contraindicated due to the increased risk of potentially fatal pulmonary artery hypertension.

The efficacy of phentermine in the clinical practice was evaluated in different studies. Kang et al. [24] evaluated the efficacy and safety of phentermine diffuse-controlled release in patients with obesity. Patients were randomized to 12 weeks of treatment with phentermine 30 mg or placebo, administered once daily in patients with obesity with controlled diabetes, hypertension, or dyslipidemia. The efficacy was evaluated by changes in body weight and waist circumference (WC) from baseline at 12 weeks and also changes in metabolic parameters, including lipid profiles and blood pressure. The participants in the phentermine group showed significant reductions in body weight ($-8.1 \pm 3.9$ kg vs. $-1.7 \pm 2.9$ kg, $p < 0.001$) and WC ($7.2 \pm 0.5$ cm vs. $2.1 \pm 0.6$ cm, $p < 0.001$) compared with those in the placebo group. Weight reductions of 5 % or greater from the baseline (95.8 % vs. 20.8 %, $p < 0.001$) and 10 % or more (62.5 % vs. 4.7 %, $p < 0.001$) were achieved in the phentermine group and placebo group, respectively. Total cholesterol (TC) and LDL cholesterol levels were significantly improved in the phentermine group. However, there were no significant differences in SBP and DBP between the groups. Dry mouth and insomnia were the most common adverse events, but these were mild to moderate and transient.

Kim et al. [25] conducted a randomized, double-blind, placebo-controlled study where 68 relatively healthy obese adults, whose BMI was 25 kg/m$^2$ or greater, received phentermine HCl 37.5 mg or placebo once daily in addition to behavioral therapy for obesity. The primary endpoints were the changes of body weight and WC from baseline in the intention-to-treat population. Mean decrease of both body weight and WC in phentermine-treated subjects was significantly greater than that of placebo group (weight: $-6.7 \pm 2.5$ kg, $p < 0.001$; WC: $-6.2 \pm 3.5$ cm, $p < 0.001$). Significant number of subjects in phentermine group accomplished weight reduction of 5 % or greater from the baseline and 10 % or more ($p < 0.001$). There were no significant differences in SBP and DBP between the groups ($p = 0.122$ for SBP; $p = 0.219$ for DBP).

Weintraub et al. [26] performed a double-blind, controlled clinical trial comparing phentermine resin (30 mg in the morning), fenfluramine hydrochloride (20 mg three times a day), and a combination of phentermine resin (15 mg in the morning) and fenfluramine hydrochloride (30 mg before the evening meal) and placebo. Eighty-one people with simple obesity (130–180 % of ideal body weight) participated. Individualized diets were prescribed and discussed again during the 24-week study period. Weight loss in those receiving the combination ($8.4 \pm 1.1$ kg) was significantly greater than in those receiving placebo ($4.4 \pm 0.9$ kg) and equivalent to that of those receiving fenfluramine ($7.5 \pm 1.2$ kg) or phentermine ($10.0 \pm 1.2$ kg) alone. Adverse effects were less frequent with the combination regimen than with other active treatments. Thirty-seven participants dropped out of the study, 18 for reasons related to drug treatment. Combining fenfluramine and phentermine capitalized on their pharmacodynamic differences, resulting in equivalent weight loss, fewer adverse effects, and better appetite control.

Vallé-Jones et al. [27] carried out a study to compare the effectiveness and tolerance of phentermine and diethylpropion in helping patients more than 20 % above their desirable weight to lose weight. Patients were allocated at random to receive either one 30-mg capsule of phentermine or one 75-mg tablet of diethylpropion daily over a period of 12 weeks. They were also asked to restrict their calorie intake to 1,500 cal per day. The results showed that there was a significantly greater weight loss in patients treated with phentermine which was particularly marked during the last 4 weeks of the study. There were significant reductions in blood pressure and heart rate in the phentermine group and of heart rate in the diethylpropion group. These were almost certainly related to weight loss rather than to a direct effect of drug treatment. Side effects were generally minor in nature, and the incidence and nature of them were comparable in the two groups.

Phentermine proved to be safe also in combination with other forms of weight control therapy like showed by Weintraub et al. [28]. One hundred and twenty-one people were enrolled in a 34-week, double-blind clinical trial and randomized to take 60-mg extended-release fenfluramine plus 15-mg phentermine resin versus placebo added to behavior modification, caloric restriction, and exercise. Participants weighed 130–180 % (154 ± 1.2 %) of ideal body weight and were in good health. By week 34, participants receiving active medication lost an average of 14.2 ± 0.9 kg or 15.9 ± 0.9 % of initial weight vs. a loss of 4.6 ± 0.8 kg or 4.9 ± 0.9 % of initial weight by subjects taking placebo ($p < 0.001$). On visual analog scales, participants rated fenfluramine plus phentermine as more helpful than placebo (50.3 ± 0.5 vs. 20.3 ± 0.3). Blood pressure decreased and pulse remained unchanged in both groups. Dry mouth was the most common adverse effect in subjects receiving fenfluramine plus phentermine; all adverse effects decreased after 4 weeks. Only nine participants left the study in the first 34 weeks. Two subjects from each group left the study as a result of adverse effects. Overall, fenfluramine plus phentermine used in conjunction with behavior modification, caloric restriction, and exercise aided weight loss and continued to be efficacious for 34 weeks.

## *Orlistat*

Orlistat 120 mg was approved as a prescription product by FDA in 1999 for obesity management in conjunction with a reduced caloric diet and to reduce the risk of regaining weight after prior weight loss. In 2007, orlistat 60 mg was approved for an over-the-counter (OTC) use for weight loss in overweight adults, 18 years and older, in conjunction with a reduced-calorie and low-fat diet. Currently, orlistat is approved for marketing in approximately 100 countries. Orlistat is the first prescription treatment for obesity that does not act as an appetite suppressant, but it works by interfering with the action of gastrointestinal lipase in the gastrointestinal tract [29].

Orlistat has a unique molecular structure, which allows it to bind to the active site of gastrointestinal lipase and block that enzyme activity. The enzyme is thus unable to break triglycerides down into their component parts. As a result of this mechanism of action, 30 % of ingested dietary fat remains undigested and unabsorbed, passing through the gastrointestinal tract unchanged. Orlistat has mainly mild to moderate gastrointestinal side effects that usually attenuate with the termination of treatment, but often not acceptable from the patients [30] and some pharmacokinetic interactions that are rare but potentially relevant, with cyclosporin [31] and warfarin [32]. Orlistat is contraindicated in individuals with chronic malabsorption syndromes or cholestasis. Orlistat is given as one capsule taken with water just before, during, or up to 1 h after each main meal. If a meal is missed or contains no fat, orlistat should not be taken. The patient should be on a diet in which about 30 % of the calories come from fat and which is rich in fruits and vegetables. The food in the diet should be spread over three main meals. Treatment with orlistat should be stopped after 12 weeks if patients have been unable to lose at least 5 % of their body weight since the start of treatment.

The most common side effects with orlistat are hypoglycemia, headache, upper respiratory infection, oily spotting from the rectum, abdominal pain or discomfort, flatus with discharge, fecal urgency, fatty or oily stools, flatulence, liquid stools, oily evacuation, and increased defecation [32]. These symptoms generally occur at the beginning of treatment and go away after some time. Orlistat should not be used in people who may be hypersensitive to orlistat or any of the other ingredients. It should also not be used in people with a long-term malabsorption disease (where nutrients from the food are not easily absorbed during digestion), in patients with a gastric by-pass surgery, or cholestasis, or who are breast-feeding. Moreover, recently, on June 2010, FDA approved a revised label for orlistat to include new safety information about cases of severe liver injury that have been reported rarely with the use of this medication [33].

Orlistat seems to be safe and well tolerated. Derosa et al. conducted several studies on orlistat [34–39], where orlistat was compared to sibutramine [34, 35] and to placebo [36, 37] or was administered together with L-carnitine [38, 39]. The authors observed a significant BMI, body weight, WC, hip circumference (HC), and waist/hip ratio (W/H ratio) improvement in both groups, but there was a significant SBP and DBP improvement in orlistat group after 12 months ($p<0.05$). A reduction of all lipid profile parameters ($p<0.05$ for all) was observed in orlistat group, while only a triglycerides reduction ($p<0.05$) was obtained in sibutramine group after 12 months. Of the 109 patients who completed the study, 48.1 % of patients in the orlistat group and 17.5 % of patients in the sibutramine group had side effects ($p<0.05$ vs. orlistat group). Side effect profiles were gastrointestinal events for orlistat and an increase in blood pressure for sibutramine, but it has been controlled by antihypertensive treatment. The vitamin changes were small and all mean vitamin and beta-carotene values stayed within reference ranges. No patients required vitamin supplementation [34, 35]. Compared to placebo [36, 37], instead, orlistat gave a significant reduction of body weight, WC, and BMI, not observed with placebo; furthermore, body weight, WC, and BMI values registered with orlistat were significantly better than the values observed in the controls after 12 months ($p<0.05$). A faster improvement of glycemic profile and fasting plasma insulin was obtained with orlistat compared to the controls. Furthermore, there was a significant reduction of lipid profile with orlistat, not reached with placebo. Orlistat was also more effective than placebo ($p<0.05$) in improving inflammatory parameters, such as adiponectin and tumor necrosis factor-α. Orlistat gave also a faster decrease of leptin and high sensitive C-reactive protein compared to the control group.

These results were confirmed by Valsamakis et al. [40]; in their study nondiabetic female subjects were treated with sibutramine 10 or 15 mg a day or with orlistat for weight loss. After 6 months, the sibutramine group had a modest mean weight loss of 5.4 % ($p<0.0001$), and WC was reduced by $4.5 \pm 1.4$ cm. There was a decrease in serum resistin, leptin, and C-reactive protein levels and a rise in serum adiponectin ($p<0.05$). Change in BMI was associated with insulin ($p=0.02$, $r=0.53$) and leptin ($p=0.01$, $r=0.58$). Change in waist was associated with insulin ($p=0.005$, $r=0.75$) and resistin ($p=0.03$, $r=20.55$). The orlistat-treated group had a mean weight loss of 2.5 %. Although this group did not show significant change in metabolic parameters, surprisingly there was a greater decrease of resistin ($p=0.02$) associated with comparable increase in adiponectin and reduction of WC and C-reactive protein.

This was in line with Kelley et al. [41]; this study was a 1-year multicenter, randomized, double-blind, placebo-controlled trial on orlistat (120 mg three times a day) or placebo combined with a reduced-calorie diet in overweight or obese adults with type 2 diabetes mellitus treated with insulin alone or combined with oral agents but with suboptimal metabolic control (glycated hemoglobin ($HbA_{1c}$) 7.5–12.0 %). After 1 year, the orlistat group lost significantly more weight ($-3.89 \pm 0.3$ % of baseline body weight) than the placebo group ($-1.27 \pm 0.3$ %, $p<0.001$). Orlistat treatment, compared with placebo, produced greater decrease in $HbA_{1c}$ ($-0.62 \pm 0.08$ vs. $-0.27 \pm 0.08$ %, $p=0.002$), fasting plasma glucose ($-1.63 \pm 0.3$ vs. $-1.08 \pm 0.3$ mmol/L, $p=0.02$), and in the required doses of insulin and other diabetic medications. Orlistat also produced greater improvements than placebo in TC ($p=0.0002$), LDL cholesterol concentrations ($p=0.001$), and LDL/HDL ratio ($p=0.01$).

The same conclusion was reached by Jacob et al. [42]: a total of 2,550 overweight or obese patients with type 2 diabetes mellitus were enrolled and randomized to treatment with orlistat 120 mg three times a day ($n=1279$) or placebo ($n=1271$) for 6 or 12 months. For the whole population, patients treated with orlistat 120 mg had significantly greater mean decrease in fasting plasma glucose compared with placebo-treated patients (−1.39 mmol/L vs. −0.47 mmol/L; $p<0.0001$). In addition, orlistat 120 mg provided significantly larger mean decrease in $HbA_{1c}$ compared with placebo (−0.74 % vs. −0.31 %; $p<0.0001$). For patients with minimal weight loss (≤1 % of baseline body weight), orlistat 120 mg still provided a significantly greater decrease in the least square mean value for both fasting plasma glucose (−0.83 mmol/L vs. 0.02 mmol/L; $p=0.0052$) and $HbA_{1c}$ (−0.29 % vs. 0.14 %; $p=0.0008$). This suggested that the improvement of glycemic control with orlistat 120 mg was independent of weight loss. Using linear regression analysis, improvement in glycemic control with orlistat 120 mg was less strongly correlated with weight loss than for placebo.

Hollander et al. [43] conducted a multicenter, 57-week randomized double-blind placebo-controlled study. Three hundred and ninety-one obese men and women with type 2 diabetes mellitus, aged >18 years, with a BMI of 28–40 kg/m$^2$, clinically stable on oral sulphonylureas, were randomized to take 120-mg orlistat or placebo three times a day with a mildly hypocaloric diet. After 1 year of treatment, the orlistat group lost 6.2 ± 0.45 % of initial body weight versus 4.3 ± 0.49 % in the placebo group ($p < 0.001$). Twice as many patients receiving orlistat (49 vs. 23 %) lost ≥5 % of initial body weight ($p < 0.001$). Orlistat treatment plus diet compared with placebo plus diet was associated with significant improvement in glycemic control, as reflected in decreases in $HbA_{1c}$ ($p < 0.001$) and fasting plasma glucose ($p < 0.001$) and in dosage reductions of oral sulfonylurea medication ($p < 0.01$). Orlistat therapy also resulted in significantly greater improvements in several lipid parameters, specifically a greater reduction in TC ($p < 0.001$), LDL cholesterol ($p < 0.001$), triglycerides ($p < 0.05$), apolipoprotein B ($p < 0.001$), and the LDL-to-HDL C ratio ($p < 0.001$). Mild to moderate and transient gastrointestinal events were reported with orlistat therapy, although their association with study withdrawal was low. Fat-soluble vitamin levels generally remained within the reference range, and vitamin supplementation was required in only a few patients.

## *Lorcaserin*

On 27 June 2012, FDA approved lorcaserin hydrochloride, as an addition to a reduced-calorie diet and exercise, for chronic weight management at the dose of 10 mg twice a day [44]. The drug has been approved for use in obese patients or in overweight adults who have at least one weight-related condition such as hypertension, type 2 diabetes, or high cholesterol.

Lorcaserin is a novel selective serotonin 2C (5-HT2C) receptor agonist. The 5-HT2C receptor in the hypothalamus modulates food intake by activating the pro-opiomelanocortin system of neurons that induces hypophagia [45]. Activation of this receptor may help a person eat less and feel full after eating smaller amounts of food. Previously available drugs that targeted this receptor, such as fenfluramine and dexfenfluramine, were effective in promoting weight loss; however, these agents were nonselective, and as a result of 5-HT2B receptor activation on heart tissue, some patients developed valvular heart disease. These drugs were subsequently withdrawn from the market [46]. When used at the approved dose, lorcaserin does not appear to activate the serotonin 2B receptor.

The approved labeling for lorcaserin recommends that the drug should be discontinued in patients who fail to lose 5 % of their body weight after 12 weeks of treatment, as these patients are unlikely to achieve clinically meaningful weight loss with continued treatment.

Regarding adverse events, the most common side effects of lorcaserin in nondiabetic patients are headache, dizziness, fatigue, nausea, dry mouth, and constipation and in diabetic patients hypoglycemia, headache, back pain, cough, and fatigue. Lorcaserin should not be used during pregnancy. Treatment with lorcaserin may cause serious side effects, including serotonin syndrome, particularly when taken with certain medicines that increase serotonin levels or activate serotonin receptors. These include, but are not limited to, drugs commonly used to treat depression and migraine. Lorcaserin may also cause disturbances in attention or memory.

The safety and efficacy of lorcaserin were evaluated in the BLOOM study (Behavioral Modification and Lorcaserin for Obesity and Overweight Management) that included 4,008 patients, aged 18–65 years, with a BMI between 30 and 45 kg/m$^2$ or between 27 and 29.9 kg/m$^2$ with an obesity-related comorbid condition [47]. Patients were randomly assigned to receive lorcaserin 10 mg twice daily, lorcaserin 10 mg once daily, or placebo. All patients received diet and exercise counseling. The ordered primary endpoints were proportion of patients achieving at least 5 % reduction in body weight, mean change in body weight, and proportion of patients achieving at least 10 % reduction in body weight at 1 year. Serial echocardiograms monitored heart valve function. Significantly more

patients treated with lorcaserin 10 mg twice daily and once daily lost at least 5 % of baseline body weight (47.2 % and 40.2 %, respectively) as compared with placebo (25.0 %, $p<0.001$ vs. lorcaserin twice daily). Least squares mean weight loss with lorcaserin twice daily and once daily was 5.8 % and 4.7 %, respectively, compared with 2.8 % with placebo ($p<0.001$ vs. lorcaserin twice daily). Weight loss of at least 10 % was achieved by 22.6 and 17.4 % of patients receiving lorcaserin 10 mg twice daily and once daily, respectively, and 9.7 % of patients in the placebo group ($p<0.001$ vs. lorcaserin twice daily). Headache, nausea, and dizziness were the most common lorcaserin-related adverse events. FDA-defined echocardiographic valvulopathy occurred in 2.0 % of patients on placebo and 2.0 % on lorcaserin 10 mg twice daily. Similar results were observed in type 2 diabetic patients: the BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) study [48] evaluated efficacy and safety of lorcaserin for weight loss in patients with type 2 diabetes. Secondary objectives included evaluations of glycemic control, lipids, blood pressure, and quality of life. This placebo-controlled trial enrolled 604 patients to placebo, lorcaserin 10 mg once daily or lorcaserin 10 mg twice daily for 1 year. Patients were treated with metformin, a sulfonylurea, or both; they had $HbA_{1c}$ 7–10 %, were 18–65 years old, and had BMI 27–45 kg/m$^2$. Patients received diet and exercise counseling. Safety monitoring included serial echocardiograms. Mean body weight was 103.6 ± 17.8 kg; BMI was 36.0 ± 4.5 kg/m$^2$. Most patients (91.7 %) took metformin; 50.2 % took a sulfonylurea. More patients lost ≥5 % body weight with lorcaserin twice a day (37.5 %, $p<0.001$) or lorcaserin once a day (44.7 %, $p<0.001$) versus placebo (16.1 %). Least square mean weight change was −4.5 ± 0.35 % with lorcaserin twice a day and −5.0 ± 0.5 % with lorcaserin once a day versus −1.5 ± 0.36 % with placebo ($p<0.001$ for each). $HbA_{1c}$ decreased by 0.9 ± 0.06 with lorcaserin twice a day, 1.0 ± 0.09 with lorcaserin once a day, and 0.4 ± 0.06 with placebo ($p<0.001$ for each); fasting glucose decreased 27.4 ± 2.5 mg/dL, −28.4 ± 3.8 mg/dL, and 11.9 ± 2.5 mg/dL, respectively ($p<0.001$ for each). Symptomatic hypoglycemia occurred in 7.4 % of patients on lorcaserin twice a day, 10.5 % on lorcaserin once a day, and 6.3 % on placebo. Common adverse events were headache, back pain, nasopharyngitis, and nausea. This study showed that lorcaserin was associated with significant weight loss and improvement in glycemic control in patients with type 2 diabetes. Compared with placebo, treatment with lorcaserin for up to one year was associated with average weight loss ranging from 3 to 3.7 %.

### *Phentermine and Topiramate Extended-Release*

On 17 July, 2012, FDA approved another antiobesity drug, a single-pill combination of phentermine and topiramate extended-release as an addition to a reduced-calorie diet and exercise for chronic weight management [49]. Like for lorcaserin, the drug has been approved for use in obese adults or overweight adults who have at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. Before July 2012, phentermine was used for short-term period to achieve weight loss in overweight or obese adults who were exercising and eating a reduced-calorie diet, while topiramate was indicated to treat certain types of seizures in people who have epilepsy and to prevent migraine headaches.

The recommended daily dose of phentermine and topiramate extended-release contains 7.5 mg of phentermine and 46 mg of topiramate extended-release. Also higher dose is available such as 15 mg phentermine and 92 mg of topiramate extended-release for selected patients. The most common side effects of phentermine and topiramate extended-release are paresthesia of hands and feet, dizziness, altered taste sensation, insomnia, constipation, and dry mouth. Phentermine and topiramate extended-release must not be used in patients with glaucoma or hyperthyroidism. Phentermine and topiramate extended-release can increase heart rate; this drug effect on heart rate in patients at high risk for heart attack or stroke is not known. Therefore, the use of phentermine and topiramate extended-release in

patients with recent (within the last 6 months) or unstable heart disease or stroke is not recommended. Regular monitoring of heart rate is recommended for all patients taking phentermine and topiramate extended-release, especially when starting phentermine and topiramate extended-release or increasing the dose. Phentermine and topiramate extended-release must not be used during pregnancy because it can cause harm to a fetus.

If after 12 weeks on the higher dose of phentermine and topiramate extended-release a patient does not lose at least 5 % of body weight, then phentermine and topiramate extended-release should be discontinued, as these patients are unlikely to achieve clinically meaningful weight loss with continued treatment.

The safety of phentermine and topiramate extended-release was assessed in the EQUIP study [50], a 56-week randomized controlled trial. Men and women with BMI $\geq$ 35 kg/m$^2$ were randomized to placebo, phentermine and topiramate extended-release 3.75/23 mg, or phentermine and topiramate extended-release 15/92 mg, added to a reduced-energy diet. Primary endpoints were percent weight loss and proportions of patients achieving 5 % weight loss. Secondary endpoints included WC, SBP and DBP, fasting glucose, and lipid measures. In the primary analysis (randomized patients with at least one post-baseline weight measurement who took at least one dose of assigned drug or placebo), patients in the placebo, phentermine and topiramate extended-release 3.75/23 mg, and 15/92 mg groups lost 1.6 %, 5.1 %, and 10.9 % of baseline body weight, respectively, at 56 weeks ($p<0.0001$). In categorical analysis, 17.3 % of placebo patients, 44.9 % of phentermine and topiramate extended-release 3.75/23 mg patients, and 66.7 % of 15/92 mg patients lost at least 5 % of baseline body weight at 56 weeks ($p<0.0001$). The phentermine and topiramate extended-release 15/92 mg group had significantly greater changes relative to placebo for WC, SBP and DBP, fasting glucose, triglycerides, TC, LDL cholesterol, and HDL cholesterol. The most common adverse events were paresthesia, dry mouth, constipation, dysgeusia, and insomnia. Dropout rate from the study was 47.1 % for placebo patients, 39.0 % for phentermine and topiramate extended-release 3.75/23 mg patients, and 33.6 % for 15/92 mg patients. Phentermine and topiramate extended-release demonstrated dose-dependent effects on weight and metabolic variables in the direction expected to be beneficial with no evidence of serious adverse events induced by treatment.

Similar results were reported in the CONQUER study, a 56-week phase 3 trial, where overweight or obese adults (aged 18–70 years), with a BMI of 27–45 kg/m$^2$ and two or more comorbidities (hypertension, dyslipidemia, diabetes or prediabetes, or abdominal obesity), were randomized to placebo, once-daily phentermine 7.5 mg plus topiramate 46.0 mg, or once-daily phentermine 15.0 mg plus topiramate 92.0 mg [51]. Primary endpoints were the percentage change in body weight and the proportion of patients achieving at least 5 % weight loss. Of 2487 patients, 994 were assigned to placebo, 498 to phentermine 7.5 mg plus topiramate 46.0 mg, and 995 to phentermine 15.0 mg plus topiramate 92.0 mg. At 56 weeks, change in body weight was −1.4 kg, −8.1 kg ($p<0.0001$), and −10.2 kg ($p<0.0001$) in the patients assigned to placebo, phentermine 7.5 mg plus topiramate 46.0 mg, and phentermine 15.0 mg plus topiramate 92.0 mg, respectively. Two hundred and four (21 %) patients achieved at least 5 % weight loss with placebo, 303 (62 %, $p<0.0001$) with phentermine 7.5 mg plus topiramate 46.0 mg, and 687 (70 %; $p<0.0001$) with phentermine 15.0 mg plus topiramate 92.0 mg; for $\geq$10 % weight loss, the corresponding numbers were 72 (7 %), 182 (37 % $p<0.0001$), and 467 (48 %; 11.7, 8.9–15.4; $p<0.0001$). The most common adverse events were dry mouth, paresthesia, constipation, insomnia, dizziness, and dysgeusia. Thirty-eight (4 %) patients assigned to placebo, 19 (4 %) to phentermine 7.5 mg plus topiramate 46.0 mg, and 73 (7 %) to phentermine 15.0 mg plus topiramate 92.0 mg had depression-related adverse events, and 28 (3 %), 24 (5 %), and 77 (8 %), respectively, had anxiety-related adverse events.

Another study [52] evaluated safety and efficacy of phentermine 15 mg plus extended-release topiramate 92 mg for treatment of moderate to severe obstructive sleep apnea (OSA) in obese adults. This phase 2, randomized, double-blind, placebo-controlled study included 2-week screening and 28-week treatment periods. Overnight polysomnography was performed at baseline, week 8, and week 28.

Investigators enrolled forty-five subjects with moderate to severe OSA not receiving positive airway pressure (PAP) treatment with BMI of 30–40 kg/m$^2$. Subjects were randomized to receive placebo ($n=23$) or phentermine 15 mg plus extended-release topiramate 92 mg ($n=22$). Both groups received lifestyle modification counseling. The primary endpoint, change in apnea–hypopnea index (AHI), significantly favored phentermine 15 mg plus extended-release topiramate 92 mg (−31.5 events/h) over placebo (−16.6 events/h) at week 28 ($p=0.0084$). At week 28, there was a 10.2 % (−10.8 kg) mean decrease in weight in the phentermine 15 mg plus extended-release topiramate 92 mg group compared with 4.3 % (−4.7 kg) in the placebo group ($p=0.0006$) and a positive, significant ($p=0.0003$) correlation between percent change in weight and change in AHI. Significant improvements in overnight oxygen saturation and reduction in blood pressure compared with placebo were observed. Phentermine 15 mg plus extended-release topiramate 92 mg was well tolerated with low adverse event rates. Phentermine 15 mg plus extended-release topiramate 92 mg induced significant weight reductions and concomitant improvements in OSA and related symptoms versus placebo.

## *Antiobesity Drugs in Type 2 Diabetic Patients: GLP-1 Receptor Agonists*

Obesity is usually associated with insulin resistance and type 2 diabetes mellitus. Diabetes is characterized by three major metabolic abnormalities: impaired insulin action, insulin secretory dysfunction, and increased endogenous glucose output [53–55]. In an attempt to address treatment concerns of many traditional medications for type 2 diabetes, in the last years, incretin-based therapies have been developed in clinical practice. Incretins are hormones that work to increase insulin secretion; there are two main incretin hormones in humans, the glucose-dependent insulinotropic peptide (GIP) and the glucagon-like peptide-1 (GLP-1). Glucagon-like peptide-1 is secreted by intestinal L-cells, mainly in response to food intake, and acts stimulating glucose-dependent insulin secretion, suppressing glucagon secretion, and moderating appetite by delaying gastric emptying and reducing hunger [56]. Glucagon-like peptide-1 agonists such as exenatide (injected twice daily) and liraglutide (injected once daily) act as incretin mimetic; they have structural similarity and bind to the receptor for GLP-1 and display a similar broad range of activities relevant to improving glycemic control. They have a much longer half-life after injection than native GLP-1 due to the absence of alanine at position 2, which is recognized by DPP-4, and this characteristic makes them resistant to DPP-4 cleavage. They appear to lower $HbA_{1c}$ levels by 0.5–1.0 %, mainly by lowering postprandial blood glucose levels [57–60].

### Exenatide

The first formulation of exenatide released, to be administered twice a day (BID), is a synthetic exendin-4, first identified and isolated in high concentrations from the salivary secretions of the Gila monster (Heloderma suspectum) within minutes of ingesting a meal [61, 62]. Exendin-4 shares 53 % amino acid sequence identity with human GLP-1 and binds directly to GLP-1 receptors [63]. Exenatide is eliminated by the kidneys exclusively by glomerular filtration and subsequent tubular catabolism [64–66]. In patients with renal dysfunction, exenatide shows reduced clearance and may thereby increase the risk of exposure-dependent side effects [67]. This formulation of exenatide should be administered twice a day, at the dose of 5 μg for the first month, followed by 10 μg twice a day by subcutaneous injections.

On the other side, exenatide LAR formulation has been developed using biodegradable polymeric microspheres that entrap exenatide [68, 69]. Exenatide is incorporated into a matrix of poly(D,L-lactide-co-glycolide), which previously has been used as a biomaterial in sutures and in

extended-release preparations that allow gradual drug delivery at controlled rates [70]. Exenatide LAR is eliminated by kidneys. It can be used at the recommended dosage of 2 mg to be administered as one injection under the skin once a week.

### Liraglutide

Liraglutide is an analog of human GLP-1 with 97 % homology to the endogenous protein 4 with one amino acid substitution (Arg34Lys) and a C-16 palmitic acid side chain attached via a glutamyl spacer. These modifications result in slower absorption from subcutaneous tissue, reversible albumin binding, and resistance to GLP-1 inactivation by DPP-4. Unlike exenatide, liraglutide is 99 % bound to albumin, with free liraglutide degraded by endogenous peptidases, and not via renal elimination [71]. Liraglutide injection produces maximal concentrations within 10–14 h after administration, with a half-life of 13 h, which gives it a pharmacokinetic profile suitable for once-daily treatment [72]. Liraglutide is metabolized in vitro by DPP-IV and neutral endopeptidase (NEP) in a manner similar to that of native GLP-1, although at a much slower rate. The metabolite profiles suggest that both DPP-IV and NEP are also involved in the in vivo degradation of liraglutide. The lack of intact liraglutide excreted in urine and feces and the low levels of metabolites in plasma indicate that liraglutide is completely degraded within the body [71]. Liraglutide is administered by the patient once a day by subcutaneous injections in the abdomen, thigh, or upper arm. It is given independent of meals and preferably at the same time each day. The starting dose of liraglutide is 0.6 mg; after at least one week, the dose can be increased to 1.2 mg, until 1.8 mg if necessary.

Several trials conducted in overweight/obese diabetic patients suggest that agonists of GLP-1 receptor have beneficial effects on metabolic regulation and could lead to weight loss, with a mean weight reduction of −3.2 kg in patients without diabetes and of −2.8 kg in those with diabetes [58–60]. Based on the available data, exenatide and liraglutide should be considered in patients with diabetes who are obese or overweight, even if further studies are needed to elucidate the effects of GLP-1 receptor agonists for the treatment of obese patients without diabetes [73].

## Drugs in Development (Table 18.2)

### *Central-Acting Drugs*

A drug initially assessed for the treatment of early as well as advanced Parkinson's [74] and Alzheimer's disease is tesofensine, a norepinephrine, dopamine, and serotonin reuptake inhibitor. At the dosages tested in the initial trials, tesofensine did not meet the predefined efficacy criteria to

**Table 18.2** Drugs in development

| Class | Drug | Mechanism of action |
|---|---|---|
| Central-acting drugs | Tesofensine | It acts as a norepinephrine, dopamine, and serotonin reuptake inhibitor |
| | Bupropion and zonisamide | Bupropion activates pro-opiomelanocortin neurons and enhances the release of the anorexiant neuropeptide a-MSH in the hypothalamus. Zonisamide is an epilepsy agent; the exact mechanism of action is not known |
| Gut hormone-based treatments | Ghrelin | It acts via the growth hormone secretagogue receptor |
| | Peptide YY | It signals the brain when to stop eating |
| | Oxyntomodulin | It is known to bind both the GLP-1 receptor and the glucagon receptor; it is a satiety signal |
| Pancreas peptides-based treatments | Pancreatic polypeptide | It may act as a circulating factor that reduces food intake |
| | Amylin | Its actions seem to depend on a direct effect on the area postrema |

proceed directly to phase III trials for these indications. However, a recent meta-analysis showed that tesofensine produced a placebo-subtracted weight loss of 4 % for >14 weeks without any diet and lifestyle therapy, similar to that of sibutramine, but with no effect on blood pressure [75]. For these reasons, tesofensine is now being developed for obesity management.

Another association in developing is bupropion and bupropion and zonisamide. Bupropion is an atypical antidepressant and smoking cessation aid that activates pro-opiomelanocortin (POMC) neurons and enhances the release of the anorexiant neuropeptide a-MSH (alpha-melanocyte-stimulating hormone) in the hypothalamus, while zonisamide is an epilepsy agent. A 12-week randomized clinical trial showed that bupropion combined with zonisamide achieved greater weight loss (7.5 %) than zonisamide alone (3.1 %) [76].

## *Gut Hormone-Based Treatments*

Gut hormone-based treatments for obesity are under investigation in phase II and III clinical trials, with particular focus on ghrelin, peptide YY, and oxyntomodulin.

Ghrelin is a 28-amino acid peptide synthesized principally in the stomach [77]; it acts via the growth hormone secretagogue receptor to stimulate food intake in humans [78]. Antagonists to ghrelin have been used in preclinical studies, paving the way for possible future evaluation as a therapy for obesity in humans [79]. On the other side, peptide YY is a short (36-amino acid) peptide released by cells in the ileum and colon in response to feeding. It exerts its action through neuropeptide Y receptors, signaling the brain when to stop eating. Peptide YY inhibits gastric motility, increases water and electrolyte absorption in the colon, and may also suppress pancreatic secretion. Obese people have low levels of the hormone, so some drug manufacturers are creating manufactured peptide YY versions that patients would inject to integrate the endogenous peptide YY.

Oxyntomodulin is co-secreted with GLP-1 and peptide YY into the circulation by intestinal L-cells after nutrient ingestion; it is known to bind both the GLP-1 receptor and the glucagon receptor, but it is not known whether the effects of the hormone are mediated through these receptors or through an unidentified receptor. Oxyntomodulin is a satiety signal; studies in humans have demonstrated that acute administration reduces food intake by 19 %. When given preprandially by subcutaneous injection three times daily, oxyntomodulin resulted in a reduction in food intake and mean weight loss of 2.8 kg over 4 weeks [80].

## *Pancreatic Peptides-Based Treatments*

Also pancreas plays a potential role in the treatment of obesity, producing peptides such as pancreatic polypeptide and amylin. Pancreatic polypeptide is principally secreted by a population of cells located at the periphery of pancreatic islets; it is released into the circulation in a biphasic manner in response to nutrient ingestion and is subject to control by the vagus nerve and a number of other factors [81]. Pancreatic polypeptide may act as a circulating factor that reduces food intake when administered to humans [82]; for this reason, a pancreatic polypeptide analog has been developed to improve the suppressor effect on appetite.

Amylin, or Islet Amyloid Polypeptide, is a 37-residue peptide hormone co-secreted with insulin from the β-cells of the pancreas. Amylin plays a role in glycemic regulation by slowing gastric emptying and promoting satiety, thereby preventing postprandial spikes in blood glucose levels [83]. These actions seem to depend on a direct effect on the area postrema. Subsequent to area postrema activation, the amylin signal is conveyed to the forebrain via distinct relay stations. Within the lateral hypothalamic area, amylin diminishes the expression of orexigenic neuropeptides [84]. Pramlintide is an amylin analog that has recently been granted the FDA approval. In addition to favorable effects on

blood glucose, pramlintide reduces food intake and has been shown to result in 1.8 kg reduction in body weight over 26 weeks in overweight diabetic subjects [85]. Further evaluation of this drug as a therapy specifically for the treatment of obesity is awaited.

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# Chapter 19
# Weight-Loss Diets: Weighing the Evidence

**Laura E. Matarese and Hossam M. Kandil**

**Abstract** The prevalence of overweight and obesity as a public health issue is well established and reflects the overall lack of success in our ability to achieve and maintain a healthy body weight. Overweight and obesity is a risk factor for several of the leading causes of death, including cardiovascular disease, diabetes mellitus, and many types of cancer. The cornerstone of treatment has been diet and exercise. An estimated 1,000 weight-loss diets have been developed with more appearing in the lay literature and the media on a regular basis. The sheer number of existing diet plans would suggest that there is no one diet that has been universally successful at inducing and maintaining weight loss. Many of these dietary programs are based on sound scientific evidence and follow contemporary principles of weight loss. Others simply eliminate one or more of the essential food groups or recommend consumption of one type of food in excess at the expense of other foods with little to no supporting evidence. The focus of this chapter is on the weight-loss diet, specifically those with the most supporting scientific evidence and those which are most likely to succeed in achievement and maintenance of desirable body weight.

**Keywords** Diet • Glycemic index • Mediterranean diet • Atkins diet • Zone diet • LEARN • Weight Watchers • Ornish

### Key Points

- The prevalence of overweight and obesity as a public health issue is well established and reflects the overall lack of success in our ability to achieve and maintain a healthy body weight.
- Overweight and obesity is a risk factor for several of the leading causes of death, including cardiovascular disease, diabetes mellitus, and many types of cancer.
- The cornerstone of treatment has been diet and exercise, and an estimated 1,000 weight-loss diets have been developed, with more appearing in the lay literature and the media on a regular basis.
- The sheer number of existing diet plans suggests that there is no one diet that has been universally successful at inducing and maintaining weight loss.
- Many dietary programs are based on sound scientific evidence and follow contemporary principles of weight loss, while others, for example, simply eliminate one or more of the essential food groups or recommend excessive consumption of one type of food at the expense of other foods, with little to no supporting evidence.

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## Trends in Adult Overweight and Obesity

The prevalence of overweight and obese individuals in the United Sates and the rest of the industrialized world has risen to alarming rates. Currently, over two-thirds of the adult population in the United States is either overweight or obese. Unfortunately, there is an equally significant epidemic of occurrence of obesity in children, which has tripled in the last 30 years. These statistics alone are evidence to the overall lack of success in our ability to achieve and maintain a healthy body weight. Overweight and obesity is a risk factor for several of the leading causes of preventable death, including cardiovascular disease, diabetes mellitus, and many types of cancer. Therefore, the preventable behaviors which lead to these causes of death is poor nutrition and lack of physical activity combined, second only to tobacco use. Obesity is a serious and complex disease resulting from the interactions between predisposing genetic and metabolic factors, a changing food supply and a rapidly changing modern environment that results in sedentary practices. The cornerstone of obesity care is assisting the patient in making healthier dietary and physical activity choices that will lead to a net negative energy balance. This chapter will review the evidence surrounding weight-loss diets.

## A Definition of Diet

Diet is defined as food and drink which is habitually consumed by an individual or population. The term "diet" is often used to refer to the weight reduction diet. An estimated 1,000 weight-loss diets have been developed with more appearing in the lay literature and the media on a regular basis. The sheer number of existing diet plans would suggest that there is no one diet that has been universally successful at inducing and maintaining weight loss. Many of these dietary programs are based on sound scientific evidence and follow contemporary principles of weight management. Others simply eliminate one or more of the essential food groups or recommend consumption of one type of food in excess at the expense of other foods with little to no supporting evidence. These are generally referred to as fad diets (Table 19.1). However, it is the combination of diet, exercise, and lifestyle modification that has been shown to be the most effective method of weight loss when 1 year of follow-up is used as the benchmark [1–4]. The focus of this chapter is on the weight-loss diet, specifically those with the most supporting scientific evidence and those which are most likely to succeed in achievement and maintenance of desirable body weight (Table 19.2). Food and beverage consumption, unlike exercise, is not optional. But the choices one makes—a serving of fresh blueberries versus a slice of blueberry cheesecake—can make a difference in the desired outcome.

**Table 19.1** Characteristics of fad diets

| |
|---|
| The diet becomes very popular (often quickly) and then may fall out of favor (sometimes just as quickly) |
| Recommendations that promise a quick fix |
| Dire warnings of dangers from a single product or regimen |
| Claims that sound too good to be true |
| Simplistic conclusions drawn from a complex study |
| Recommendations based on a single study |
| Dramatic statements that are refuted by reputable scientific organizations |
| Lists of "good" and "bad" foods |
| Recommendations made to help sell a product |
| Recommendations based on studies published without review by other researchers |
| Recommendations from studies that ignore differences among individuals or groups |
| Eliminated one or more of the five food groups |

**Table 19.2** Comparison of weight-loss diets

| | Diet | Advantages | Disadvantages | Exercise | Behavioral modification |
|---|---|---|---|---|---|
| Very low carbohydrate | Atkins | • Rapid initial weight loss<br>• Emphasis on healthy fats<br>• High satiety value<br>• Slow introduction of complex carbohydrates | • Halitosis from ketone production<br>• Must adjust insulin for reduction in body weight and carbohydrate intake<br>• Low fiber—may cause constipation | • Suggests walking as the best way to begin<br>• Discussion of aerobic versus anaerobic activities<br>• Assessment of max heart rate, best frequency, duration, and intensity of workouts | • Encourages lifelong changes for sustained weight loss |
| Low glycemic | Zone | • Rapid initial weight loss<br>• Emphasis on healthy fats<br>• High satiety value | • Complex—must adhere to caloric ratio of carbohydrate, protein, and fats (40:30:30)<br>• Must weigh food | • Walking for the calorie-burning and hormonal benefits, but for fat-burning, you have to eat a Zone snack both 30 min before and 30 min after exercising | • No. Diet is designed to get client into "the Zone" requiring a regimented, one-size-fits-all method of eating |
| | South Beach | • Rapid initial weight loss<br>• Emphasis on whole grains, fruits, and vegetables | • Claims that the quantity of food does not need to be limited | • Minimal. General advice such as some form of regular aerobic exercise, strength training and stretching, and even in short doses | • No |
| | Sugar Busters | • Eliminates consumption of refined sugar | | • Recommended but no formal program, just advice on how to calculate your ideal heart rate, general recommendations to work out on a regular basis, for 20-min, four times a week | • None |
| | Nutrisystem | • Use of prepackaged foods—no decisions to make | • Use of prepackaged foods can be limiting and does not teach food choices<br>• Expensive | • Beginner, intermediate, and advanced plans all outline regimens of aerobics, resistance training, and yoga | • Limited—change poor eating habits and begin to understand appropriate portions |

(continued)

**Table 19.2** (continued)

| | Diet | Advantages | Disadvantages | Exercise | Behavioral modification |
|---|---|---|---|---|---|
| Low fat | Ornish | • Results in significant weight loss | • Extremely limited and difficult to follow<br>• Poor long-term compliance<br>• Low fat often resulted in consumption of increased calories | • No specific fitness plan but recommends gradually building up to 30–60 min of walking or other moderate activity each day | • Stress management<br>• The choice-based program emphasizes becoming aware of what is eaten |
| | LEARN | • Results in significant weight loss<br>• Flexible food choices | • Very low fat which may be difficult to follow long term | • Includes exercise | • Intensified structured approach to health behavior modification with a focus on healthy eating, exercise, coping patterns, and sustained weight loss |
| | Weight Watchers | • Nutritionally balanced | • Can potentially abuse point system | • Some. Workout ideas, demonstrations online<br>• Program includes general guidelines from the US Centers for Disease Control and Prevention and the American College of Sports Medicine | • Healthful behavior strategies<br>• Website offers articles to help avoid common mental pitfalls that can sabotage weight loss |
| Mediterranean diet | | • Nutritionally balanced<br>• Not restrictive | • Definition of Mediterranean diet varies | • General—30 min of exercise per day in small increments whether you are dieting or not<br>• 45–60 min of aerobic activity each day for weight loss<br>• Includes a 3-day exercise plan | • Indirectly—suggestions to use smaller plates and eat slowly |

## Determining the Appropriate Diet Prescription

Obesity is a complex disease and to think that a healthy body weight is simply a matter of caloric restriction and increased energy expenditure is an oversimplification. Yet, there is no doubt that the diet prescription plays a pivotal role in the success of the weight-loss program. At the most basic level, weight gain can be considered a result of increased energy intake, decreased energy expenditure, and increased energy storage. However, the biochemical, physiological, psychological, emotional, economic, and social factors surrounding these mechanisms are multifaceted and complicated. As a result, there is no one diet prescription which can be used universally for all individuals. Different people will respond to different diet prescriptions based on their individual metabolic makeup, comorbid factors, and lifestyle behaviors.

## Dietary Macronutrients

The sheer act of altering the macronutrient content of the diet to affect weight loss is complex and makes the comparison of diets difficult. A carbohydrate is not simply a uniform organic compound. For example, when considering changes in the carbohydrate content of the diet, it may be based on the glycemic index (GI) or glycemic load, the fiber content of the specific carbohydrate, or the complex carbohydrates versus refined. Yet, these are all carbohydrates which potentially can be altered in the diet. These carbohydrates will vary in their effects on blood sugar, nutrient density, and hormone levels that affect tissue metabolism. The same is true for fat. A fat is simply not one nutrient but rather can be considered as monounsaturated, polyunsaturated, saturated fats, and *trans* fats. They may include omega-3, omega-6, or omega-9 fatty acids. Different fatty acids have significant effects on inflammation, a major component of obesity. Protein sources may be derived from plant, marine, or animal sources. It should also be noted that these macronutrients cannot be considered in isolation. As you reduce the percentage of one of these macronutrients in the diet, the percentage of the other two macronutrients will increase.

## Diet Composition and Metabolic Rationale

### *Low-Carbohydrate Diets*

Rapid weight loss has been demonstrated with the use of low-carbohydrate diets. These can be further categorized into very-low-carbohydrate diets such as Atkins which generally has 20–25 g of carbohydrate in the initial phases of the diet or moderate-carbohydrate diets including Zone and South Beach. The Zone diet prescribes a ratio consisting of a lower total carbohydrate and higher protein content of 40:30:30. South Beach employs a phased approach with the initial phase similar to Atkins but then evolves into a more moderate diet consisting of high-fiber carbohydrates using low-glycemic index foods. The glycemic index and Mediterranean diets, although not specifically categorized as high in protein and low in carbohydrate, result in a moderately high level of protein simply by limiting refined carbohydrates. The rationale for a carbohydrate restriction is that, in response to lower glucose availability, there will be reduced insulin concentrations which in turn will shift metabolism from lipogenesis to lipolysis. Energy is derived by ketogenesis from dietary fat, protein, and adipose stores. The exact carbohydrate level required to produce this metabolic shift is thought to be between 20 and 50 g

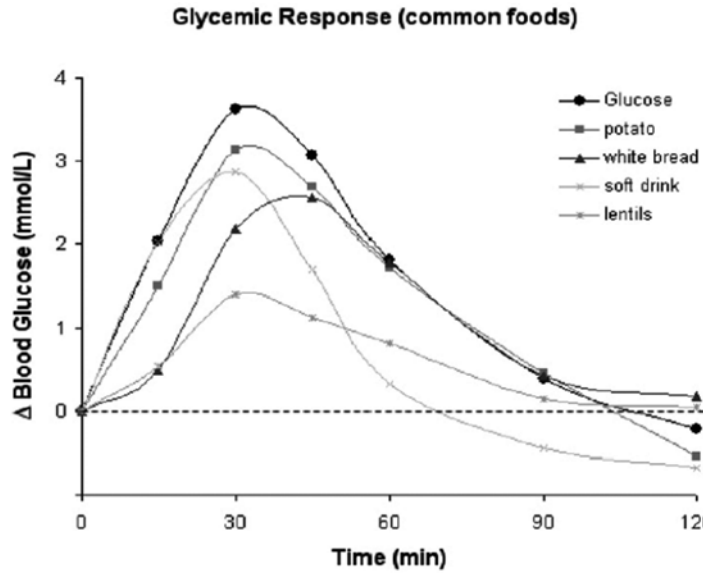


**Fig. 19.1** Effects of high- and low-glycemic index. With kind permission from Springer Science, Zacharias E. The Mediterranean Diet 2012, pp. 127–139

per day in the initial phases of the diet in comparison to the carbohydrate content of the typical Western diet which often exceeds 300 g per day. The higher protein and fat intake along with the production of ketones results in a higher satiety value, and individuals generally consume less calories overall. Once the desired weight loss is achieved, the carbohydrate content is slowly increased until the patient finds the carbohydrate level which results in weight maintenance. This level will be different for each individual and there is no way to predict the exact grams of carbohydrate that will result in equilibrium and body weight stability.

There have been several randomized controlled trials comparing very-low-carbohydrate diets to traditional calorie-restricted low-fat diets [5–7]. Short-term weight loss at 3 and 6 months was significantly greater with the very-low-carbohydrate diet in all studies. However, the differences in weight loss at 1 year were not significant [5]. The low-carbohydrate diet was associated with a greater decrease in serum triglycerides and increase in high-density lipoprotein (HDL) cholesterol [5–7].

## *Low-Glycemic Index/Load Diets*

The glycemic index (GI) was originally developed to help individuals with diabetes manage their carbohydrate intake relative to insulin requirements. The index is a ranking of carbohydrate foods which measures the rate at which the blood glucose levels rise when a particular food is ingested as well as how quickly the blood glucose levels drop (Fig. 19.1). Diets with a high-glycemic load (the mathematical product of the glycemic index and the carbohydrate) [8] result in higher postprandial insulin concentration, calorie for calorie, than those with a low-glycemic load [9, 10]. Pure glucose has a rating of 100; thus, the closer a food is to 100, the higher the GI rating. Foods with a low GI rating will be absorbed more slowly, keeping blood glucose levels lower and more sustained. Typically, foods are rated high (>70), moderate (56–69), or low (less than 55). Diets such as South Beach, Zone, Sugar Busters, and NutriSystem utilize the GI approach and are low in sugar and starch but not low in total carbohydrate. The diets are relatively high in fiber which ultimately lowers the glycemic load. In addition to the lower spike in blood glucose, low-glycemic foods are thought to be more satisfying

than high-glycemic foods since they take longer to absorb and help increase the satiety value of the diet. Most, but not all, foods on the lower end of the GI scale tend to be healthier, nutrient rich, less processed, and higher in fiber—such as whole fruits, vegetables, grains, and beans. Foods high in fiber can be very filling, especially when paired with protein.

Ludwig et al. examined glycemic response, blood sugar, and insulin levels at breakfast in a group of pediatric subjects randomized to receive low- versus high-GI foods [11]. The hormonal and metabolic responses to the low- and high-GI meals were markedly different. Serum insulin concentrations were high following ingestion of the high-GI meal due to the rapid absorption of glucose. By contrast, plasma glucagon levels were suppressed, most likely because of the low protein content of the meal and the inhibitory effects of high plasma glucose and insulin concentrations. Additionally, the high-GI group had a spike in counter-regulatory (plasma epinephrine and growth hormone) hormones that trigger hunger. When the children in the high-GI group were given free access to lunch, they ate 81 % more calories than the low-GI group.

Differences in hormonal response may partially explain the observed variability in dietary weight-loss trials. In an 18-month trial, Ebbeling et al. demonstrated in adults that weight loss was greater with the low-glycemic load diet than the low-fat diet which was associated with higher insulin concentrations [12]. Additionally, a low-glycemic load diet had beneficial effects on HDL cholesterol and triglyceride concentrations but not on low-density lipoprotein (LDL) cholesterol concentration.

Others have argued that it is calorie restriction and not the macronutrient component of the diet which results in weight loss. The effects of a high-glycemic versus a low-glycemic dietary macronutrient pattern in a calorie-restricted diet were evaluated in a randomized controlled trial in 34 healthy overweight adults over the course of 1 year [13]. There was no difference in group mean values for energy intake, hunger, satiety, metabolic rate, weight and body fat loss, and cardiovascular risk factors. Therefore, the effect was due to the lower total calorie intake irrespective of GI.

Fabricatore and colleagues evaluated the effects of low-glycemic load versus low-fat diets in obesity and type 2 diabetes [14]. Seventy-nine obese adults with type 2 diabetes were randomized to receive low-fat or low-glycemic load dietary instruction, delivered in 40-week lifestyle modification programs with identical goals for calorie intake and physical activity. Changes in weight, HbA1c, and other metabolic parameters were compared at weeks 20 and 40. Weight loss did not differ between groups. Participants in the low-fat and low-glycemic groups lost $5.7 \pm 0.6$ % and $6.7 \pm 0.7$ % of initial weight, respectively, at week 20 ($p = 0.26$). At week 40, reductions were $4.5 \pm 1.2$ % and $6.4 \pm 1.3$ %, respectively ($p = 0.28$). Subjects on the low-glycemic load diet had larger reductions in HbA1c than those on the low-fat diet at week 20 and week 40. This occurred despite the lack of significant differences in body weight, fasting glucose, and dietary fiber between the two groups. This finding suggests that the quality and quantity of carbohydrate consumed can significantly enhance the effect of weight loss on HbA1c in patients with type 2 diabetes.

The GI is not a perfect tool and has been the subject of criticism. For example, brown and white rice rank comparably on the index scale as do white and whole wheat bread, yet clearly the whole grain choices are healthier. There are some scores which are confusing and inconsistent. Carrots, for example, are a nutrient-rich, high-fiber vegetable that can have a GI ranking of 47, plus or minus 16 depending on how the food is prepared and how much the food is processed. Some candy and confections that include nuts have a better GI score than a potato because the composite score of the candy is made up of the lower carbohydrate content of the nuts plus the other ingredients in the candy. There are also variations within a food; ripe bananas have higher GI scores than underripe bananas. Pasta which is cooked al dente will rank lower than fully cooked pasta. Furthermore, dietary foods are not consumed in isolation. When carbohydrates are paired with other foods, it impacts the glycemic load. Thus, ingestion of cheese and crackers together will produce a different GI than cheese or crackers alone. The fat content and food temperature will affect gastric emptying and GI.

## *Low-Fat and Very-Low-Fat Diets*

The low-fat and very-low-fat diet has been the mainstay of weight-loss diets for several decades. Indeed many people have been able to gain some control over their weight by lowering their fat consumption. Of the macronutrient portion of the diet, fat is the most calorically dense with 9 kcal/g. The low-fat diet generally contains between 20 and 30 % of calories from fat and the very-low-fat diet contains less than 19 % of calories that come from fat. This means, of course, that the carbohydrate and protein content of the diet will be higher. These diets tended to be lower in calories when properly initiated and resulted in weight loss when done correctly. In addition to weight loss, the low-fat diet was also associated with a reduction in comorbid conditions. Ornish was able to demonstrate a reversal in coronary artery disease at 1 and 5 years [15, 16]. The diet was low fat and nearly vegan and included exercise and stress management versus usual care. The largest study of low-fat diet in almost 50,000 postmenopausal women came from the low-fat arm of the Women's Health Initiative in which 20 % of the calories came from fat with emphasis on fruits, vegetables, and grains [17]. After 8 years, there was no difference in cancer rates or incidence in cardiovascular disease and there was poor weight loss. It was concluded that it was difficult to adhere to the diet. Most women only achieved 24 % fat consumption, and after 8 years on the study, they drifted up to 29 % fat intake. In addition to the fact that the diet was difficult to sustain, it ignored the type of fat so individuals may be following a lower level of fat, but the fat may have included harmful fats such as *trans* fats.

The effect of reducing total fat intake on body weight was evaluated in a systematic review and meta-analysis [18]. Thirty-three randomized controlled trials of 73,589 participants and ten cohort studies were included. Diets lower in total fat were associated with lower relative body weight, but the size of the effect varied. Greater reduction in total fat intake and lower baseline fat intake were associated with greater relative weight loss. Lower total fat intake also led to lower body mass index and waist circumference. Reductions in total fat intake were associated with small but statistically significant reductions in total cholesterol, LDL, and ratio of total-to-HDL cholesterol and in systolic and diastolic blood pressures.

One problem with low-fat diet was that the principles of the diet were misinterpreted and people assumed that they could eat any level of calories, as long as it was low fat. According to the CDC, energy intake increased by about 335 kcal per day from the years 1971 to 2000 with a significant increase in carbohydrate [19].

## *LEARN Diet*

LEARN is an acronym that stands for the five fundamental components of the program: Lifestyle, Exercise, Attitudes, Relationships, and Nutrition. The LEARN diet is one of the most comprehensive behavioral approaches for weight control and dieting and has been shown to result in weight loss in patients with cardiovascular disease. The diet itself is low in fat with only 10 % coming from saturated fat and high in carbohydrates. The recommended carbohydrate level is between 55 and 60 %. The composition of the diet is similar to that of the Ornish diet plan. This diet plan embraces a comprehensive approach with a strong emphasis on lifestyle modification. Aggarwal and colleagues compared changes in body weight in a cohort of patients with cardiovascular disease participating in traditional cardiac rehabilitation followed by the LEARN program [20]. There was a significant reduction in body weight ($203.3 \pm 30.7$ versus $190.1 \pm 30.4$ lb, $p < 0.001$) and BMI ($32.0 \pm 3.9$ versus $29.5 \pm 3.8$ kg/m$^2$, $p < 0.001$) following the LEARN program.

## *Weight Watchers*

Weight Watchers is one of the most recognized and oldest commercial weight-loss programs. The program has changed over the years but has remained steadfast in its goal of offering weight-loss guidance in a group support environment while emphasizing a balanced diet and encouraging exercise. The overall program is based on calorie reduction. Foods are categorized and assigned a point value based on their calorie, fat, and fiber content. The program offers flexibility in food choices as long as the individual stays within the assigned daily points. The disadvantage to this, however, is that one could easily consume all the prescribed points in the form of chocolate cake or potato chips. Because of this, Weight Watchers changed the point system in 2013. The new program contains an entirely different counting system which encourages people to use the points wisely by eating foods rich in protein and fiber which have a high satiety value and help to lose weight in a healthier and more nutritious way. Participants are still encouraged to make wise, healthy food choices and incorporate exercise into their daily routines. Group support is provided at local meetings and via the Internet. This allows for the introduction of behavioral modification techniques as well as emotional support.

Weight Watchers was one of the first commercial weight-loss programs to test its effectiveness in a randomized controlled trial. Heshka and colleagues conducted a 2-year, multicenter randomized trial to compare weight loss achieved by a commercial program, Weight Watchers, to traditional self-help approaches [21]. After 1 year, participants in Weight Watchers lost 4.3 kg as compared to 1.3 kg in the group who received two 20-min counseling sessions and provision of self-help resources. Additionally, those in the Weight Watchers group maintained a weight loss of 2.9 kg (versus 0.2 kg) after 2 years.

The Lighten Up randomized controlled trial compared a range of 12-week commercial and National Health Service (NHS) weight reduction programs with traditional self-help programs [22]. The NHS programs consisted of a group weight-loss program and two primary care programs—one led by a nurse and one led by a pharmacist. The participants in the self-help group were provided with 12 vouchers to a local fitness center. At 12 weeks, all programs achieved significant weight loss [range 1.37 kg (NHS) to 4.43 kg (Weight Watchers)], and all except NHS programs resulted in significant weight loss at 1 year. At 1 year, only the Weight Watchers group had significantly greater weight loss than did the self-help group (2.5 kg greater loss). There have been several other follow-up studies by the NHS to examine the effects of referral to commercial weight-loss programs. Each has demonstrated that referrals from primary care practitioners into a pragmatically delivered weight management program led to a clinically significant loss with Weight Watchers demonstrating be greatest weight loss for the least cost [23, 24].

## *Mediterranean Diet*

The Mediterranean diet includes vegetables, fruits, legumes, whole grains, nuts, olives, and olive oil along with some cheese, yogurt, fish, poultry, eggs, and wine in moderation. These foods form the basis of the plan and provide a rich source of micronutrients, antioxidants, vitamins, minerals, and fiber that work in a synergistic fashion to protect against chronic disease. There is no single Mediterranean diet. Instead, it is a concept of eating based on the dietary patterns of countries bordering the Mediterranean Sea. Most of the foods included in the diet are fresh, seasonal whole foods while limiting processed and convenience food items. Preparation methods tend to be simple—baked, broiled, or poached; foods are rarely deep-fried. Only small amounts of saturated fat, sodium, concentrated sugars, and meat are part of the plan. However, it is more than a diet and includes a lifestyle

which encourages leisurely dining and regular physical activity, which are an important part of the equation. The diet is not considered a weight-loss diet per se. Rather, it is a healthy diet plan that has been shown to reduce risk factors for heart disease and other chronic illnesses. However, it has been shown to result in weight loss, particularly when exercise is included.

The Lyon Diet Heart Study was a randomized controlled trial of 605 free-living subjects with known coronary heart disease [25]. Subjects were randomized to receive the Mediterranean diet or usual post-infarction low-fat diet. Although the study was planned to be long-term 5-year trial, it was terminated at 27 months' mean follow-up time because the benefits in the experimental group were so striking and included a 70 % reduction in all-cause mortality including cancer, reduced cardiovascular disease events, and better weight loss than the control diet. The experimental group consumed significantly less lipids, saturated fat, cholesterol, and linoleic acid but more oleic and alpha-linolenic acids which was confirmed by measurements in plasma. With the mean follow-up time of 46 months per patient, the initial beneficial effects of the Mediterranean diet continued compared with the group consuming the prudent low-fat diet [26].

## Randomized Controlled Trials of Multiple Diet Interventions

There have been a number of randomized controlled trials which have attempted to evaluate the efficacy and/or superiority of one diet over another.

### *Macronutrient Content*

The optimal macronutrient distribution to induce weight loss and improve metabolic risk factors has been debated and the subject of numerous investigations. To determine if differences in the macronutrient content of a weight reduction diet resulted in differences in weight loss, body composition, and risk factors for diabetes and cardiovascular disease, Hu and colleagues performed a meta-analysis of randomized controlled clinical trials for diets low in carbohydrate (≤45 %) versus low fat (≤30 %) [27]. Twenty-three trials with a total of 2,788 participants were included in the analysis. Both the low-carbohydrate and low-fat diets resulted in a decrease in body weight, waist circumference, blood pressure, total-to-HDL cholesterol ratios, total cholesterol, LDL cholesterol, triglycerides, blood glucose, and serum insulin levels. Additionally, both diets resulted in an increase in HDL cholesterol. However, participants on low-carbohydrate diets had greater increases in HDL cholesterol and greater decreases in triglycerides but experienced less reduction in total and LDL cholesterol compared with persons on low-fat diets. This suggests that the low-carbohydrate diets are as effective in reducing weight and improving specific metabolic risk factors and may be more efficacious in certain individuals.

One of the concerns with the evaluation of the studies on macronutrient content is the length of time the diet is prescribed and if there are differences in short-term versus long-term outcomes. The short-term effects of an energy-restricted low-fat diet were compared to an equivalent energy-restricted low-carbohydrate diet in a group of overweight men and women [28]. Over the course of 10 weeks, energy restriction achieved by a very-low-carbohydrate diet was equally effective as a low-fat diet strategy for weight loss, body fat reduction, and improvements in blood pressure and triglycerides. Significant improvements in total cholesterol values were observed in the low-fat group. Fasting insulin levels were significantly lower in the low-carbohydrate diet as compared with the low-fat group. This resulted in a significant decrease in the insulin-to-glucose ratio for the low-carbohydrate group after diet intervention. Thus, a low-fat regimen may be preferred when reduction of blood cholesterol is a

primary goal, whereas the low-carbohydrate regimen may be more appropriate when improvement in insulin sensitivity is the target. This study evaluated short-term effects. However, a vital question is whether overweight people have a better response in the long term to diets that emphasize a specific macronutrient composition. Sacks et al. randomly assigned 811 overweight adults without diabetes or cardiovascular disease to one of four diets [29]. Rather than selecting a specific popular diet, the targeted percentages of energy derived from fat, protein, and carbohydrates in four diets were 20, 15, and 65 %; 20, 25, and 55 %; 40, 15, and 45 %; and 40, 25, and 35 %. The diets consisted of similar foods and met guidelines for cardiovascular health. The participants were offered group and individual instructional sessions for the entire 2-year study period. At 6 months, all participants had lost an average of 6 kg, which represented 7 % of their initial weight, but they began to regain weight after 12 months. After 2 years, weight loss was greatest in those assigned to the 25 % protein group. Satiety, hunger, satisfaction with the diet, and attendance at group sessions were similar for all diets; attendance was strongly associated with weight loss (0.2 kg per session attended). The diets improved lipid-related risk factors and fasting insulin levels. The authors concluded that reduced-calorie diets result in clinically meaningful weight loss regardless of which macronutrients they emphasize.

The effects of protein content and glycemic index in maintenance of weight loss were evaluated in the European Diet, Obesity, and Genes (Diogenes) dietary-intervention study [30]. A total of 773 participants were randomized to one of the five diets: a diet that was low in protein (13 % of total energy consumed) with a low-glycemic index, a diet that was low in protein with a high-glycemic index, a diet that was high in protein (25 % of total energy consumed) with a low-glycemic index, a high-protein and high-glycemic-index diet, or a control diet. The control diet, which followed dietary guidelines in each participating country, had a moderate protein content and did not include instructions to participants with respect to the glycemic index. After 26 weeks, a modest increase in protein content and a modest reduction in the glycemic index led to an improvement in study completion and maintenance of weight loss.

## *Popular Diets*

In order to assess adherence rates and the effectiveness of four popular diets for weight loss and cardiac risk factor reduction, Dansinger and colleagues randomly assigned overweight or obese adults with known hypertension, dyslipidemia, or fasting hyperglycemia to receive Atkins, Zone, Weight Watchers, or the Ornish diet over the course of 1 year under normal free-living conditions [31]. All of the diets resulted in modest statistically significant weight loss at 1 year, with no statistically significant differences between diets. In each diet group, approximately 25 % of the initial participants sustained a 1-year weight loss of more than 5 % of initial body weight, and approximately 10 % of participants lost more than 10 % of body weight. Overall dietary adherence rates were low, although increased adherence was associated with greater weight loss and cardiac risk factor reductions for each diet group. The discontinuation rates among the diets were 50 % for Ornish, 48 % for Atkins, and 35 % for both Zone and Weight Watchers. Each of the diets achieved modest statistically significant improvements in several cardiac risk factors although these reductions were associated with weight loss regardless of diet type. Thus, it appears that it is the actual weight loss and adherence level rather than diet type that was the key determinant of clinical benefits.

The A to Z study was designed to test the 12-month effectiveness of four different weight-loss diets among 311 overweight or obese, nondiabetic, premenopausal women under free-living conditions [32]. Participants were randomly assigned to follow the Atkins, Zone, LEARN, or Ornish diets. They were asked to read the respective diet book and received weekly instruction for 2 months and then an additional 10-month follow-up. After 12 months, the Atkins group had a mean weight loss of 4.7 kg while the other three groups had mean losses of 1.6–2.6 kg. Women in the Atkins group also had more

favorable outcomes for metabolic effects at 1 year than women assigned to the Zone, Ornish, or LEARN diets. Adherence to the various dietary regimens was not optimal and reflected the real-world challenges associated with reading and following guidelines in popular diet books. However, Gardner and colleagues were able to demonstrate comparable or greater weight loss with the Atkins diet in the absence of adverse metabolic effects. Of the four diet groups, the Zone diet, characterized by a moderate but not extreme reduction in carbohydrate—particularly through a reduction in refined carbohydrate—a low nutrient density, and moderately increased protein intake, provided the most optimal micronutrient levels during energy restriction [33]. In a secondary analysis, the level of dietary adherence and long-term compliance was evaluated [34]. Regardless of the assigned weight-loss diet, 12-month weight change was greater in the most adherent compared to the least adherent tertiles. These results suggest that strategies to increase compliance may be as important as the specific macronutrient composition of the diet itself in supporting long-term success.

Many of the comparative trials evaluating effectiveness and safety of weight-loss diets have been limited by short follow-up times and high dropout rates. In a 2-year interventional trial, Shai et al. randomly assigned 322 moderately obese subjects to one of the three diets: low-fat, restricted calorie; Mediterranean, restricted calorie; or low carbohydrate, nonrestricted calorie [35]. The rate of adherence to the assigned study diet was 95.4 % at 1 year and 84.6 % at 2 years. The mean weight loss was 2.9 kg for the low-fat group, 4.4 kg for the Mediterranean-diet group, and 4.7 kg for the low-carbohydrate group ($p<0.001$). Additionally, the relative reduction in the ratio of total cholesterol to HDL cholesterol was 20 % in the low-carbohydrate group and 12 % in the low-fat group ($p=0.01$). Among the 36 subjects with diabetes, changes in fasting plasma glucose and insulin levels were more favorable among those assigned to the Mediterranean diet than among those assigned to the low-fat diet ($p<0.001$).

## Prescribing Weight-Loss Diets for Successful Outcomes

Ultimately, the best diet is the one the patient will follow under normal free-living conditions. A significant problem with weight-loss diets is the lack of compliance and long-term adherence. Regardless of the macronutrient content of the diet, persistence predicts success. One way to improve dietary adherence rates in clinical practice may be to employ a broad spectrum of diet options in order to better match individual patient food preferences, lifestyles, and metabolic risk profiles.

One cannot overlook the laws of thermodynamics. Calories count and overeating leads to fat storage and weight gain. However, the population is very heterogeneous and there is a great deal of variation in metabolic response to different diet prescriptions. For example, induction of weight loss in those with insulin resistance seems to be more favorable with a low-carbohydrate diet [5, 6, 31, 33, 36, 37]. Thus, the diet should be individualized for each patient depending on their BMI, metabolic risk factors, and lifestyle as well as cultural, religious, and food preferences. It is difficult to predict metabolic response. Therefore, a careful and detailed diet and activity history will provide some insight as to the eating patterns which led the patient to the development of obesity. Each of these diets, if implemented correctly and under medical supervision can be safe, result in weight loss, improved metabolic risk factors while supplying necessary nutrients.

A strong educational component is essential for any diet program which is undertaken. This should include not only the mechanics of the diet but also portion control, eating in restaurants, and how to change behaviors. The patient should be taught to develop an eating plan for lifelong health. It is important to help the patient find a balance between food and physical activity for overall health and fitness.

A comprehensive lifestyle modification program which includes diet, exercise, and behavior therapy will aid in achieving long-term and sustained weight management [38] (Chap. 14). The behavior therapy component employs techniques to help obese individuals modify eating, activity,

and cognitive habits that contribute to poor choices and excess weight. Comprehensive lifestyle modification programs typically provide weekly individual and/or group sessions designed to modify eating and daily activity habits. Specific goals are set for each patient along with self-monitoring by the use of body weight, daily food, and activity logs. The programs are often enhanced with the addition of Internet-based programs, text messaging, social network mediums, telephone follow-up, and other print materials.

## Conclusion

Obesity is a serious and highly prevalent disease associated with increased morbidity and mortality. Primary treatment should be directed at achieving and maintaining desirable body weight. Body weight can be reduced with a number of scientifically based weight-loss diets if implemented correctly and with adequate compliance. The weight-loss diet should be individualized for each patient based on BMI, metabolic risk factors, lifestyle, and cultural, religious, and food preferences. A strong educational component is essential to include not only the mechanics of the diet but also portion control, eating in restaurants, and how to change behaviors for lifelong health. It is important to help the patient find a balance between food and physical activity for overall well-being and fitness. The use of behavioral modification will aid in compliance.

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# Chapter 20
# Commercial Weight Loss Programs

**Leslie C. Redmond, Scott Kahan, and Lawrence J. Cheskin**

**Abstract** Commercial weight loss programs have taken over the weight loss industry as widely accepted and relatively affordable options as a means to lose weight. The need for these programs varies from underequipped physicians to providing reasonably priced alternatives to clinical support. In this chapter, we'll explore the various types of commercial programs available and the differences between them, ending with a look at how commercial weight loss program providers and consumers can work together to meet consumer demand and deliver outcome-based results.

**Keywords** Weight loss • Weight management • Commercial weight loss programs • Internet-based programs • Weight Watchers

### Key Points

- Commercial weight loss programs have taken over the weight loss industry as widely accepted and relatively affordable options as a means to lose weight.
- One-third of Americans are currently obese, with approximately 40 % of women and 24 % of men trying to lose weight at any given time—creating a large market for the weight loss industry.
- Weight loss of even 5–10 % of initial body weight can significantly decrease comorbidities of overweight/obesity.
- The major commercial weight loss programs include Weight Watchers, Nutrisystem, OPTIFAST, Mediafast/Take Shape for Life, Jenny Craig, and LA Weight Loss.

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- While many of the available commercial weight loss programs offer similar services, there are significant differences as some programs offer comprehensive advice on physical activity while others do not, and others place the most emphasis on a behavioral component.
- The Institute of Medicine has also recommended that the following be considered as mandatory up-front program disclosures to consumers to include a statement of the program approach and goals, staff credentials, a statement of client population and experience over a 9-month period, program costs, and preprogram procedures recommended for clients.

## What Are Commercial Weight Loss Programs?

In the realm of weight management, weight loss is almost always included as the initial step in the long-term weight management process. Whether an individual needs to lose 10 or 100 lb for improved health, the weight loss component is essential in setting the stage for effective and successful long-term weight management.

But where to start? Individuals seeking to lose weight are often so overwhelmed by the many options available to them that they may feel like giving up before they even begin. The seemingly obvious solution would be for these individuals to seek out information and advice from their primary care physicians. Unfortunately, primary care physicians often feel underequipped to provide overweight or obese clients with the information and support that they need. To help fill this gap, commercial weight loss programs are often turned to for assistance with initial weight loss efforts. They ideally provide safe, effective, and easy to follow weight loss strategies to consumers.

## Why Do Commercial Weight Loss Programs Exist?

One-third of Americans are currently obese, with approximately 40 % of women and 24 % of men trying to lose weight at any given time [1]. In response, an entire weight loss industry has emerged and flourished. However, many individuals may be uninformed and ill-prepared to make decisions on their own regarding which weight loss method may be best for them [2]. Ideally, in the medical model of care for people suffering from the myriad medical and social consequences of obesity, the primary care physician who first diagnoses an individual as being overweight or obese will be the one to make recommendations and give advice regarding the best approaches to achieving a healthy weight.

Unfortunately, this is not always the case. An evaluation of provider-initiated weight loss interventions found that the most common advice given to patients was very basic and superficial: *increase activity, follow a low-fat diet, and appreciate the benefits of weight loss and aerobic exercise* [3]. Providers identified lack of knowledge about weight loss interventions and lack of educational materials as barriers to weight loss counseling [3]. Primary care providers also frequently reported that while the diagnosis of the overweight or obesity is within their scope of practice, the actual management of the condition is better handled by other health-care professionals, such as behavioral therapists, registered dietitians, or exercise physiologists [3]. However, patients typically do not know where or how to find these other professionals nor are they able to afford what will often be out-of-pocket expenses. The weight loss industry recognized this need for affordable yet effective weight loss options and has thrived as the demand for weight loss solutions has expanded, along with the prevalence of the affected population.

The first commercial weight loss program with staying power was Weight Watchers, founded in 1963. Developed by Jean Nidetch, the program began as a weekly meeting of friends in Nidetch's Queens, New York home to discuss how best to lose weight [4]. The weekly meetings turned into what is known today as Weight Watchers, with millions of men and women enrolled worldwide [4]. Weight Watchers groups are lead by successful program participants; the program is overseen by a Scientific Advisory Board [4].

## Available Commercial Weight Loss Programs

Since the founding of Weight Watchers, a number of other commercial weight loss programs have emerged. In addition, there are numerous clinical weight loss programs. It can be difficult to determine what exactly qualifies as a commercial weight loss program, as some are better defined as clinical programs; the primary distinguishing factor is that programs fall under the clinical definition if they are based on physician/other medical health-care provider's supervision and/or require physician referral for entry into the program. Commercial programs are also by definition for profit, while clinical programs are generally not. Table 20.1 identifies and characterizes some of the best-known commercial weight loss programs that have also been studied and shown to have reasonably high success rates among participants.

**Table 20.1** Well-known commercial weight loss programs

| Program | Founded | Approach |
|---|---|---|
| Weight Watchers [5] | 1963 | *Diet*: low calorie, exchange diet; traditional food<br>*Physical activity*: "Get Moving" booklet<br>*Behavioral component*: behavioral weight control methods<br>*Support*: group sessions and weekly meetings |
| Nutrisystem [6] | 1972 | *Diet*: glycemic index-based meal replacements<br>*Physical activity*: *My Daily 3* personalized fitness plans<br>*Behavioral component*: counselor available online<br>*Support*: online group support; online dietitian |
| OPTIFAST [7] | 1974 | *Diet*: low calorie diet; meal replacements social support emphasized<br>*Support*: group sessions; weekly classes; telephone support<br>*Physical activity*: physical activity modules<br>*Behavioral component*: lifestyle classes; stress management and |
| Medifast/Take Shape for Life [8] | 1980 | *Diet*: low calorie diet; meal replacements ± traditional foods<br>*Physical activity*: components available<br>*Behavioral component*: components available<br>*Support*: included in Take Shape for Life, clinics |
| Jenny Craig [9] | 1985 | *Diet*: low calorie diet; meal replacements<br>*Physical activity*: audiotapes for walking<br>*Behavioral component*: manual on weight loss strategies<br>*Support*: individual sessions; weekly contact |
| LA Weight Loss [10] | 1989 | *Diet*: low calorie diet; traditional foods<br>*Physical activity*: optional walking videotape<br>*Behavioral component*: counseling sessions<br>*Support*: individual sessions three times per week |

## What Makes a Commercial Weight Loss Program Successful?

Just because a commercial weight loss program is developed based on scientific evidence and is supervised by highly qualified medical professionals does not guarantee success for participants. While many of the available commercial weight loss programs offer similar services, there are significant differences. For example, some programs offer comprehensive advice on physical activity while others do not, and others place the most emphasis on a behavioral component. Does the program offer online services, or are participants required to meet in person? How much weight is lost by the average participant? Staff qualifications should also be considered. The following sections will address these areas.

## Physical Activity

Most health-care professionals agree that for successful long-term weight control, both diet and physical activity must be addressed. While initial weight loss can certainly be achieved with dietary changes alone, at least one study has found that individuals seeking to lose weight who engage in regular physical activity in addition to maintaining a healthful diet achieve an average 20 % initial weight loss, as well as 20 % greater sustained weight loss after 1 year, as compared to individuals seeking to lose weight via diet alone [11]. (The importance of physical activity to weight control is discussed in another chapter of this book.) Of the major commercial weight loss programs described in Table 20.1, physical activity is encouraged in most, yet considered optional. Having an optional exercise component may be the very reason that a consumer chooses a particular weight loss program. In some cases, structured exercise may be intimidating to overweight individuals, or the consumer might not be mentally prepared to tackle both a change in diet and a challenging exercise program. The option to choose a program tailored to a consumer's particular wants is one of the advantages that commercial weight loss programs can offer.

## Behavioral Component

It has been shown that the most successful weight loss programs include a behavioral component as a primary focus [12]. (The importance of behavioral therapy to weight control is discussed in another chapter of this book.) Behavioral therapy in commercial weight loss can come in many forms, including group support meetings, e-mail with a behavioral counselor, or online self-monitoring journals. In Table 20.1, it is evident that behavioral changes are considered in most programs; however, the importance placed on this component varies. Like physical activity, it appears that for most commercial weight loss programs, the behavioral component is available to those who want it, but is not required. Although some might view this as undesirable, it is important to remember that one of the primary reasons that commercial weight loss programs exist is because medically supervised programs are simply unaffordable for many patients. As such, commercial weight loss programs are often less expensive than their clinical alternatives, though sometimes this lower price comes at the expense of fewer services offered [13]. Generally, the more highly qualified the staff and the more services offered (i.e., behavioral counselors), the higher the price tends to be.

## Internet Based Versus Non-Internet Based

There is some available evidence comparing the effectiveness of Internet-based programs to programs that require meetings in person. Research shows that while non-Internet-based programs are usually the most effective, Internet-based programs can also provide valuable services, as long as they incorporate a structured group atmosphere [14], self-monitoring, cognitive restructuring, stress management, social support, physical activity, and relapse prevention with the support of a behavioral counselor [12]. One pilot study compared two completely Internet-based weight loss programs: Vtrim (considered a clinical program; with a therapist-led structured behavioral curriculum) and eDiets (considered a commercial program; without a structured behavioral curriculum). Results were that while both groups showed significant weight loss, participants randomized to the Vtrim group lost significantly more weight than the eDiets group at 6 months and maintained a greater weight loss at 12 months [15]. These results can be interpreted in more than one way. First and foremost, this research showed that Internet-based programs can be successful. Another conclusion that could be drawn is that medically supervised programs are more effective than commercial programs. But it can also be concluded that successful weight loss was still achieved in the commercial program, providing evidence that these programs can in fact be effective for those who are unable or unwilling to take part in a clinical program. Ultimately, the choice between Internet-based or non-Internet-based may have less to do with which has been shown to be more effective and more to do with what fits in the most with a patient's lifestyle. A patient could enroll in the most successful program available, but if they cannot attend the meetings or meet the requirements, then failure may be unavoidable. Online amenities such as electronic self-monitoring, message boards, group chat, and e-mail with medical professionals could provide very feasible options [16, 17].

## What Is the Available Evidence?

At first glance, commercial weight loss programs appear to provide a magic solution: one look at a program's website will give customers all the anecdotal evidence they need to convince them that the program works. However, anecdotal evidence often does not translate to effectiveness. Actual outcome data of commercial weight loss programs is rarely published.

## Commercial Weight Loss Versus Traditional Weight Loss

Even if all commercial weight loss programs met the expectations of consumers and showed significant outcome-based results, some still question whether the same results couldn't just be obtained without subscribing to a program ("self-help"). Current research does not appear to support this idea. One study showed that after 26 weeks, subjects randomized to a commercial weight loss program (Weight Watchers) achieved greater decreases in body weight and body mass index as well as mean waist circumference, fat mass, and serum homocysteine levels, as compared to subjects randomized to a self-help program consisting of completely self-directed weight loss following one initial meeting with a nutritionist [18]. The same authors conducted a similar study with analysis at 2 years and found that their results were in line with their first trial [19]. Another larger study found that participants randomized to a commercial program (Weight Watchers) lost twice as much weight as those randomized to the standardized care group (as defined by national treatment guidelines), as well as greater

reductions in waist circumference and fat mass [13]. However, analysis of weight maintenance was not performed. A meta-analysis of major commercial weight loss programs in the United States confirmed this finding that structured commercial programs result in greater weight loss than self-help programs [20].

Supporters of commercial weight loss programs argue that such programs, especially those that provide complete meal replacements, ensure that clients achieve safe and effective weight loss without depriving them of essential nutrients, while self-directed weight loss programs using traditional foods may result in nutrient deficiencies. Available research appears to support this theory.

One study has shown that participants randomly assigned to either a 1-year meal replacement program or a 1-year traditional food program did not significantly differ in terms of weight lost or macronutrient intake; however, the traditional food group did have significantly lower intake of several vitamins and minerals [21]. If the ultimate goal of weight loss is improved health, then it seems counterproductive to engage in a self-help program that will shed pounds but deprive the body of essential nutrients at the same time, which would ultimately increase the risk of poor health outcomes. It is important to note that in this particular study, both groups were in fact supervised by registered dietitians, therefore is not completely analogous to an entirely self-directed weight loss program using traditional foods.

Critics of commercial weight loss programs argue that patients who are able to achieve successful weight loss when provided with complete meal replacements may not be able to maintain weight loss once they attempt to transition back to traditional foods. Current research does appear to suggest that weight is often regained after transitioning back to traditional food; however, that same research shows that significant weight loss is still maintained. One such study compared the efficacy of a meal replacement plan (Medifast) and a traditional food-based plan after a period of weight loss and weight maintenance. Researchers found that weight loss was significantly increased in the Medifast group as compared to the traditional food group [22]. The study also showed that while significantly more weight was regained during the weight maintenance phase, overall weight loss was still significantly higher in the Medifast group [22]. Even with this evidence, the debate over meal replacements versus traditional food use for weight loss will likely remain controversial. In response, more commercial weight loss programs that use meal replacements are beginning to incorporate transitional periods during which consumers continue to be provided with support and services as they make the transition back to traditional food.

## Understanding What Consumers Need and What Programs Offer

Before commercial weight loss programs can be most effective in helping customers successfully lose and maintain weight, a thorough analysis to identify what consumers want versus what the programs offer is needed. It is also important to evaluate whether or not the weight loss associated with commercial programs is sustainable in the long run. In 1992, the National Institutes of Health (NIH) held a *Technology Assessment Conference on Methods of Voluntary Weight Loss and Control* and found that participants who remain in the controlled settings of weight loss programs lose approximately 10 % of their weight, but one-third to two-thirds of the weight is regained within 1 year, and almost all is regained within 5 years [2]. To help address these issues, representatives from academia, government organizations, the weight loss industry, and consumer advocacy groups met in Washington, DC, to discuss effective strategies for combating the steadily climbing obesity rates at a conference entitled Commercial Weight Loss Products and Programs—What Consumers Stand to Gain and Lose [2].

## What the Consumers Want

The consumer panelists represented at the conference argued that commercial weight loss programs withhold information, fail to collect data, and only disclose partial data [2]. They also felt that complete and accurate data should be mandatorily provided in the following areas: program cost and duration, potential health risks and complications, staff credentials, outcome data on average weight loss achieved by participants, and short- and long-term maintenance success [2]. They also suggested that if providers were unwilling to provide this information, then the government should require its dissemination via legislation or mandatory regulations under the Federal Trade Commission Act [2].

## What the Providers Want

While the providers at the conferences agreed with some of the consumers' demands, they also argued that collecting certain data (most notably, outcome data) would be difficult and costly and that low long-term success outcomes might discourage people from trying to lose weight at all [1]. The collection and dissemination of data could be good for some providers but problematic for smaller providers to obtain [1]. It was ultimately suggested that data should be accumulated in a cooperative effort and disseminated about programs generically rather than on a program-specific basis [1].

## What the Science Says

The science panel chimed in to emphasize that evidence shows that weight loss of even 5–10 % of initial body weight can significantly decrease comorbidities of overweight/obesity, but this is often out of line with what dieters expect or desire [1]. They suggested that the message to encourage weight loss should be reformulated to emphasize the health benefits of modest weight loss rather than the lofty weight loss goals that many dieters envision [1]. The Food and Nutrition Board at the Institute of Medicine (IOM) has also indicated that the goal of weight loss programs should be refocused from weight loss alone, which is often appearance based, to weight management and achieving the best weight possible in the context of overall health [23].

The IOM has also recommended that the following be considered as mandatory up-front program disclosures to consumers [23]:

- A statement of the program approach and goals
- Staff credentials
- A statement of client population and experience over a 9-month period
- Program costs
- Preprogram procedures recommended for clients

While this list is a good start, each item needs to be looked at individually to ensure proper interpretation. For example, the significance of advanced degrees and the meaning of certification and registration as it pertains to staff credentials could be potentially misleading to consumers if they are unaware of what they mean. In addition, consumers need to understand that average outcome data of client population and experience over a 9-month period may not coincide with the success rates that they have envisioned for themselves based on what the media depicts. In fact, a consumer perception study conducted on consumers averaging about 220 lb has shown that respondents' dream weight

would be 135 lb, which equates to a 39 % reduction [1]. This is nearly three times the amount that research has shown commercial weight loss programs are capable of safely achieving in the most successful clients [2]. Respondents also reported that they would be "happy" with a 32 % reduction, would "accept" a 25 % reduction, and would be "disappointed" with a 17 % reduction [2]. What this ultimately means is that according to this survey, 67 % of consumers would be "disappointed" with the 10–15 % weight loss achievable under the most effective programs [2]. Clearly, there needs to be a coordinated effort among physicians, providers, and consumers to develop successful programs that also align with consumers' goals.

## How to Improve?

Conference participants eventually settled on a three-pronged action plan that included the formation of a coalition to develop guidelines or standards for the voluntary disclosure of information deemed necessary for consumers to effectively evaluate weight loss programs and products, the formation of a coalition to develop a successful message for educating consumers and corresponding consumer education materials, and an agreement to explore further sources for research initiatives [2].

## What's Next?

As American consumers become more aware of the health risks associated with overweight and obesity, they will increasingly seek out ways to avoid such risks. Commercial weight loss programs have a substantial impact on the problem, but it is clear that there is much work to be done. Changing the way that consumers view weight loss is essential, starting with defining success as a measureable decrease in health risks, as opposed to an unrealistic image defined by the media. In addition, commercial weight loss programs need to devote both time and money to provide consumers with the information and data that they need to make informed and educated decisions about their weight loss options. With these improvements, more commercial weight loss programs could very well be recognized and recommended by health-care providers as essential tools in the weight management field.

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# Chapter 21
# Academic Programs for Weight Control

**Danielle Flug Capalino and Lawrence J. Cheskin**

**Abstract** Hospital- or university-based, medically supervised weight loss programs are far less commonly used by the general public than commercial programs, but offer certain features that are unusual in commercial programs. Their success rates vary but generally provide the most comprehensive care available, utilizing a multidisciplinary team of health-care professionals.

**Keywords** Medical supervision • Weight loss • Multidisciplinary • Team approach

### Key Points

- It is difficult to quantify the number of noncommercial programs in the United States or internationally as there is no comprehensive list published.
- Hospital- or university-based, medically supervised weight control programs are far less commonly used by the general public than commercial programs but offer certain features that are unusual in commercial programs.
- Aside from the composition of the treatment team of professionals, programs vary in the methods used to assess and treat obesity such as metabolic testing, meal replacements, group meetings, and residential programs.
- The interdisciplinary team of professionals often includes a combination of dietitians, exercise physiologists, medical doctors, and behavioral therapists.
- In the Look AHEAD trial, over 5,000 overweight or obese adults with type 2 diabetes were treated with either Intensive Lifestyle Intervention (ILI) participants lost on average 8.6 % of body weight.
- Meal replacements provide food for the person trying to manage their weight so that cooking is not a barrier to success. Their use varies among institutions.
- The higher the total percentage of weight lost, the greater the likelihood of maintaining a 5–10 % loss.

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- Evidence from the National Weight Control Registry (NWCR) shows that 60–90 min of exercise per day is typically what is needed to maintain long-term weight loss.
- The Institute of Medicine's Food and Nutrition Board published the Criteria for Evaluating Weight-Management Programs which includes benchmarks for long-term weight loss sustained for at least one year along with a reduction in at least one related comorbidity.
- The success rates of academically based weight management centers vary, but they generally provide the most comprehensive care available, utilizing a multidisciplinary team of health-care professionals.

## Introduction

Chapter 20 in this book focuses on commercial weight loss programs that have the largest place in the market. Another avenue to control excess weight is hospital-, university- or clinic-based medically supervised programs. Though the specifics of the individual programs differ (and will be explored in this chapter), the defining features of so-called "noncommercial" or "clinical" weight loss centers are that they are medically supervised, provide personalized behavioral management, and offer a collaborative approach of different health practitioners, as well as being generally not for profit. This discussion will be focused on behavioral and nutritional and medical counseling and not focus on pharmaceuticals or surgical interventions, though these are part of many such programs.

It is difficult to quantify the number of noncommercial programs in the United States or internationally as there is no comprehensive list published. Most programs are based in hospitals, and in fact, there are programs at many of the major hospitals in the United States. In addition, programs have different focus areas. We will highlight some of the most well-known programs and analyze the literature that has been published from and about noncommercial weight loss centers. However, given the diversity of the programs, the best way to garner information has been through the websites of various programs and contacting them directly. There is not a body of academic literature looking at outcomes of such centers; instead, searches were conducted by searching authors affiliated with a weight loss center to distinguish which studies would be appropriate for the analysis.

The most recent data available suggests that only a small percentage of people who seek weight loss participate in a university-based program. Of 20,000 adults maintaining significant weight loss, only 5 % had done so through a hospital- or university-based program [1]. Though most research takes place within such settings, the data is limited by the small number of people enrolled. Patients seeking weight loss at university-based programs have been shown to have higher rates of disordered eating and psychopathology and multiple previous failed attempts at weight loss [2]. Thus, while most research studies take place within the setting of a hospital or university, the populations served may represent a more severe form of obesity and its comorbidities and thus may not be representative of the general obese population.

## Interdisciplinary Team

Weight loss centers tend to take an interdisciplinary team approach. The team of professionals often includes a combination of dietitians, exercise physiologists, medical doctors, and behavioral therapists. Sometimes pharmacists or surgeons will be part of the team if pharmaceuticals or surgical interventions are utilized. Following are more in-depth descriptions of the different personnel that weight loss programs often utilize:

Registered dietitians (RD) are credentialed by the Accreditation Council for Education in Nutrition and Dietetics (ACEND) and are trained to create balanced meal plans and work with patients to

discover things like "trigger foods" and disordered eating patterns, such as meal skipping or bingeing. A skilled dietitian can work with a patient to help them lose weight by creating a meal plan or guiding the use of meal replacements. Once weight is lost, caloric needs change, so that continued work with an RD is helpful in devising an appropriate maintenance diet.

An exercise physiologist will work one-on-one with patients to create an exercise plan that will help them lose and/or maintain weight loss. Programs need to be tailored not only calorically, based on metabolic rate, but also need to take into account the physical abilities of the client. The plans do not take a "one-size-fits-all" approach. Some clients may not be mobile, others marathon runners. It is best practice to tailor these plans to the individual, taking into consideration their access to facilities for exercise and level of motivation for physical activity and using that information to come up with a plan that is physically appropriate as well as feasible. As part of the team, the exercise physiologist may also serve as the point person for their clients and can sometimes also serve as the client's personal trainer (or work with the client's trainer). Evidence from the NWCR, which tracks over 10,000 individuals who have lost at least 30 lbs and kept it off for at least one year, shows that 60–90 min of exercise per day is typically what is needed to maintain long-term weight loss [3]. Of the people in the NWCR, 90 % report using a combination of diet and exercise to lose and maintain weight loss [3].

Though weight loss is rooted in the amount of calories that are consumed and spent, psychological factors play a big role in disrupting the energy balance equation. Behavioral change is explored in depth in Chap. 16, but it is important to acknowledge the critical role of a behavioral counselor/therapist in the weight loss center setting. Though an RD can develop a meal plan, a therapist is often needed to get to the root of what is triggering eating behaviors or what is preventing a person from adhering to a diet. Once the root causes are addressed, it can be much easier for a dieter to apply the lessons learned about nutrition.

Therapy and dietary coaching can be done in person or, with the expansion of online access, virtually. A recent NEJM study concluded, in a comparison of in-person and remotely based counseling (without face-to-face contact), that obese patients were able to lose and maintain weight loss over a 2-year period even without face-to-face contact [4].

## Dieting Methods

Aside from the composition of the treatment team of professionals, programs vary in the methods used to assess and treat obesity. For instance, methods may include metabolic testing, meal replacements, group meetings, and residential programs.

Different forms of metabolic testing are used in weight loss centers to estimate the resting metabolic rate (RMR). Measuring RMR can be a very useful tool in designing meal and exercise plans because there is then individual-specific data on which to base the caloric needs to lose weight, and the rate of weight loss can be predicted based on this evaluation. Estimation formulas may be used, often in concert with measurements made via indirect calorimetry. Metabolic testing can be a very useful tool for clients, as they then have knowledge of what their daily energy needs are and what amount of calories can be consumed to lose weight. Repeating the metabolic testing after a period of weight loss can help define changes in metabolic rate that are likely to occur during dieting and determine the level of intake needed to maintain the weight lost.

Though meal replacements are commercial products, the use of the products is a feature of many noncommercial weight management programs. The aim of meal replacements is to provide food for the person trying to manage their weight so that cooking is not a barrier to success. Additionally, since choice is limited, if the person is struggling to make healthful decisions, meal replacement as an option simplifies the process of meal planning in the setting of a low-calorie diet.

**Table 21.1** Major US weight management programs

| Name and location | Services offered | Structure | Pricing | Insurance |
|---|---|---|---|---|
| Albert J. Stunkard Weight Management Program—Health First, University of Pennsylvania, Philadelphia, PA | Medically supervised | Meal replacements | Not stated | Does not accept insurance |
| Duke Diet and Fitness Center, Raleigh, Durham, NC | Medical doctors, nutritionists, behavioral counselors, exercise physiologists | Lifestyle change residential program for varying time, also a family support program | Varies by time frame; 2-week program is $4,400 | Does not accept insurance; Medicare covers a small portion of fees |
| Columbia University Obesity Nutrition Research Center, New York, NY | Weight loss experts, including a behavioral therapist, registered dietitian, and exercise physiologist | 52-week weight loss groups for adults who have more than 50 pounds to lose. Resting metabolic rate, bone density, and bioelectrical impedance, Bod-Pod, underwater weighing, hydrostatic weighing, DXA, and 3-D body scanning available | $50 per week and a one-time fee of $75 for an individual screening appointment with staff before start | Does not accept insurance |
| Johns Hopkins Weight Management Center, Baltimore, MD | Physician, dietitian, exercise physiologist | Orientation session followed by 4-h comprehensive meetings with each discipline; meal replacements or food-based diets; appetite medications sometimes used | $400 for overview, no monthly billing, pay for meetings or individualized services, food | Does not accept insurance |

As demonstrated by the chart, there is no "typical day" in a noncommercial weight loss center, as each has a somewhat different approach and staffing. Each has behavior modification as a central component not only to enable a patient to lose weight but also to be able to sustain the changes to keep it off long term

Some of the better-known products are Medifast, Optifast, Health Management Resources (HMR), Advanced Health Systems, and ProtiDiet. Some of these use a very-low-calorie diet approach (defined as less than 800 kcal per day) and must be followed under medical supervision. The majority of these are done with low-calorie diets, defined as 800–1,200 kcal per day [5].

Though not a first line of treatment, if a person has failed other dietary attempts and is deemed medically appropriate, appetite-suppressing or fat-blocking prescription medications may be used to facilitate weight loss. At the time of this writing, there are 4 FDA-approved medications: orlistat (Xenical), phentermine, lorcaserin (Belviq), and the combination of phentermine and topiramate (Qsymia). Pharmacotherapy is explored in detail in Chap. 18 of this book.

See Table 21.1 for an overview of major weight management programs in the United States.

## Attrition

It is important for developing and improving programs to understand the factors that influence attrition. Additionally, any claims about success or failure of a weight loss program are dependent on completion rates of the program. Thus, it is a critical question to determine why people drop out of programs and what influence this has on the results that only capture completers.

A study by Pekarik et al. looked at 52 women in a university-based weight loss program to answer these questions. Based on earlier literature, it was established that there may be a difference in people who drop out at different points in the process—characterized as early versus late dropouts. Marked differences were found between early dropouts and late dropouts, but the late dropouts were similar to the completers. The early dropouts were characterized as having higher anxiety scores, lower breath of interests, lower energy levels, less organizational skills, and a higher rate of depression [6].

While there are some behaviors clearly identified as highly prevalent among members of the NWCR, including regular exercise, eating breakfast, and regularly weighing themselves, there is a dearth of research on predictors of long-term weight maintenance. In general, the higher the total percentage of weight lost, the greater the likelihood of maintaining a 5–10 % loss. For example, if a person loses 25 % of weight, it may be easier to maintain 5–10 % than if an individual loses 9 % [7]. In addition, adopting behavioral techniques including cognitive restraint was related to successful weight loss in a large sample of obese patients [8].

## Outcomes

Unfortunately, outcomes for weight loss studies are not uniformly reported. Some authors use BMI, others amount of weight lost, and others percentages. Lack of consensus definitions is a limiting factor in comparing efficacy of programs. The Institute of Medicine's Food and Nutrition Board published the Criteria for Evaluating Weight-Management Programs [9] to attempt to resolve this issue. The authors defined long-term weight management as greater than or equal to 5 % weight loss and/or a reduction of BMI by 1.0 or more units, sustained for at least one year. Improvements in health associated with weight loss should produce a reduction in at least one related comorbidity. As such, in addition to weight loss, proper evaluation of programs involves looking at the ability to reduce biochemical markers or medications associated with comorbid conditions (e.g., type 2 diabetes).

Though studies on weight loss are often set in university-based weight management centers, literature specific to success of such centers is not typically published. In part, it is the nature of the field. The results that are published are often funded studies that take place in the setting of a hospital- or clinic-based weight loss center. But there is a distinct difference between specific trials that take place in a hospital weight loss center and the centers' overall success. Further, the studies that are published in peer-reviewed journals are infrequently long-term result analysis.

Unpublished data is perhaps the best way to assess success rates of weight loss centers, though such an analysis is limited by institutions' willingness to provide such information. For instance, Duke advertises an average weight loss of 5 % of initial body weight in 4 weeks for their clients. Duke also reports but does not quantify statistics on improvement of diabetes regulation, blood pressure, cholesterol, and other comorbidities. A study of Duke participants showed that after one year, 80 % had maintained and/or continued to lose weight and 85 % reported significant improvements in their health and quality of life.

At the Johns Hopkins Weight Management Center, unpublished data indicates that the average weight loss achieved was 38 lbs (15 %) and, of those on respective medications, that 57 % of participants were able to reduce or discontinue medication for hypertension, 55 % were able to reduce or stop a statin drug, and 50 % were able to reduce or stop medications for type 2 diabetes.

As a basis for comparison, academically developed programs like the Diabetes Prevention Program (DPP) and Look AHEAD have both published extensively. The DPP looked at over 3,000 individuals with impaired glucose tolerance and studied the effect of a lifestyle intervention (the active arm in the trial) on weight loss. Those in the behavioral arm had a goal weight loss of 7 % body weight in the first 6 months, which was achieved by 49 %, and 37 % maintained that loss for one year [10]. In the Look AHEAD trial, over 5,000 overweight or obese adults with type 2 diabetes were treated with either ILI involving group and individual meetings to achieve and maintain weight loss through decreased caloric intake and increased physical activity, or a Diabetes Support and Education (DSE) condition. In the ILI active arm, participants lost on average 8.6 % of body weight [11].

## Discussion

Though university- or hospital-based weight management centers play a small role in the treatment of obesity overall, they are the main sites of research on the topic. Outcomes from multiple peer-reviewed studies show that substantial weight loss and maintenance is attainable in this setting. The methods used in such studies outline the best practices known in the field. To return to our definition of a non-commercial weight management center, these centers use a multidisciplinary approach. It appears that this integrative model, treating an individual through multiple modalities, can be effective in adopting the behavioral changes needed to sustain long-term weight loss.

Although most peer-reviewed literature on weight loss has taken place in a hospital- or university-based setting, the results are not necessarily broadly applicable. Most research on behavioral treatment has been conducted in university-based programs. Future research might focus more on determining how these behavioral techniques can be best applied in a real-world setting and also on predictors of success among individuals treated at these centers.

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# Chapter 22
# Pharmaconutrition for the Treatment of Obesity

**Ryan T. Hurt, Thomas H. Frazier, and Stephen A. McClave**

**Abstract** Obesity is rapidly becoming the leading cause of preventable death with the incidence of obesity doubling over the past 30 years. There are at least 60 known obesity-associated comorbid medical conditions in addition to 12 different types of cancer. Despite the rising trend of obesity, there are very few FDA-approved pharmacological treatments for weight reduction. Patients often turn to alternative therapies including dietary supplements, nutraceuticals, and pharmaconutrition. The purpose of this chapter is to describe the clinical evidence for a number of pharmaconutritional supplements for the treatment of obesity. These supplements include green tea, green coffee extract, protein, and L-leucine.

**Keywords** Obesity • Pharmaconutrition • Green tea • Green coffee extract • Protein • L-leucine

### Key Points

- Obesity is rapidly becoming the leading cause of preventable death in the USA, second to smoking-related disorders.
- A conservative estimate would place the health-care burden for obesity at $150 billion per year.
- Despite the rising trend of obesity, there are very few FDA-approved pharmacological treatments for weight reduction; thus, alternative therapies are often sought by patients, including dietary supplements, nutraceuticals, and pharmaconutrition.
- Obesity may be associated with a low-grade inflammatory response which may contribute to adverse sequelae and poor outcomes and become a target of immunonutrition therapy.
- Pharmaconutrients with anti-inflammatory actions that can potentially benefit obesity and or its adverse sequelae include omega-3 PUFAs, arginine, green coffee extract, green tea (EGCG), leucine, SAM-e (betaine), carnitine, magnesium, curcumin, vitamin D, zinc, α-lipoic acid, and probiotics.

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## Introduction

Obesity is rapidly becoming the leading cause of preventable death in the USA, second to smoking-related disorders. The incidence of obesity in adults in the USA has doubled over the past 30 years. Approximately 70 % of adults in the USA are considered overweight or obese as of 2010 [1]. Obesity rates have been projected to continue to rise with an estimated increase of 33 % in obesity prevalence by 2030 [2]. A conservative estimate would place the health-care burden for obesity at $150 billion per year [3, 4]. There are over 60 known obesity-associated comorbid medical conditions in addition to 12 different types of cancer [5]. These associated medical conditions, such as diabetes mellitus, coronary artery disease, and nonalcoholic fatty liver disease (NAFLD), can lead to increased morbidity and mortality and complicate medical management [6, 7]. Despite the rising trend of obesity, there are very few FDA-approved pharmacological treatments for weight reduction; thus, alternative therapies are often sought by patients, including dietary supplements, nutraceuticals, and pharmaconutrition [8].

It has been estimated that approximately two thirds of adults use dietary supplements, with the majority being multivitamins, calcium, and vitamin D [9]. As the obesity epidemic continues to increase, patients are increasingly turning to highly commercialized dietary supplements, such as green tea and green coffee extract (GCE) to help them lose weight. Sales of weight-loss supplements in the USA are approximately $2 billion per year and will more than likely increase as more adults become overweight and obese [10, 11]. Dietary supplements are often promoted through marketing and are perceived by the patients as requiring less effort than lifestyle modification such as caloric restriction or exercise [11]. The purpose of this chapter was to examine the antiobesity properties, basic science data, clinical data, and possible side effects of four commonly used dietary supplements. These supplements were chosen from the list of many potential pharmaconutrients (see List 22.1) for obesity, because they have both basic science and multiple clinical studies supporting their use for weight loss. These supplements include green tea, GCE, specialized proteins, and L-leucine.

**List 22.1 Pharmaconutrients with at least some animal and/or clinical data supporting their use in obesity or metabolic syndrome**

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| Omega-3 PUFAs |
| Arginine |
| Green coffee extract |
| Green tea (EGCG) |
| Leucine |
| SAM-e (betaine) |
| Carnitine |
| Magnesium |
| Curcumin |
| Vitamin D |
| Zinc |
| α-Lipoic acid |
| Leucine |
| Probiotics |
| Garcinia Cambogia |

## Obesity

The definition of obesity used for this chapter is based on the definition utilized by the World Health Organization (WHO) and the National Institutes of Health (NIH) using the body mass index (BMI). The recommended classifications based on BMI are as follows: underweight, BMI $\leq$ 18.49 kg/m$^2$;

normal weight, BMI ≥ 18.5–24.9 kg/m$^2$; overweight, BMI ≥ 25.0–29.9 kg/m$^2$; obesity class I, BMI ≥ 30–34.9 kg/m$^2$; obesity class II, BMI ≥ 35–39.9 kg/m$^2$; and obesity class III, BMI ≥ 40 kg/m$^2$ [12]. Furthermore, class III obesity has been referred to as morbid, severe, and super obesity. The BMI is not a perfect measure of obesity and may not be an accurate measurement of associated comorbidity in tall, short, or muscular individuals.

There are a large number of diseases and comorbid conditions associated with obesity in adults. These associated conditions include diabetes, atherosclerosis, hypertension, hyperlipidemia, nonalcoholic fatty liver disease (NAFLD), and obstructive sleep apnea, to name a few. It is these associated comorbidities which are responsible for the increased morbidity and mortality in obese individuals [6, 7, 13]. Numerous large epidemiologic studies have found that obesity is associated with increased all-cause mortality [6, 7]. Furthermore, obesity is associated with cause-specific mortality including heart disease and diabetes [14]. In addition, there are at least 12 types of cancers which are associated with obesity including breast, colon, esophageal, and renal cancers [7].

## Obesity-Associated Inflammation

Obesity may be associated with a low-grade inflammatory response which may directly or indirectly contribute to adverse sequelae and poor outcomes [15]. Lifestyle habits that lead to an increase in BMI likewise contribute to increasing inflammation. Inflammation is increased by inactivity and ingestion of trans fat, saturated fat, and omega-6 fatty acids. Increased leptin levels, high plasma triglycerides, and hyperglycemia with the production of advanced glycation end products also correlate with increased inflammation [15]. Evidence of increased inflammation is seen by the association of central adiposity and increased inflammatory cytokines, a relationship that is not seen with truncal obesity [16, 17]. Even some patients with a normal BMI, but an increased waist/hip circumference, will show evidence of increased inflammation [17].

Obesity has been associated with increased C-reactive protein (CRP) levels. This increased CRP levels (an independent risk factor of cardiovascular disease) may be partially responsible for the obesity-associated cardiovascular risk. A recent meta-analysis evaluated obese subjects and CRP levels in various obese populations [18]. Data from 51 cross-sectional studies that used BMI, waist circumference (WC), or waist-to-hip ratio (WHR) as measure of obesity were evaluated. Obesity was associated with elevated levels of CRP, and the association was stronger in women and those of European decent. There were no significant differences in the anthropometric measurements (WC, WHR, or BMI) [18]. When weight is lost in obesity, the inflammatory response is decreased. This principle was demonstrated in a prospective study of 60 obese women who underwent bariatric surgery [19]. The stated aim of the study was to evaluate changes in the proinflammatory profile of morbidly obese patients after weight loss following bariatric surgery. Twelve months after surgery, there was a significant decrease in levels of IL-6 ($p < 0.001$), hs-CRP ($p < 0.001$), insulin ($p < 0.001$), and homeostasis model assessment (HOMA; $p < 0.001$) [19]. In addition, correlations were seen between BMI and IL-6 levels ($r = 0.53$, $p < 0.001$) and BMI and CRP levels ($r = 0.40$, $p = 0.004$).

In addition to CRP, IL-6, and TNF-α, specific adipocyte cytokines called adipokines (leptin and adiponectin) are involved in obesity-associated inflammation and the metabolic consequences (altered lipid metabolism and insulin sensitivity) of obesity [15].

## Green Tea

Green tea, or *Camellia sinensis*, is a rich source of both flavonoids and flavonols [20]. Catechins are the predominant form of flavonols and probably the primary antiobesity ingredient of green tea. The catechins include epigallocatechin gallate (EGCG), catechin 3-gallate (CG), epigallocatechin (EGC),

epicatechin gallate (ECG), and epicatechin (EC) [21]. EGCG is the most abundant and studied catechin and is the most pharmacologically active with the greatest antiobesity effect [22]. One cup of green tea contains approximately 50 mg of EGCG [23, 24].

Green tea or EGCG has been shown to decrease obesity-associated inflammation. A recent study demonstrated that green tea extract can modulate adipocyte inflammatory signals [25]. Rats were fed a low-fat diet or high-fat diet containing no green tea extract, green tea extract at 1 %, or green tea extract at 2 % for 8 weeks [25]. Compared to the high-fat group with no green tea extract, the green tea extract group had significantly lower levels of TNF-α protein expression. Green tea or EGCG has been shown to decrease proinflammatory cytokines including TNF-α, IL-2, IL-6, and IL-1β in a number of obese and diabetic animal models [26–28]. EGCG increased the anti-inflammatory adiponectin in one study but had no effect in others [29–31].

Green tea, green tea extract, and EGCG are the most clinically studied pharmaconutrients for weight loss [32]. There have been two meta-analyses examining the role of green tea for weight reduction in overweight or obese patients [32]. The first of these included 11 prospective studies with green tea, green tea extract, or EGCG-caffeine in normal, overweight, and obese subjects. The main finding was that green tea significantly decreased overall body weight (mean = −1.31 kg; $p < 0.001$) [32]. Because caffeine may play a role in weight loss, the second meta-analysis included 15 randomized prospective studies of green tea with and without caffeine [33]. Of the 15 RCTs included in the analysis, seven were catechins + caffeine versus caffeine control, six were catechins + caffeine versus caffeine-free control, and two were caffeine-free catechins versus caffeine-free controls. The main findings were that green tea catechins + caffeine significantly decreased BMI (mean = −0.55; 95 % CI, −0.65, −0.40), total body weight (−1.38 kg; 95 % CI, −1.70, −1.06), and waist circumference (−1.93 cm; 95 % CI, −2.82, −1.04) compared to caffeine alone [33]. Green tea catechins + caffeine also significantly decreased total body weight (−0.44 kg; 95 % CI, −0.72, −0.15) when compared with caffeine-free control subjects. The studies which evaluated green tea catechins without concomitant caffeine did not show a significant reduction of any of the assessed anthropometric endpoints.

Because many of the studies in the meta-analyses included subjects who had normal BMI measurements, it is difficult to make conclusions about the weight-loss potential of green tea. Furthermore, the ability of green tea catechins to reduce obesity-associated comorbid conditions and inflammation cannot be clearly evaluated from the meta-analyses. One recent small, randomized prospective trial evaluated the effects of green tea or green tea extract in metabolic syndrome [34]. Thirty-five subjects with metabolic syndrome who were overweight or obese were randomized to receive four cups of green tea, two capsules of green tea extract, or four cups of water per day for 8 weeks. Subjects in the green tea and green tea extract groups had significant reduction in body weight and BMI compared to placebo ($-1.9 \pm 0.6$ kg, $p < 0.05$, and $-2.5 \pm 0.7$ kg, $p < 0.01$).

## Green Coffee Extract

GCE has recently received increased interest from the popular press and population at large as a potential weight-loss supplement. GCE is derived from unroasted coffee beans. Like green tea, GCE can contain naturally occurring caffeine [35]. GCE contains high levels of chlorogenic acid, a polyphenol and potent antioxidant, which is thought to be the main antiobesity component of GCE [35, 36]. The roasting of coffee beans can limit the concentrations of chlorogenic acids [35].

GCE and chlorogenic acids have been studied in animal models of obesity [37, 38]. The first of these studies examined the effect of GCE on fat accumulation and body weight in mice [37]. A mouse model (ddY) which replicates metabolic syndrome (elevated triglycerides, increased fasting blood glucose, and visceral fat) was used to study the effects of GCE on visceral fat and lipids. Animals were fed a standard diet containing GCE for 2 weeks. The main findings were that 0.5 and 1 % GCE

reduced visceral fat and overall body weight [37]. In addition, 2 weeks of GCE reduced hepatic and serum triglycerides. The authors interpreted the results to suggest that GCE is possibly effective against weight gain and fat accumulation by inhibition of fat absorption and activation of fat metabolism in the liver [37]. A subsequent study investigated the efficacy of chlorogenic acid or caffeic acid on body fat in a high-fat (37 % calories from fat) diet-induced mouse model of obesity [38]. Both caffeic acid and chlorogenic acid significantly lowered body weight and visceral fat mass from baseline. In addition, chlorogenic acid lowered serum leptin, insulin, cholesterol, and triglyceride levels compared to the high-fat control group. They also lowered triglyceride (in plasma, liver, and heart) and cholesterol (in plasma, adipose tissue, and heart) concentrations [38]. Adiponectin levels were significantly elevated in the chlorogenic acid group but not the caffeic acid group. Both caffeic acid and chlorogenic acid significantly inhibited fatty acid synthase (FAS), 3-hydroxy-3-methylglutaryl-CoA reductase, while they increased fatty acid beta-oxidation activity and peroxisome proliferator-activated receptor-alpha (PPAR-α) expression in the liver [38]. This study supported the hypothesis that chlorogenic acid (the active component of GCE) improved body weight, lipid metabolism, and obesity-associated adipokine levels [38].

There are a number of clinical studies evaluating the effects of GCE or chlorogenic acid on weight. The first of these was a meta-analysis which combined a number of smaller GCE studies which had evaluated GCE for a potential weight-loss supplement [39]. The study identified five eligible trials, with three meeting inclusion criteria. The main findings were that treatment of GCE resulted in a significant decrease in body weight (mean difference −2.47 kg; 95 % CI, −4.23, −0.72) when compared to placebo [39]. Subsequently, a 22-week crossover study was conducted to examine the efficacy and safety of GCE in reducing weight and body mass [36]. A total of 16 overweight adult subjects received high-dose GCE (1,050 mg), low-dose GCE (700 mg), or placebo in separate 6-week treatment periods followed by a 2-week washout period. The primary outcomes focused on the anthropomorphic measurements of body weight, BMI, and percent body fat [36]. The main findings of the study were significant reductions in body weight (−8.04 ± 2.31 kg), BMI (−2.92 ± 0.85 kg/m$^2$), and percent body fat (−4.44 ± 2.00 %). The significant decreases in these anthropomorphic measurements came when subjects were taking the GCE [36]. Six subjects shifted from overweight (BMI 25–29.9 kg/m$^2$) to the normal BMI (20–24.9 kg/m$^2$) [36]. These observed study results and the meta-analysis were consistent with the animal studies, suggesting that GCE may be an effective weight-loss dietary supplement.

## Specialized Proteins

There has been a large amount of clinical interest in specialized protein supplementation with obese patients in the ambulatory setting. High-protein diets appear to be associated with greater satiety than normal diets and make up a significant portion of calories in a number of popular diet strategies [40]. There are two major types of dietary protein which has been studied extensively, soy and whey. There are a number of potential antiobesity components in protein. Isoflavones have anti-inflammatory properties which may be beneficial in obesity. The branched-chain amino acid L-leucine is found in protein in high concentrations, and it has effects on satiety.

There are a large number of animal studies demonstrating the antiobesity and anti-inflammatory properties of protein. In a recent study, obese Zucker fa/fa rats were fed casein (controls) or casein supplemented with soy isoflavones for 6 weeks [41]. Animals fed the isoflavones had decreased levels of TNF-α and decreased plasma levels of IL-1β and MCP-1. Isoflavone-fed animals had lower levels of the liver enzymes ALT and AST in the plasma [41]. In a previous animal model, similar results were demonstrated. Rats fed a soy diet had less hepatic lipid deposits than controls fed a casein-based protein diet [42]. Animals fed the soy protein had decreased leptin levels, smaller adipocytes, lower

body fat content, decreased brown adipose tissue, and overall decreased weight gain compared to animals fed casein [42].

Soy protein has been shown to be beneficial in a number of smaller clinical studies [43–45]. In a multicenter, randomized prospective human cohort study, 87 healthy obese women were randomly assigned to a 1,200 kcal diet and exercise group or a 1,200 kcal diet, exercise, and soy isoflavone extract group for 6 months [45]. Mean serum leptin and TNF-α levels decreased after 6 months in both groups, but only women in the soy isoflavone group showed a significant increase in mean levels of adiponectin [45].

A prospective trial randomized overweight and obese subjects to a soy-based hypocaloric diet versus a similar placebo diet for 12 weeks [43]. The soy group demonstrated greater weight loss, lower total serum cholesterol levels, and lower LDL cholesterol levels compared to placebo. A separate study randomized obese and overweight subjects to one of three treatment groups for 6 months: lifestyle education, soy protein diet, or soy protein diet with a physical activity program [44]. Those subjects in both the protein groups had significantly greater weight reduction and body fat mass than those subjects randomized to lifestyle education alone [44].

In addition to vegetable-based protein, there is some limited evidence that whey protein has some potential benefits over soy protein [46]. A prospective trial evaluated the role of various protein diets on satiety and biomarkers such as ghrelin and GLP-1, randomizing patients to a single casein-, whey-, or soy-enhanced breakfast. The whey-based meal had significantly higher levels of L-leucine than the soy- or casein-based meals. The whey-based meal better increased satiety as measured by an appetite scale. One of the potential mechanisms to explain the enhanced benefits observed with the whey protein is the increased levels of L-leucine, which may enhance the metabolic mammalian target of rapamycin (mTOR) pathway in the hypothalamus inducing satiety.

## L-Leucine

L-Leucine is one of the three branched-chain amino acids (BCAAs), along with valine and isoleucine. L-Leucine is not metabolized in the liver but directly in the skeletal muscle, and it can cross the blood-brain barrier [47, 48]. Of the three BCAAs, only L-leucine has activity with the mTOR pathway, which is involved in protein synthesis and satiety [48]. As a result of the skeletal muscle mTOR activity, L-leucine is involved in the activation of skeletal muscle protein synthesis [49]. In addition to the enhanced protein synthesis, L-leucine may affect the regulation of food intake via the hypothalamic neurons in the arcuate nucleus (ARC) which express mTOR. L-Leucine is a potent and selective stimulator of mTOR and thus may play a role in stimulating satiety [48]. To optimize muscle protein synthesis, it has been estimated that adults should consume at least 2.5 g of L-leucine with each meal [50, 51]. The main source of L-leucine in the human diet is protein.

There are many animal studies evaluating the effects of L-leucine on obesity and the metabolic syndrome [52, 53]. A recent study examined the effect of L-leucine supplementation during aging. As mammals age, they are at risk for sarcopenia (and obesity increases this risk) [54]. Six-month-old rats were divided into three groups. The first group was an adult group euthanized at 26 weeks of age, the second was fed a leucine-supplemented diet (4 % leucine) for 40 weeks, and the third received a control diet for 40 weeks [52]. Body weight and fat were lower in the leucine-fed animals compared with the control group, but still higher than in the adult group. The lipid and glycemic profiles were altered in both the control and leucine groups, potentially because of the effects of aging. However, leucine supplementation did not affect the changes in protein status parameters associated with aging.

Another recent study examined the effect of casein, skim milk, or leucine and high or low calcium levels on adiposity and insulin sensitivity [53]. Sprague–Dawley rats were fed a high-fat/high-sucrose

(HFHS) diet for 6 weeks. Rats were randomly assigned to one of six HFHS diets for 8 weeks where dietary protein was provided as casein, skim milk, or casein enriched with leucine and contained either low calcium or high calcium [53]. Animals fed leucine had significantly greater insulin sensitivity than those fed casein or skim milk ($p<0.05$). Two important genes responsible for insulin sensitivity, hepatic insulin receptor substrate (IRS) and protein kinase B (Akt), were altered in the liver in response to leucine supplementation [53]. Both skim milk and leucine diets had significantly lower body weight compared to casein ($p<0.05$). Skim milk and leucine both reduced fat mass; however, only leucine improved insulin sensitivity [53]. In addition to the effects on protein synthesis and satiety, leucine may have an effect on insulin sensitivity.

There have been a number of human trials evaluating L-leucine and its effect on obesity, metabolic syndrome, and obesity-associated inflammation. A recent prospective randomized trial evaluated the effects of a pharmaconutritional supplement containing 2.25 g leucine and 30 mg pyridoxine (vitamin B6) [55]. Twenty overweight or obese subjects were randomized to receive leucine + vitamin B6 or placebo three times/day for 4 weeks without caloric restriction. In addition to the clinical arm, the investigators evaluated the effects on isolated adipocytes [55]. Leucine decreased FAS expression and triglyceride content in adipocytes. Administration of leucine + vitamin B6 increased fat oxidation; decreased respiratory quotient; improved HOMA(IR); reduced oxidative and inflammatory biomarkers such as plasma MDA, TNF-α, CRP; and increased adiponectin. The authors concluded that L-leucine positively affected the obesity-associated inflammation [55].

An earlier cohort trial studied the effects of BCAA on body weight. The stated objective of the study was to examine the association between dietary BCAA intake and risk of overweight status/obesity among multiethnic populations from China, Japan, the UK, and the USA [56]. The cross-sectional study cohort included 4,429 men and women aged 40–59 years with no previous diagnosis of diabetes. Compared with those in the first quartile, the OR (95 % CI) of overweight status from the second to fourth quartiles of BCAA intake were 0.97 (0.80–1.17), 0.91 (0.75–1.11), and 0.70 (0.57–0.86). In addition, BCAA intake and obesity were also inversely associated ($p=0.03$) [56]. This data suggested that higher dietary BCAA intake was associated with lower prevalence of overweight status/obesity among healthy adults. Since leucine is the most biologically active of the three BCAAs, it is likely the effect was due to leucine and not valine or isoleucine.

## Other Potential Candidates

There are a number of other potential pharmaconutrients that may induce weight loss in patients with metabolic syndrome or obesity. We have listed a number of candidates, but there may potentially be many more yet to be discovered (List 22.1). Resveratrol is naturally found in the skin of grapes and the Japanese knotweed [57], and a number of animal studies have shown a beneficial effect from this agent on obesity and the metabolic syndrome [58–61]. One such study demonstrated lower concentrations of triglycerides, total cholesterol, free fatty acids, insulin, and leptin found in obese Zucker rats that received resveratrol [58]. Furthermore, the elevated hepatic lipid content was significantly lower in obese rats treated with resveratrol. Despite the large number of basic science studies with resveratrol though, there is a lack of clinical data.

Low levels of vitamin D have been associated with a significant number of diseases including obesity [62]. The exact potential antiobesity mechanism is not completely understood. A recent meta-analysis evaluated the small number of clinical trials involving the effect of vitamin D and/or calcium supplementation on obesity [63]. Obesity often coexists with low calcium intake and vitamin D insufficiency. A total of 15 RCTs on calcium with or without vitamin D and seven on vitamin D alone met the inclusion criteria [63]. The authors found that the data on vitamin D supplementation for weight

loss were too few to make substantial conclusions. Some studies supported the hypothesis that vitamin D supplementation could be beneficial in weight loss, but the data lacked statistical power. As is true with many pharmaconutrients, large prospective randomized controlled trials are needed to confirm a benefit in obesity. However, such trials are expensive, and the monetary support needed to conduct the appropriate large pharmacological studies is lacking.

## Conclusions

Many overweight or obese individuals may turn to dietary supplements as a way to augment their diet as a way to reduce their weight. Nutrient concentrations in dietary supplements are often manyfold higher than the levels typically consumed in a typical Western ad-lib diet. A wide range of these dietary supplements are currently sold over the counter. Because of variation in the phenotypic expression of obesity, treatment with pharmaconutrition should be individualized. Unlike the heavily regulated pharmacological treatments for obesity, dietary supplements are limited only by the provisions of the Dietary Supplement Health and Education Act (DSHEA) of 1994. As a result, dietary supplements often have manufacturing abnormalities, fluctuations in purity, and high potential for contaminants. Dietary supplements are often combined with other products routinely sold in nutrition supplement stores, and as a result, it is difficult to determine which specific agent is producing the antiobesity effect. Despite these limitations, there are a number of pharmaconutritional agents that have potential for improved clinical outcomes in overweight and obese individuals. Combining these agents may provide synergy and improved weight-loss potential.

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# Chapter 23
# Endoscopic Approaches to Obesity

**Andrea True Kelly and Mark DeLegge**

**Abstract** The prevalence of obesity is on the rise and is associated with significant morbidity, mortality, and health-related costs to both patients and society. Investigations for safe and effective treatments for obesity have significantly increased. Current treatments are generally divided into two categories: (1) conservative (e.g., diet, exercise, drugs) and (2) surgical management (e.g., gastric bypass). Long-term success via conservative means is low. While surgical gastric bypass leads to significantly greater and sustained weight loss in obese patients, it is often associated with serious adverse events and high costs. Many patients in need are also not suitable candidates for these more invasive procedures due to comorbidities.

In an effort to capitalize on the efficacy of surgical weight loss treatments while reducing medical risks and costs, investigation into endoscopic and transoral approaches for the treatment of obesity has intensified. Endoscopic approaches primarily include restrictive (e.g., intragastric balloons, gastric stapling) or malabsorptive (e.g., duodenal-jejunal sleeve) devices and procedures. These less invasive approaches allow for outpatient or short-stay procedures and allow for treatment of individuals with comorbidities, older age, and super or mild obesity that are often excluded from surgical procedures. Efficacy observed with endoscopic methods typically lies between that observed for conservative and surgical approaches, with an improved safety profile over surgical procedures. Several of these endoscopic approaches are available worldwide but not in the USA, partly due to high regulatory hurdles for efficacy imposed by the Food and Drug Administration (FDA). Reimbursement coverage for these devices and procedures also remains a challenge.

**Keywords** Obesity • Endoscopy • Minimally invasive • Gastric balloon • Duodenal sleeve • Gastric plication

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## Abbreviations

| | |
|---|---|
| BMI | Body mass index |
| CCK | Cholecystokinin |
| CDC | Centers for Disease Control and Prevention |
| CDRH | Centers for Devices and Radiological Health |
| EVG | Endoluminal vertical gastroplasty |
| EWL | Excess weight loss |
| FDA | US Food and Drug Administration |
| GERD | Gastroesophageal reflux disease |
| GES | Gastric electrical stimulation |
| GI | Gastrointestinal |
| HbA1c | Hemoglobin A1c |
| HDL | High-density lipoprotein |
| IGB | Intragastric balloon |
| LDL | Low-density lipoprotein |
| LGBP | Laparoscopic gastric bypass |
| T2DM | Type 2 diabetes mellitus |
| WHO | World Health Organization |

### Key Points

- Obesity is on the rise and is associated with significant morbidity, mortality, and costs to both patients and society.
- Current treatments are generally divided into two categories: (1) conservative (e.g., diet, exercise, drugs) and (2) surgical management (e.g., gastric bypass).
- Long-term success via conservative means is low, and although surgical gastric bypass leads to significantly greater and sustained weight loss, it is often associated with serious adverse events and high costs.
- Many patients are not suitable candidates for these more invasive procedures due to comorbidities.
- In an effort to capitalize on the efficacy of surgical weight loss treatments while reducing medical risks and costs, investigation into less invasive endoscopic and transoral approaches for the treatment of obesity has intensified.
- Endoscopic approaches primarily include restrictive (e.g., intragastric balloons (IGBs), gastric stapling) or malabsorptive (e.g., duodenal-jejunal sleeve) devices and procedures, which allow for outpatient or short-stay procedures and allow for treatment of individuals with comorbidities, older age, and super or mild obesity that are often excluded from surgical procedures.
- Efficacy observed with endoscopic methods typically lies between that observed for conservative and surgical approaches, with an improved safety profile over surgical procedures.
- Several of these endoscopic approaches are available worldwide but not in the USA, partly due to regulatory hurdles imposed by the Food and Drug Administration (FDA), and reimbursement coverage for these devices and procedures also remains a challenge.

## Introduction

Obesity is complex metabolic disease of excessive fat accumulation associated with significant morbidity, mortality, and health-related costs. Clinically defined by a body mass index (BMI) of 30 kg/m$^2$ or more, obesity is associated with premature death from numerous causes. This growing pandemic is the fifth leading risk for death globally; 2.8 million adults die each year from preventable obesity-related conditions including type II diabetes mellitus (T2DM), cardiovascular diseases, and certain cancers [1]. In 2008, more than 500 million adults were considered obese, and the prevalence of super obesity (BMI $\geq$ 50 kg/m$^2$) increased from 0.9 to 6.2 % over a 40-year period. Children also suffer from obesity, and obesity noted in adolescence is significantly associated with an increased risk of severe obesity in adulthood [2]. In 2010, 40 million children under the age of 5 were already considered overweight. The World Health Organization projects that by 2015 approximately 2.3 billion adults will be overweight and greater than 700 million will be obese worldwide [1].

The race for safe and effective treatments for obesity has intensified. Current treatments are generally divided into two categories: (1) conservative management (e.g., diet, exercise, behavioral, pharmacologic/drug therapy) and (2) surgical management (open and laparoscopic; e.g., gastric bypass, gastric banding). Finding safe and effective long-term drug therapies for the treatment of obesity has been a challenge. In 2011, the FDA declined to approve three new diet pills and forced the withdrawal of another (sibutramine) from the market. One new drug (Qsymia™; phentermine and topiramate, extended release) was approved by the FDA in 2012 for patients with a BMI $\geq$ 30 or 27 kg/m$^2$ with one weight-related morbidity along with a low-calorie diet and exercise. However, long-term success achieved via conservative means is generally low. While surgical gastric bypass leads to significantly greater and sustained weight loss in obese patients, it is often associated with serious adverse events and high costs. In addition, many patients in need of surgical treatment of obesity are not suitable candidates for such procedures.

In an effort to capitalize on the efficacy of surgical weight loss treatments while reducing medical risks and costs, investigation of endoscopic and transoral approaches for the treatment of obesity has increased. Endoscopic approaches for weight loss typically include restrictive (e.g., IGBs, gastric stapling) or malabsorptive (e.g., duodenal-jejunal sleeve or endoluminal bypass) devices and procedures. These less invasive approaches, as compared to surgery, allow for outpatient or short-stay procedures and treatment of individuals who are currently excluded from more invasive surgical procedures such as those with multiple comorbidities, older age, and super or mild obesity. In addition, endoscopic approaches may be used before bariatric surgery in order to reduce overall risks and improve the efficacy of these more invasive, longer-term surgical approaches.

Unfortunately, most endoscopic methods/devices are not available commercially in the USA, but several are available worldwide. Industry attributes this to high regulatory hurdles imposed by the US FDA Center for Devices and Radiological Health (CDRH), the division of the FDA responsible for granting medical device marketing approvals (e.g., 510(k), pre-market approval) [3]. In addition, lengthy FDA device registration review times nearly double that of other developed countries also has an impact. While the speed at which the CDRH reviews device applications is finally starting to improve, thanks to changes and innovative programs recently implemented by the agency (e.g., Medical Device Innovation Initiative), a backlog of applications remain. However, with continued demonstration of safety and efficacy and greater communication and collaboration between device developers and the FDA, several of these important endoscopic approaches should be commercially available in the USA within 5 years.

## Overview of Obesity and Satiety

Simply stated, the fundamental cause of obesity is an energy imbalance between calories consumed and calories expended. Globally, the obesity pandemic has been spurred by the increased intake of energy-dense foods that are high in fat, salt, and sugar but low in vitamins, minerals, and other micronutrients. This, coupled with a decrease in physical activity and sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization, helped elevate obesity to the leading health concern facing the USA [4].

Overeating is a leading contributor to the development of obesity, and satiety is an important and related paradigm. Understanding and exploiting the mechanisms behind satiety may hold the key to successful endoscopic approaches for the treatment of obesity. The mechanisms behind significant weight loss observed during surgical gastric bypass procedures are complex and still a subject of scientific investigation. Fundamentally, the means by which food is received and processed by the digestive system is altered by gastric bypass in three ways: (1) food intake is restricted due to the creation of a small gastric pouch, (2) food is excluded from the stomach and proximal bowel, and (3) undigested food is exposed to the jejunum. These changes result in a high level of satiety or the perception of feeling full and satisfied between meals. This ultimately leads to less food intake, weight loss, and important metabolic changes that decrease comorbid conditions, particularly type 2 diabetes. Endoscopic obesity procedures attempt to mimic one or all of these alterations.

The relationship between postprandial antral distention and sensory fullness has long been recognized in satiation [5, 6]. The satiety response is induced by a complicated neuromuscular and hormonal regulatory system between the stomach, gastrointestinal (GI) tract, hypothalamus, and the vagus nerve [7, 8]. In vivo electrophysiological studies have proven the existence of two classes of upper gastrointestinal vagal nerve endings: (1) tension receptors that are exclusively sensitive to gastric muscular contractions and distention and (2) gastric mucosal receptors that respond to gastric mucosal stroking and chemical stimuli induced by the presence of food [9].

In addition, cholecystokinin (CCK) is an important mediator in the satiety response. This gut peptide has both direct and indirect actions that inhibit food intake, which are likely mediated through different sites. Production of CCK occurs in response to a high-fat meal arriving in the small intestine and by stimulation of gastric mechanoreceptive fibers through the action of gastric distention. The satiety signal is delivered through gastric vagal afferent fibers to the medial hypothalamus via CCK. Numerous studies have concluded that inhibition of food intake and the induction of satiety result from the physiological actions of endogenous CCK [10–12]. Similarly, the 28-amino acid "hunger-stimulating" peptide, ghrelin, which is produced mainly by P/D1 cells lining the stomach and epsilon cells of the pancreas, also plays a role in satiety [13]. Ghrelin levels increase before meals and decrease after meals. Following gastric bypass, ghrelin levels are reduced in patients and lead to satiation before it would normally occur [14].

Navigating these complex neuromuscular regulatory mechanisms is critically important for current restrictive-type endoscopic methods including IGBs and endoluminal suturing/stapling, which allow the "satiety signal" to be sent with less food intake. Other endoscopic approaches to the treatment of obesity focus on malabsorption of food to prevent caloric utilization by the body (e.g., endogastric liners/sleeves), similar in concept to gastric bypass. Thus, it stands to reason that future endoscopic devices and procedures that target multiple pathways in this complex satiety system should have improved efficacy over current methods.

Other important procedures that are not covered in this endoscopic review that are also less invasive than the classic surgical procedures include laparoscopic gastric banding, vagal nerve stimulation, and gastric pacing/electrical stimulation.

## Endoscopic Devices and Approaches

### *Restrictive Approaches*

#### Intragastric Balloons

Overview

One of the first available endoscopic gastric restrictive techniques performed involved insertion of an IGB device. Since then, IGB placement has become the most common endoscopic procedure performed for the treatment of obesity. The IGB represents a reversible endoscopic approach for weight loss that is available worldwide, with the exception of the USA.

These devices were first evaluated with small-volume balloons of approximately 220–250 $cm^3$ [15]. Early trials using air-filled polyurethane balloons with sharp ridges failed to demonstrate significant efficacy vs. sham procedures and were associated with significant complications including gastric mucosal ulceration and bleeding, gastric perforation, and balloon deflation with small bowel obstruction [16]. Research and renewed interest in gastric space-occupying devices resulted in design and material improvements that have led to smooth, spherical, saline, or air-filled silicone devices that are longer lasting and better tolerated. These devices are inserted into the stomach under endoscopic guidance, generally under deep sedation. The typical patient BMI at implantation ranges from 27 to 60 $kg/m^2$ [17, 18]. The procedure lasts approximately 15–30 min, and complication rates associated with the actual IGB placement procedure itself are low. Placement is completed via an outpatient procedure, and patients generally require a prescription for an antiemetic upon discharge given that nausea and vomiting frequently occur following the procedure.

Weight Loss with IGBs

While results of certain randomized, prospective, controlled trials have demonstrated safety and efficacy compared to sham procedures, overall the results of IGB for weight loss have been variable. The duration of IGB gastric placement is 3–6 months for most devices, and additional balloon placements can be repeated out to 12 months [19, 20]. The greatest weight loss noted with IGBs generally occurs in the first 3 months. Patients with weight loss ≥6.5 kg at 3 months are more likely to exhibit weight loss at 6 and 12 months. Repeat IGB placement for an additional 9 months in patients who experienced successful weight loss with the first IGB placement resulted in weight loss of 20.5 % (25.6 kg) after 1 year. Other factors associated with successful weight loss were being female and adherence to a weight loss program with a lower-calorie diet, exercise, and behavior modification [21].

Results from randomized, double-blind, placebo-controlled trials [21] and recent reviews [22–24] have shown that 6-month balloon placement induced a mean weight loss of 15 kg (range 9–21 kg) or 34 % excess weight loss (EWL) (±4.8 %; $P>0.001$) when compared to sham procedures [25]. In a 12-month trial, an average weight loss of 24 kg was achieved [19]; however, 15 % of balloon-treated subjects showed no or insufficient weight loss, and early balloon removal was reported in 3–7 % of patients [21, 26, 27]. In a meta-analysis that included over 3,500 patients, the average reported weight loss at 6 months was 14.7 kg or 32.1 % of excess body weight (EBW) [27]. However, efficacy results have also varied; two other sham-controlled trials failed to demonstrate a benefit of IGB placement on early weight loss or other body measurements compared to controls [21, 28]. Mechanistically, a temporary increase in pre- and postprandial satiety, which was maximal at 4 weeks after the intervention, has been reported [28].

### Metabolic Endpoints Noted with IGBs

Data on metabolic abnormalities and comorbidities with IGB placement in over 1,000 patients showed improvements in T2DM (improvements in glucose control and hemoglobin (Hb) A1c levels) and hypertension in 87 % and 94 % patients, respectively [25, 29]. Moreover, the positive effect of IGB placement on diabetes remained up to a year after balloon removal in about 1/3 of the diabetic patients studied [30]. Weight loss resulting from IGB placement has also led to improvements in lipid profile (low-density lipoproteins, cholesterol, and triglycerides) and obstructive sleep apnea [18, 21].

### Weight Loss Maintenance with IGBs

A concern with a temporary procedure such as IGB placement is the risk of weight regain after removal. Indeed, one report showed that 28–80 % of patients regained their lost weight after only 1 year [20]. Other studies have shown an average remaining weight loss of 9 kg or 27 % EWL, representing 10 % of the total weight loss [31]. Two years after IGB removal, one study showed that >10 % EWL was maintained by 47 % of patients, while >15 % EWL was maintained by 33–38 % [20, 21]. In a study of 100 patients with IGB placement for 6 months, Dastis et al. [32] showed that at balloon removal, the average weight loss was 12.6 kg. Follow-up showed that EWL >10 % was maintained in 24 % of patients after 2.5 years, while an average of 12.6 % EWL was achieved after 4.8 years. At 5 years post-balloon removal, 40 % of the IGB population opted for a surgical bariatric procedure.

A meta-analysis by Imaz et al. showed that 1 year after treatment, 143 patients lost a mean of 15.9 kg at balloon removal. However, the 133 patients that were followed 1 year after balloon removal had regained 6.3 kg, representing 39.6 % of the weight lost at balloon removal [27].

### Comparison of IGB to Surgical Gastric Bypass

Compared to gastric bypass, the majority of studies have shown that IGB placement leads to a lesser degree of weight loss. A mean loss of 14.7 kg is typical at IGB removal (~6 months) [27] vs. 20–30 kg weight after bariatric surgery, which is maintained up to 10 years [33]. A recent study in Turkey compared laparoscopic gastric bypass (LGBP) with two consecutive IGB placements. A total of 32 patients were studied: 16 patients underwent LGBP and the other 16 patients underwent balloon placement for 6 months followed by placement of a second balloon for another 6 months. Excess weight loss observed between the two groups at 6 months was not significantly different, but at 12 and 18 months, patients in the balloon group had significantly higher weight loss compared to the LGBP group. According to this report, endoscopic management of obesity is at least comparable to surgical management [34].

Given the apparent transient nature of weight loss noted with temporary IGB placement, some clinicians have recommended the IGB as a pretreatment to allow for more invasive bariatric surgery in patients whose risk of surgery is compromised by their significant weight. Exclusion of patients from surgical bypass often relates to the surgical risks present in super- or mega-obese patients who also have obesity-related comorbidities (e.g., diabetes, hypertension). Studies in super obese patients (BMI $\geq$ 50) have shown that even partial weight loss with IGB placement can lessen the surgical risks noted when undergoing bariatric surgery in this population. This may be due to a reduction in visceral fat, which makes laparoscopic approaches easier and also decreases the rate of conversion to open procedures and the need for two-stage surgeries [35].

Promising results were obtained in super-super obese patients (BMI > 60 kg/m$^2$) with IGB placement followed by LGBP surgery. A recent report by Zerrweck et al. demonstrated that weight loss with an IGB prior to LGBP in super-super obese patients significantly reduced excess BMI and was associated with a shorter operative time and a lower overall risk of significant adverse outcomes [36].

Specifically, the IGB was maintained during 155 ± 62 days and induced a loss of 5.5 ± 1.3 kg/m$^2$ (11.2 ± 3.2 % of excess BMI) at the time of LGBP. This was associated with a decrease in systolic blood pressure and gamma-glutamyl transpeptidase level ($P < 0.05$ vs. baseline). Operative time was lower in the IGB group (146 ± 47 vs. 201 ± 81 min in controls; $P < 0.01$), and significant adverse events occurred less frequently after LGBP in the IGB group (2 vs. 13 in controls; $P < 0.05$). All patients were alive at 1 year, and overall weight loss was similar in both groups (52.4 ± 17.3 vs. 50.3 ± 12.7 % of excess BMI loss in controls; NS).

The IGB may also serve as a "segway" for the reconsideration of bariatric surgery in patients who initially considered surgery but refused. In a study of patients who qualified but initially refused bariatric surgery and underwent IGB placement, a greater understanding of the potential benefits of weight loss interventions was demonstrated, and many reconsidered bariatric surgery following IGB placement [37].

### General Safety and Tolerability of IGBs

Newer IGBs are generally well tolerated. Some of the more commonly reported complications include dyspepsia and emesis (up to 7.4 % of subjects), especially during the first 2 weeks of placement [38]. Results from a large case series and meta-analysis of nearly 3,500 patients showed that adverse experiences observed with IGBs included the following: esophagitis (1.27 %), balloon rupture (0.36 %), and gastric outlet obstruction (0.76 %) [39, 40]. Another meta-analysis showed that complication rates leading to early balloon removal occurred in 4.2 % of patients and nearly 43 % of these early removals were voluntary [27]. Other adverse events and reasons for early removal included deflation (0.1 %), gastric perforation (0.2 %), gastrointestinal tract obstruction (0.6 %), and gastric ulceration (0.1 %). Death related to IGB placement has also been observed but is rare (0.07 % of subjects) [22, 23, 27, 41].

### Examples of IGBs

The most common gastric balloon on the market internationally is the Orbera™ balloon (formerly the BioEnterics Intragastric Balloon or BIB, Allergan, Irvine, California, USA). Others include the Heliosphere Bag® (IHB, Helioscopie Medical Implants, Vienne, France), the volume-adjustable Spatz™ Adjustable Balloon System® (Jericho, NY, USA), the Silimed Balloon (Silimed, Rio de Janeiro, Brazil), the Stationary Antral Balloon (SAB; JP Indústria Farmacêutica, Ribeirão Preto, Brazil), and the ReShape Duo® (California, USA).

### Orbera™ Intragastric Balloon

The Orbera™ by Allergan (formerly BioEnterics Intragastric Balloon; BIB) is a spherical, large-capacity (600–800 mL) silicone polymer balloon available commercially outside of the USA and is the most widely studied IGB. The deflated balloon is preloaded on a catheter, which is passed transorally into the esophagus. Once the balloon has been passed, an endoscope is passed along side it to ensure accurate placement of the balloon in the fundus. Under direct visualization, the balloon is then inflated by the injection of saline solution mixed with methylene blue through the external portion of the catheter. The Orbera™ balloon can remain in place for a maximum of 6 months given that the risk of spontaneous balloon deflation increases at time points, thereafter. If inadvertent balloon rupture does occur, methylene blue is released and systemically absorbed, leading to a change in urine color. This intuitive mechanism alerts the patient to notify their clinician for immediate follow-up.

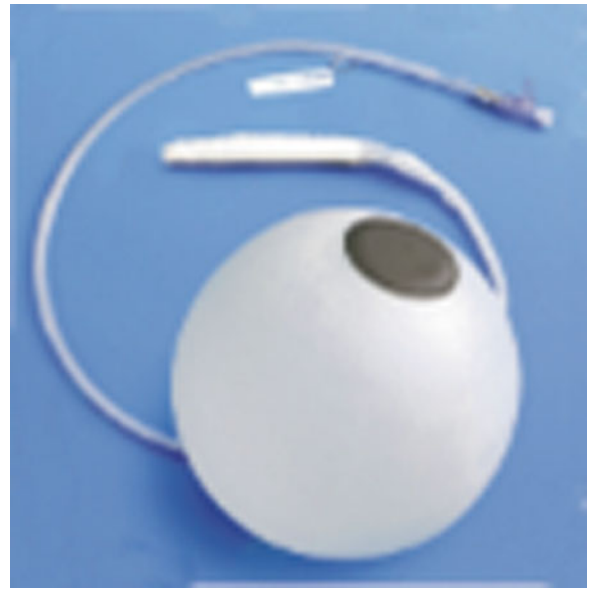

**Fig. 23.1** Heliosphere IGB System

Compared with conservative measures, retrospective studies have shown that BIB placement resulted in a significantly greater decrease in BMI at 6 months (35.4 vs. 38.9 kg/m$^2$) [42] but was not as effective in reducing BMI at 6- and 12-month follow-ups compared to surgical sleeve gastrectomy [30, 43].

### Heliosphere Bag®

Another endoscopic IGB design is the Heliosphere Bag® (Helioscopie Medical Implants, Vienne Cedex, France); see Fig. 23.1. It is an air-filled balloon with a gold coating on the internal surface to impede air leakage that was introduced in 2004. The time to endoscopic placement was reported at 8 min, but issues with balloon positioning at placement were noted. These included balloon deflation and patient discomfort due to the large balloon size and decreased flexibility [44]. Nausea and vomiting were commonly observed post-procedure (80 % of patients), which lead to severe dehydration in 6 % of patients. Weight loss was 6, 7, and 10 kg at 1, 2, and 4 months, respectively. Another study reported by Forestieri et al. in 100 patients demonstrated that in patients who were discharged on a 1,000 kcal diet following HB placement, mean weight loss observed at 6 months was 17.5 kg [45]. Adverse events included balloon deflation and migration into the small intestine ($n=1$) and partial balloon deflation ($n=3$) due to a manufacturing welding problem, as noted in the resulting medical device alert issued in 2009 for possible bowel obstruction.

A double-blind, comparative study of the BIB vs. the HB was been performed in 33 patients [46]. At 6 months, weight loss was similar between the two balloon devices. However, two of the HB devices deflated and migrated distally into the small intestine, and an additional four HB devices were removed due to patient intolerance.

### Spatz™ Adjustable Balloon System

The Spatz™ Adjustable Balloon System® is currently available worldwide, with the exception of the USA, and offers a unique adjustable IGB design approved for up to 1 year of implantation. Over 180

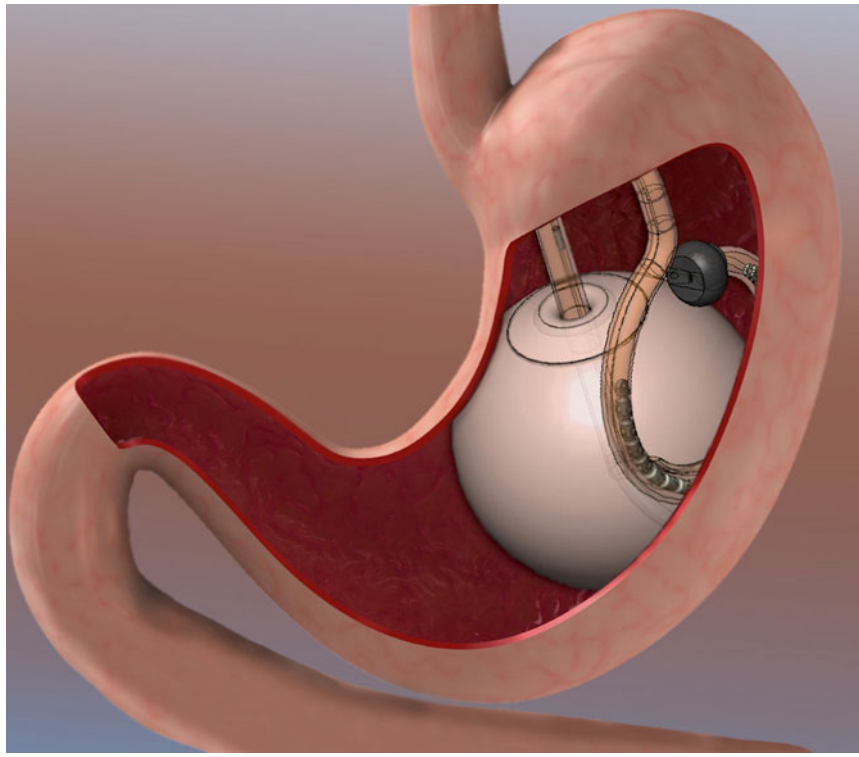

**Fig. 23.2** Spatz™ Adjustable Balloon System®

patients were registered in a clinical registry in Spain, and results have shown weight loss of 14.8 (36.2 % EWL), 21.1 kg (45.7 % EWL), and 26.7 kg (57.1 % EWL) at 12, 24, and 36 weeks, respectively [19]. Downward adjustment (balloon volume reduction) for intolerance (mean 160 $cm^3$) in the first 2 weeks alleviated symptoms (nausea/vomiting) and yielded continued weight loss of 3.9 kg/month. Upward adjustment (mean 186 $cm^3$) at weight loss plateau (mean 3.2 months) yielded an additional weight loss of 1.7 kg/month; see Fig. 23.2.

### Stationary Antral Balloon

An alternative endoscopic balloon design currently under development is the Stationary Antral Balloon (SAB; JP Indústria Farmacêutica S.A., Ribeirão Preto, São Paulo, Brazil). This pear-shaped balloon device is filled with 150–180 $cm^3$ of saline and is attached to a 30 cm duodenal stem with a 7 g metallic weight. The stem and metallic weight are meant to keep the balloon in the antrum without migration, capitalizing on the relationship between antral distention and sensory fullness. Twenty-six patients received the device for an average of 4 months, and the median weight loss observed was 6.5 kg. Spontaneous balloon deflation was noted in four patients, with two-fourth patients expelling the balloon rectally. One of the deflated balloons migrated back into the stomach where it was retrieved endoscopically. One balloon migrated down to the small intestine where it caused an obstruction and resulted in a surgical removal [47].

**Fig. 23.3** ReShape Duo® IGB

ReShape Duo®

Another alternative endoscopic balloon with a double-balloon design currently under development is the ReShape Duo® (ReShape Medical, California, USA); see Fig. 23.3. The double-balloon device is placed in a 15–30-min outpatient procedure and is meant to prevent migration of the device if one of the balloons deflates. Results from a phase I clinical trial in 30 patients showed that the mean EWL observed after 6 months of balloon placement was 31.8 ± 21.3 % with the ReShape Duo® and 18.3 ± 20.9 % in the control group. Follow-up at 1 year showed that the treatment group maintained 64 % of their weight loss [48]. The ReShape Duo® has been used successfully in Europe since 2007 and is currently being evaluated as part of a clinical study for future FDA approval in the USA.

## Endoluminal Suturing

Other endoscopic techniques for weight loss have not been studied as extensively as the IGBs; no meta-analyses have been performed, and many of these devices have not been extensively studied in randomized, controlled, multisite clinical trials. One restrictive endoscopic approach to weight loss that has been studied in clinical trials is endoluminal suturing, also known as endoluminal vertical gastroplasty (EVG). The aim of this somewhat challenging gastric plication technique is the creation

of a restrictive gastric pouch via suturing that limits food intake. This reduced size proximal gastric pouch creates an effect similar to what is observed with laparoscopic banding to achieve satiety.

### EndoCinch™

The most broadly utilized endoluminal suturing device system is the EndoCinch™ system (C.R. Bard, Murray Hill, NJ). This device was initially investigated for the treatment of gastroesophageal reflux disease (GERD), but issues with long-term durability were observed [49]. It has also been used in the repair of gastrogastric fistulas following bypass surgery [50]. Fogel et al. first described the utilization of the EndoCinch™ for the treatment of obesity in 2008. The EVG procedure for weight loss involved configuration of one continuous suture running through 5–7 stitch points in a cross-linked fashion from the proximal fundus to the distal body [51]. After all the stitches are placed and visualized, the suture is tightened, bringing the anterior and posterior gastric wall faces together to create the EVG.

Results reported out to 12 months in 59 of 64 patients treated with the EndoCinch™ method in an uncontrolled study. The mean preoperative BMI was 39.9 kg/m$^2$ and the procedure took approximately 45 min. Results showed that patients had a significant reduction in BMI at 12 months (mean [SD] BMI 39.9 ± 5.1 vs. 30.6 ± 4.7 kg/m$^2$; $P < 0.001$) and a % EWL (SD) of 21.1 ± 6.2, 39.6 ± 11.3, and 58.1 ± 19.9 at 1, 3, and 12 months, respectively. The greatest reduction in % EWL (85.1 ± 24.0) was noted in patients with a BMI <35 kg/m$^2$ [51].

No serious adverse events with the EndoCinch method were noted; however, on repeat endoscopy, it was observed that some of the patients had loosening or breaking of the sutures. It is unclear what effects suture failing will ultimately have on longer-term weight loss and/or safety. Randomized, prospective sham-controlled trials are necessary to confirm the results of this observational trial.

### Restore Suturing System™ Transoral Gastric Volume Reduction (TRIM)

Another technique known as the transoral gastric volume reduction or TRIM procedure was performed using the Restore Suturing System™ (RSS; Bard-Davol, Warwick, RI). This device is a single-intubation, multistitch, endoscopic suturing system where the device capsule is placed on the end of a standard endoscope and the suturing system is placed through the working channel of the endoscope; see Fig. 23.4a–d. This device was studied in a pilot nonrandomized safety and feasibility trial at two institutions, and a total of 18 patients were enrolled [52]. This study demonstrated that an average of six plications were successfully placed in all patients with a procedure time of 125 ± 23 min. After the procedure, common complaints included nausea, vomiting, and abdominal discomfort. The first ten patients enrolled were kept overnight according to the study protocol, and the remaining eight patients were discharged on the day of the procedure and there were no serious adverse events noted [52].

At the 12-month follow-up ($n = 14$), decreases in the mean weight (11.0 ± 10.0 kg, $P = 0.0006$), mean BMI (4.0 ± 3.5 kg/m$^2$ $P = 0.0006$), and mean waist circumference (12.6 ± 9.5 cm, $P = 0.0004$) were observed. The mean EWL at 12 months was 27.7 ± 21.9 %. The proportion of patients with an EWL of ≥20 % or ≥30 % was 57 % and 50 %, respectively [53].

The mean systolic and diastolic blood pressure of patients treated with the TRIM procedure decreased by 15.2 mmHg ($P = 0.0012$) and 9.7 mmHg ($P = 0.0051$), respectively. No device or procedure related serious adverse events were noted. Endoscopy at 12 months showed partial or complete release of plications in 13 patients [53].

## Endoluminal Stapling

Another restrictive endoscopic method involves gastric stapling. Similar to gastric plication, endoscopic stapling procedures aim to create a restrictive proximal gastric pouch. Endoluminal gastric

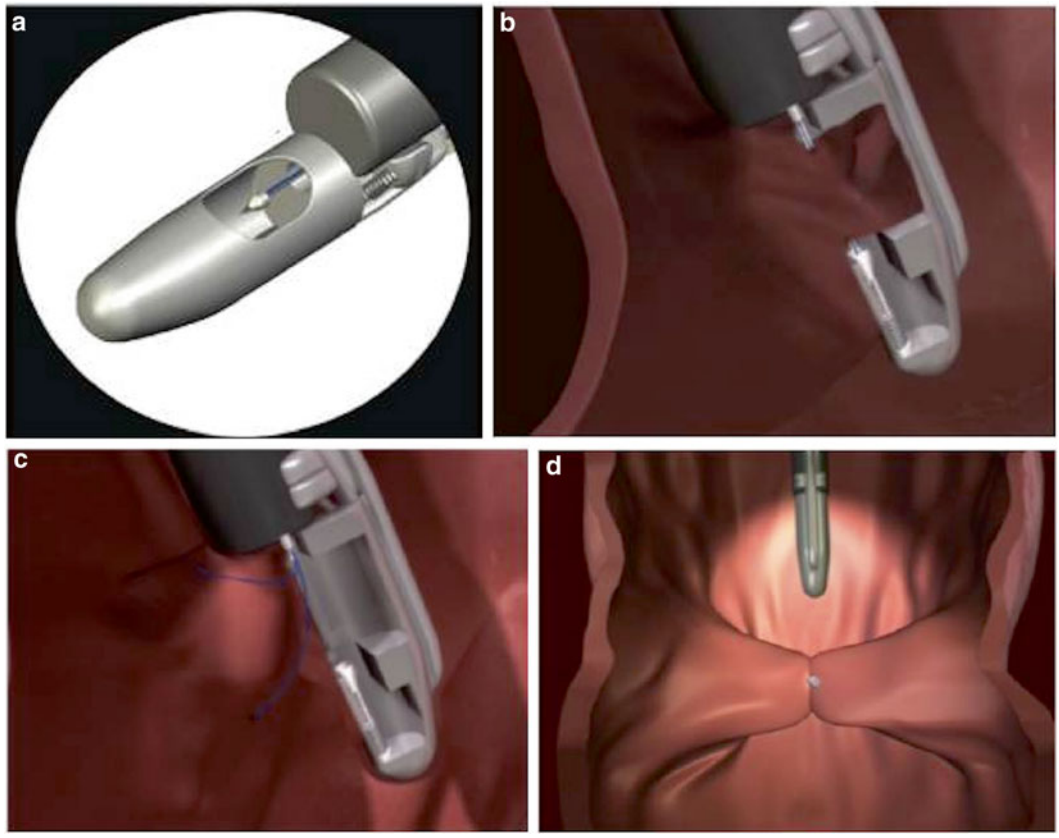


**Fig. 23.4** Restore Suturing System™ TRIM procedure (from Brethauer et al., 2010). (**a**) Needle with suture passes through tissue. (**b**) Capsule applied to tissue, and suction applied. Needle drives suture and suture tag through muscular wall of stomach and deposits tag in end of capsule. (**c**) Tag and suture are retrieved from end of capsule by activating plunger on device. Capsule is then positioned for next suture placement. (**d**) Once the plication has been approximated, the fastener is deployed, and the suture cut with activation of the fastening device. Another suturing device is then placed down the working channel, and the steps are repeated

stapling was first performed in 2007, and various locations, techniques, and devices have been used since (e.g., the transoral endoscopically guided stapling system, TOGA®, Satiety, Inc., Palo Alto, CA, USA; Eagle Claw, Olympus, Tokyo, Japan; EndoCinch™, C.R. Bard, Inc., Murray Hill, NJ, USA; SurgASSIST, Power Medical Interventions, Inc., New Hope, PA, USA; BaroSense Articulating Circular Endoscopic Stapler, Menlo Park, CA, USA).

### Transluminal Oral Gastroplasty (TOGA®)

Extensive clinical testing and early promise was demonstrated with transluminal oral gastroplasty (TOGA®) (Satiety, Inc., California, USA). The TOGA® procedure involves the utilization of an endoscopic stapling device on a flexible shaft for transoral formation of a proximal gastric sleeve [54]. Similar to endoluminal stapling, this reduced size proximal gastric pouch limits the amount of food eaten to achieve satiety.

Early clinical success with this device was observed. The first prospective human TOGA® trial was performed in 31 patients with a BMI of 43.3, and mean reported EBW loss was 16 %, 23 %, and 25 %

at 1, 3, and 6 months, respectively [55]. A second human study of the TOGA® procedure was performed in 11 patients, and weight loss of 19 %, 34 %, and 46 % at 1, 3, and 6 months, respectively, was observed [56]. After the procedure, no serious adverse events were noted, and common complaints in these studies included nausea, vomiting, and abdominal discomfort.

As of July 2010, over 180 patients were treated with the TOGA® system in Italy and Belgium as part of a pivotal clinical trial with the primary endpoint of % EWL in up to 60 months, and patients were expected to participate in post-procedure nutritional/dietary counseling. Fifty-three patients were available at the 12-month follow-up [57]. Excess BMI loss was reported at 33.9 %, 42.6 %, and 44.8 % at 3, 6, and 12 months, respectively. At 12 months, excess BMI loss was 52.2 % for patients with a baseline BMI of <40.0 and 41.3 % for patients with a baseline BMI of ≥40.0 ($P<0.05$). At 12 months, Hb A1c levels decreased from 7.0 % at baseline to 5.7 % ($P=0.01$); triglyceride levels decreased from 142.9 to 98 mg/dL ($P<0.0001$); high-density lipoprotein levels increased from 47.0 to 57.5 mg/dL ($P<0.0001$). One case of respiratory insufficiency and asymptomatic pneumoperitoneum were noted and were treated conservatively [57]. An apparent device malfunction leading to esophageal perforation was also noted in at least one patient, resulting in a lawsuit filed against Satiety, Inc. [58]. In 2012, Nanni et al. reported the results of 29 patients treated with the TOGA® system, 20 with LGBP, and 30 with biliopancreatic diversion (BPD) [59]. At the 2-year follow-up, greater reductions in BMI were noted in both the LGBP and BPD groups with a higher percentage of these patients reaching a BMI <35 compared to the TOGA® group.

These disappointing longer-term efficacy results have reportedly led to the sale of Satiety, Inc.'s assets and intellectual property rights [60]. The TOGA® system has been granted a CE mark, but it is still not available for sale in the EU or rest of world. FDA approval has not been granted, and it appears that commercial advancement of this system is on hold.

### Transoral Endoscopic Restrictive Implant System (TERIS™)

Another stapling system is the Transoral Endoscopic Restrictive Implant System (TERIS™, BaroSense, Inc., Redwood, CA, USA). This is a relatively new technique combining staples with a prosthesis at the level of the cardia. Restriction is created by means of five silicone anchors placed through full-thickness, transmural plications in the cardia just below the gastroesophageal junction, leaving a 10 mm restricting orifice in the middle [55, 56]. A study in 13 patients with BMIs between 40 and 50 kg/m$^2$ or between 35 and 40 kg/m$^2$ with obesity-related comorbidities showed a median EWL of 28 % at 3 months and a mean decrease in median BMI from 42.1 to 37.9 kg/m$^2$. Another randomized, uncontrolled, open-label study of 20 patients showed a median EWL of 21 and 26 % with the TERIS™ at months 3 and 6, respectively. However, one procedure was abandoned due to gastric perforation related to stapler malfunction, and two cases of pneumoperitoneum requiring percutaneous intervention were noted [61, 62]. A total complication rate of 25 % resulted in device withdrawal, and adjustments to the system are under development.

### StomaphyX™

An additional stapling device commonly used for the treatment of GERD (StomaphyX™, EndoGastric Solutions, Redwood City, CA, USA) was used in a study of patients following vertical banded gastroplasty (VBG). Patients receiving VBG may develop pouch complications such as dilation and staple-line dehiscence, which may contribute to weight regain. If conservative measures fail, open revisional surgery of the pouch or conversion of the VBG to Roux-en-Y gastric bypass is considered. StomaphyX™ is an endoscopic device used with a conventional gastroscope for the approximation of tissue in gastric pouches or across gastroenteric anastomoses to enhance restriction. A small study of

14 patients showed that it may be safely used for reduction of pouch size for endoluminal pouch revision following failed VBG [63].

Significant reductions in weight and BMI were appreciated pre- and postoperatively (119.5 ± 25.9 vs. 109.6 ± 24.4 kg; 43.4 ± 9.7 vs. 39.8 ± 9.1 kg/m$^2$, respectively). There was no correlation between preoperative pouch status and weight loss. Three patients had two separate StomaphyX™ procedures performed. Only minor complications (headache, back pain) were identified [63].

Another novel restrictive approach is the Expandable Tissue Anchors system (USGI Medical Incorporated, San Clemente, CA, USA), consisting of two rated polyester expandable anchors with nitinol springs that are joined together over a polyester suture through the stomach wall. These expandable anchors distribute force over a much larger surface area than staples or sutures alone, and evaluation in prospective observational and randomized clinical trials is warranted [64].

## Malabsorptive Approaches

### *Endoluminal Bypass*

One of the components of weight loss seen with the surgical Roux-en-Y gastric bypass is the act of bypassing the duodenum from the food stream. Even prior to the initiation of weight loss, this duodenal bypass creates a rapid improvement in glucose tolerance and diabetes although the exact mechanisms behind this are unclear. This effect may partially relate to modulations in neuroendocrine systems [65]. According to a meta-analysis published in JAMA in 2004 [66], patients who had gastric bypass had an average excess weight loss of 68 %. In addition to weight loss, a high percentage of patients also showed improvement or resolution in the following comorbidities: T2DM (86 %), hypertension (79 %), hyperlipidemia (70 %), and obstructive sleep apnea (86 %).

An attempt to mimic some of the success of open gastric bypass with endoscopic procedures resulted in the introduction of prosthetic devices that bypass the duodenum and proximal jejunum such as the EndoBarrier® Gastric Liner (GI Dynamics, Inc., Lexington, MA, USA) and ValenTx bypass sleeve. These endoscopic-placed devices induce weight loss via malabsorption.

#### EndoBarrier® Gastric Liner

The EndoBarrier® Gastric Liner (EGI) sleeve is a 60 cm fluoropolymer liner that is anchored in the duodenum and passes distally into the proximal jejunum. Results of the first human open-label study of 12 patients with the EGI sleeve were published in 2008 [67]. Ten of 12 patients had the device in place for 12 weeks. The average EBW loss at 12 weeks was 23.6 %. All four diabetic patients had normal plasma glucose levels at 12 weeks. Two partial pharyngeal tears occurred during device removal. Adverse events included episodes of abdominal pain, nausea, and vomiting within the first 2 weeks, and no severe adverse events were noted.

Another study of the EGI system was reported by Gersin et al. [68]. An EWL of 11.9 % was noted in patients who maintained the sleeve for 12 weeks compared to an EWL of only 2.0 % in the sham group. Unfortunately, one-third of the patients who received the EGI required early removal due to gastrointestinal bleeding, abdominal pain, nausea, or vomiting.

An additional multicenter trial with DJBS was reported by Schouten et al. [69]. Thirty patients underwent sleeve implantation, and 11 patients adhering to a diet plan served as controls. Mean EWL at 3 months was 19 % for the device and 6.9 % for the controls. Four of the attempted sleeve placements were unsuccessful, and four other DJBS devices had to be removed early due to dislocation,

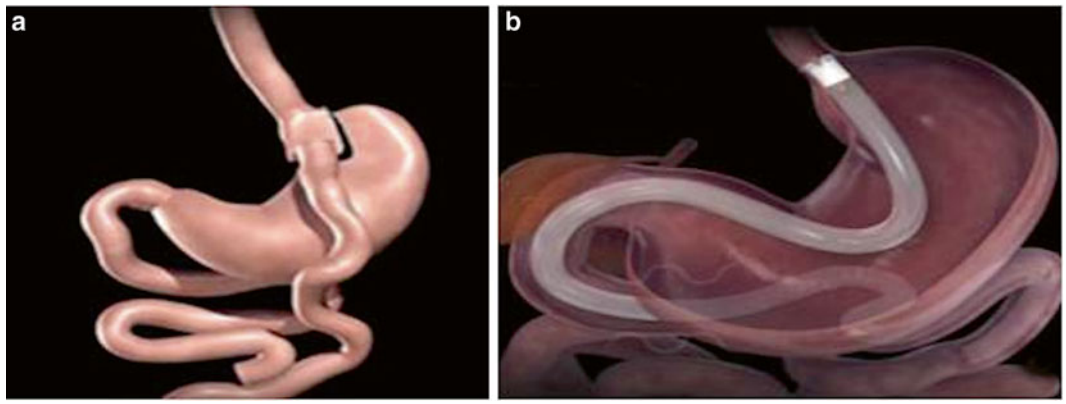


**Fig. 23.5** (**a**) Roux-en-Y gastric bypass. (**b**) ValenTx endoluminal bypass sleeve

sleeve migration, obstruction, or continuous abdominal pain. Further trials with this device to assess safety and efficacy will be required to obtain marketing approvals.

### ValenTx Endoluminal Bypass Sleeve

The ValenTx (ValenTx, Inc., Carpinteria, CA, USA) endoluminal bypass therapy also mimics the permanent anatomical changes made by the Roux-en-Y gastric bypass procedure with an adjustable, removable, and replaceable device. This endoluminal bypass sleeve system is 120 cm in length and is attached to the distal esophagus placed by a combination of endoscopy and laparoscopy and has the potential to be completed solely via endoscopy in the future (see Fig. 23.5a for an illustration of Roux-en-Y gastric bypass (a) and Fig. 23.5b for comparison to the ValenTx sleeve (b)). The ValenTx is not yet FDA approved and is currently under clinical investigation.

In a collaborative study led by physicians from the University of California San Diego Medical Center, the Imperial College of London, and the Hospital San Jose Tec de Monterrey in Monterrey, Mexico. A total of 22 patients were implanted, and 17 patients (77 %) maintained the device and achieved a mean EWL of 39.5 %. In addition to weight loss, all seven diabetic patients in the study maintained normal fasting blood glucose levels without antihyperglycemic medications during the trial [70].

## *Other Less Invasive Endoscopic Approaches Influencing Gastric Function*

### TransPyloric Shuttle™ (TPS)

The TransPyloric Shuttle™ (BARONova, Inc., Goleta, CA, USA) is another temporary medical device that is endoscopically placed and removed from the stomach. The TPS™ is designed to self-position across the pylorus, creating an intermittent obstruction to outflow that may result in delayed gastric emptying. This may serve to induce early satiation and/or to prolong satiety.

BARONova's website states that the shuttle has been "studied in both animals and humans with favorable results," and a trial of up to 50 patients in Australia investigating the safety and impact of the device on EWL at 12 weeks (ENDObesity™ I study) has been conducted. The study enrolled patients with a BMI between 30 and 50 kg/m$^2$ and was completed as of 2012, but there are no peer-reviewed publications documenting results, as of yet. According to the company, who received an investment from Allergan in 2008, data from 20 patients in the trial are locked, and publication of results is pending [71].

**Table 23.1** Overview of endoscopic methods for weight loss

| Approach | Subjects | Procedure (1) Sedation (2) Implantation time | Weight loss | Other endpoints | Complications |
|---|---|---|---|---|---|
| Intragastric balloons | $N \geq 100{,}000$<br>BMI: 29–60 kg/m$^2$ | (1) Midazolam<br>(2) Implantation in ≤20 min | 15 kg (range 9–21 kg) or 2–10 BMI points in 6 months; average 24 kg after 1 year | T2DM and hypertension ameliorate/resolve in a minority; dyslipidemia improves in 50 %; 11 % remains unchanged | Dyspepsia<br>Persistent emesis<br>Esophagitis<br>Distal migration<br>Small bowel obstruction |
| Gastric plication (suturing/stapling) | $N = >100$<br>BMI: 30–51 kg/m$^2$ | (1) Under general anesthesia<br>(2) Average 125 min (range 60–140 min) | 24–46 % EWL in 6 months; 23–53 % EWL in 1 year; note: location of the plication affects result | Requires further investigation | Vomiting<br>Nausea<br>Stomachaches<br>Gastric perforation<br>Obstruction |
| Duodenal-jejunal bypass/sleeves | $N = 500$<br>BMI: 40–60 kg/m$^2$ | (1) Under general anesthesia<br>(2) Implantation and explantation in 15–45 min | 12–40 % EWL or 8–17 kg in 3 months | T2DM remission | Vomiting<br>Nausea<br>Abdominal pain<br>Mucosal tear<br>GI bleeding<br>Migration/obstruction |

Adapted from Verdam et al. [22]

## Overall Summary

Temporary endoscopic approaches to the treatment of obesity can play an important role in managing weight loss alone or prior to more invasive and longer-lasting surgical procedures such as gastric bypass. See Table 23.1 for a summary of endoscopic approaches to weight loss. Long-term clinical data on the safety, efficacy, and durability of endoscopic methods and devices in appropriately designed clinical trials are being published.

More work is needed to confirm early observational studies and compare these approaches to appropriately define the roles and populations most suitable for each for these methods in the treatment of obesity. With improved communication and collaboration with the FDA and continued demonstration of safety and efficacy, several of these important and less invasive approaches already commercially available in other countries should be available in the USA within the next 5 years.

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# Chapter 24
# Surgical Management of Weight Loss

**Dustin M. Bermudez, Sebastian DeMarco, Emily Cunningham, and Walter Pories**

**Abstract** For millennia, severe obesity and type 2 diabetes (T2DM) were considered hopeless diseases. Without effective treatments, patients endured dietary limitations, drugs and injections with the recognition that early death, blindness, amputation and renal failure were the unavoidable outcomes. Bariatric surgery has sharply changed this dismal picture. Within only a few days these operations are followed by rapid, full and durable remission not only of T2DM and severe obesity but also of hypertension, dyslipidemias, polycystic ovary syndrome, non-alcoholic hepatic steatosis, gastro-esophageal reflux, sleep apnea. However, as in other therapies, there are also complications. The early ones are similar to other abdominal operations; the late complications are just now becoming more clear. This chapter will review bariatric surgery, its indications, and the major operations and provide an overview of early and late outcomes.

**Keywords** Obesity • Type 2 diabetes mellitus • Bariatric surgery

### Key Points

- Obesity has become a national epidemic and a disease of global magnitude. The numbers of patients with obesity have grown exponentially in the last 10 years to the degree that the Centers for Disease Control and Prevention reports that one third of the US population is obese.
- Traditional therapies of diets, exercise, behavioral modification, and drugs have had little effect, especially in the severely obese.
- Bariatric surgery now provides the most effective treatment of obesity and type 2 diabetes mellitus (T2DM), with major impact on many of the other complications of the metabolic syndrome.

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- Depending on the insurance carrier, patients generally need to meet multiple criteria before being considered for bariatric surgery so that their likelihood of benefit is outweighed by potential risk.
- Criteria for the three bariatric operations that require stapling (Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic diversion with duodenal switch) of the gut generally include a BMI $\geq$ 40 kg/m$^2$ or a BMI $\geq$ 35 kg/m$^2$ with comorbidities of morbid obesity. For adjustable gastric banding operations, however, the requirement has been lowered to a BMI $\geq$ 30 even without comorbidities.
- Other novel surgical approaches include intragastric balloon, gastric plication, endoluminal therapy, and gastric pacing.
- Prior to surgery, a thorough nutritional assessment is undertaken, and a dietitian may be involved to help educate the patient about their postoperative diet.
- Education of the patient, family, referring physician, and the colleagues who will be following the individual after bariatric surgery is critical.
- The clinician needs to be astute for the complications of bariatric surgery.

## Introduction

Obesity has become a national epidemic and a disease of global magnitude. The numbers of patients with obesity have grown exponentially in the last 10 years to the degree that the Centers for Disease Control and Prevention reports that one third of the US population is obese [1]. The prevalence of diabetes has grown by more than 50 % in that time period as well [2]. Unfortunately, the traditional therapies of diets, exercise, behavioral modification, and drugs have had little effect, especially in the severely obese [3]. The introduction of bariatric surgery has changed this picture. Operative approaches now provide the most effective treatment of obesity and type 2 diabetes mellitus with major impact on other expressions of the metabolic syndrome including hypertension, polycystic ovary syndrome, dyslipidemias, nonalcoholic steatohepatitis, gastroesophageal reflux disease, degenerative arthritis of weight-bearing joints depression, stress incontinence, cardiopulmonary failure, and even the prevalence of solid cancers [4, 5, 6]. In this chapter, we will detail the indications, surgical approaches, outcomes, and complications of bariatric surgery.

## Obesity: A Global Pandemic

Obesity has become a global pandemic. Seventy-two million Americans are now considered obese, and almost 135 million are considered to be overweight [7]. These numbers are higher than ever before. Not only are adults affected by obesity, but increasingly so is our youth. Over 17 % of children in 2010 are considered obese [8]. The prevalence of obesity in adolescents and children has also more than tripled in the last 20 years.

The cause of the morbid obesity epidemic is controversial and likely multifactorial, with increased consumption of high-caloric foods, modern food processing, easy availability of food, decreased food costs, a more sedentary lifestyle, cessation of smoking, genetics, and possibly even environmental exposures to a variety of culprits such as pesticides, herbicides, fertilizers, and other ecologic pollutants. Despite the indistinguishable causes, there is clear evidence to the impact of this growing trend. Hand in hand with growing numbers of obese individuals is an explosion of patients with diabetes, hypertension, dyslipidemias, obstructive sleep apnea, polycystic ovary syndrome, and cardiopulmonary failure—and this is only a partial list of the "comorbidities of obesity," a group of diseases often

**Table 24.1** Manifestations of the metabolic syndrome

| | |
|---|---|
| Neurologic | Pseudotumor cerebri, stroke |
| Cardiovascular | Hypertension, coronary artery disease, hyperlipidemia |
| Pulmonary | Obstructive sleep apnea, pulmonary hypertension, cor pulmonale |
| Endocrine | Hypogonadism, polycystic ovarian syndrome, hyperinsulinemia, insulin resistance, diabetes mellitus |
| Alimentary tract | Nonalcoholic steatohepatitis (NASH), cirrhosis, cholangiocarcinoma |
| Hematologic | Elevated C-reactive protein, more inflammatory cytokines |
| Renal | Chronic kidney disease, microalbuminuria |
| Rheumatologic | Hyperuricemia/gout, weight-bearing arthralgia |

pooled into the poorly defined term "the metabolic syndrome." Table 24.1 has an extensive list of the diseases associated with the metabolic syndrome. The prevalence of patients suffering from these comorbidities has seen a similar rise in their incidence. The number of diabetics alone has tripled over the last 30 years [9].

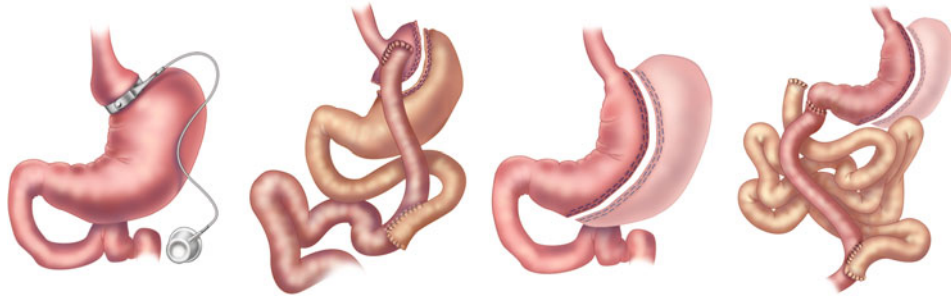
The precise definition of the metabolic syndrome is still somewhat controversial. "Comorbidities of obesity," however, is an even broader term than that of the metabolic syndrome though there is no definite consensus on its definition either. The International Diabetes Federation (IDF) in 2006 offered an outline of the definition of the metabolic syndrome [10]. Specifically, the IDF described the metabolic syndrome as increased waist circumference (that is ethnicity specific) plus two of the following criteria: triglycerides >150 mg/dL (or treatment for hypertriglyceridemia), HDL < 40 mg/dL in men or 50 mg/dL in women (or treatment for low HDL), systolic blood pressure >130 mmHg or diastolic blood pressure greater than 85 mmHg (or treatment for hypertension), or fasting plasma glucose greater than 100 mg/dL.

Diets, exercise, behavioral modification, and drugs can be effective treatment for individuals who are overweight or class 1 obese, but in the severely obese, even if the therapy is intensive, the weight loss is limited and not maintained. Bariatric surgery has sharply changed this picture with the introduction of four operations that, even though distinctly different, are remarkably effective not only in the remission of obesity but also in the resolution of its comorbidities.

## Bariatric Surgery

The derivation of "bariatric" is from the Greek words "baros" for weight and "iatrikos" for treatment. The surgical approaches to severe obesity developed in response to the frustration of clinicians in the 1950s that were confronted with the inability to help these unfortunate individuals to lose weight. By 1980, the gastric bypass and the gastric band were in initial trials that determined these operative approaches were effective. In the first decade of this century, sharp improvements in assuring the safety of the operations were achieved. Four major bariatric operations are now commonly performed: (1) adjustable gastric banding (AGB), (2) sleeve gastrectomy (SG), (3) Roux-en-Y gastric bypass (RYGB), and (4) biliopancreatic bypass with duodenal switch (DS). Remarkably, and in great part due to the certification process for "Bariatric Surgery Centers of Excellence" by the American Society for Metabolic and Bariatric Surgery (ASMBS), the four operations are far safer than other routine abdominal operations with 90-day mortality rates of 0.3 %, the same as routine cholecystectomy [11]. Sketches of these operations, their impact on weight loss, and the remission of T2DM are shown in Fig. 24.1.

**Four Accepted Bariatric Operations in US**
Meta-analysis: All articles in English, 1991 – 2006,
621 studies, 888 treatment arms, 135,246 patients



| | Adjustable gastric band | Gastric bypass | Gastric sleeve | Duodenal switch |
|---|---|---|---|---|
| XS WT loss | 46.2% | 57.9% | ? 60% | 63.6% |
| Stop T2DM | 56.7% | 80.3% | ? 80% | 95.1% |

Buchwald H, Estock K, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantie JP, Sledge J.
Meta-analysis of Bariatric Surgery and Diabetes, Am J Med (2009) 122:248 - 256

**Fig. 24.1** Four accepted bariatric operations in the United States

## Preoperative Workup and Patient Selection

Depending on the insurance carrier, patients generally need to meet multiple criteria before being considered for bariatric surgery so that their likelihood of benefit is outweighed by potential risk. Table 24.2 details the key elements of these patient selection criteria. Criteria for the three bariatric operations that require stapling of the gut, i.e., SG, RYGB, and DS, generally include a BMI $\geq$ 40 kg/m$^2$ or a BMI $\geq$ 35 kg/m$^2$ with comorbidities of morbid obesity. For AGB operations, however, the requirement has been lowered to a BMI $\geq$ 30 even without comorbidities [12].

Patients who have BMIs less than 35 kg/m$^2$ and morbidities of obesity can also benefit from bariatric surgery, but this is still controversial, and few carriers are willing to cover operations for patients who do not meet the current BMI criteria [13–15].

The arbitrary nature of the selection process leads to some patients being disadvantaged from the outset. For example, in a group studied by Jackson et al., males with a BMI of 35 had a percent body fat mass of 35 %, while females, at the same BMI, had a percent body fat mass of 46 % [16]. Furthermore, the BMI discriminates against Asians and African Americans. Stevens et al. reported that at a similar BMI of 27.5, for example, while 26 % of Caucasian females had hypertension, 34 % of African Americans and 44 % of Chinese Asians had the disease [17]. Similarly, at the same BMI, 12 % of the Caucasians had diabetes, while 15 % of African Americans and 17 % of Chinese Asians were so afflicted. Additionally, the BMI discriminates against older individuals whose weight often decreases along with increased lipid deposition in muscle and other tissues.

Finally, BMI also fails to allow for fitness. One of our study subjects at East Carolina University was a 20-year-old student with a height of 5′8″ who weighed 308 lbs and presented with a BMI of 47.0—clearly a candidate for bariatric surgery according to the current health insurance guidelines. He'd be hard to convince. He was our fastest running back, and his body composition studies revealed that only 7 % was fat.

As it stands today, a young, unfit Caucasian woman has ready access to bariatric surgery, while an African American woman who may be far more ill with uncontrolled diabetes and crippling

**Table 24.2** Preoperative criteria for bariatric surgery

| | |
|---|---|
| Body mass index | Significant controversy: BMI > 40 kg/m$^2$ or BMI > 35 kg/m$^2$ with comorbidities |
| Psychiatric | Needs to be cleared as good candidate |
| Nutrition | Needs to be educated on post-bariatric diet |
| Cardiac | Will need preoperative clearance if significant comorbidities |
| Pulmonary | Consider IVC filter for BMI > kg/m$^2$, if significant need for CPAP need to rule out cor pulmonale and pulmonary hypertension |
| Gastrointestinal | Need preoperative upper GI series or endoscopy to evaluate anatomy preoperatively |
| Hepatic | Evaluate gallbladder for cholelithiasis and liver for cirrhosis and nonalcoholic steatohepatitis |
| Nutrition | Replete any deficiencies preoperatively |

osteoarthritis of her weight-bearing joints will be denied the only effective treatment for her metabolic syndrome. Recently, in recognition of this concern, the Food and Drug Administration lowered the BMI required for adjustable gastric bands to 30. It is a good start, but clearly there are people with the metabolic syndrome but due to BMI requirements are denied access to their best chance at treatment.

## *Nutritional Assessment*

Prior to surgery, a thorough nutritional assessment is undertaken, and a dietitian may be involved to help educate the patient about their postoperative diet. Despite being overweight, the majority of these patients are malnourished, especially in select vitamins and trace elements even before surgery [18, 19]. Bariatric surgery, an intervention designed to induce malnutrition, can make these nutritional deficits even worse. This potential for exacerbation of underlying vitamin and mineral deficiencies underscores the importance of nutrition assessments both preoperatively and postoperatively. Key vitamins that need to be delivered at supratherapeutic doses include vitamin B12, B1 (thiamine), B6, and folate as well as key minerals including calcium, iron, zinc, and chromium [20]. Accordingly, these patients should be reminded often that they must supplement their diets with vitamins and minerals for the rest of their lives. It is likely but not proven that post-bariatric hypoglycemic attacks and neuropathies are due to underdiagnosis of micronutrient deficiencies.

Patients are generally advanced slowly through a progressive postoperative diet from soups to soft foods and to regular food but will need to avoid simple sugars along the way to prevent dumping syndrome and its sequelae. Dumping syndrome occurs when undigested food is "dumped" into small intestine. The etiology for dumping syndrome, however, is still controversial, but there are indications that glucose may play a role since about four out of five bariatric surgical patients cannot tolerate sweets due to diarrhea, cramping, bloating, nausea, vomiting, dizziness, and fatigue. This tendency to "dump" may be one of the reasons why RYGB patients change their diets following surgery and why the RYGB is such a successful operation.

## *Preoperative Education*

Education of the patient, family, referring physician, and the colleagues who will be following the individual after bariatric surgery is critical. The key elements are: (1) severely obese patients are sick, burdened with comorbidities and, therefore, challenging surgical risks; (2) while the operations induce dramatic weight loss and remission of diabetes and other comorbidities, most patients do not return to normal weight but remain at least overweight or obese (an observation that denies the general

impression that bariatric surgical patients can't eat normal amounts; in fact, most post-RYGB patients still consume more calories than lean individuals); (3) although the surgery is safe with a 90-day mortality of 0.3 % when performed in a certified Center of Excellence, it is also associated with dangerous short- and long-term complications, albeit rare, that must be dealt with promptly by an experienced bariatric surgeon; and (4) patients' psychological states improve sharply along with their weight loss, remission of disease, and improved quality of life, but many of these individuals still need professional help in addressing such challenges as family relationships, sexuality, clothing, diet, and working environments.

The patient's family needs not only to be educated about the procedure but also in full support of the patient's decision to undergo bariatric surgery. If the spouse does not concur, if siblings continue to raise doubts, and if the children are not supportive, it is best to postpone the surgery until everyone is on board to get the best results.

## *Preoperative Workup*

There are few strict contraindications to bariatric surgery. Patients with unresolved major psychiatric disorders or resistant eating disorders such as bulimia nervosa are not candidates for weight loss surgery. Neither are patients with active alcohol or drug use problems. There are no fixed age parameters or medical comorbidities or previous operations that truly preclude bariatric surgery. Although the general guidelines have limited the surgery to 18–65, there are now numerous reports of successful outcomes in adolescents and patients in their 70s [21–26]. Bariatric surgery has also been performed on patients with cirrhosis [27] and those with cardiovascular disease although with higher, but still acceptable, complication and mortality rates [28].

In addition to a through history, physical examination, and routine imaging and laboratory studies including Hg/HCT and a complete metabolic panel, many patients will also have an evaluation of their stomach and upper gastrointestinal tract. Esophagogastroduodenoscopy (EGD) and/or an upper gastrointestinal series (UGI) is usually performed prior to surgery [29, 30]. These studies document anatomic abnormalities that might complicate the surgery, such as a hiatal hernia, a neoplasm, or an ulcer of the stomach. If a hiatal or paraesophageal hernia is present, it can and should be repaired at the same time as the weight loss surgery. Most patients will also undergo a right upper quadrant abdominal ultrasound to evaluate for cholelithiasis and hepatic steatosis. Patients who have had deep venous disease may also be evaluated for possible inferior vena cava filter placement.

The decision to place an IVC filter preoperatively is controversial. Recent studies demonstrate that IVC filter placement may do more harm than good [31]. Earlier studies, however, demonstrate benefits when the patient has a BMI > 60 kg/m$^2$ or deemed high risk [32].

## *Psychological Assessment*

Psychological evaluation prior to surgery is an important part of the preoperative evaluation process—those who fail or do poorly on this evaluation will have a much greater risk of recidivism, complications, and weight regain. Most candidates for bariatric surgery have a history of psychological disorders [33]. About 25 % of severely obese women have a history of sexual or other physical abuse [34]; a large number have addictive personalities with histories of alcohol and/or drug abuse and/or binge eating [35, 36]. All encounter bias in the family, school, and workplace and social activities such as church [37, 38]. In addition, these individuals may be mentally ill with schizophrenia or too intellectually challenged to understand bariatric surgery and its outcomes. In general, patients with

drug or alcohol abuse and/or major psychological disease are not acceptable surgical candidates until their problems have been treated and controlled. Judgment, however, should be cautious. In many cases, the psychological problems are due to the obesity and the way these patients are treated by society. In most cases, there is a major improvement in the mental health of bariatric surgery patients with the dramatic loss of weight and remission of comorbidities.

## The Roux-en-Y Gastric Bypass

The current model of the RYGB has been utilized since 1980. Considered by many to be the "gold standard" for weight loss surgery procedures, there is an increasingly large body of evidence demonstrating its beneficial impact on the natural history of morbid obesity.

### *Technique*

The overall objective of the RYGB is to limit intake with a small pouch, about 30 mL in volume, and interfere with digestion with the bypass of almost all of the stomach, the entire duodenum, and about 150 cm of proximal ileum. Several approaches are used to perform a RYGB. The anastomosis between the stomach and small intestine (gastrojejunostomy), about 10–12 mm in diameter, may be stapled or hand sewn. The Roux limb may be brought up to meet the stomach in an antecolic or retrocolic fashion (in front of or behind the mesentery of the transverse colon). Furthermore, the Roux limb (portion of the small intestine divided and anastomosed directly to the stomach) can be fixed on the anterior aspect of the stomach (antegastric) or on the posterior side of the stomach wall (retrogastric).

The length of the Roux limb may also vary. The longer the length of the Roux limb, the greater the degree of malabsorption. Most surgeons prefer a Roux limb that is 75–150 cm in length. A "long-limb" bypass is one with a Roux limb 150–200 cm in length. Generally used in the "super obese" (BMI > 50 kg/m$^2$), the long-limb bypass promotes faster and more substantial weight loss [39]. Choban et al. demonstrated that patients with a BMI greater than 50 kg/m$^2$ who underwent long-limb bypass lost more than 50 % of their excess weight by 18 months postoperatively [40]. There is, however, conflicting evidence in the literature as to whether a longer limb has an impact on long-lasting obesity [41].

Here we will describe an antecolic, antegastric technique, which is the most frequently employed in the United States. The small vertical gastric pouch is typically 30 mL in volume. This neo-stomach is then anastomosed directly to the small intestine, i.e., the alimentary limb. Bile and pancreatic secretions are diverted from the digestive process until the two limbs are rejoined into a "common channel" that is generally 75–100 cm in length from the ileocecal valve. Figure 24.2 details the anatomy of a gastric bypass.

### *Outcomes*

The RYGB is currently the most frequently utilized weight loss surgery in the United States [42]. Overall outcomes for a gastric bypass patient are excellent. Studies have demonstrated that following gastric bypass, approximately 50–75 % of excess weight loss (EWL) occurs within the first 1–2 years. Sustained weight loss can be seen over 10 years after surgery [43]. Diabetes has been demonstrated to resolve in over 83 % of patients and at least improve in over 85 % [44]. There has

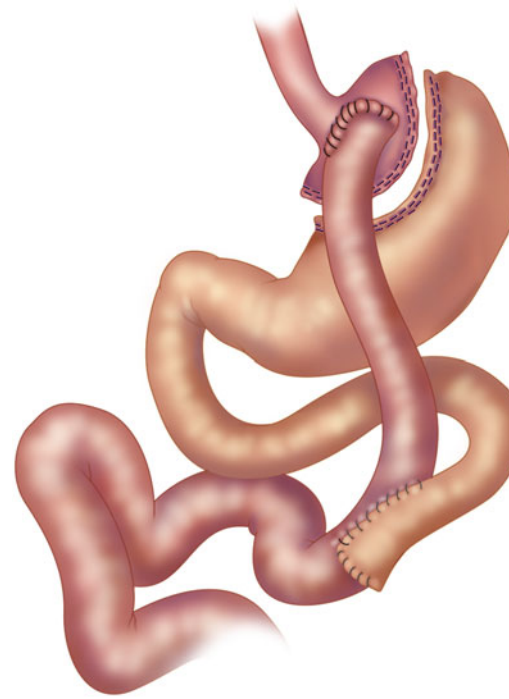


**Fig. 24.2** The Roux-en-Y gastric bypass

also been demonstrated an 80 % reduction in mortality in diabetic patients who had undergone gastric bypass [45]. Similarly, there was a reduction of death from diabetes by 92 %, coronary disease by 56 %, and cancers overall by 60 %. A prospective randomized controlled clinical trial found that there were significantly greater weight loss, significantly lower hemoglobin A1c, and superior glycemic control in diabetic patients who had undergone bariatric surgery (either sleeve gastrectomy or RYGB) when compared with patients who had undergone intensive medical therapy alone [46]. Mingrone et al., also in prospective, randomized controlled trials, had similar findings 2 years after bariatric surgery (RYGB and DS) with 75 and 95 % of patients, respectively, having resolution of their diabetes when compared to medical therapy alone that did not demonstrate cure in any of its patients [47].

## Sleeve Gastrectomy

The principle of the gastric sleeve is to reduce the gastric conduit to a tube, about the thickness of a thumb, and to excise most of the stomach, thus sharply reducing the secretion of HCL, pepsin, ghrelin, gastrin, and mucus. The sleeve gastrectomy is a fairly new procedure especially in comparison to other bariatric operations. Approximately 36 % of bariatric procedures performed in US academic medical centers from 2008 to 2012 were sleeve gastrectomies [48]. Figure 24.3 demonstrates how the stomach appears after surgery.

It was developed initially as part of a staged procedure in the super obese to precede the duodenal switch (see below) as described by Hess and Marceau in the early 1990s [49, 50]. While restrictive in nature, its effects appear to be greater than just limiting oral intake probably due to the resection of the grinding and endocrine areas of the stomach.

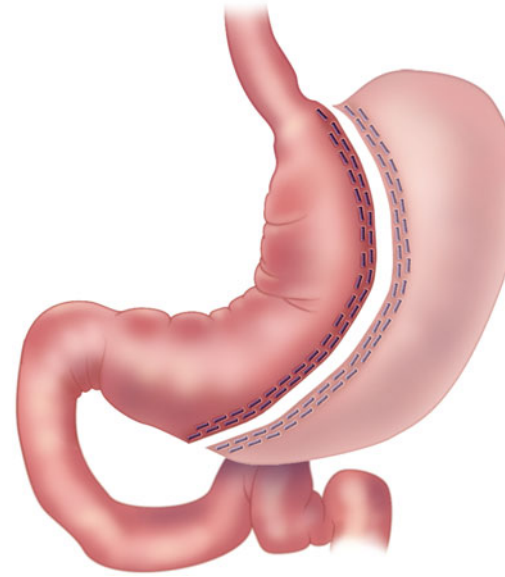


**Fig. 24.3** Sleeve gastrectomy

### *Technique*

The greater curve of the stomach is freed from adjacent greater omentum all the way up to the angle of His at the gastroesophageal junction. The greater curve of the stomach is resected either with or without buttressing material. The distal end of the staple line is begun 3–5 cm proximal to the pylorus. This allows for better preservation of pyloric function and minimizes risk of dumping syndrome.

### *Outcomes*

The impact of the gastric sleeve on weight loss, inducing remission of diabetes, and other comorbidities is remarkably similar to that of the gastric bypass for still unexplained reasons. After 2 years, there can be upwards of 65 % of EWL following SG [51].

## Adjustable Gastric Banding

The principle of the gastric band is to restrict food intake with the construction of a small gastric pouch, about 30 mL, and limiting outflow with a 10 mm gastric outlet controlled by a balloon that can be filled or emptied from a subcutaneous reservoir. The gastric band has been in use in the United States for nearly three decades. Introduced in 1990, the band has become one of the most frequently performed bariatric procedures in the United States. About 23 % of all bariatric procedures were AGBs in 2008 [52].

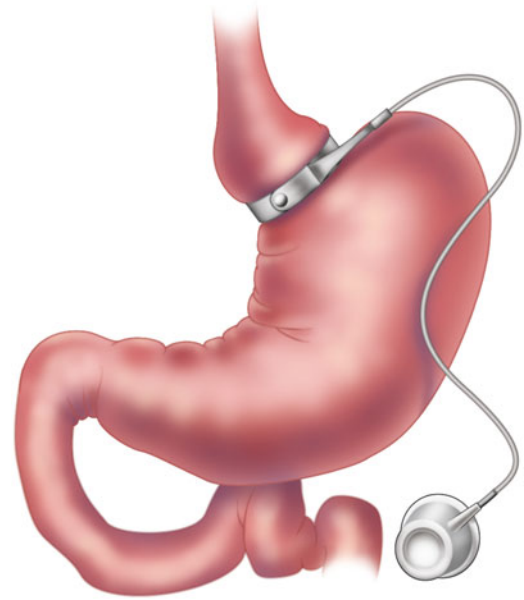


**Fig. 24.4** Adjustable gastric banding

## *Technique*

The AGB is illustrated in Fig. 24.4. The angle of His and the hepatogastric ligament are both opened. The band, a silicone and inflatable device with a buckle, is placed behind the stomach with minimal dissection. Once locked into place, the fundus of the stomach is sutured to itself over the band to prevent slippage and migration of the AGB. Tubing that feeds into the inflatable balloon portion of the band is accessed through a subcutaneous port. The band is placed around the fundus and lesser curve of the stomach, ideally allowing only about 30 mL of fluid in the stomach above the band.

## *Outcomes*

The AGB, more than any of the other widely adopted bariatric procedures, is dependent on a very committed patient who will strictly adhere to the commonly accepted post-AGB diet regimen. In those who were closely observed, studies have demonstrated EWL averaging 50.3 % at 2 years post surgery [53]. However, there is considerable variability in the percent EWL achieved.

The AGB is frequently compared to the RYGB. RYGB patients had better weight loss and higher incidence of resolution of comorbidities such as hypertension and diabetes at one year than AGB patients [54]. Perioperative complications following AGB were lower than RYGB patients. Reoperation rates, however, were significantly higher in the AGB group with compared to RYGB (16 % vs. 27 %). The use of the AGB has dropped sharply because it has not lived up to its initial claims. Weight loss is frequently unsatisfactory; the remission of comorbidities is low, and about 5 % require reoperation every year [55, 56].

## Biliopancreatic Diversion with Duodenal Switch

The objective of the biliopancreatic diversion with duodenal switch (DS) is to combine the gastric sleeve with the exclusion of the duodenum, jejunum, and much of the ileum from contact with food, leaving only about 100 cm as a "common channel." It is the most aggressive of the bariatric operations offered in the United States today. Initially, it was introduced as biliopancreatic diversion only. DeMeester et al. addressed this as an approach to promote an exclusively malabsorptive phase to weight loss surgery [57]. Hess et al. refined this operation to include a sleeve gastrectomy and preservation of the pylorus (unlike the RYGB) [57]. This allowed for both a gastric restrictive phase to the operation and the malabsorptive phase but minimized the risk for dumping syndrome.

### *Technique*

The procedure, detailed in Fig. 24.5, is carried out by first removing approximately 75 % of the stomach off of the greater curvature—similar to the sleeve gastrectomy. This allows for the restrictive phase of the procedure. Next, the duodenum is divided distal to the first portion but proximal to the ampulla of Vater. The proximal end of the duodenum is then anastomosed to the small bowel via a Roux limb, thus creating a duodenojejunostomy. This will become the alimentary limb of the DS. The distal end of this is left as a duodenal stump. The downstream jejunojejunostomy is used to put the duodenum and jejunum back in continuity and allow for adequate digestion.

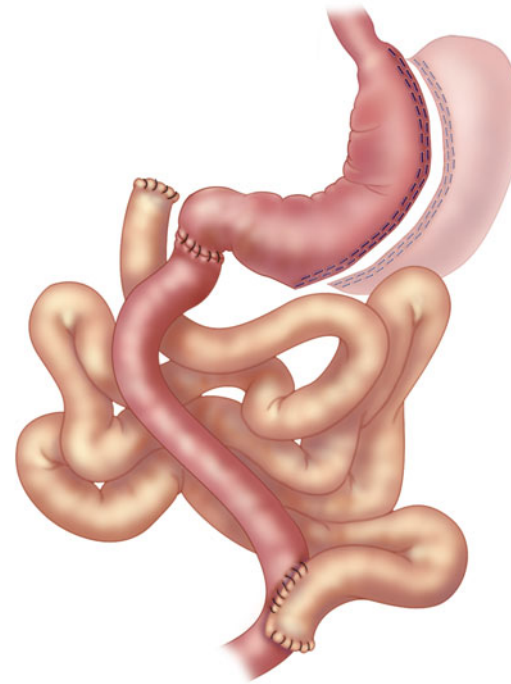


**Fig. 24.5** Biliopancreatic diversion with duodenal switch

### *Outcomes*

Weight loss following DS is dramatic with average EWL at 10 years at approximately 70 %. Almost all lose their comorbidities with some reports demonstrating a greater than 95 % success rate at the elimination of diabetes and hypertension. There have been reports of almost no marginal ulcers or episodes of dumping syndrome (presumably due to presence of the pylorus) [58, 59].

## Novel Approaches to Bariatric Surgery

Several newer surgeries and endoscopic procedures have been introduced as the incidence of those undergoing bariatric operations has blossomed. While these procedures account for less than 1 % of the bariatric operations performed in the United States, they are worthwhile to address briefly as they make any discussion of bariatric operations more complete.

### *Intragastric Balloon*

Not currently approved for use in the United States, the intragastric balloon is a temporary device used to restrict food intake. It is introduced into the stomach endoscopically and acts as a "space-occupying" foreign body that leads to earlier satiety. Complications include perforation, bowel obstruction, ischemia and necrosis of the gastric wall, and, of course, lack of weight loss. Two randomized double-blind controlled trials have been performed in Europe that indicate average weight loss is 15 kg over a 6-month period [60, 61]. Long-term data are lacking as it is a relatively new procedure. Major issues with the gastric balloon are that it is only a temporary maneuver to promote weight loss. Current recommendations are that it be removed approximately 6 months after its endoscopic placement [62].

### *Gastric Plication*

Similar to the SG in terms of the mechanism by which it promotes weight loss, it is unlike the SG in that it is reversible. Very little data is available to demonstrate the efficacy and safety of gastric plication. Brethauer et al. have demonstrated its safety in the obese population [63]. Efficacy in the long term for these patients is lacking though data does demonstrate that patients still lose about 30 % of their excess body weight. It is still considered an investigational procedure.

### *Endoluminal Therapy*

Primarily reserved for revisional bariatric surgery, the StomaphyX device is the first of its kind approved for endoluminal bariatric surgery. It pleats the mucosa and bowel wall with deployable fasteners. This allows an endoscopic approach to narrow the gastrojejunostomy and promote earlier satiety [64]. It is also still considered an investigational procedure.

### *Gastric Pacing*

The motility of the stomach and its feedback to the central nervous system indicating satiety are mediated by a neuronal mechanism. A gastric pacemaker can theoretically augment or abrogate these signals [65, 66]. This device can be implanted in the wall of the stomach laparoscopically or even endoscopically. It is currently being tested in Europe and Canada with some encouraging results. It functions by different mechanisms. The first mechanism is through disruption of gastric motility. This delays the clearance of food in the stomach, thus prolonging the sensation of satiety. The second mechanism by which gastric pacemakers function is through vagal nerve stimulation. This will promote the signal indicating satiety though the gastric lumen may not be distended with food. Although fascinating in terms of physiologic studies, pacing procedures have virtually been abandoned. They are also considered investigational procedures.

## Complications of Bariatric Surgery

While complications are not common following bariatric surgery, they are real and need to be considered prior to operation so that a full assessment of risks and benefits to surgery can be carried out.

Following a large amount of weight loss, internal hernias (i.e., a segment of intestine that is blocked internally) may occur. Such an intestinal loop may necrose in a matter of hours. Accordingly, patients with intermittent abdominal pain, especially after eating, need to be evaluated promptly. Any severe abdominal pain lasting over an hour requires immediate consultation with a bariatric surgeon. Delay in diagnosis can lead to a large amount of necrotic small bowel, sepsis, and death if not reduced surgically. Data has a small range of its prevalence following surgery—from less than 1 % to over 2 % after surgery [67, 68].

Marginal ulcers (i.e., mucous erosion of the jejunum) just beyond the gastrojejunostomy are another complication of gastric bypass surgery. Patients with Helicobacter pylori infections, who use nonsteroidal anti-inflammatory drugs (NSAIDs), smoke tobacco, and/or use steroids, are at greater risk of developing these ulcers [69]. Aside from chronic pain, these ulcers can create a robust inflammatory reaction at the level of the anastomosis, leading to stricture, bleeding, or perforation. Usually managed in a nonoperative fashion with proton pump inhibitors, they can sometimes require surgical revision if severe enough.

Malnutrition is perhaps the most serious and common complication following bariatric surgery. Following operations that are designed to induce weight loss, these deficits can worsen if patients are not vigilant with vitamin supplementation. Daily multivitamins and trace elements are essential to avoid beriberi, pellagra, kwashiorkor, Wernicke-Korsakoff syndrome, and neuropathies. In addition, there is some early evidence that the episodic hypoglycemia seen after bariatric surgery may also be due to trace element deficits. Complete vitamin and mineral supplements such as Centrum or One-A-Day multivitamin and mineral at two capsules per day will prevent these complications. Overall, however, the risk of a major complication over two decades following gastric bypass is less than 5 %.

Complications following sleeve gastrectomy are rare but serious. The staple line along the greater curve of the stomach can potentially leak. This requires an emergent return to the operating room for repair. Case series have some variability in their incidence—highest recorded being 2.4 % [70]. Other complications such as wound infection, hemorrhage, pulmonary embolus, and respiratory failure were similar to that of the bypass except for intestinal obstruction which is rarely seen following the gastric sleeve [71]. There is also evidence that many gastric sleeve patients develop significant reflux with esophagitis. There have also been early report that the long gastric scars can twist and/or stenose gastric tubes as they heal and contract.

The gastric banding procedure has been performed with less frequency in recent years as numerous complications have been seen in the postoperative period [72]. Approximately 50 % of bands placed in the last 5 years are being removed [73]. A slipped band occurs when the stomach herniates superiorly through the lumen of the band, thus obstructing the flow of food and promoting severe reflux. Two to three anti-obstructing stitches are placed in the stomach to prevent this from occurring. Esophageal dysmotility and pseudoachalasia occur when the band becomes too tight that it obstructs the passage of food through its lumen. Another complication, though rare, is gastric erosion. Occurring about 5 % of the time in patients who have had it longer than 5 years, it can be a morbid complication [49, 74]. Most of the time, the band is removed, and, if there is a perforation in the stomach, it can be closed. Frequently, patients are being converted over to other, more durable weight loss surgeries. Despite the potential for complications and need for the removal of the band, the placement of an AGB is the safest procedure available with a mortality rate of 0.17 % at 1 year [75].

Numerous issues may arise following DS. Many of them have already been discussed previously under the heading of gastric bypass. The incidence of anastomotic leak, malnutrition, vitamin deficiency, and electrolyte imbalances occurs with far greater frequency in DS patients.

## Resolution of Diabetes Following Gastric Bypass

Following bariatric surgery, many patients were found to have resolution of their comorbidities. Several studies discovered that they would resolve prior to profound weight loss. One of the most highly investigated instances of this phenomenon is the resolution of diabetes following RYGB. Pories et al. were the first to describe in 1982 the resolution of diabetes mellitus following RYGB (also known as the Greenville Obesity Procedure) [76]. While resolution of diabetes does occur with SG, AGB, and DS, the majority of the data pertain to the RYGB experience.

Pories et al. first noted that there was a resolution of hyperinsulinemia following gastric bypass in 1992 [77]. Fasting blood sugars were drawn before and after gastric bypass. The level of fasting serum glucose as well as serum glucose 180 min after a glucose meal was significantly decreased [78]. Gastric bypass essentially reverses diabetes as serum fasting glucose is normalized to less than 125 mg/dL postoperatively. Amazingly, this change begins within a few short days postoperatively. Hyperinsulinemia is also quickly resolved postoperatively, but insulin resistance remains for months after. The weight loss itself from bariatric surgery results in the improvement of end-organ insulin sensitivity [79].

This suggests the cause of type 2 diabetes is due to insulin hypersecretion, with insulin resistance being a protective factor against this elevated insulin level. Thus, bariatric surgery “cures” type 2 diabetes by restoring normal insulin levels via the reduction of contact time between food and the gut. Arterburn et al. state that the future of diabetes is treatment with an operation and not a medicine [80].

## Conclusions

The prevalence of obesity, diabetes, and other sequelae of the metabolic syndrome have grown exponentially. The true pathophysiologic mechanism by which this occurs, however, remains to be seen. What is clear is that bariatric surgery can allow for drastic weight loss. It is the most effective weight management tool available to patients. The impact of gastric banding, duodenal switch, gastric bypass, and sleeve gastrectomies, however, does not stop at simple weight loss. Fertility, glycemic control, resolution of hypertension, obstructive sleep apnea, and weight-bearing arthralgia are just a

few of the many documented benefits of bariatric surgery. The term bariatric may be a misnomer—we propose these operations are better categorized as "metabolic" surgeries as their impact is indeed multifactorial.

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# Chapter 25
# Complications of Bariatric Surgery

**Leonardo Claros and Scott Shikora**

**Abstract** The number of bariatric surgeries being performed has dramatically increased over the last decade. The purpose of this chapter is to make all clinicians that provide care for the bariatric patient to be familiar with the commonly occurring potential complications in both the short and long term that are associated with these procedures. It is important for all providers to be able to recognize, understand, and treat these complications when they occur to ensure not only the patients safety but long-term success.

**Keywords** Bariatric surgery • Complications • Gastric bypass • Sleeve gastrectomy • Adjustable gastric banding • Leaks • Fistulas • Ulcers • Stenosis • Prolapse • Slippage • Infection • Bleeding • Dumping syndrome • Intussusception

### Key Points

- The number of bariatric surgeries being performed has dramatically increased over the last decade.
- Clinicians who provide care for the bariatric patient must be familiar with the commonly occurring potential complications in both the short and long term that are associated with these procedures.
- Early complications can include venous thromboembolism (VTE), infections, bleeding, anastomotic leaks, nausea/vomiting, dehydration, and dumping syndrome.
- Late complications may include anastomotic (marginal) or peptic ulcers, stenosis, fistulas, nutritional deficiencies, weight loss failures, gastric band prolapse (slippage), intestinal obstruction, and intussusception.
- It is important for all providers to be able to recognize, understand, and treat these complications when they occur to ensure not only the patient safety but long-term success.

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## Introduction

Over the last couple of decades, there has been a dramatic increase in the number of bariatric operations performed not only in the USA but around the world as well.

It has been estimated that in the past year, as many as 200,000 operations were done in the USA and a similar number outside the USA. Since its inception in the 1950s, bariatric surgery has undergone continuous improvement and has evolved into a very innovative field that offers sustainable and meaningful weight loss as well as improvement (and even remission) of a number of related health conditions.

Bariatric procedures have long been considered high risk for a variety of reasons. Firstly, obese patients often have significant health issues. Secondly, performing surgery on obese individuals is technically challenging due to their body habitus and intra-abdominal adiposity. Lastly, bariatric surgical procedures are complex gastrointestinal operations. However, when these operations are done in accredited centers with highly trained and skilled surgeons, multidisciplinary teams, and committed administrations, the results are excellent and the morbidity surprisingly low. These good outcomes are the result of comprehensive preoperative screening and preparation, skilled surgical technique, and excellent perioperative care. However, despite these improvements complications and even devastating complications may still occur both shortly after surgery and in the long term.

The incidence and severity of these untoward events can be minimized by a familiarity of the potential complications that may develop; an understanding of the signs, symptoms, and risks; and the knowledge of how to manage them when they occur. As more and more bariatric surgery is being performed, it is highly likely that all clinicians, not just the bariatric surgeons, will need to manage these patients. Furthermore, it is highly likely that the surgeon would be most responsible for the early complications and the patient's other clinicians, the long-term issues. Therefore, it is of utmost importance that not only bariatric professionals but also all health-care professionals that could potentially care for bariatric patients recognize the signs and symptoms, be familiar with the appropriate diagnostic maneuvers, and institute the correct treatment in a timely fashion.

This chapter will cover early and late complications associated with bariatric surgery.

We will mainly focus on the three main performed surgeries in the USA: the Roux-en-Y gastric bypass (RYGBP), vertical sleeve gastrectomy (VSG), and the adjustable gastric banding (AGB).

## Classification

We will classify the complications of bariatric surgery on early and late according to the time of presentation. For the sake of this chapter, early complications are those that most often occur within 30 days of surgery and late complications as those that occur mainly after 30 days. Please keep in mind that those designations are purely arbitrary but help frame the understanding of the risks of bariatric surgery and will hopefully help the nonbariatric surgeon clinician with bariatric patient care. Please also note that there may be some overlap for certain complications. For example, venous thrombosis most often occurs within the first 30 days after surgery (early) but can occur for several months after (late).

### *Early Complications*

#### Venous Thromboembolism

One of the most common causes of mortality after bariatric surgery remains the dreaded VTE whose prevalence has been reported to be as high as 20–30 % in the obese population. In the present-day practice of bariatric surgery, the incidence of symptomatic VTE has been generally reported at 1–2 %

[1, 2]. However, according to one of the largest retrospective and multicentric studies published by the University of California and the Irvine Medical Center where they examined data from over 300,000 bariatric patients who underwent surgery, and concluded that the incidence of in-hospital VTE was only 0.17 % with the highest rate observed in open gastric bypass (0.45 %). The VTE incidence was significantly lower in laparoscopic compared with open gastric bypass (0.13 % versus 0.45 %, respectively, $P < 0.01$) [3]. A different meta-analysis found that the incidence was 0.5 % [4]. Unfortunately, it is difficult to know the true incidence of VTE as most of the reports only studied patients who were symptomatic. Asymptomatic events were only recorded in a minority of the published studies.

As with all patients, it is very important to take the appropriate measures to prevent this occurrence. There are several published recommendations, but to date there is no consensus or standard of care when it comes to VTE prophylaxis in the morbidly obese. Over 90 % of bariatric surgeons utilize some form of thromboprophylaxis. Additionally, over 70 % use both mechanical and chemical prophylaxis [5]. The ASMBS Clinical Issues Committee published a position statement recommending the use of lower extremity sequential compression devices and early ambulation, as they were easy to implement. In addition, routine administration of chemoprophylaxis, if not contraindicated, was recommended for all bariatric surgery patients. However, recently the need for chemical anticoagulation has been questioned [6]. Unfortunately the choice, dosage, and duration of anticoagulation administration remain controversial. Further, the role for vena caval filters, used for patients unable to receive chemoprophylaxis and for those at very high risk, is also not well elucidated.

In order to diagnose this complication, a high index of suspicion must be maintained. Often these patients will present with unilateral leg swelling (DVT), tachycardia, and/or hypoxia (PE). Additionally, they may also demonstrate hypocarbia due to hyperventilation. Although these findings are suggestive of VTE, they are by no means exclusive as the patient could have sustained other complications that can manifest similar signs and symptoms such as a cardiac event, hemorrhage, or gastrointestinal leak. The acute onset as opposed to a more gradual one might aid with the differential, but an aggressive assessment usually by radiographic imaging is a must under these circumstances. The traditional gold standard for the diagnosis of a VTE had been a pulmonary angiography. In recent years and with the advent of better CT scanners, there has been a shift toward a computed tomographic angiography (CTA). Whenever possible and if the patient is stable, a CT scan of the chest and abdomen would be the most helpful diagnostic examination as it could potentially rule out an intra-abdominal source as well. The negative predictive value of a normal chest CTA is greater than 99 % [7].

The treatment and management of a patient with a VTE require anticoagulation. When the diagnosis is not clear (i.e., due to inability to obtain a CTA), treatment will be largely based on the clinical suspicion. If the patient remains tachycardic, bleeding and other causes have been ruled out, and the CT examination is negative, it is often our practice to explore the patient in the OR. If no evidence of leak or intra-abdominal sepsis is found at surgery, then anticoagulation might still be indicated. If the patient on the other hand has a low or moderate clinical suspicion of a VTE, additional supportive testing may be obtained such as ventilation perfusion scanning or lower extremity ultrasonography.

Some clinicians advocate for the use of inferior vena cava (IVC) filters preoperatively in high-risk patients. This is largely controversial and yet unproven. A small series from George Washington University Medical Center concluded that if filters are to be placed in this high-risk group of patients, they should be removed after the risk of VTE has passed [8]. However, there is no true measure for determining when the risk has passed, and some events occur months after surgery. In 2008 and 2009, the American Association of Clinical Endocrinologists (AACE), the Obesity Society (TOS), and the American Society for Metabolic and Bariatric Surgery (ASMBS) published a set of recommendations where they stated that filters should be considered for patients with a history of prior PE, prior iliofemoral DVT, evidence of venous stasis, known hypercoagulable state, or increased right-sided heart pressures [9]. However, as stated above, the role for vena caval filters in the bariatric patient population is poorly defined.

## Infection

The incidence of infection largely varies from hospital to hospital, from surgeon to surgeon, from patient to patient, and also from procedure to procedure [10, 11].

It is well known though that the obese population, as proven in most analysis, are at higher risk for developing infections [12–14] as they have a compromised inflammatory response and healing process [15, 16]. Many of the comorbidities commonly seen in these patients contribute to this higher risk for developing infections. These comorbidities include conditions such as diabetes mellitus and obesity hypoventilation syndrome that result in hyperglycemia and low oxygen tension in the tissues. It is believed that the bactericidal activity of the neutrophils is largely dependent on superoxide radical production, which is dependent on the oxygen partial pressure in the tissues. Tight and adequate early control of post-op hyperglycemia has been shown to lower rate of infections [17].

After a bariatric procedure patients are at risk for two types of infections; surgical site infections and intra-abdominal infections. A surgical site infection, i.e., wound infection, occurs in about 1–11 % of cases depending on the reference [1, 18, 19]. The incidence of abdominal wall infection is frequently higher after open surgery when compared to laparoscopic approaches. It is also much easier to manage a small-infected trocar site rather than a long abdominal wall incision.

Intra-abdominal infections, most commonly as a result of a gastrointestinal perforation and leak, could become lethal complications and need to be promptly diagnosed and treated. The index of suspicion must be high in a postoperative patient that develops tachycardia, tachypnea, hypoxia, fever, and/or chills. Oliguria and hypotension are late signs. Patients may also appear anxious or demonstrate what bariatric surgeons refer to as the "feeling of doom" or the fear of dying. Although diagnostic imaging (CT scanning or GI fluoroscopy) can usually make the diagnosis, if there is a high index of suspicion, the patient should not undergo imaging but go to surgery in a timely fashion. Time is important. Delay in therapy can result in a more devastating outcome. On occasion, diagnostic imaging will be nonspecific or not diagnostic. In our practice if the diagnostic imaging is otherwise negative but the patient is concerning, we have a low threshold to take the patient to surgery for exploration. In most cases a diagnostic laparoscopy would be feasible and preferable over an open laparotomy.

The goal of surgical exploration is primarily to control the sepsis. The intra-abdominal fluid is aspirated and the abdomen is irrigated clean. The leak should be located and the drains placed in the region. Although suture repair is attractive and usually attempted, the repair will often break down. The patient will recover and heal with adequate drainage tubes, antibiotics, and nutritional support.

## Bleeding

The incidence of postoperative bleeding following bariatric surgery varies in the literature and is often quoted between 1 and 4 % [20]. Patients with postoperative hemorrhage will often present with signs and symptoms including tachycardia, decreased urine output, a falling hemoglobin level, and pale appearance. Hypotension and dizziness would suggest a significant bleed. The bleeding most commonly arises from the staple lines, but it could potentially result from an intra-abdominal injury to organs such as the liver or spleen. Additionally, for anastomotic procedures such as the gastric bypass, bleeding may also occur within the GI tract from the anastomoses and manifest as gastrointestinal bleeding (GIB). It is important to make the distinction of whether the bleeding is from an intra-abdominal or intraluminal source. However, the distinction could be quite challenging. Most morbidly obese patients will rarely demonstrate abdominal distention until a significant amount of bleeding has occurred. If a drain was left in place at surgery, high bloody drain output may support the diagnosis. On the other hand if the patient presents with hematemesis or passing blood or clots per rectum, there may be a GIB. On occasion, gastric bypass patients with GI bleeding may also develop signs of bowel obstruction as a clot formed in the gastric pouch might organize and act as a "cork" at

the level of the jejuno-jejunal anastomosis (most of the time) or even at the level of the gastrojejunal anastomosis. It is much less common for symptoms of obstruction to present after the gastric sleeve where hematemesis would be a cardinal sign of staple-line bleeding. Additionally, GIB after a gastric sleeve is very uncommon as there are no anastomoses. Serial blood testing is important not only for diagnosing but also for monitoring bleeding. A low falling serum hematocrit or hemoglobin may confirm that bleeding has occurred. Stable numbers over time may suggest that the bleeding has spontaneously ceased. However, a normal lab value obtained shortly after surgery may not be reliable. A thorough physical examination and a carefully obtained history can help localize the potential site of GIB even without the need of diagnostic tests [21].

The management of GIB in bariatric patients depends entirely on the hemodynamic stability of the patient. If the patient is stable, general support measures and an expectant approach will usually be sufficient. On the other hand if the patient is hemodynamically compromised, the general principles of resuscitation for any post-op bleeding patient must be instituted. It is important to secure good peripheral access and start IV resuscitation promptly. Transfusions of blood products and correction of any coagulopathy should be instituted as indicated. Surgical exploration would be necessary if the patient becomes hemodynamically unstable or the bleeding does not appear to be resolved after a few hours of observation.

If the patient is having active hematemesis, a diagnostic endoscopy may be warranted. This procedure is best done in the operating room with the patient intubated in order to protect his or her airway. Bedside therapeutic endoscopies are discouraged in this specific population. The endoscopy not only is valuable for localizing the bleeding but also could utilize therapeutically the many endoscopic modalities that control bleeding such as clip placement, electrocautery, or chemical injection that are currently available. Additionally, the clot could be successfully evacuated from the pouch further preventing the possibility of an obstruction. If the bleeding source could not be identified or controlled endoscopically, a surgical exploration is the next step whether this is done laparoscopically or in an open fashion would depend on the situation at hand and the experience of the surgeon. For GIB, the staple lines should be over sewn [21]. Intra-abdominal bleeding should be treated as indicated as it would after any abdominal surgery.

## Leaks

Gastrointestinal leaks are one of the most common causes of mortality and morbidity after bariatric procedures. They are among the most feared complications that a clinician caring for these patients can deal with. For the gastric bypass, the literature reports an incidence that ranges between 0 and 5.6 % in different series [1, 22, 23]. However, 1–2 % would be a reasonable estimation of the current incidence. For the sleeve gastrectomy, the incidence is reported to be 1.2–2.7 % [24]. Leaks after AGB are very uncommon. They may occur secondary to unintentional injury or perforation of the stomach during band placement.

After a gastric bypass, a leak occurs most commonly at the gastrojejunal anastomosis, but it could also occur at any of the staple closures of the gastric pouch, the gastric remnant, or the jejuno-jejunal anastomosis. It can even occur anywhere on the gastrointestinal tract due to an unrecognized injury during the operative procedure. On the other hand for gastric sleeves, it occurs most commonly on the uppermost end of the staple line but could also occur anywhere along the staple line or anywhere in the GI tract.

As described above, the clinical presentation for leaks often poses a diagnostic challenge as the physical examination of the morbidly obese surgical patient is unreliable and many patients will demonstrate nonspecific signs or symptoms. The most common sign of leak is a prolonged tachycardia of 120 beats per minute (BPM) or greater. This heart rate needs to be thoroughly evaluated with a high index of suspicion for a leak. However, leaks can occur at lower heart rates. In the morbidly obese,

peritoneal signs may be absent, and radiographic evaluation may not demonstrate the leak. For example, a water-soluble contrast study can view the pouch, gastrojejunal anastomosis, and proximal Roux limb well, but the study will rarely demonstrate a leak at the level of the jejuno-jejunal anastomosis and never at the gastric remnant since this portion of the stomach is excluded from the oral contrast bolus. A CT scan might be helpful if the patient fits on the scanner, but the patient's size is a great rate-limiting factor to obtain a good quality study or even any computed tomography images at all. When obtainable, the CT can usually demonstrate that a leak has occurred but not always locate where the leak occurred. As stated earlier, the diagnosis of leak is truly a clinical diagnosis. Patients that "do not look well" or have the appearance of "impending doom" should be given consideration for exploration. Patients who are hemodynamically unstable warrant early exploration. Hypoxemia, oliguria, and hypotension occur later as sepsis develops. The morbidity and mortality increase when these signs are observed.

The optimal management of a leak usually involves an early diagnosis and prompt surgical exploration. As stated above, the exploration involves the clean out of the contamination, identification of the leak, and adequate drainage. Leak repair is often attempted but rarely successful. If the leak is controlled with drainage, it will often heal over time. Antibiotic administration and nutritional support are also required. Enteral nutrition is preferred over parenteral, and a feeding gastrostomy or jejunostomy should be considered at time of surgery.

For patients with small, contained leaks who are hemodynamically stable, surgery may be avoided. There is a growing literature regarding the endoscopic placement of stents. When in good position, it would interrupt the contamination and allow patients to eat. However, the patient may still require percutaneous drainage of the collection and antibiotics.

Surprisingly, the leaks seen in the gastric sleeve are much more difficult to manage than those after gastric bypass. The leaks are likely caused by the same mechanisms as with the gastric bypass, i.e., injury to the tissue, mechanical staple-line failures. While the presenting signs and symptoms would be similar to that seen after gastric bypass, sleeve leaks tend to be more resistant to healing.

The newly created gastric pouch is elongated and narrow. The resistance of the flow through a narrow and long tube is directly proportional to the fourth power of its radius and inversely proportional to the length of the tube (Poiseuille's law). In simple terms we have created a high-pressure system, and the most common site for a leak after a sleeve gastrectomy is proximally close to the angle of His. Less commonly they could happen distally close to the pylorus. Endoscopic stenting has been described as an alternative to surgery for leaks if the patient is stable.

If the leak does not heal after several months, surgery is indicated. Leaks may sometimes heal with closure and patching. However, persistent leaks may require gastrectomy and reconstruction, proximal leaks by gastrectomy and esophagojejunostomy, and distal leaks by partial gastrectomy and conversion to a gastric bypass [25].

### Nausea and Vomiting

Nausea and vomiting are common occurrences after all bariatric surgery. Most of the time immediately after surgery, this is related to the anesthetics, the analgesics, and/or the surgical trauma to the GI tract. Adequate postoperative antiemetics should be implemented. However, the clinician must always be vigilant to rule potential obstructive sources. After the immediate postoperative period, most cases of nausea and vomiting are due to dysfunctional eating habits, such as overeating, eating too fast, or not chewing food well. This is particularly true when the nausea and vomiting occur frequently but not consistently or do not seem to be related to any particular food. However, other causes must be ruled out such as dumping syndrome, medication intolerance, anastomotic strictures, marginal ulcers, intestinal obstruction, band prolapse, or an overly tightened band. A thorough history may help differentiate causes. For example, a patient who develops progressive solid food intolerance

approximately 4–6 weeks after surgery, which necessitates a change in diet to only liquids, may have an anastomotic stricture. Patients who experience solid food intolerance accompanied by postprandial, burning pain in the left upper abdomen may have an anastomotic ulcer. In contrast, a patient who gets nauseated or vomits only on occasion without any obvious pattern is most likely to be eating incorrectly (e.g., too quickly, excessive volume of food).

## Dehydration

Mild dehydration is commonly seen in the early postoperative period after all of the bariatric procedures. As with any other surgical patient, it is mainly due to decreased fluid intake. Unlike other surgical procedures, the current bariatric procedures all reduce gastric capacity. Due to the limited gastric capacity, patients have difficulty drinking the necessary amount of fluid as they can only take in small volumes of fluid at a given time. This is particularly a problem shortly after surgery and in warm climates. Over time patients do adapt to the very small gastric capacities, and this problem becomes less common. Also vomiting or diarrhea may exacerbate fluid losses. Patients with intestinal illnesses that result in vomiting and diarrhea may have difficulty maintaining their hydration. On the basis of body weight, obese patients require a greater amount of fluid per day than their lean counterparts to maintain normal fluid balance. This volume is obtained directly from the liquid consumed and indirectly from the water constituent of the food eaten. Standard fluid recommendations are impossible given the heterogeneity of the patients. In addition, there are no mathematical equations that accurately estimate fluid needs in the obese population. Patients are often instructed to use thirst and urine concentration as a guide for fluid intake and to monitor their hydration status via awareness of potential signs of dehydration, such as dizziness, dry mouth, dark urine, and dry skin. It is our practice to teach our patients that fluid status can be managed by encouraging them to travel with a fluid source (i.e., sports bottle) and drink continuously throughout the day one swallow at a time until the symptoms of dehydration are relieved. Once dehydrated, these patients have great difficulty "catching up" because they cannot drink fluid quickly. For those patients with vomiting and inability to tolerate oral intake, intravenous fluids may be necessary to restore their intravascular depletion. Dehydration may also cause nausea, which may exacerbate intolerance to the diet or fluids. It is therefore critical that patients drink enough fluid postoperatively to prevent dehydration. An intake of approximately 64 oz of fluid a day is generally recommended. However, some patients may even require more, especially if they are extremely heavy, physically active or live in a warm climate. Patients should be frequently reminded that meeting their fluid goal takes precedence to food, including even protein intake. Whenever possible, postoperative patients who are unable to ingest adequate protein from solid foods alone should include high-protein, low-carbohydrate liquid supplements in their diet to better meet fluid and protein needs.

## Dumping Syndrome

Dumping syndrome is a condition that is most commonly seen after the gastric bypass, less commonly with the sleeve as the pyloric sphincter is preserved, and rarely seen with the adjustable banding. After gastric bypass, the ingested foods enter the small intestine largely undigested. Concentrated sweets are the usual cause for the dumping syndrome. Two stages of dumping syndrome have been described. "Early" dumping begins concurrently or immediately succeeding a meal. Symptoms of early dumping include nausea, vomiting, bloating, cramping, diarrhea, dizziness, and fatigue. It is felt to be the result of hypovolemia. The concentrated sweets represent a hyperosmotic load that when rapidly emptied into the jejunum results in the diffusion of fluid into the lumen of the intestine resulting in osmotic diarrhea, distension of the small bowel leading to crampy abdominal pain, and hypovolemia resulting

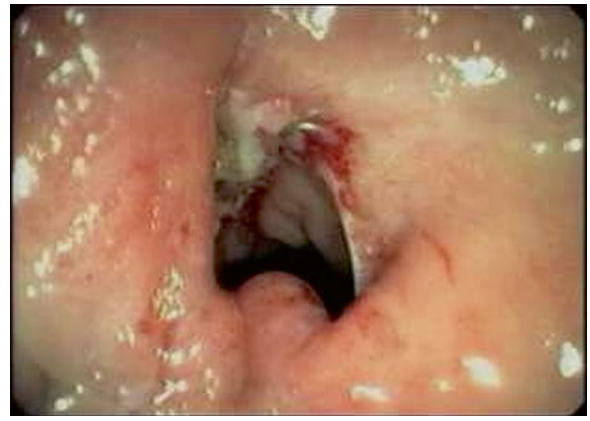

**Fig. 25.1** Marginal ulcer

in dizziness. "Late" dumping occurs approximately 90–180 min after a meal. The symptoms of late dumping include weakness, sweating, and dizziness and are due to hypoglycemia. The carbohydrate load in the small intestine stimulates an exaggerated insulin release that ultimately results in symptomatic hypoglycemia. Many patients experience both types.

To avoid experiencing dumping syndrome, it is important to instruct patients to avoid certain foods such as those that contain added sugars, simple carbohydrates, and concentrated fats. Patients who suffer from dumping syndrome are counseled accordingly. Additionally, whenever possible, they should increase their soluble fiber intake [26]. Patients suffering from dumping syndrome should also evaluate their supplements. Some nutritional supplements contain sugars. Patients taking these supplements may experience dumping syndrome even though their diets are appropriate. They should only select supplements that only contain approximately 13 g (or less) of "sugars" per serving.

Most patients will benefit from simply altering their diets. For those patients who experience severe symptoms that are refractory to dietary changes, a trial of medications such as octreotide or acarbose will usually be effective [27]. On rare occasions, severe, intractable dumping syndrome may require reversal of the bypass.

## *Late Complications*

### Ulcers

In general, ulcers after a bariatric surgery will be either anastomotic (marginal ulcers) or peptic. Peptic ulcers occur in the distal gastric antrum or duodenum as they would occur in people who have not had bariatric surgery. After the AGB, the incidence of peptic ulcer disease is similar to that of nonbariatric patients. However, after a GBP it seems to occur at a lower incidence than the general population. Printen et al. reported an incidence of peptic ulcers of 0.26 % in over 3,000 gastric bypasses [28].

On the other hand, marginal ulcers after a GBP have a variable incidence reported to be between 1 and 16 % [29–31]. The marginal ulceration represents a mucosal erosion on the intestinal side of the anastomosis with the gastric pouch (Fig. 25.1).

The intestinal mucosa is normally not exposed to gastric acid, which gets neutralized by the alkaline biliopancreatic secretions. Unlike the stomach, which is resistant to acid, the intestinal mucosa has no natural barriers and is more prone to ulceration. The causes of marginal ulceration after gastric bypass are multifactorial. It has been associated with the use of nonabsorbable suture material [32],

gastric pouch size greater than 50 cc [33, 34], nonsteroidal anti-inflammatory drug use [35], *Helicobacter pylori* [36], tobacco smoking [37], ischemia, and Roux limb tension.

Patients with marginal ulcers will usually present with burning, upper epigastric pain. Some may complain of substernal chest pain or pain that radiates to the back. Nausea, vomiting, and food intolerance are also commonly seen with marginal ulcers. Massive upper GIB is uncommon but can also be seen often as a late manifestation of untreated or unrecognized ulcer disease.

The evaluation of a patient who presents with symptoms suggestive of ulceration is very straightforward. A barium swallow could be used as a diagnostic test that is noninvasive and simple to perform although it is not very sensitive and could miss small or shallow ulcers. Upper endoscopy is the gold standard for diagnosis. If the ulceration is found, the treatment usually involves the removal of the irritant that is causing it such as NSAIDS or tobacco and the prescription of either a histamine receptor antagonist or a proton-pump inhibitor along with a coating agent such as sucralfate. Most ulcers will heal with conservative therapy. However, those secondary to ischemia, enlarged pouches, or gastrogastric fistula [1] tend to be more refractory and will often require revisional surgery.

### Stenosis

All of the current bariatric procedures rely on small pouches or narrow pouch outlets as key components to maintain durable weight loss. The RYGBP is comprised of a small gastric pouch that has a narrow anastomosis to the jejunum. The pouch is generally 15–30 mL and the anastomosis 1–1.5 cm in diameter. The sleeve is essentially a long narrow tube whose overall capacity is estimated to be 120–150 mL. The same concept applies to the AGB. The gastric pouch is about 15 mL and the narrow outlet adjusted by tightening the band. However, the outlet may become abnormally narrow from inflammation, ulceration, swelling, or ischemia with scarring. In this setting, patients will have progressively worsening food intolerance leading to frequent and often progressive vomiting. Initially, the difficulty will be with certain solid foods such as bread or beef. In severe cases, it will progress to include all solid food and even liquids. Constant and progressive symptoms are characteristic of stenosis, while episodic or transient vomiting is more likely from dietary indiscretion. If not properly treated or recognized, these complications could lead to dehydration, and if chronic, protein-calorie malnutrition and vitamin or thiamine deficiency.

An outlet narrowing is called a stricture or stenosis. Anastomotic (gastrojejunostomy) stenosis occurs in 1–15 % of patients who undergo RYGBP and typically occurs within 2 years of the procedure [38] although most seem to occur within the first 4–8 weeks after surgery [39]. Some may also occur years later often as the result of chronic or recurrent ulceration. It is controversial whether the anastomotic technique, i.e., circular versus linear stapled versus hand sewn and retrocolic versus antecolic, truly alters the incidence of stenosis for the RYGBP.

While sleeve gastrectomies do not have anastomoses, the sleeve itself may stenose in about 2 % of patients. Strictures may be due to the healing of a leak, a twisting of the sleeve, or to inadvertently creating it too narrowly. Most early stenosis occurs at the incisura of the stomach. Stricture may occur as a result of ulceration and subsequent healing although the exact incidence of this complication is unknown yet.

Anastomotic strictures can usually be diagnosed by history alone. UGI fluoroscopy can also be helpful in demonstrating narrowing of the sleeve gastrectomy, the gastric pouch, or the gastrojejunal anastomosis. Upper endoscopy is the best test as it is not only diagnostic but also therapeutic. An experienced endoscopist should be able to recognize the stricture and then balloon dilate it. Balloon dilatation with a through-the-scope balloon is highly effective in reestablishing an adequate lumen and resolving the patient's symptoms. The goal of dilatation is to follow a stepwise approach dilating the stricture to a final lumen of 12 mm. The majority of strictures are successfully corrected with one endoscopic balloon dilatation for the RYGBP [40, 41] and 1.6 dilations for the VSG [42]. However, a serious complication of balloon dilatation is acute perforation.

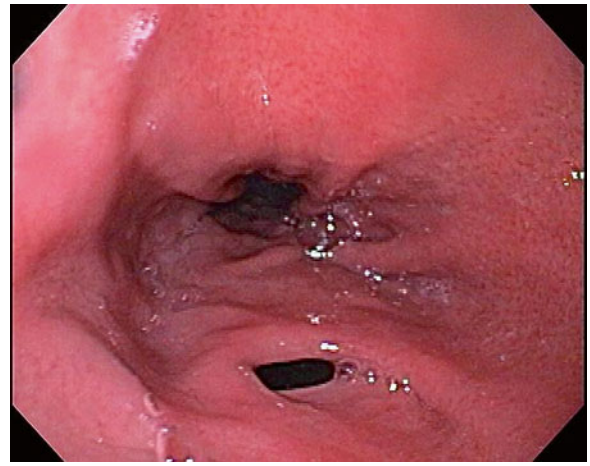

**Fig. 25.2** Fistula

On occasion multiple dilatations may be necessary. In some cases, the structure may be very fibrotic and not amenable to balloon dilatations. Those patients will likely require surgical revision.

Gastric sleeve strictures can also be balloon dilated or stented endoscopically. However, they are less likely to be successfully managed nonoperatively and more likely to require surgery than gastric bypass strictures. While stricturoplasty has been described [43], depending on the location, conversion to gastric bypass or gastrectomy with esophagojejunostomy may be necessary.

Outlet stenosis is uncommon with the AGB, but it can result from fibrotic reaction around the band compressing the lumen. It may occur as a result of band erosion into the lumen, which incites an inflammatory response and fibrosis. In these cases revisional surgery and removal of the band might be the only treatment.

## Fistulas

Gastrogastric fistula after gastric bypass is an abnormal communication between the gastric pouch and the excluded gastric fundus (Fig. 25.2). This complication is usually followed by weight gain and/or marginal ulceration. The incidence reported in the literature is extremely wide, ranging from as low as 0 % in some series to up to 49 % in other ones [32, 44]. The higher fistula rates were usually from the earlier studies analyzing the experience of open gastric bypass that employed a stapling device that did not cut the pouch free from the rest of the stomach. Noncutting staple lines were like seams and had a high likelihood of dehiscing over time. The more contemporary fistula rate for gastric bypasses created with a cutting stapler has been closer to 1 %. The cutting stapler separates the pouch from the fundus. The subsequent healing dramatically reduced the likelihood or late failure. Recent publications describing predominantly or exclusively cut staple lines have quoted the incidence to range from 0.4 to 6 % [30, 45]. Gastrogastric fistula after cut staple lines has been attributed to two main causes: (1) it was a technical complication derived from the incomplete division of the stomach during the creation of the pouch, and (2) it occurred after a staple-line failure, resulting in a leak with an abscess, which then drained into the distal stomach forming the fistula. There is a well-documented association between gastrogastric fistulas and marginal ulceration in the bariatric population. Studies have reported rates as high as 53.3 % of marginal ulceration when associated with fistulas [46]. While the likelihood of preventing the formation of gastrogastric fistula is remote, there have been multiple attempts with an assortment of technical modifications to decrease the incidence. The use of sealants, over sewing the staple lines, and the use of buttressing material have all been advocated, but none of these techniques have been proven to prevent fistula [47–51].

Diagnosing a gastrogastric fistula is not a complicated endeavor. An UGI fluoroscopy is the gold standard. A CT scan can demonstrate the communication between the gastric pouch and the gastric remnant but suffers from a high false-negative rate as it cannot differentiate between a fistula and contrast reflux into the excluded fundus. Esophagoduodenoscopy can be useful for characterizing the size and location of the fistula, but it is invasive, expensive, and may miss small fistulas. It may also diagnose concomitant marginal ulcers.

Not all fistulas require treatment. Many may be found incidentally if asymptomatic patients were evaluated. Conservative treatment with antacid medications and observation is not unreasonable as long as the patient is not gaining weight or is symptomatic and found to have intractable marginal ulceration. Otherwise the treatment of fistulas has traditionally been surgical. Revisional surgery to resect the gastrogastric fistula is extremely challenging and is associated with a high incidence of staple-line leak or fistula recurrence. Salimath et al. suggest resecting the upper excluded fundus to reduce the risk of recurrence [52].

Recently, endoscopic suturing and stapling techniques are being developed and used to treat fistulas. However, the early results are promising but not conclusive. More research and validation are necessary before this treatment can be considered conventional and not experimental.

### Nutritional Deficiencies

In order to better understand the potential deficiencies that can develop after surgery, it is also important to remember where along the gastrointestinal tract the macro- and micronutrients are absorbed. Procedures that reroute the nutrient stream away from the gastric acid and/or the proximal small intestine can be assumed to put patients at risk for developing deficiencies, such as iron, vitamin B12, folic acid, and calcium. Some nutrients are preferentially absorbed more proximally in the GI tract and others more distally. In addition, certain nutrients require specialized mixing for maximal absorption. For example, iron represents both. It is preferentially absorbed in the proximal small intestine and is best absorbed after contact with an acid environment. Therefore, the type and severity of nutrient deficiency will vary according to the operative procedure performed.

The gastric restrictive procedures, including the RYGBP, rarely cause protein-calorie malnutrition. The weight loss seen is predominantly from fat with only minimal changes in lean body tissue. However, in patients with dysfunctional eating habits such as anorexia or the avoidance of protein food sources and in patients with protracted vomiting, protein malnutrition can occur. Unfortunately, diagnosing protein malnutrition may be challenging. Clinical signs of protein malnutrition can be challenging to observe in overweight patients. Additionally, serum protein levels will often stay in the normal ranges until late [53, 54].

Therefore, for all bariatric patients, dietary monitoring is important during weight loss and the long term. Patients are instructed to follow a high-protein diet to include approximately 60–80 g of protein daily. Protein intake guidance should not be driven only by serum protein levels but more importantly by diet history.

Severe calorie deficiency (cachexia) is also unusual after bariatric surgery but may be seen in patients with protracted vomiting, diarrhea, or anorexia. Treatment includes nutritional supplementation (even involuntary if necessary), correction of any underlying anatomical abnormalities (i.e., stricture, obstruction), and/or psychological intervention as indicated. For the most extreme or intractable cases, surgical reversal may be necessary.

Vitamin and/or mineral deficiencies are prevalent after all bariatric procedures and in particular gastric bypass [55–58]. After surgery, all patients may be at risk for an array of dietary vitamin and/or mineral deficiencies and therefore should comply with lifelong supplementation and surveillance. Of note, micronutrient deficiencies may develop slowly and not become evident until years after surgery. Therefore, patients need to be followed yearly and lifelong.

The gastric restrictive procedures like the AGB generally cause fewer micronutritional deficiencies. This is presumably because nutrients are not diverted from the duodenum and gastric mixing is essentially normal. However, deficiencies may develop in those patients with intractable vomiting or among those with suboptimal nutrient intake. Intake may be inadequate since the meal size is dramatically reduced and because many patients change their dietary choices. For example, many of these patients do not tolerate red meat, so they may avoid meats altogether. Gastric bypass patients will be at risk for deficiencies for the same reasons as the restrictive procedure patients but will be at additional risk due to the fact that the nutrient stream bypasses the fundus, duodenum, and proximal jejunum causing malabsorption of iron, folate, calcium, and vitamin B12. While the VSG does not alter the intestinal tract, vitamin deficiencies similar to the gastric bypass have been described. This may be due to the reduction of gastric acid and changes in gastrointestinal motility noted after the sleeve gastrectomy. For all bariatric patients, serum levels need to be aggressively followed yearly, and supplementation should be prescribed judiciously. Since many bariatric programs rely on different supplementation protocols, there is no consensus as to what represents the optimal regimen. The ASMBS has recently published recommendations for surveillance and supplementation based on the prevailing literature and best practice [11].

### Weight Loss Failure

Weight loss failure occurs in some patients after all of the current bariatric operations. After RYGBP approximately 20–25 % of patients will exhibit significant weight regain [59]. The exact failure rate of the VSG is too early to know. However, it was quoted to be around 15 % from the Spanish National Registry for Bariatric Surgery [60]. The failure rate for the band is also highly quoted at 25–37 % depending on the study reporting it [61–63].

Few failures can be traced to technical errors. In most cases, dietary noncompliance and/or adverse behavioral changes are to blame. In many cases, patients chronically overeat, graze, and/or abuse calorie-dense foods, candies, or sweets. These patients often complain of increasing appetite, increasing meal capacity, and gradual weight gain. Many have also reduced their physical activities.

The treatment for patients who “fail” bariatric surgery is controversial. Revision is an option but carries a higher morbidity than the original procedure. There is no controversy concerning possible revision for disrupted anatomy such as a gastrogastric fistula or a massive gastric pouch. However, revisional surgery is controversial when the original operation is relatively intact. Many surgeons would opt to revise the prior procedure or to convert to a more radical operation. However, there are few publications to support that volume reducing a mild or even moderately dilated pouch or revising a dilated anastomosis will lead to meaningful and sustainable weight loss for the RYGBP. Limb lengthening is also poorly studied. While dramatically decreasing the common channel thus enhancing the malabsorptive component of the operation will likely succeed in achieving weight loss, it may do so at increased nutritional risks.

On the other hand the conversion from a sleeve to a gastric bypass has been described, and it is feasible although long-term results are also lacking. For the AGB, removing the band and conversion to a gastric bypass, sleeve, or duodenal switch has been reported to achieve good results [64, 65].

As most weight loss failure after bariatric surgery is behavioral and rarely anatomical, it is important to fully assess the patient being considered for revisional surgery. Dysfunctional eating habits and maladaptive behavior need to be identified and corrected. It is not unreasonable to give the patient a 6–12-month period of aggressive dietary, behavioral, and even pharmacologic therapy before considering surgery. Some patients will be able to achieve their weight goals and forego surgery altogether. In this process, some patients will also be deemed unsuitable for revisional surgery.

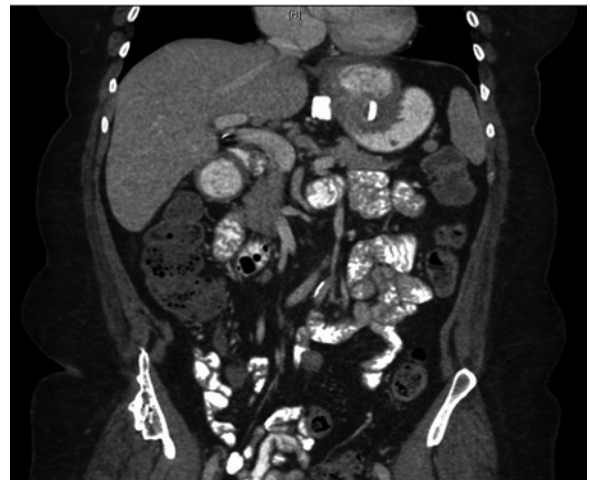

**Fig. 25.3** CT scan of a band prolapse

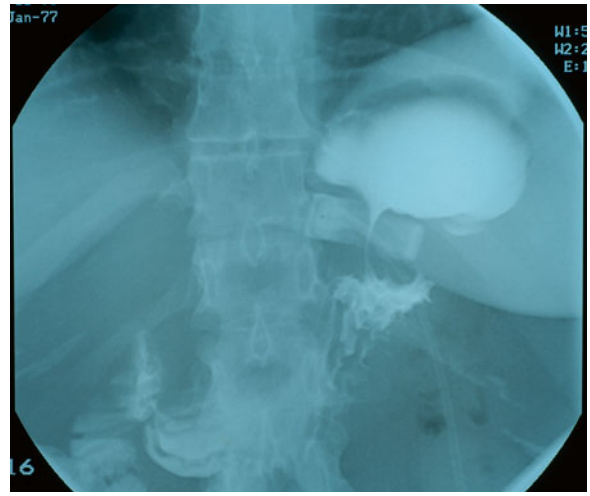


**Fig. 25.4** Band prolapse on a fluoroscopy with oral contrast

## Adjustable Gastric Band-Specific Complications

The FDA approved the utilization of AGB in 2001. Currently today, there are only two bands available in the USA: the LAP-BAND® System (Inamed Corporation, Santa Barbara, CA) and the Ethicon Endo-Surgery Curved Adjustable Gastric Band® formerly known as Realize Band (EES, a Johnson & Johnson company, Cincinnati, OH). Although gastric banding is a much simpler and safer procedure than sleeves and bypasses, it is not free of risk.

There are a number of complications associated with the adjustable banding.

The most common patient complaint is nausea and vomiting followed by gastroesophageal reflux disease. These problems generally occur as a result of noncompliance and overeating. However, they may also be due to anatomical issues such as overfilling of the band, improper placement of the band, band erosion, or prolapse.

Band prolapse (or slippage) is a condition in which the band slides down the stomach compared to its initial position. The stomach that was below the band could also be pushed upward through the band as a result of vomiting or increased pouch pressure from overeating. In both causes the gastric pouch becomes enlarged and floppy appearing (Figs. 25.3 and 25.4). It also doesn't empty well

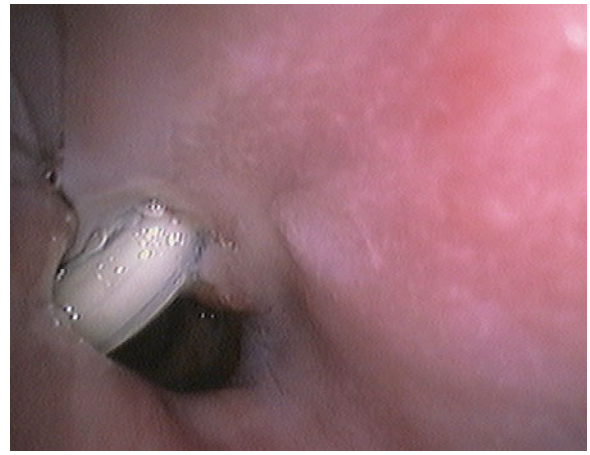

**Fig. 25.5** Band erosion

leading to heartburn, nausea, and vomiting. The incidence of band prolapse is currently about 2–3 % [66]. It has dropped significantly after a change in the operative technique from a perigastric placement to a pars flaccida approach [67, 68]. The diagnosis is best made radiographically. A simple abdominal film will demonstrate an abnormal tilt to the band. An UGI fluoroscopic study will show pouch size and whether it is obstructed. If the patient is clinically stable, the initial treatment usually involves deflating the band. If the symptoms are relieved, the patient can then be followed for several weeks. The prolapse may resolve spontaneously. If band deflation fails to achieve improvement or the patient complains of abdominal pain or demonstrates signs and symptoms of peritonitis, the patient should be surgically explored to correct the prolapse, and if not feasible, the band would need to be removed.

Another complication that can develop with AGB is band erosion into the lumen of the stomach (Fig. 25.5). Although the actual etiology is not known, it has been thought to be the result of an injury to the wall of the stomach at the time of surgery or having the band adjusted too tightly around the stomach. The rate of erosion varies from 0.5 to 4.7 % [68–71]. An eroded band rarely results in perforation and peritonitis and often is an incidental finding in an asymptomatic patient. The band being a foreign object creates a strong inflammatory reaction and the stomach, omentum, liver, or any other tissue in the proximity will often adhere to the band covering it. As the erosion slowly occurs, these tissues seal the space overlying the band, and there is no free extravasation of stomach contents. When symptomatic, band erosion results in heartburn, nausea, vomiting, abdominal pain, or the lack of restriction as if the band had been removed. Additionally, band erosion may present as a late port-site infection. The tubing that connects the band to the port acts as a highway for transporting oral flora to the port and its surrounding soft tissue. The treatment for band erosion is removal of the band as salvage is not possible due to the fact that the band is a contaminated foreign body that has eroded into the stomach and will not clear the contamination with conservative management such as antibiotics.

Currently the AGB has developed a growing rate of patient dissatisfaction. Despite its simplicity and safety, the success rate for weight loss and resolution of comorbid medical conditions lags behind the other procedures. While there are many patients who have done well and are satisfied with their bands, a significant number of patients have had little or no weight loss or chronic symptoms. One of the most common reasons for patients requesting to have their bands be removed is band dissatisfaction. In one study, 24 % of bands were explanted per patient's request, the rest for band problems such as erosions and prolapses [72, 73]. In a series by Tucker et al., 22 % of patients had band explantation. Thirty-nine percent of these failures were weight related, and 16 % were for poor quality of life [74].

### Intestinal Obstruction

Since the VSG and the AGB do not require any small bowel manipulation, intestinal obstruction is extremely rare and only occurs after generic causes such as abdominal wall herniation or adhesions. However, after RYGBP there are several potential causes for intestinal obstruction. The incidence of intestinal obstruction after RYGBP is reported to occur from 1.1 to 10.5 % [1, 20, 75–78]. A 1–2 % incidence would be an acceptable average. Small bowel obstruction (SBO) after laparoscopic surgery is mainly caused by nonadhesive disease as compared to open surgery where SBO secondary to adhesions is more common. Laparoscopic operations, in general, result in fewer intra-abdominal adhesions. However, after laparoscopic surgery, patients are at higher risk of SBO from internal herniation (i.e., mesenteric soft tissue defects created by the surgery and exacerbated by the resultant weight loss) when compared with open. Additionally, the laparoscopic approach results in a lower incidence of incisional hernias (0.7 %) [1] when compared to open gastric bypass where the rate of incisional hernias has been reported to range from 15 to 20 % [79, 80]. Intestinal obstruction from laparoscopic trocar sites may be uncommon but must be taken seriously. The trocar sites create small fascial defects that could allow for a loop of bowel to get trapped inside causing intestinal incarceration and/or strangulation. With the advent of better technology and bladeless trocars, the risk has decreased.

In addition to adhesions, ventral hernias, and internal hernias (IH), other causes of SBO include the formation of mesocolic constrictions, anastomotic strictures, intussusception, intestinal volvulus, and kinking of the bowel at the site of the jejunojejunostomy. The bottom line is that SBO can be seen after any RYGBP procedure whether performed open or laparoscopic; only the etiology of the SBO may be different. All SBOs, regardless of the etiology, behave in a similar fashion and warrant the same treatment.

The symptoms of an SBO after bariatric surgery are the same as those from any abdominal surgery and include abdominal bloating, discomfort, nausea, and vomiting. The symptoms may be different depending on the site and cause of the obstruction. For example, the vomiting would be bilious if the obstruction is distal to the jejunojejunostomy anastomosis preventing the contents from both the Roux limb and biliopancreatic limb from going distally and causing the bile from the biliopancreatic limb to reflux retrograde up the Roux limb and into the pouch.

Internal hernias (IH) constitute a common cause of intestinal obstruction after bariatric surgery both laparoscopic and open. IH are mesenteric defects created during a gastric bypass procedure. These defects include the transverse mesocolic window (for the retrocolic technique), the jejunojejunostomy mesenteric defect, and the space between the transverse mesocolon and the mesentery of the Roux limb (the Petersen defect). Although most bariatric surgeons close these spaces at time of surgery, the significant weight loss seen with the RYGBP leads to recreation and even enlargement of these spaces.

Unlike SBOs after other surgical procedures, an SBO after gastric bypass could be an operative emergency. The gastric remnant has no means to decompress and could represent a blind loop obstruction with impending necrosis and perforation. For this reason bilious vomiting after a gastric bypass should warrant prompt evaluation and, often, early surgical correction. Many of the adverse outcomes in bariatric patients admitted to nonbariatric surgeons with SBO result are from a delay in operative correction. Nasogastric decompression, the mainstay of treatment for SBO in nonbariatric patients, is ineffective for bariatric patients for decompressing the biliopancreatic limb and remnant. Bariatric patients treated in such a manner are at risk for gastric perforation and/or intestinal infarction.

Although most patients with SBO can be diagnosed by history and physical exam, a CT scan is probably the best modality for identifying the site and cause. CT scanning is usually performed to assist with the diagnosis. A “swirl” sign on CT imaging is almost pathognomonic of an internal hernia. A negative CT scan does not completely rule out an SBO. Surgeons need to use their clinical acumen to determine whether to explore or observe the patient. For patients with signs and symptoms of peritonitis, patients should not delay surgery for X-rays but instead go to surgery immediately. The

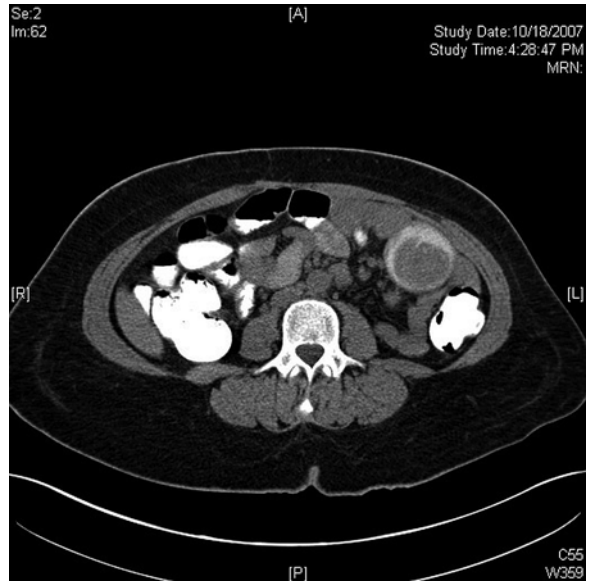


**Fig. 25.6** Target sign on a CT scan of an intussusception

morbidity of SBOs in RYGBP patients remains high, with the incidence of perforations at 9.1 % and death at 1.6 % [81]. The operative treatment can be done laparoscopic in most cases even when the gastric bypass was done open. Surgical treatment includes correcting the cause of the obstruction (lysing the adhesion, reducing the internal or ventral hernia, untwisting the volvulus, etc.). Additionally, all hernia spaces should be investigated and all mesenteric defects closed.

Meticulous closing of mesenteric defects with running nonabsorbable sutures at the time of the original surgery has been shown to decrease the incidence of these hernias [77, 81]. However, even when these spaces are closed, they may reopen particularly since patients will lose a significant amount of weight and the fatty tissue of the mesenteries will shrink.

### Intussusception

Although the reported incidence of intussusception following gastric bypass is relatively low at about 0.1–0.3 % [82], it is expected that this number would increase as more bariatric operations are being performed. The etiology of intussusception is believed to be due to a postoperative intestinal motility disorder which develops secondary to ectopic pacemakers or migratory motor complexes in the Roux limb. Another theory states that the substantial weight loss seem with the gastric bypass causes a thinning of the mesentery that may lead to a less resistance to invagination creating a zone of enteric instability [83].

The well-known triad of abdominal pain, bloody stools, and a palpable mass that is commonly seen with intussusception in nonbariatric patients is rarely seen in gastric bypass patients, and therefore, it is important to combine a thorough clinical history, physical exam, radiographic images, and a low index of suspicion to diagnose the condition [84]. The diagnosis can be relatively straightforward when on a CT scan, and a classic "target sign" is demonstrated. The management of an intussusception after gastric bypass is controversial. It generally occurs at the lower small bowel to small bowel anastomosis. Some surgeons advocate resection and reconstruction of this anastomosis over small bowel pexy [85–87] (Fig. 25.6).

## Conclusions

Bariatric surgery has evolved over the last 50 years into a well-established specialty. As the approaches are becoming less invasive and the health benefits becoming increasingly more recognized, an ever growing number of morbidly obese patients will undergo these surgical procedures. To obtain good results in the long term, it is of utmost importance that all health-care providers who take care of these patients have an understanding of the potential adverse effects. Early recognition and the appropriate early intervention are keys to minimizing the incidence and severity of these untoward events and maximizing the good results.

The purpose of this chapter is to make all clinicians that provide care for the bariatric patient to be familiar with the commonly occurring potential complications in both the short and long term that are associated with these surgeries. It is important for all providers to be able to recognize, understand, and treat these complications when they occur to ensure the patients' success.

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# Part IV
# Integrative Medicine and Obesity

# Chapter 26
# Prevention Strategies for Obesity Among Children and Adults

**Sara N. Bleich, Pooja Singal, and Tiffany L. Gary-Webb**

**Abstract** This chapter synthesized the evidence related to obesity prevention interventions in the clinical, school, worksite, and community settings. Overall, there are not enough studies with consistent methods and outcomes to determine the impact of obesity prevention programs on body weight among adults or children. Of the four settings examined, the largest body of evidence was available for the school setting. This literature suggests that combined intervention approaches which include nutrition and physical activity, as well as a reduction in sedentary activities, result in significant reductions in body weight, particularly among older children (e.g., high school students). We also found that federal guidelines map well to best available evidence on obesity prevention, with the exception of the school setting, where more recent research reflects a need to update guidelines. Going forward, more research and consistent methods are needed to understand the comparative effectiveness of obesity prevention programs, particularly among populations at highest risk for excess body weight. In addition, published details on the processes required to implement obesity prevention interventions are needed in order to increase the translatability of the research and guide effective programs and policy.

**Keywords** Obesity prevention • Adults • Children • Federal guidelines • Avoidance of weight gain

### Key Points

- There are not enough studies with consistent methods and outcomes to determine the impact of obesity prevention programs on body weight among adults or children.
- Of the four settings examined, the largest body of evidence was available for the school setting.
- The studies suggest that combined intervention approaches that include nutrition and physical activity, as well as a decrease in sedentary activities, result in significant reductions in body weight, particularly among older children (e.g., high school students).

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- Federal guidelines map well to best available evidence on obesity prevention, with the exception of the school setting, where more recent research reflects a need to update guidelines.
- Going forward, more research and consistent methods are needed to understand the comparative effectiveness of obesity prevention programs, particularly among populations at highest risk for excess body weight.
- Published details on the processes required to implement obesity prevention interventions are needed in order to increase the translatability of the research and guide effective programs and policy.

## Introduction

Childhood obesity—defined as a body mass index (BMI) at or above the 95th percentile of the sex-specific Centers for Disease Control and Prevention (CDC) BMI-for-age growth charts—affects one in five children and adolescents in the United States [1]. Since 1980, rates of obesity tripled for children ages 2–5 years old and adolescents aged 12–19 years old and quadrupled for children 6–11 years old [2]. Adult obesity—defined as a BMI at or above 30 kg/m$^2$—affects roughly one third of US adults and has doubled in since 1980 [3]. In both adults and children, obesity disproportionately impacts females, minorities, and low socioeconomic status (SES) groups [3, 4].

Obesity greatly increases the risk for several adverse health conditions (e.g., heart disease, type 2 diabetes, certain cancers, and stroke) [5–8] and is a leading cause of preventable death [9]. The adverse affects of obesity are not only medical; excess body weight has also been shown to affect quality of life in both adults and children [10]. Obesity and its associated conditions are estimated to cost between $147 billion annually, approximately 10 % of all medical spending [11]. The increase in obesity costs has been primarily driven by an increase in obesity prevalence (not per capita costs among the already obese) [11], pointing to the importance of obesity prevention. Interventions to produce weight loss have been plentiful yet overall have had modest effects [12]. Therefore, strategies for prevention hold promise to help curb the obesity epidemic, particularly because preventing weight gain may have fewer barriers to implement than achieving weight loss after there is already a weight problem.

Primary prevention of obesity has received widespread attention in recent years, most recently in the report by the Institute of Medicine entitled, *Accelerating Progress in Obesity Prevention: Solving the Weight of the Nation* [13]. This chapter identifies obesity prevention strategies for children and adults. We limit the discussion of obesity prevention to avoidance of weight gain (not stabilization of weight or weight maintenance in those who may be healthy weight after weight loss). The main reason for this focus is the limited evidence base about specific interventions to help children or adults achieve the goal of long-term maintenance of a healthy weight, although research is underway in this area [14].

The first section of this chapter provides a framework for obesity prevention. The next section provides an overview of federal recommendations for obesity prevention. It then discusses obesity prevention strategies in the clinical setting, schools, the workplace, and the community. For each setting, the strength of the evidence is described. The chapter concludes with a summary of the evidence base for obesity prevention activities.

## Framework for Obesity Prevention

Figure 26.1, developed by the Institute of Medicine [15], provides a framework for understanding obesity prevention strategies.

This framework indicates that obesity prevention directly results from changes in structural, institutional, systemic, or environmental factors which, in turn, impact cognitive, social, and behavioral

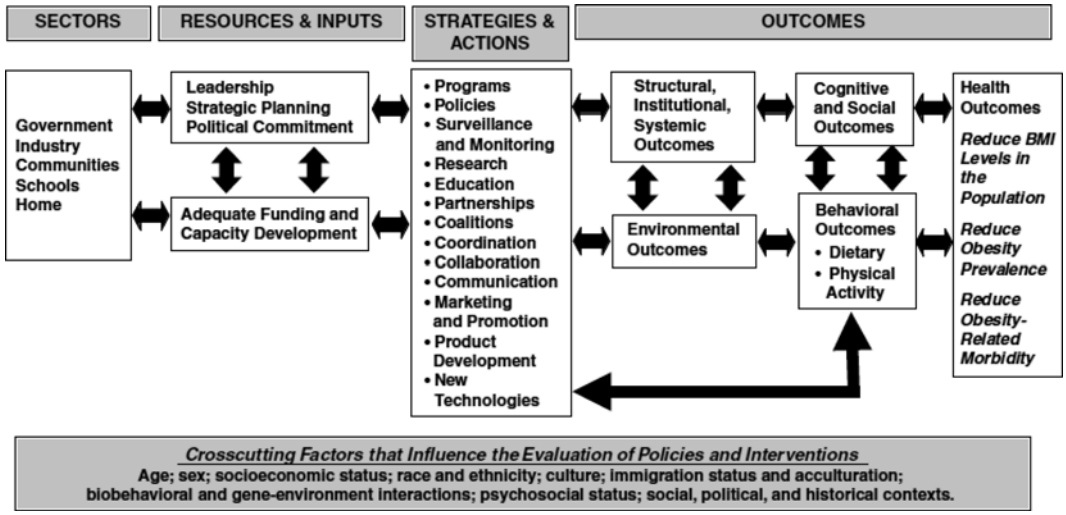


**Fig. 26.1** A framework for understanding obesity prevention strategies [15]. Reprinted with permission from the National Academies Press, Copyright 2007, National Academy of Sciences

outcomes in individuals. A host of strategies and actions which impact obesity prevention can be undertaken by a variety of sectors (e.g., government, community, schools) with diverse resources. This model emphasizes that many strategies undertaken to prevent obesity will not have a direct impact on BMI, but rather on pathways that alter energy intake, physical activity, or weight control.

## Federal Guidelines for Obesity Prevention

The United States lacks a set of uniformly accepted guidelines for obesity prevention, with considerable variation at the local, state, and national level. This section provides a brief overview of national guidelines for obesity prevention by setting: clinical, school, worksite, and community. Specific details about these recommendations can be found in the Appendices A and B.

### *Clinical*

The United States Preventive Services Task Force (USPSTF), which provides guidelines on clinical preventive healthcare services, recommends that physicians screen all patients [ages 6 and older) for obesity [16, 17]. According to these guidelines, clinicians should offer or refer obese patients to intensive, multicomponent behavioral intervention [16]. Currently, there is no federal clinical prevention guideline for healthcare professionals to follow. However, several clinical trials suggest that weight loss medication combined with behavioral weight loss interventions (such as dietary changes) is successful, at least in the short term [14, 18].

### *School*

The Centers for Disease Control and Prevention (CDC) provides nine recommendations for obesity prevention in schools (detailed in the Appendices A and B) which broadly focus on promoting healthy

eating (e.g., improving the school meal program), physical activity (e.g., developing comprehensive physical activity programs), and community partnership (e.g., partner with families and communities to implement relevant policies) [19].

### *Worksite*

The CDC provides recommendations for worksite obesity prevention interventions which combine both healthy eating and physical activity and facilitate behavior change through educational, behavioral, or environmental strategies [20]. These recommendations have been used to create a free web-based resource, called "CDC's LEAN *Works!* Leading Employees to Activity and Nutrition," which offers employers interactive tools and evidence-based resources to design effective worksite obesity prevention and control programs [21].

### *Community*

The CDC recommends six strategies for obesity prevention in the community setting [22]: (1) to promote the availability of affordable healthy food and beverages, (2) to support healthy food and beverage choices, (3) to encourage breastfeeding, (4) to encourage physical activity or limit sedentary activity among children and youth, (5) to create safe communities that support physical activity, and (6) to encourage communities to organize for change. The CDC also developed a guide to help communities implement these recommendations [23]. Of note, the report acknowledges that the evidence to support the recommendations were not based on studies of at least 1 year duration that measured weight as an outcome, but on short-term changes in food choices or use of environmental modifications to facilitate physical activity [22].

While the types of prevention strategies are not uniform across the four settings, not surprisingly, there is a common emphasis on improvements in healthy eating and physical activity, the major contributors to obesity.

## Evidence on the Obesity Prevention Interventions

In this section, we provide a brief overview of evidence about obesity prevention interventions by setting. For each setting, we summarized the overall body of evidence, provided an example of an obesity prevention program, and identified key limitations to the literature. If available, we also provided information on subpopulations. To gather this evidence, we primarily relied on systematic reviews, meta-analyses, and reviews of obesity prevention programs conducted from 2005 forward in PubMed. The search results are provided in Appendix B. We included only those reviews where body weight (e.g., BMI, percent obese) was the primary outcome. Search terms generally included "obesity prevention" and the setting (e.g., obesity prevention and schools). We also used sources cited within these papers. For settings where systematic reviews were limited, we collected evidence from individual articles. Based on these criteria, we used roughly one review along with individual articles in the clinical setting, 16 reviews for the school-based setting, three reviews for the workplace setting, and eight reviews for the community setting.

## *Obesity Prevention in Clinics*

While only one systematic review was identified describing effective clinic-based obesity prevention interventions, an expert committee convened in 2005 by the American Medical Association (AMA), in collaboration with the Health Resources and Service Administration (HRSA) and the Centers for Disease Control and Prevention (CDC), created a list of practical recommendations pediatricians could make to their patients [24]. The guidelines consisted largely of diet-related recommendations, with a few focused on physical activity. The recommendations were based on several levels of evidence: (1) *consistent evidence*, meaning that multiple studies generally showed a consistent association between the recommended behavior and either obesity risk or energy balance; (2) *mixed evidence*, meaning that some studies demonstrated evidence for weight or energy balance benefit while others did not report a significant outcome or that there were few studies or small sample sizes; and (3) *suggestions*—meaning that studies examining the association between the recommendation and weight-related outcome were few, had small sample sizes, or without clear findings, but that the expert committee still believed could support the achievement of healthy weight and were unlikely to cause harm.

Recommendations pediatricians should give to children that are backed by consistent evidence include the following: minimize sugar-sweetened beverages, such as soda, sports drinks, and punches; decrease television viewing (and other forms of screen time) to ≤2 h per day (or no television viewing if the child is ≤2 years of age); eat breakfast daily; limit eating out at restaurants, particularly fast food restaurants; involve the whole family in lifestyle changes, including healthy family meals; allow the child to self-regulate his or her meals and avoid overly restrictive feeding behaviors (CE for children ≤ 12 years of age); and limit portion size (the USDA provides recommendations about portions, which may differ from serving sizes on nutrition labels, and a product package may contain ≥1 serving size).

The only recommendation backed by mixed evidence was to encourage consumption of diets with recommended quantities of fruits and vegetables, as specified by the USDA's Dietary Guidelines for Americans [24]. Suggested recommendations include eating a diet rich in calcium, fiber, and balanced micronutrients; breastfeeding exclusively to 6 months of age and maintaining breastfeeding after introduction of solid food to 12 months of age and beyond; promotion of vigorous physical activity for at least 60 minutes a day; and limiting consumption of energy-dense food [24].

The evidence for interventions further suggests that clinicians use patient-centered counseling techniques, including motivational interviewing, to help engage patients as partners in their health and identify their own motivations for making change. In addition, they recommend that BMIs be calculated and plotted at least annually and that the information should be integrated with other information on growth pattern, familial obesity, and other medical risks to assess the child's obesity risk [24].

No information on relevance of these recommendations for various subgroups was available.

## *Obesity Prevention in Schools*

Evidence related to the impact of school-based interventions on obesity prevention is mixed; some studies show a positive impact, others show a negative impact, and others show no result. Overall, this literature suggests that among children ages 3–18, nutrition and physical activity interventions result in significant reductions in body weight compared with control (standardized mean difference (SMD) = −0.29, 95 % confidence interval (CI) = −0.45 to −0.14) and that parental or family involvement of nutrition and physical activity interventions also induced weight reduction (SMD = −0.20, 95 %CI = −0.41 to 0.00) [25]. The authors of this systematic review used SMD because the trials included in their analysis assessed weight loss in different ways such as BMI and weight. Larger

effects on body weight have been demonstrated in interventions targeting children and adolescents (versus preadolescents) and females. Intervention components which appear to have a significant and positive impact on obesity prevention in the school setting include longer duration (interventions lasting at least 1 year) [26] of combined diet and physical activities, a family component, and education programs which increase self-efficacy among children and their parents [27, 28].

Some examples of successful obesity prevention interventions in schools include encouraging children to consume fewer carbonated beverages [29], encouraging children to play board games designed to increase student knowledge about healthy diets [30, 31], providing parents with clear nutritional guidelines such as traffic light techniques to characterize the foods their children [30], increasing physical activity during regular physical education classes, offering more opportunities for physical activity before and after school [32], and the incorporation of behavioral change lessons into the school curriculum (e.g., self-monitoring, goal setting) [33]. Educational interventions encouraging a reduction in television and video game use have been shown to result in significant changes in BMI [34, 35].

Obesity prevention activities in schools do not have the same impact on all children. For example, some evidence suggest that girls respond better to educational components of interventions (e.g., sessions integrated into classrooms educating students on decreasing television viewing, decreasing consumption of high-fat foods, increasing fruit and vegetable intake, and increasing physical activity), while boys appear to be more influenced by structural and environmental changes (e.g., increasing physical activity during physical education class and increasing physical activity on campus during leisure periods throughout the school day) [35–37]. However, other studies have shown that interventions increasing physical activity have a significant impact on the BMI among girls, but not in boys, particularly those girls less than 9 years of age [33, 38].

Evidence also suggests that the impact of obesity prevention interventions differs by age. For example, research has shown that high school students benefit more from obesity prevention interventions than middle school students [39] and that interventions involving middle school children are more effective than interventions involving children less than 7 years of age [29, 33, 37]. Another example is that classroom instruction and physical education promotes moderate to vigorous physical activity for older children, especially for teenage girls, while younger children benefit from behavior change programs that reduce sedentary behavior [33].

Among racial/ethnic groups, some culturally relevant interventions have demonstrated effectiveness. For example, dance for health, a 12-week dance and health education intervention targeted at African American and Hispanic seventh graders resulted in a significantly lower BMI for the girls in the intervention [40]. Other culturally relevant interventions have not demonstrated effectiveness. For example, the Stanford Girls Health Enrichment Multi-Site (GEMS) Study which examined the impact of a community- and family-based obesity prevention program for low-income African American girls among 261 African American girls aged 8–10 years. The intervention randomized families to one of two interventions: (1) after-school hip-hop, African, and step dance classes and a home-/family-based intervention to reduce screen media use or (2) information-based health education and found that the program did not significantly reduce body weight. Few studies analyzed the success of universal obesity prevention programs among ethnic or racial subgroups [26, 38].

Key limitations to obesity prevention programs in schools include the large degree of methodological heterogeneity among studies and small sample sizes [26, 33, 37, 38]. It is also difficult to define a decrease in BMI as a success in universal programs that also consist of children of normal BMI [26].

### *Obesity Prevention in the Workplace*

Moderate evidence suggests that workplace obesity prevention programs targeting both diet and physical activity with 6–12 months of follow-up significantly reduce body weight and BMI, 1 kg

(2.2 lb) and 0.3 kg $m^2$, respectively [41–43]. Most worksite obesity prevention studies combine informational and behavioral strategies (e.g., messages about healthy eating and physical exercise or skills and approaches to increase self-awareness and self-efficacy) to influence diet and physical activity [43]. There is limited evidence to draw conclusions about differential effects by program focus (nutrition and physical activity) or program component (information, behavioral skills, or environmental and policy). While relatively fewer studies have focused on modifications to the work environment (e.g., cafeteria, exercise facilities) to promote healthy choices, evidence suggests that adding an environmental component to a physical activity and diet intervention in the worksite may reduce body weight by an additional 0.3 kg (~0.7 pounds) [43]. The available literature also indicates that more intensive modes of intervention increase program impact. For example, offering structured programs (i.e., scheduled sessions) is more effective than unstructured approaches; similarly information plus behavioral counseling confers more benefit than providing information alone [41].

The evidence base related to obesity prevention in the workplace suggests six promising practices, each of which is associated with an approximately 5-lb decrease in body weight: (1) enhanced access to opportunities for physical activity combined with health education, (2) exercise prescriptions alone (offering specific recommendations about frequency, intensity, and type of exercise), (3) multicomponent educational practices (providing information about health promotion and risk reduction, alongside exercise or nutrition prescriptions and other brochures), (4) weight loss competitions with incentives (without teaching behavioral management skills, modeling, or demonstrating), (5) behavioral practices with incentives, and (6) behavioral practices without incentives [42]. The range of cost-effectiveness estimates from the few studies with this information varies from $1.44 to $4.16 per pound of weight loss [44, 45]. Other evidence suggests that workplace wellness programs are associated with a 28.3 % reduction in sick leave and a 5.6:1 return on investment, a 26.1 % reduction in medical cost, and a 30 % reduction in direct medical and workers' compensation claims [46]. This evidence supports the growing trend among employers of adopting wellness programs as a means to lower health costs and increase productivity of workers [41].

To our knowledge, there are no obesity prevention programs focused on the workplace which examine whether the impact of the interventions differs by demographic characteristics (e.g., ethnicity, SES, or age). However, the findings appear to be applicable to both male and female employees across a range of worksite settings [41].

There are several limitations to this body of evidence. Relatively few studies focused on obesity prevention have been conducted in the worksite setting, especially studies examining the impact of policy, environmental, or media strategies on obesity prevention [41, 42]. The available evidence often uses a population-based approach which does not allow for the calculation of individual-level weight loss, making it difficult to know whether many people lost a little weight or a few people lost a lot of weight [41, 42]. Also, weight loss is usually reported as an overall average without consideration of possible heterogeneity across subpopulations, making it difficult to know whether various obesity prevention interventions have differential impacts on higher-risk populations [41]. There is also considerable heterogeneity between studies with respect to length of follow-up, study design, intervention type, and outcomes studied [43]. Despite these limitations, multiple reviews, using differing methodologies, at different points in time, draw similar conclusions [41–43].

## *Obesity Prevention in the Community*

Community-based obesity prevention interventions are becoming popular with the recognition that the drivers of the obesity are increasingly being identified in the environment [47–50]. This shift

towards a stronger community focus is echoed by the recent Institute of Medicine report—Accelerating Progress in Obesity Prevention—which recommends a comprehensive approach to childhood obesity prevention which includes the community [13]. The limited evidence base is mixed; some studies show a reduction of body weight, while others show no effect. Successful community-based interventions have the following components: focus on multiple behaviors (e.g., healthy eating, physical activity, sedentary behavior) [46], inclusion of upstream and environmental changes that facilitate the implementation of those healthy behaviors (e.g., increasing affordability and availability of healthy food in community stores, improving walkways and cycle routes, and providing safe and affordable venues of physical activity at community recreation centers) [51], and bringing together key stakeholders (e.g., community members, prominent leaders, families, schools, etc.) [52].

An example of a successful community-based obesity prevention intervention is the statewide program in Delaware which aims to modify children's behavior through an easy-to-remember prescription for a healthy lifestyle, 5-2-1-Almost None, which encouraged children to do the following daily: eat at least five servings of fruit and vegetables, engage in no more than 2 h of recreational time in front of television or computer screens, participate in at least 1 h of physical activity, and consume almost no sugar-sweetened beverages [53]. They worked with schools (e.g., improving wellness policies aimed at increasing physical exercise and healthy eating by increasing evidence-based physical activity programs, adding fitness equipment, providing physical activity breaks for students, stocking healthy snacks in vending machines, incorporating games and contests for healthy eating, and using an approved snack list), childcare providers (e.g., policy/regulation changes that encourage the 5-2-1-Almost None strategy through increased opportunities for physical activity and increased provision of healthy food), and primary care settings (e.g., shifting from just identifying obesity to universal assessment, preventive health messages based on guidelines consistent with the 5-2-1-Almost None messaging that show up in the EMR and early interventions). The preliminary results suggest that the initiative stopped the increase in overweight and obese children over a 2-year period.

Another example of a successful community-based obesity prevention intervention is Shape Up Somerville, which engaged children, parents, teachers, school food service providers, city departments, policy makers, healthcare providers, before- and after-school programs, restaurants, and the media [54]. Intervention activities took place before school (healthy foods in breakfast program, Walk to School campaign), during school (healthy lunch and snacks sold, taste tests and new recipes, physical activity lessons, new play equipment at recess, development of school "wellness" policy), after school (cooking lessons and promotion of healthy eating, increased physical activity), at home (parent outreach and education through bimonthly newsletter and free coupons, family events, and child's "health report card"), and within the community (community advisory council, farmers markets, SUS-"approved" restaurants, fitness fairs, city ordinances on walkability/bikeability, and resource guides). This intervention significantly decreased BMI *z*-score (percentile relative to some specified distribution of BMI-for-age) in children at high risk for obesity by −0.1005.

Although most community-based prevention studies focus on school-aged children, recent evidence suggests that these interventions may also be successful in preschool children [43, 55]. The limited evidence related to community-based obesity prevention interventions among targeted subpopulations does not show an impact on body weight [56].

Key limitations to community-based obesity prevention interventions include the small evidence base; the length, most are short term, making it difficult to assess long-term impact on obesity prevalence [51, 55, 57], the complexity of interventions which makes it difficult to isolate the impact of individual components [58]; lack of consistency in study design which reduced comparability [52]; insufficient knowledge about the process and quality of the intervention implementations which make it difficult to assess the real-world effectiveness [55]; and limited data for racial and ethnic minorities who are at higher risk for obesity.

## Consistency Between Federal Guidelines and Obesity Prevention Studies

Federal guidelines on obesity prevention map well to the available evidence on effective interventions in the community and worksite settings which were released in 2007 and 2005, respectively. For the school setting the most recent federal guidelines were released in 2005. Since then, evidence from meta-analyses and systematic reviews (in 2009 and onwards) suggests that in addition to promoting multicomponent interventions with a family component, the most successful interventions should also last for at least 1 year and work to enhance participant's actual and perceived self-efficacy [21–23]. This new evidence in the school setting suggests a need to update federal guidelines for prevention. In the clinical setting, the most recent USPSTF recommendations are from 2010 to 2012 and contain little information on obesity prevention. In general, obesity prevention research is receiving increasing attention from the academic community, and the number of relevant studies is increasing rapidly. Going forward, it will be important for federal guidelines to keep pace with the changing science.

## Conclusion

This chapter synthesized the evidence related to obesity prevention interventions in the clinical, school, worksite, and community settings. Overall, there are currently not enough studies with consistent methods and outcomes to determine the impact of obesity prevention programs on body weight among adults or children. Of the four settings examined, the largest body of evidence was available for the school setting. This literature suggests that combined intervention approaches which include nutrition and physical activity, as well as a reduction in sedentary activities, result in significant reductions in body weight, particularly among older children (e.g., high school students). School-based obesity prevention programs appear to have a greater impact when they are reinforced by a community or family component. Similarly, community-based childhood obesity prevention interventions were more successful when they involved multiple settings.

According to one systematic review [59], the effectiveness of obesity prevention programs in the pediatric population (e.g., the number of studies that produced significant intervention effects) is 21 % [59] which is similar to other public heath prevention programs such as HIV (22 %) [60] and eating disorders (25 %) [61] but lower than the effectiveness of smoking prevention programs (60 %) [62]. The average effect size for obesity prevention programs is also similar to the effect size observed for other public health programs [59].

In conclusion, obesity prevention programs implemented in the school setting focused on both diet and physical activity may moderately prevent weight gain among children with larger effects observed for programs targeting adolescents (versus preadolescents) and females. The available data is insufficient to determine the impact of obesity prevention programs on body weight in the other settings included in this review which suggests the need for more research. Going forward, more research and consistent methods are needed to understand the comparative effectiveness of obesity prevention programs, particularly among populations at highest risk for excess body weight. In addition, published details on the processes required to implement obesity prevention interventions are needed in order to increase the translatability of the research and guide effective programs and policy.

# Appendix A

**Table 26.1** Federal guidelines by setting

| Sector | Target | Federal agency | Guidelines/recommendations |
|---|---|---|---|
| Clinical | Children | USPSTF [63] | *As of January 2010*, the USPSTF recommends that clinicians screen children aged 6 years and older for obesity and offer them or refer them to comprehensive, intensive behavioral interventions to promote improvement in weight status. No evidence was found regarding appropriate intervals for screening |
| | Children | Expert committee convened by AMA, HRSA, and CDC [64] | 1. Consume ≥5 servings of fruits and vegetables every day (ME)[a]. Families may subsequently increase to nine servings per day, as recommended by the USDA. The USDA website (www.mypyramid.gov) recommends the number of cups of fruits and vegetables per day according to age, ranging from two cups per day for 2-year-old children to 4.5 cups per day for 17- and 18-year-old youths<br>2. Minimize sugar-sweetened beverages, such as soda, sports drinks, and punches (ME). Ideally, these beverages will be eliminated from a child's diet, although children who consume large amounts will benefit from reduction to one serving per day<br>3. Decrease television viewing (and other forms of screen time) to ≤2 h per day (CE)[b]. If the child is ≤2 years of age, then no television viewing should be the goal. To assist with this change, the television should be removed from the room where the child sleeps<br>4. Be physically active ≥1 h each day (ME). Unstructured play is most appropriate for young children. Older children should find physical activities that they enjoy, which may include sports, dance, martial arts, bike riding, and walking. Activity can be structured, such as a dance class, or unstructured, such as dancing to music at home, and children can perform several shorter periods of activity over the day<br>5. Prepare more meals at home rather than purchasing restaurant food (ME)<br>6. Eat at the table as a family at least five or six times per week (ME)<br>7. Consume a healthy breakfast every day (ME)<br>8. Involve the whole family in lifestyle changes (CE)<br>9. Allow the child to self-regulate his or her meals and avoid overly restrictive feeding behaviors (CE for children ≤ 12 years of age)<br>10. Help families tailor behavior recommendations to their cultural values (suggest) |
| | Adults | USPSTF [65] | *As of June 2012, the* USPSTF recommends screening all adults for obesity. Clinicians should offer or refer patients with a body mass index (BMI) of 30 kg/m$^2$ or higher to intensive, multicomponent behavioral interventions |

(continued)

**Table 26.1** (continued)

| Sector | Target | Federal agency | Guidelines/recommendations |
|---|---|---|---|
| Schools | Children | CDC [66] | 1. Use a coordinated approach to develop, implement, and evaluate healthy eating and physical activity policies and practices<br>2. Establish school environments that support healthy eating and physical activity<br>3. Provide a quality school meal program and ensure that students have only appealing, healthy food and beverage choices offered outside of the school meal program<br>4. Implement a comprehensive physical activity program with quality physical education as the cornerstone<br>5. Implement health education that provides students with the knowledge, attitudes, skills, and experiences needed for healthy eating and physical activity<br>6. Provide students with health, mental health, and social services to address healthy eating, physical activity, and related chronic disease prevention<br>7. Partner with families and community members in the development and implementation of healthy eating and physical activity policies, practices, and programs<br>8. Provide a school employee wellness program that includes healthy eating and physical activity services for all school staff members<br>9. Employ qualified persons, and provide professional development opportunities for physical education, health education, nutrition services, and health, mental health, and social services staff members, as well as staff members who supervise recess, cafeteria time, and out-of-school-time programs |
| Workplace | Adults | CDC [67] | Programs combining nutritional and physical activity in interventions that employ:<br>1. Informational and education strategies to increase knowledge about a healthy diet and physical activity (e.g., lectures, written materials, educational software)<br>2. Behavioral and social strategies that target the thoughts (e.g., awareness, self-efficacy) and social factors that affect behavior changes (e.g., individual or group behavioral counseling, skill-building activities such as cue control, rewards or reinforcements, inclusion of co-workers or family members to build support systems)<br>3. Policy and environmental strategies that make healthy choices easier and target the entire workforce by changing physical or organizational structures (e.g., improving access to healthy foods, as in cafeterias and vending machines; providing more opportunities to be physically active, as by providing on-site exercise facilities)<br>4. Other policy strategies may also change rules and procedures for employees such as health insurance benefits or costs or money for health club memberships<br>5. Worksite weight control strategies may occur separately or as part of a comprehensive worksite wellness program that addresses many health issues |

(continued)

**Table 26.1** (continued)

| Sector | Target | Federal agency | Guidelines/recommendations |
|---|---|---|---|
| Community | All ages | CDC [68] | 1. Communities should increase availability of healthy food and beverage choices in public service venues<br>2. Communities should improve availability of affordable healthier food and beverage choices in public service venues<br>3. Communities should improve geographic availability of supermarkets in underserved areas<br>4. Communities should provide incentives to food retailers to locate in and/or offer healthier food and beverage choices in underserved areas<br>5. Communities should improve availability of mechanisms for purchasing food from farms<br>6. Communities should provide incentives for the production, distribution, and procurement of foods from local farms<br>7. Communities should restrict availability of less healthy foods and beverages in public service venues<br>8. Communities should institute smaller portion size options in public service venues<br>9. Communities should limit advertisements of less healthy foods and beverages<br>10. Communities should discourage consumption of sugar-sweetened beverages<br>11. Communities should increase support for breastfeeding<br>12. Communities should require physical education in schools<br>13. Communities should increase the amount of physical activity in PE programs in schools<br>14. Communities should increase opportunities for extracurricular physical activity<br>15. Communities should reduce screen time in public service venues<br>16. Communities should improve access to outdoor recreational facilities<br>17. Communities should enhance infrastructure supporting bicycling<br>18. Communities should enhance infrastructure supporting walking<br>19. Communities should support locating schools within easy walking distance of residential areas<br>20. Communities should improve access to public transportation<br>21. Communities should zone for mixed-use development<br>22. Communities should enhance personal safety in areas where persons are or could be physically active<br>23. Communities should enhance traffic safety in areas where persons are or could be physically active<br>24. Communities should participate in community coalitions or partnerships to address obesity |

[a]Denotes consistent evidence
[b]Denotes mixed evidence

## Appendix B

**Table 26.2** Search strategy

| Setting | Search terms used | Number of articles identified | Number of review articles used |
|---|---|---|---|
| Clinical | Obesity prevention and clinic | 0 | 1 |
| School | Obesity prevention and school | 35 | 16 |
| Workplace | Obesity prevention and worksite | 32 | 3 |
| Community | Obesity prevention and community | 41 | 8 |

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# Chapter 27
# Dietary Supplements for Obesity and the Metabolic Syndrome

**Kavita Poddar, Gerard E. Mullin, and Lawrence J. Cheskin**

**Abstract** Obesity is recognized as a public health threat that is engulfing the nation and the world. Since it is associated with a number of adverse health consequences, losing weight is often needed. This can be accomplished through a variety of interventions, ranging from surgery, to prescribed diet and exercise plans, to consuming over-the-counter supplements available for weight loss. Most individuals would be delighted to find a relatively effortless way to lose weight in "weight-loss pills." People are attracted by the prospect of over-the-counter diet pills in part due to ease of access. The present review examines the scientific evidence concerning various weight-loss agents that are available over the counter or in food stores. The review provides a starting point to make informed choices, as well as advice for incorporating healthy alternatives in the diet.

**Keywords** Weight loss • Over-the-counter supplements • Obesity • Diet pills

### Key Points

- Obesity is recognized as a public health threat that is engulfing the nation and the world.
- Since obesity is associated with a number of adverse health consequences, losing weight is often needed.
- Weight loss can be accomplished through a variety of interventions ranging from surgery to prescribed diet and exercise plans to consuming over-the-counter supplements available for weight loss.
- People are attracted by the prospect of over-the-counter diet pills in part due to ease of access.
- Given the medical and psychosocial impact of being obese and the difficulty in making sustained improvements in diet and physical activity, individuals often turn to complementary therapy and

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alternative medicine (CAM) and/or over-the-counter (OTC) weight-loss products consisting of single or multiple dietary supplements (e.g., herbs, vitamins, minerals, amino acids).

- Approximately 25 % of US adults reported using different forms of complementary and alternative medicine for health promotion.
- While the Dietary Supplement Health and Education Act (DHSEA) of the US Food and Drug Administration (FDA) regulates the dietary supplements marketed, there is no requirement for the manufacturers to demonstrate efficacy or safety of their products.
- Dietary fiber supplements may provide adjunctive benefit for weight loss/weight maintenance in those seeking to lose weight by increased satiety, reduced appetite, blockage of dietary fat absorption, and reduction of cardiovascular risks.
- Chitosan is the deacetylated form of chitin, a substance that is found in crab, shrimp, and lobster shells and is present in abundance in nature that is felt to block lipid absorption. Starch blockers such as *Phaseolus vulgaris* has not shown to be beneficial for weight loss.
- Caffeine intake alone does not seem to be effective in moderate doses (<300 mg/day), but in combination with green tea, catechins have been shown to produce positive effects on weight loss and weight maintenance via increased metabolism.
- Several clinical trials indicate that green tea when consumed in amounts that provide >500 mg/day of catechin may help in body weight and fat reduction.
- Ginseng and chromium that modulate carbohydrate metabolism have not been proven to promote sustained weight loss.
- Supplements purported to interfere with fat synthesis hydroxycitric acid (HCA), conjugated linoleic acid (CLA) lack substantive evidence in clinical trials to support their use.
- "Diet pills" such as *Ephedra* has been proved to be a hazardous supplement and has even been attributed to a number of deaths.

## Introduction

Overweight and obesity is a global threat which continues to expand worldwide and represents a major public health challenge [1, 2]. In recent years, statistics on obesity trends in the USA are providing conflicting reports [3–5]. While some reports indicate that the overweight and obesity is increasing [3], other reports suggest that rates are stabilizing [5]. Nonetheless, it is important to recognize that the rates are unacceptably high. Moreover, physical, psychological, and economic [6–8] health effects associated with obesity cannot be ignored, as obesity-related comorbidities are rising congruently with rates of obesity [9–11]. While the etiology of this global epidemic is multifactorial [12–15], unfavorable shifts in diet and exercise habits worldwide are undoubtedly major contributors to the spread of this disease [16, 17].

It is well known that maintenance of lost weight is often more challenging than losing weight; most dieters relapse/regain most weight lost quickly [18–20]. Given the medical and psychosocial impact of being obese [6–11], and the difficulty in making sustained improvements in diet and physical activity [18–20], individuals often turn to complementary therapy and alternative medicine (CAM) and/or over-the-counter (OTC) weight-loss products consisting of single or multiple dietary supplements (e.g., herbs, vitamins, minerals, amino acids). Overweight and obese individuals are often delighted to believe that there is a relatively effortless way to lose weight. CAM using natural and herbal products is being used extensively by Americans, not only to promote health but in many cases to treat illnesses [21, 22]. Billions of dollars are being spent on such products [23, 24]. Approximately 25 % of US adults reported using different forms of complementary and alternative medicine for health promotion according to Davis et al's report in 2007 versus almost 17 % who used it for treating an illness [21]. Barnes et al. [24] reported that approximately two-thirds of adults in the USA have used some form

of CAM in the past year for treating illnesses (which includes prayer), and approximately one-third of adults have used at least one form of service defined as alternative therapy. Data from the 2007–2010 NHANES survey suggested that US adults tend to use dietary supplements to promote health rather than supplement their diets with nutrients [25]. Use of CAM therapies have been reported for weight loss in individuals who have tried alternative methods to lose weight, indicating its use as an adjunctive therapy [22]. Common use of OTC dietary supplements to treat obesity has been reported in middle-aged women and has made more than one serious attempt to lose weight [26]. Disturbing is that users of OTC dietary supplements often assume that they have been evaluated for safety and efficacy by the FDA and express the belief that they are safer than prescription medications [26] and provide energy and vitality, among other beneficial and even miraculous outcomes [27]. While the Dietary Supplement Health and Education Act (DHSEA) of the US Food and Drug Administration (FDA) regulates the dietary supplements marketed, there is no requirement for the manufacturers to demonstrate efficacy or safety of their products [28]. However, manufacturers cannot include ingredients that have not been approved [28]. Harel et al. [29] identified more than 200 supplements that were recalled because they included ingredients that were not approved by the FDA. Few scientifically rigorous studies have been conducted to assess the efficacy, safety, and quality of these supplements.

This chapter aims to evaluate those supplements touted as useful for weight loss, utilizing published data to reach a conclusion regarding the effects on weight loss. Healthcare providers should use their best judgment in deciding whether to recommend, caution, or discourage the use of certain supplements presented in this review. Moreover, it is best that those who choose to use these products be monitored by a healthcare provider to ensure safety. Most of the products discussed in this chapter are available in the market without users meeting the criteria for recommended use. Finally, supplement users may be taking prescription medications; thus, the potential for drug/nutrient interactions needs to be considered.

The following sections outline, by category of purported action, some commonly used agents for weight loss.

## Supplements Professing to Increase Satiety

### *Dietary Fibers*

*Dietary fibers* consist of intrinsic and intact carbohydrates in plants, and *functional fibers*, which are carbohydrates that have a beneficial physiological effect in humans [30, 31]. Fibers are generally not digestible by the human digestive system, but may be acted upon by gut microflora [30, 31]. Fibers are classified as soluble or fermentable fibers and insoluble fibers, which can be fermented by gut microflora to provide bulk [30, 31]. Soluble fibers are natural gel-forming fibers like pectin, gum, and mucilage, and insoluble fibers are structural fibers like cellulose, lignin, and some hemicelluloses [30, 31]. Fibers add bulk, thereby decreasing the energy density of foods [32–36]. Insoluble fiber has shown to decrease subjective appetite, and thereby food intake by exerting a hygroscopic effect, by which they slow the absorption of energy-dense macronutrients [37]. Fiber-rich diets have been shown to provide higher satiety than a low fiber diet, both during a meal and between meals [38]. In addition, high intake of dietary fiber may aid in weight loss and weight maintenance among obese individuals [39] and is associated with lower body mass index [33, 34]. Moreover, high fiber intake is associated with a several health benefits, which include reduced risk of developing coronary heart disease, hypertension, stroke, improved insulin sensitivity, and dyslipidemias [39]. Thus, dietary fiber supplements may provide adjunctive benefit for weight loss/weight maintenance in those seeking to lose weight. To this effect, several weight-loss products contain sources of soluble fiber. Examples include *psyllium*, *konjac root fiber*, *chitin*, *and guar gum*.

## *Psyllium*

Psyllium is derived from the seed husk of *Plantago psyllium*. It is one of the most widely used fiber supplements and often better tolerated than other fiber supplements [40]. Psyllium may help in lowering or improving the risk factors associated with the development of cardiovascular diseases, diabetes, and metabolic syndrome [41–46]. Psyllium may help in modulating obesity and body weight via inducing greater satiety by bulking, forming a gel, and increasing viscosity of the gastric contents [47–49]. It has been shown to have significant beneficial effects on body composition in obese individuals, which include BMI and waist circumference improvements, while generally causing minimal abdominal discomfort with supplementation of ~3.5 mg per meal [44–46]. Pal et al. [46] compared the effects of four different diets in overweight and obese adults (BMI between 25 and 40 kg/m$^2$): a control diet (with placebo), a psyllium fiber diet (FIB), a healthy diet plus placebo (HLT), and a healthy diet plus psyllium fiber supplement (HLT FIB) [46]. Groups with psyllium fiber diet were asked to have 12 g psyllium three times a day before main meals. They found that both diets containing psyllium (FIB and HLT FIB) significantly reduced body weight (>2.0 kg; $p=0.007$ and >2.5 kg; $p<0.001$, respectively) and percentage of total body at >2.0 %, $p=0.002$, and >2.5 %, $p<0.001$, respectively, compared with the control group after 12 weeks [46]. Similarly, other studies have shown improvements in BMI and waist circumference when supplemented with ~3.5 g psyllium TID before meals [44, 45] or improved weight loss (−4.52 kg) when supplemented with up to 3 g/day BID [49]. One study showed that psyllium supplementation up to 6 g/day in the form of capsules improved overall percent body in adolescents and was well tolerated [48]. While some studies support the role of psyllium in potentially treating obesity [44–46], others refute this [50–53]. One double-blind, placebo-controlled study, which included 125 normal weight and overweight patients with type 2 diabetes (control group, mean BMI 28.6 ± 6.5, and psyllium group, mean BMI 29.1 ± 6.3 kg m$^2$) observed no significant changes in body weight when psyllium (15 g day) was supplemented in the diet for 6 weeks [50]. Similarly, other randomized studies have also found no effect on body weight or body composition [51–53]. The lack of effect in these last studies may be because the participants were in the healthy weight range or slightly overweight; however, improvements in metabolic risk factors were still evident [51–53]. Some studies highlight that psyllium supplement in doses ranging from ~3.0 to 15 g per day may be tolerated well without abdominal discomfort [44–48, 51–53]. The data presented thus far make it difficult to draw a conclusion on the effect of psyllium on body weight due to several inconsistencies. Moreover, the studies had varied methodologies in which different confounding factors may or may not have been considered. These include different medications, overall calorie intake, starting BMI, length of the study, and doses of psyllium, thereby making it difficult to unravel the true effect of psyllium. Overall, while there is a controversy regarding the effect of psyllium in body composition, it seems to have positive impact on health risks, suggesting that its use is often beneficial and can be recommended for most patients.

## *Konjac Root Fiber (Glucomannan)*

Konjac is a local plant of Asian countries and contains glucomannan (*Amorphophallus konjac*) which is a fermentable, highly viscous dietary fiber [54]. In Asia, the konjac tuber has been used for centuries as an herbal treatment. In addition, several traditional foods such as jelly, tofu, and noodles are made using konjac tuber. Konjac flour is used as a food stabilizer, gelling agent, and supplement [54]. The USDA has approved it for use in meat as a binder, but in spite of it being recognized as food, glucomannan is not granted generally recognized as safe (GRAS) status [55]. There is some evidence of its benefit in improving cardiovascular risk factors like serum cholesterol, blood glucose, blood

pressure, insulin resistance, and to some extent, weight loss [56–59]. Proposed mechanisms of action via which glucomannan may promote weight loss include lowering energy density, promoting satiety, delaying gastric emptying, and reducing fat absorption in the intestines [54]. One study in obese women reported that without dietary restriction, 3 g of glucomannan per day for 8 weeks decreased mean body weight by 5.5 lb ($p = 0.005$) [59]. Similarly, a single blind study showed significant weight loss (−1.4 kg) with 3 g of glucomannan supplementation for 4 weeks [60]. Weight loss was even greater (−2.4 kg) when participants consumed glucomannan in conjunction with calorie restriction [60]. Similar results were observed in yet another study (−2.2 kg $p = 0.001$) [61]. In contrast, one study reported that body weight was not affected when 8–12 g of glucomannan was given to overweight adults [57]. Similarly, another found that a combination of psyllium (3 g/day) and glucomannan (1 g/day) showed no effect on body weight [49]. However, studies do corroborate the effects of glucomannan in improving metabolic parameters associated with the development of CVD [49, 56–58]. Glucomannan may produce modest weight loss; nonetheless, larger clinical trials are needed to further support its role in body weight regulation.

Reported adverse effects of glucomannan in the capsule form include gas, bloating, and mild diarrhea [62]. Some reports of esophageal obstruction when glucomannan is ingested in the tablet form were reported, as the tablets swell before reaching the stomach. Fortunately, glucomannan is no longer available in the tablet form [63, 64]. Glucomannan may also reduce the bioavailability of certain medications and may lower blood glucose levels; thus, caution needs to be exercised in the use of this supplement [62]. To conclude, konjac root (glucomannan) may be an effective adjunct therapy for weight loss. The limited available data warrant additional trials to establish its role, and its safety, before it can be recommended.

## *Guar Gum*

*Guar gum* is a plant-based dietary fiber, derived from the Indian cluster bean (*Cyamopsis tetragonolobus*) [65]. Similar to other dietary fibers discussed, it is a soluble fiber that may be beneficial for reducing body weight [66]. Besides weight loss, it is being investigated for its efficacy in the treatment of metabolic disorders like type 2 diabetes and hypercholesterolemia [66]. Its proposed mechanism for weight loss includes induction of greater satiety associated with its gel-forming property and increased viscosity of the bowel content [66–68]. While a few clinical trials suggest that guar gum may positively impact body weight [69–71], its efficacy is debatable as substantial evidence from recent studies found no benefit in weight loss [67, 68]. Most studies conducted have not used body weight as the primary outcome measure [68–71] and are decades old [69–71]. Other studies, including a study by Kovacs et al. [67] that tested the effect of *guar gum* on body weight as the primary outcome measure, found no changes in body weight. Pittler et al. [72] conducted a meta-analysis and concluded that guar gum was not effective for weight loss, but adverse events like abdominal pain, flatulence, diarrhea, and cramps were associated with its intake. Since the publication of this meta-analysis, only one study has tested the effect of guar gum on body weight in overweight adults; it also found no significant effect [67].

## *Conclusion to Fiber Supplementation*

While dietary fiber intake is associated with several health benefits, data on dietary fiber intake indicate that the average American is far from consuming the recommended levels (25 g/day for adult

women; 38 g/day for adult men) of fiber [39]. This is likely due to typical American diets lacking adequate amounts of whole grain foods, fruits, vegetables, and legumes [73–75]. Dietary fiber supplements may provide an adjunctive benefit for weight loss/weight maintenance via mechanisms that include increased satiety, reduced appetite, and blockage of dietary fat absorption. While some gastrointestinal discomfort/bloating may accompany acute increases in extract-based or high dietary fiber intake, in general, fiber supplementation does not bring about significant adverse effects. Moreover, dietary fiber is an alternative medicine that can be obtained from a wisely selected regular diet, rather than supplements.

## Supplements That May Block Dietary Fat Absorption

### *Chitosan (Chitin)*

Chitosan is the deacetylated form of chitin, a substance that is found in crab, shrimp, and lobster shells and is present in abundance in nature [76]. Chitosan is a polysaccharide that is indigestible by the human gut. The exact mechanism of action in promoting weight loss is not well understood; however, it has been proposed that negatively charged lipid molecules bind to the positively charged tertiary anion group of chitosan polysaccharide, thereby preventing fat absorption and binding bile acids in the intestinal lumen for excretion [77]. In addition to weight control, it has been theorized that due to the proposed mechanism of action, chitosan may be useful in treating hypercholesterolemia [76, 77]. One randomized, double-blind, placebo-controlled trial examined the effect of chitosan (3 g per day) on weight loss in 59 obese participants who consumed a high fat diet and found that the chitosan group lost 1 kg ($p < 0.005$) and BMI decreased by 0.3 kg/m$^2$ ($p < 0.01$), but some reported gastrointestinal adverse effects including bloating, flatulence, increased stool bulk, nausea, and heartburn [78]. Mhurchu et al. [79] evaluated chitosan in 250 obese participants. This double-blind, placebo-controlled trial randomized patients to receive 3 g of chitosan per day or placebo in addition to standardized dietary and lifestyle advice. At the end of 24 weeks, the chitosan group lost more weight than placebo (−0.39 versus +0.17 kg, $p = 0.03$). More than 30 participants in the chitosan group reported minor gastrointestinal-related adverse events [79]. Similar to these results, a meta-analysis reviewed 14 studies of the effect of chitosan on weight loss and concluded that it caused a small net effect of approximately 1.7 kg [80]. Additional high-quality clinical trials reviewed have shown to cause clinically insignificant (−0.6 kg) weight loss with chitosan treatment as compared to those from lower quality studies (−2.3 kg weight loss) [80]. Overall, human studies have yielded mixed results [78–81] and have been conducted on a small scale and over a short duration [82]. Pittler et al. [81], however, found no effect of chitosan in a small RCT [81]. Only one study has reported significant improvements in body composition with chitosan (3 g/day) in overweight adults over a 60-day period [83]. In this randomized, double-blind, placebo-controlled trial, 150 overweight adults were randomized to three groups: 3 g of chitosan per day and a behavior modification program, placebo and a behavior modification program, or a minimum intervention control group. The chitosan group showed a significant reduction in weight compared to control (−2.8 versus −0.6 lb, $p = 0.03$), a decrease in percent body fat (−0.08 % versus +0.4 %, $p = 0.003$), and a decrease in fat mass (−2.6 versus + 0.6 lb, $p = 0.001$). In summary, chitin/chitosan may have some weight reduction and cholesterol-lowering effects, but these effects are not clinically significant at reasonable doses (3–6 g/day). Further studies are needed to support the claim that chitosan may help in weight loss.

## Supplements That Block Dietary CHO Absorption

### *Phaseolus vulgaris*

*Phaseolus vulgaris* is an α-amylase inhibitor extracted from white kidney beans from South America, Central America, and Mexico and now grown worldwide for its edible bean [84]. Red and black varieties of this particular bean are available. Color and size of the beans are important characteristics, as color indicates concentration of polyphenolic compounds such as anthocyanins, flavonol glycosides, and proanthocyanidins (condensed tannins) [85]. *P. vulgaris*, also known as the common bean, is believed to be a functional food due to the presence of phytochemicals, lectins, phytic acid, dietary fibers, unsaturated fatty acids, and trypsin inhibitors [86]. Evidence from in vivo studies suggests that *P. vulgaris* inhibits the digestive enzyme alpha-amylase and prevents starch absorption, potentially resulting in weight loss [87, 88]. Suppression of starch absorption in turn may result in lower blood glucose and delay gastric emptying, thereby increased satiety, resulting in lower calorie intake [89, 90]. Limited clinical trials in humans show that *P. vulgaris* may have beneficial effect on weight loss [91–93]. A double-blind, placebo-controlled trial of 50 obese subjects [91] found that after 8 weeks of *P. vulgaris* supplementation at 3,000 mg/day, decreases in body weight (average 3.79 lb) and reductions in triglyceride levels (−26.3 mg/dL) were observed. The same group conducted another 4-week double-blind, placebo-controlled trial of 25 adults and showed that white bean extract supplementation (2,000 mg/day) led to significant decreases in body weight (6.0 lb) and waist circumference (2.0 in.) [92]. Yet another study showed that consuming *P. vulgaris* (445 mg) in a supplement helped in weight reduction (2.73 kg), decreasing fat mass (2.4 kg), and other measures of body composition in overweight individuals [93]. A more recent meta-analysis of six randomized controlled trials concluded that there was a nonsignificant difference in weight loss between *P. vulgaris* and placebo groups, but a significant reduction in body fat favoring *P. vulgaris* compared to placebo. However, the studies were flawed in methodology, making the results nonreliable, therefore inconclusive on the effects in weight loss [94]. More data on *P. vulgaris* extract use for weight loss may be helpful. Though no side effects have been reported, there is not enough data to support its role at this time.

## Supplements to Increase Metabolism

### *Caffeine*

History of caffeine use worldwide goes thousands of years back. Common beverages and drinks such as coffee, tea, sodas, energy drinks, and products containing cocoa or chocolate have this active ingredient. In addition, caffeine is also found in a variety of medications and dietary supplements. It was often present in products that contained *Ephedra* alkaloids for purposes of weight loss before *Ephedra* was restricted [95]. Caffeine is a naturally occurring alkaloid found in varying amounts in more than 60 plants with roasted coffee beans and tea leaves being the world's primary sources. In the USA, most of the dietary caffeine consumed is in the form of coffee and tea [95]. Caffeine content of different beverages varies with coffee having highest amount of caffeine compared to tea which has higher than soft drinks. Amount of caffeine present in coffee and tea depends on factors like type of plant, conditions in which it is grown, and the method used for brewing. An average one cup of coffee contains ~100 mg of caffeine [95]. In the tea category, yerba mate tea has highest content of caffeine with an average of 78 mg/8 oz [95]. Caffeine is consumed by 8 in 10 individuals worldwide and 9 in 10 adults in North America. On an average, American adults consume >250 mg caffeine per day. Caffeine

is rapidly and completely absorbed by the body, with 100 % bioavailability. Once absorbed, caffeine antagonizes adenosine receptors in the brain thereby resulting in sleep inhibition with subsequent increased alertness. This effect of caffeine on mind and body has resulted in its increased popularity worldwide. Besides stimulating the central nervous system, caffeine is a popular mood enhancer and exercise performance booster [95]. Caffeine may help in reducing symptoms associated with Parkinson's disease [96] and may aid in preventing sunlight-induced skin cancer [97]. Additional probable health benefits being speculated with coffee consumption include reduced risk of type 2 diabetes [98] and weight management [99, 100]. The effect of caffeine in weight loss has been assessed in conjunction with compounds like catechins, which are found in green tea [99–101]. Caffeine consumption, when contained in green tea, has been associated with weight loss and weight maintenance [99–101]. One meta-analysis of 15 studies showed that caffeine in combination with green tea catechins was associated with decreased BMI, body weight, and waist circumference [99]. Westerterp-Plantenga et al. [100] reported that when overweight and slightly obese individuals consumed a mix of 270 mg epigallocatechin gallate (EGCG) + 150 mg caffeine per day, they lost significant body weight of >5.5±1.8 kg; ($p < 0.001$). The authors concluded that high caffeine intake was associated with weight loss via thermogenesis and fat oxidation. Moreover, habitual caffeine consumption was associated with weight maintenance [100]. Similar results were confirmed in a meta-analysis of 11 studies wherein the authors reported that EGCG-caffeine mixture had positive effects on weight loss and weight maintenance [101]. While studies with caffeine show beneficial effects on body weight, most of them that have been conducted are in combination with teas and/or *Ephedra*, making it difficult to assess the independent effect of the caffeine consumption. It is proposed that caffeine may assist in weight loss by increasing metabolic rate, energy expenditure (EE), lipid oxidation, and lipolysis and thermogenesis, all favorable components in regard to weight management and possible weight loss in humans [102–105]. It is important to note that favorable effects of caffeine are seen with limited (<300 mg/day) caffeine intake and in combination with other polyphenols. Moreover, studies have reported adverse events with higher consumption of caffeine (>300 mg/day) which include tremors, insomnia, and dizziness [106–108]. In summation, caffeine intake alone does not seem to be effective in moderate doses (<300 mg/day). Most of the effects of caffeine on weight loss have been in conjunction with other compounds like teas (and *Ephedra* which had adverse effects). Consuming more than three cups of coffee and caffeinated sweetened beverages can easily raise daily caffeine intake to over 300 mg/day. This level of intake may impart weight loss benefits, but may add calories to the diet which in turn may negate its effect.

## *Green Tea* (Camella sinensis)

*Camella sinensis leaves*, which are native to Eastern Asia, are used to produce green tea and are believed to improve health in that part of the world [109]. It is grown on large scale in tropical countries, and processing of the *Camella sinensis* leaves produces three different types of teas, namely, green tea (~20 % of total tea, is produced worldwide and mainly consumed in Asian countries), black tea (>75 % of total, is produced worldwide and is consumed largely by western countries), and oolong tea (2 % of total, produced worldwide and consumed mainly in southern China) [109]. Tea leaves contain polyphenols, majority of which is catechins with smaller quantities of caffeine. The quantity of catechins versus caffeine present in tea depends on the way different teas are brewed and have undergone partial fermentation and oxidation processes [109]. The major catechin in green tea is (−) EGCG, with lesser amounts of catechin, epicatechin, gallocatechin, gallocatechin gallate, and epicatechin gallate [110]. Major health benefits attributed to the consumption of green tea are associated with these active compounds and are attributed largely to the antioxidant capacity of these compounds. Health benefits also depend on the amount of tea consumed, along with the type of tea and

the bioavailability of the catechins [109, 110]. Some of the potential health benefits for which teas and particularly green tea are known include prevention of cardiovascular risk factors, weight loss, and protective effects against neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [111, 112]. Clinical trials are evaluating the effects of green tea for cancer-protective, cardioprotective, anti-diabetic, metabolic syndrome protective, antioxidant, and weight loss effects [113–116]. Several clinical trials indicate that green tea when consumed in amounts that provide >500 mg/day of catechin may help in body weight and fat reduction [116–123]. Mechanisms via which green tea may assist in weight/fat loss include increased energy expenditure and fat oxidation by inhibition of lipogenesis, synergistic effect of caffeine with catechins in green tea to increase fat oxidation and energy expenditure, and upregulation of enzymes involved in hepatic fat oxidation [124]. Hursel et al. [101] conducted a meta-analysis of 11 clinical trials to understand the role of green tea on body weight regulation. The authors concluded that catechins in green tea were associated with significant decreases in body weight (−1.31 kg; $p<0.001$) and body weight maintenance after a period of WL. Moreover, high habitual caffeine intake (>300 mg per day) was not associated with significant weight change (−0.27 kg) when compared to those who had low habitual intake (<300 mg per day) where weight loss was −1.60 kg; $p=0.09$. Other meta-analysis of randomized clinical trials reported that green tea preparations induced statistically insignificant weight loss (ranging from −0.04 to −3.5 kg), reduction in BMI (ranging from no effect to −1.3 kg/m$^2$), and waist circumference changes ranging from gain of 1 cm to a loss of 3.3 cm in overweight or obese adults while had no effect on weight loss maintenance [125]. There were some adverse events reported in which two required hospitalization and the remaining were mild to moderate. Some research has been conducted with green tea added to a combined diet-and-exercise weight-loss program to test the effect on weight loss and reported no benefit [120, 126]. While some studies on green tea suggest that it may favor weight loss [100, 122, 123, 127, 128], in reality it may serve as an adjunct therapy for weight loss.

On final note regarding the safety of green tea, one study reviewed the safety of green tea extracts and found that liver damage may be a potential adverse effect when consumed on an empty stomach [129]. Frank et al. [130] on the other hand reported that green tea catechin extract (714 mg/day) supplementation in healthy individuals is not associated with liver damage. Daily dosage of 800 mg/day of EGCG capsules for ~1 month may be well tolerated without any harmful effects. An average daily intake of up to five cups per day of green tea will provide about 250 mg/day of catechins [129].

## Supplements to Modulate Carbohydrate Metabolism

### *Ginseng*

Ginseng is a traditional herbal medicine commonly used in countries including Korea, China, and Japan over thousands of years. Different forms of ginseng extracts exist, which include Chinese or Korean ginseng (Panax ginseng), Siberian ginseng (Eleutherococcus senticosus), American ginseng (Panax quinquefolius), and Japanese ginseng (Panax japonicas) [131]. Ginseng is being studied for potential health benefits which include antidiabetic effect [132] and delaying/protecting against neurodegenerative disorders like Parkinson's, Alzheimer's, Huntington's disease, and multiple sclerosis [133]. Some research indicates that this herb may prevent acute respiratory illness [134], may have cardioprotective effects [135], and may aid in weight loss [136–138]. A more recent review of randomized clinical trials that evaluate the impact of ginseng in health reported that ginseng potentially may be helpful in improving glucose metabolism and in moderating the immune response, thereby benefit individuals with diabetes and respiratory illnesses [139]. Some studies in animal models indicate that ginseng may have potential as an adjunct therapy for weight loss [137, 140]; however,

clinical trials are needed to extrapolate these results in humans. Studies suggest that Panax ginseng root extract may produce weight and fasting glucose-lowering effects in an obese insulin-resistant rat model by inhibiting pancreatic lipase enzymes [136, 137]. The major bioactive components of *ginseng* responsible for health benefits are the ginsenosides, which are a group of saponins that possess pharmacologic properties, thereby may have clinical usage [131]. To date only one double-blind, placebo-controlled clinical trial has reported that ginseng therapy may have an effect on body weight [141]. This study showed that 200 mg of ginseng supplementation improved mood, fasting blood glucose levels, and reduced body weight among patients with type 2 diabetes [141]. However, it is difficult to draw the conclusion that ginseng had the weight loss effect in the intervention group as the placebo group also lost weight. Moreover, the study did not use body weight as a primary end point.

### *Chromium*

Chromium (Cr) picolinate is an essential trace metal found in foods like eggs, cereals, nuts, and vegetables [142] and is essential for carbohydrate and fat metabolism [143]. Chromium picolinate is commonly available as OTC supplements and has been purported to aid in weight loss via mechanisms which include increased insulin sensitivity [144], increased metabolic rate [145], decreasing food cravings [146], and potentiating insulin actions [147]. While chromium supplementation may have positive effect on weight loss [148], clinical relevance is questionable due to small effect [149]. Most of the studies on chromium in weight loss suggest that chromium picolinate in daily dosages of 200–400 μg do not have any differences in weight loss between the treatment and placebo groups [150, 151]. One study assessed the effects of chromium picolinate supplementation (1,000 μg/day) on weight loss in healthy overweight adults and concluded that it did not affect weight loss [152]. Adverse effects of chromium supplementation reported include watery stools, vertigo, headaches, and urticaria [149]. Anderson et al. [153] did not report any significant adverse effects with 1,000 μg of chromium supplementation; however, there are concerns that chromium may cause free radical damage [154], rhabdomyolysis [155], and renal failure [156].

## Supplements to Reduce Fat Synthesis

### *Hydroxycitric Acid (Garcinia cambogia)*

Hydroxycitric acid (HCA) is derived from a tropical fruit grown in India called Malabar tamarind (*Garcinia cambogia*). Several species of *Garcinia cambogia* exist, and many small and complex compounds called xanthones and their derivatives have been isolated from different species of *Garcinia cambogia* which have biological properties. However, isolation of HCA from a few species of Garcinia has caught attention by health professionals [157]. Research on physiological effects of *Garcinia cambogia* indicates that it has an effect on fatty acid synthesis and lipogenesis, thereby affecting appetite and aiding in weight loss [158]. HCA has shown to inhibit ATP, a citrate oxaloacetate lyase enzyme which plays a key role in fatty acid synthesis when carbohydrate is available in abundance and thereby inhibits lipogenesis [158]. When taken on empty stomach, HCA extracts have shown to exhibit concentration-dependent release of serotonin in the brain which may suppress appetite [159]. Preuss et al. [159] reported that HCA supplementation (2,800 mg per dose) three times taken 30–60 min before meals resulted in >5 % body weight loss and BMI reductions of 5.2 % at the end of 8 weeks. In addition, food intake, total cholesterol, LDL, triglycerides, and serum leptin levels

reduced significantly, and there were no adverse effects reported [159]. Enough evidence to support the effect of HCA in weight loss is lacking [160–162] with one group of researchers demonstrating that weight loss efficacy of this compound was evident when it was administered in combination with other active agents [163]. Further evidence to support the role of HCA in fat oxidation is contradictory with some suggesting that HCA may alter fat oxidation and energy expenditure [164] while others showing no effect of HCA on fat oxidation [165]. While several in vitro and in vivo studies support the role of HCA in weight loss and fat oxidation [158, 159], more clinical trials are needed for a definitive effect in humans regarding weight loss.

### *Conjugated Linoleic Acid*

Conjugated linoleic acid (CLA) is polyunsaturated fatty acids (PUFA) which possess a single pair of conjugated double bonds. Several isoforms of CLA exist with 18:2 *cis*-9, *trans*-11 (c9, t11) being the natural form and 18:2 *trans*-10, *cis*-12 (t10, c12) the synthetic form. Ruminant meat (beef and lamb) and dairy products (milk and cheese) are main dietary sources of CLA [166]. Research shows that CLA may have beneficial role in health promotion and have anticancer, anti-diabetogenic, and anti-atherosclerotic properties. In addition the role of CLA has been assessed in immune modulation and potentially weight regulation [167]. While most of the research with CLA shows promising results in relation to the health conditions mentioned above, they have been conducted using in vivo and in vitro models [167]. In humans, evidence supporting the role of CLA in health is not consistent. Different CLA isomers may exert different health benefits with t10, c12-CLA isomer showing positive impact on weight loss in humans versus the natural form (c9, t11) which has shown to have no benefit. Several mechanisms have been proposed via which CLA may exert anti-obesity effects. In short, CLA decreases energy intake, increases energy expenditure, and reduces fat synthesis [168, 169]. Research in humans has not produced dramatic results seen in animals [170–176]. There seems to be inconsistency between human clinical trials and animal studies with regard to CLA supplementation for weight loss. While results in human trials may be inconclusive, it could be due to differences in age, gender, and CLA dose and isomer form. There are some research indicating that certain CLA isomers negatively affect blood lipids and increase insulin resistance [170], thereby limiting the efficacy of CLA for weight and fat loss.

## Conclusion

The data presented from published double-blind RCTs, systematic reviews, and meta-analyses are encouraging in some cases, but with limited evidence. There is little convincing evidence that any specific dietary supplement is effective in reducing body weight. Before advising individuals whether to use or not to use these supplements, healthcare professionals should rely on evidence for the product's safety and efficacy. Provided there is strong evidence suggesting that any product may be safe and effective, it may be reasonable to recommend it. However, it would be appropriate to discourage the use of products when there is evidence that a product is not safe or not effective. Chitosan and guar gum appear to be ineffective for weight loss and lack convincing evidence of efficacy. For chromium, CLA, ginseng, glucomannan, green tea, HCA, L-carnitine and psyllium, there is insufficient or contradictory evidence, suggesting that healthcare professionals should caution individuals who decide to take them. When using any of these alternative therapies as adjuncts for weight control, bear in mind that consumers often have the notion that natural equals safe. Though derived from natural sources, they may nonetheless exhibit powerful pharmacologic effects and are thus still "medicines." For

example, foxglove, the plant origin of digitalis, has well-known toxic effects comparable to those seen with pharmacologic digitalis dosing. Another formerly common product, *Ephedra*, has been proved to be a hazardous supplement and has even been attributed to a number of deaths.

The major goal of this review was to answer the many questions and concerns regarding the use of "natural" diet pills as weight loss aids. Diet pill manufacturers use several key advertising strategies to incite consumer interest in their products. The current literature available about weight loss supplements is modest. It is important to highlight that perhaps the most general and safest alternative/herbal approach to weight control is to substitute low-energy-density foods for high-energy-density and processed foods, thereby reducing total energy intake [73–75]. Low-energy-dense foods have many health-promoting effects since they are mostly plant based. One may be able to achieve weight loss or at least assist weight maintenance without cutting down on the volume of food consumed nor compromising its nutrient value.

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# Chapter 28
# Obesity and the Stress Connection: Mind–Body Therapies for Weight Control

**Steven Gurgevich and James P. Nicolai**

**Abstract** This chapter addresses the nature in which the stress connection influences obesity and offers ways to use the many mind–body stress management techniques to facilitate weight reduction programs. The dynamics that cause obesity and its effects involve very complex biological, genetic, metabolic, behavioral, emotional, social, and cultural factors. The role and effects of stress on all aspects of obesity are clearly negative. Stress plays a role in potentiating obesity, maintaining obesity, and undermining the obese person's power to reduce weight. The list of the more common mind–body modalities include visualization, breathwork or breathing exercises, hypnosis and guided imagery, cognitive–behavioral therapy, therapeutic journaling, affirmations and self-talk, meditation, mindfulness techniques, therapeutic social and group support, and mindful exercises like yoga and qiqong. Since stress relief is a natural outcome of using mind–body methods, better-managed stress through the use of these techniques may allow individuals to have greater clarity to articulate and implement therapeutic strategies for weight reduction. The research on mind–body therapies' effectiveness in treating obesity is in short supply and quite often weak in isolating clear and empirically measurable relationships. Nevertheless, approximately 55 million American adults have used at least one mind–body therapy in the last 12 months according to data generated in 2007. At the present time, there remains a great need for empirical research studies and findings that clarify the application of mind–body therapies to reduce obesity.

**Keywords** Breathwork • Breathwalking • Clinical hypnosis • Guided imagery • Cognitive behavioral therapy (CBT) • Mindfulness meditation • Therapeutic journaling

### Key Points

- The dynamics that cause obesity and its effects involve very complex biological, genetic, metabolic, behavioral, emotional, social, and cultural factors.
- The role and effects of stress on all aspects of obesity are clearly negative: Stress has a role in potentiating obesity, maintaining obesity, and undermining the obese person's power to reduce weight.

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- Cortisol regulates glucose metabolism, insulin release, and immune functions; regulates blood pressure, sugar cravings, appetite, thyroid function, sleep and the inflammatory response; and manages fat storage and energy-excess levels when stress adversely affects these functions setting the stage for obesity.
- Stress reduction is a key component to any weight-loss program.
- The more common mind–body modalities to reduce stress and balance cortisol production include visualization, breathwork or breathing exercises, hypnosis and guided imagery, cognitive–behavioral therapy, therapeutic journaling, affirmations and self-talk, meditation, mindfulness techniques, therapeutic social and group support, and mindful exercises like yoga and qiqong.
- Since stress relief is a natural outcome of using mind–body methods, better-managed stress through the use of these techniques may allow individuals to have greater clarity to articulate and implement therapeutic strategies for weight reduction.
- Approximately 55 million American adults have used at least one mind–body therapy in the last 12 months according to data generated in 2007.
- There is a great need for empirical research studies and findings that clarify the application and effectiveness of mind–body therapies to reduce obesity.

## Introduction

We live in a world where obesity is a global epidemic. At one time, and still in some places, just getting enough to eat was the most basic problem of survival. Today, one-third of all women and one-quarter of all men in America are on a diet. In the USA alone, over 60 billion dollars per year are spent on weight-loss products. Various studies estimate that up to two-thirds of those dieting will gain back more weight when they stop their diet programs than when they began them. Lifestyle estimates are that the average American consumes 150 lb of sugar a year, that is, 22 teaspoons of sugar a day. Traditionally, or perhaps historically, our sustenance was based on foods high in nutrition and low in calories. Now, our foods are low in nutrition and high in calories. Most Americans are overfed and starving to death. It is no surprise that the Journal of the American Medical Association (JAMA) recently reported that 74.1 % of men and 64.5 % of all women, over 20 years of age, are overweight (BMI > 25) and that 35.9 % of men and 36.3 % of women are obese (BMI > 30) [1]. Since 2006, the American Psychological Association has published their findings of an ongoing survey report called "Stress in America." Their research published in 2010 targeted, in part, stress and factors of weight and obesity. Responses of both adults and children about the various impacts of stress included its effects on body weight, obesity, eating behaviors, emotional symptoms, lifestyle, and well-being with breakdowns for health, ethnicity, gender, generations, and geographic locations [2]. The most recent findings published in 2012 now show, "A growing number of Americans (53 %) are citing personal health and their family's health as a source of stress" and yet "Eating well and exercising (54 % each) are ranked at the bottom in terms of importance when compared with other aspects of well-being…" [2].

We can blame the food industry for doing an excellent job of designing and selling "products" that make the consumer continuously buy and eat more than they need. The food industry knows how to make foods appealing, tasty, and irresistible to the consumer and to keep them coming back for more despite the consequences of an obesity epidemic. But we cannot put all the blame on the commercialization of the food industry, our movement away from the farm, the invention of "food-like substances," or even food industry's influence on government regulation of what is allowed to be sold and consumed as food. The behavior, mindset, and lifestyle of the present generation are a vital part of the dynamics of obesity and weight-related illness. And "stress" plays a larger role than we realize.

In the 1950s, Thomas Holmes, a physician and researcher, studied the connection between stress and tuberculosis. By 1956 the term "stress" became a part of American speech. The link between chronic stress and illness is now well established and documented by more than enough research. Many medical, psychological, behavioral, and alternative technologies have evolved to mitigate the effects of stress on illness. This chapter addresses the nature in which the stress connection influences obesity and offers ways to use the many mind–body stress management techniques to combat the dynamics of the obesity/stress connection.

## Part I: Obesity and the Stress Connection

Stress is the body's reaction to a perceived threat or change—real or imagined—that produces a series of adaptations, which may be physical, mental, emotional, or behavioral. Events, circumstances, and thoughts that cause a stress response or adaptive response in the body are a normal part of life occurrences. The "forced adaption" required to deal with positive or negative stressors in life over time may either create adaptive patterns and personal strengths or may lead to maladaptive stress-coping styles that can cause illness, adversely affect mood and behavior, disturb sleep, and cause weight gain. The human body is designed to respond to stress by activating the hypothalamic–pituitary–adrenal (HPA) axis. In response to stressors, the hypothalamus stimulates the pituitary gland, which, in turn, secretes adrenocorticotropic hormone (ACTH), stimulating the adrenal glands to produce a variety of different steroid hormones. Of the nearly 30 steroid hormones produced by the adrenal cortex, the principal ones include aldosterone (a mineralocorticoid), sex hormones and their precursors (DHEA, androstenedione), and cortisol. Whereas the mineralocorticoids are in charge of regulating intracellular concentrations of potassium and sodium, along with maintaining water balance, and the sexual hormones play a variety of roles during the life cycle of the individual, the primary chronic stress hormone is cortisol (acute stress hormones include adrenaline and noradrenaline produced by the adrenal medulla). Cortisol enables the body to maintain steady supplies of blood sugar, which helps the person cope with the necessary energy demands that come from prolonged stressors. Cortisol is an important hormone that is vital to proper glucose metabolism, insulin release, immune functions, regulation of blood pressure and the inflammatory response, managing fat storage and energy, to mention only a few. Under normal circumstances, the HPA axis operates according to a circadian rhythm of cortisol production, with the highest levels occurring shortly after awakening and progressively decreasing until they are lowest during the first several hours of sleep. However, cortisol has been called "the stress hormone" because it is secreted in higher levels during the body's "fight or flight" response and is responsible for several stress-related changes in the body. We think of sympathetic arousal as the turning on of the "fight or flight" response and the parasympathetic response of restoring the body back to balance as the "relaxation response." Simply put, when a threat or danger is present, the stress response system goes into action with sympathetic arousal, and when the danger passes the parasympathetic nervous system then produces the "relaxation response" to restore the body back to normal homeostasis. That is how it should work. But when individuals are under prolonged or chronic stress, they are vulnerable to the negative effects of sustained elevation of cortisol levels. This can suppress thyroid function, create blood sugar imbalances, decrease bone and muscle mass, elevate blood pressure, impair cognitive performance, suppress or diminish immunity, slow wound healing, and increase abdominal fat [3].

Studies have shown that cortisol is also associated with increased appetite, cravings for sugar, and weight gain. In addition, cortisol also influences other appetite-regulating hormones such as leptin (which tells the brain that we are full and to stop eating) and neuropeptide Y (NYP). Neuropeptide Y is released during stress and has been found to unlock certain receptors in fat cells, causing them to increase mainly in size, but also in number, encouraging fat accumulation (adipogenesis) [4]. The hormones leptin and ghrelin are called the "hunger hormones" because they work to decrease or increase appetite,

respectively. Studies have also addressed how stress responses can disrupt the hypothalamus' activity for regulation of food intake and energy balance, as well as insulin and leptin resistance in obesity [5–8].

Disturbed sleep is frequently associated with stress. There is now convincing evidence that sleep plays a role in energy balance, hunger, and appetite and is one of the factors contributing to obesity. The National Sleep Foundation polls show that over the past 50 years, Americans have gone from an average of 8–9 h of sleep per night to an average of 6 h and 40 min of sleep in 2008 [9]. It is suspected that many people today are only in bed for 5–6 h on a regular basis. Meticulous studies conducted by Eve Van Cauter, PhD, at the University of Chicago have shown that decreased sleep duration may significantly affect the risk of weight gain and obesity and reduced sleep increasing appetite via a decrease in leptin and an increase in ghrelin, along with a reduction in insulin sensitivity [10–15]. The symptoms of poor sleep not only cause persons to feel fatigued but may also cause them to confuse tiredness with feelings of hunger and the need to eat more.

The physical act of eating may also be used as a stress-coping mechanism. Stress usually alters eating behavior by promoting the urge to under-eat or overeat in certain individuals. With more severe and chronic life stress, associations can be created to foods higher in sugar and fat, which causally links chronic stress to continued weight gain and obesity [16, 17]. Eating to celebrate, avoid, or mitigate emotional stress is called emotional eating [18–20]. Emotional hunger differs from physical hunger. Emotional hunger (and eating) is caused by stress and the many hormonal and metabolic dynamics of stress discussed earlier. It also reflects eating to avoid or "stuff" emotional states of anxiety, depression, anger, sadness, loneliness, boredom, or simply feeling "empty." The question about what you are eating becomes the question of "what is eating you?" The "comfort from eating" when under emotional stress and the indulgence or craving for "comfort foods" is fairly common to most of us. However, when the occasional or more normal forms of emotional eating become habitual, more severe, or out of control, the presence of a clinical eating disorder may be diagnosed. This may include binging, purging, bulimia, obsessive eating, secretive eating, anorexia, and more. The "Eating and Appraisal Due to Emotions and Stress Questionnaire" (EADES) is a 24 question instrument designed to assess the extent to which a person uses food to cope with emotional stress and eating behavior and can be useful in weight-management screening and referral purposes [21, 22].

Obesity and depression both share dysregulation of the HPA axis. Epidemiological surveys suggest that adolescents with depression are at greater risk of obesity, and obese individuals are more likely to experience depression than non-obese persons [23, 24]. Cushing's syndrome is a clear example of how the hyperactivity of the HPA axis treatment with corticosteroids and cortisol excess result in both obesity and mood disturbance. It is also clear that from a psychological perspective, being obese sets a host of emotional stressors into play that can cause depression, such as self-image issues, physical illness or limitations to activity, sociocultural reactions and stereotyping, social isolation, and the self-reinforcing dynamics on both mood and the body's stress chemistries. It is also seen that some individuals on antidepressant medications may experience the side effects of weight gain. This vicious cycle can make eating hazardous and lends a new view of "comfort food" [25].

The relationship between obesity and the stress connection, so far, has included the role of normal physiological stress responses seen in the HPA axis, sympathetic arousal, and stress hormones, along with hunger/satiation biochemistry. It is also mediated by the effects of shortened sleep, the influence of psychosocial factors, emotional eating with its potential risk of advancing to an eating disorder, depression, and medication effects that may contribute to weight gain and obesity via the stress connection. There are perhaps many other avenues of exploration, but it should be obvious that the stress response has many dynamics that can affect the body's BMI, eating behaviors, moods, self-image, and physical health. Before moving on to mind–body strategies for mitigating the stress connection, it should be mentioned, without greater detail, that many other stress connection factors have been similarly studied. Relationships have been found between obesity and chronic job stress [26–29], social stress [30, 31], posttraumatic stress disorder (among military veterans, for instance) [32], and other specific stress categories.

## Part II: Mind–Body Strategies for Influencing the Obesity/Stress Connection

The dynamics that cause obesity and the effects of obesity involve very complex biological, genetic, metabolic, behavioral, emotional, social, and cultural factors. The role and effects of stress on all aspects of obesity are clearly negative. The mechanisms of stress responses and resultant effects, almost without exception, have negative influences on one's physical, mental, and emotional well-being. And as reviewed in Part I, stress plays a role in potentiating obesity, maintaining obesity, and undermining the obese person's power to reduce weight and its effects. The research on mind–body therapies' effectiveness in treating obesity is in short supply and quite often weak in isolating clear and empirically measurable relationships. Nevertheless, approximately 55 million American adults have used at least one mind–body therapy in the last 12 months, as reported by the National Institute of Health's National Centers for Complementary and Alternative Medicine (NCCAM) 2007 National Health Interview Survey [33]. It is probable that this number has increased. It would seem that the interest and use of mind–body therapies remain strong. Hopefully, this interest will translate into more robust research methodologies that report and explain the effectiveness of these methods. However, at the present time (2013), there remains a great need for empirical research studies and findings that clarify the application of mind–body therapies to reduce obesity.

## Varieties of Mind–Body Modalities

All mind–body modalities share a salient feature: accessing the mind–body connection to affect therapeutic physical and mental responses that act upon the body to produce greater comfort and healing. The list of mind–body modalities is growing as new variants among them evolve into a wide array of "psychological therapeutic technologies." Although many of the mind–body methods can produce therapeutic benefits, the empirical evidence and clarity of the mechanisms of action and causal effect have not been researched and presented yet. This does not mean that the mind–body techniques are invalid (although some may be), but only that the research, empirical findings, and complexities of measurement and methodology have not caught up. This has not curtailed their clinical use or the trend for these mind–body therapies to evolve, to refine their techniques, and to be presented in training workshops for professional and nonprofessional practitioners.

The list of the more common mind–body modalities include visualization, breathwork or breathing exercises, hypnosis and guided imagery, cognitive–behavioral therapy, therapeutic journaling, affirmations and self-talk, meditation, mindfulness techniques, therapeutic social and group support, and mindful exercises like yoga and qiqong. This list is not exhaustive, as there are many variants and methods, but the ones listed here are the most common methods and categories of mind–body therapies.

Most mind–body therapies are not new. Records of using medical hypnosis date back to the ancient Egyptians; the "sleep healing temples" of Asklepios in ancient Greece, Franz Anton Mesmer's clinic in the late 1700 France; and the widespread use of various therapies in India and England, France, Portugal, and Germany in the mid- to late 1800s. Mindfulness physical exercises such as Tai Chi and qigong date back to ancient China. And as noted earlier, 55 million American adults have used at least one of the mind–body methods in the previous 12 months according to data collected over 6 years ago.

Even though sufficient research has not provided rationale for a scientific "seal of approval," the clinical results being achieved keep the interest and use growing; and the reputable research results that have been reported and published are predominately favorable toward these mind–body therapies.

There are many benefits to exploring these modalities. A brief list of advantages shows mind–body methods to be:

- Simple, requiring little or no equipment
- Economical and relatively inexpensive
- Noninvasive
- Easy to learn and use
- Available to all ages
- Compatible with other therapies used simultaneously
- Appropriate for those with mobility limitations
- Free from negative side effects

The most common results of each mind–body modality are relaxation, tranquility, and a feeling of well-being in addition to the desired therapeutic outcome of its application. These relaxation response effects are most enjoyable and perceived as a positive experience, which adds to the reinforcement for compliant and continued use. Another benefit of mind–body applications is the apparent synergistic or additive effects perceived when combining these with other therapeutic modalities. One meta-analysis reported a specific benefit of hypnosis when combined with cognitive behavioral therapy in the treatment of obesity [34]. One of the authors of this chapter, with others, published an article on the combined benefit of hypnosis with acupuncture suggesting that the combined effects were greater than the sum of the parts [35].

## Strategy and Goals of Mind–Body Therapy

Since stress relief is a natural outcome of using mind–body methods, the first step in using these modalities should be directed toward achieving greater balance and control over the effects of stress. As individual stress responses are better managed, the person may find themselves having greater clarity to articulate and implement a therapeutic strategy to reduce obesity. Generally, mind–body methods require repetition or regular practice, which enhances the person's skill set for reducing stress responses and applying these methods toward meeting weight and hunger management goals. No therapy, mind–body or medical, is a "magic bullet" that will conquer both stress and obesity. But the mind–body skills obtained can be valuable in addressing the many facets of the stress response as well as the many activities required to lose weight.

The goal of mind–body therapy should not be simply to target greater success implementing diet and exercise programs. Rather, the goal in using these methods should be to create lifelong patterns of proactive choices, in the face of varying levels of stress, which ultimately achieve and maintain the healthy weight desired. Dr. Andrew Weil has addressed this goal quite well saying, "You cannot get down to your ideal weight and stay there by making resolutions to diet, going on the latest fad diet, joining a diet center, or buying pills and drinks that promise magical results. You can do it only by changing your ways of eating permanently, by building up good, sensible food habits that you can stick with for the rest of your life" [36]. Mind–body methods can play a powerful role in addressing the mental, emotional, and behavioral factors and issues that have blocked achieving the goal as articulated by Dr. Weil.

## Target Applications of Mind–Body Therapy for Stress and Obesity

Stressful events in life are inevitable; they are built in to the life experience. We cannot expect mind–body therapies to change the events that are "stressful," but these modalities can be effective in changing one's responses to them. It is very difficult, if not impossible, to experience the "relaxation response"

and "stress" simultaneously. Relaxation and the stress response are two distinctively different biochemical or neuroendocrine states within the body. All of the following mind–body modalities can be learned and practiced to promote greater relaxation and lessen stress response patterns.

Breathwork–breathing techniques are simple, have no cost, and can be done anywhere. The simplest version is "taking a fuller, deeper, more rhythmically even breath and exhaling with the intention of releasing or "letting go" of tension, worry, or troublesome thoughts of the moment". In addition to breathwork, there are many other breathing exercises that can be learned and practiced to produce a conditioned relaxation response. Even individuals with limiting or compromised pulmonary conditions can perform and benefit from breathwork techniques. Dr. Nicolai teaches an active form of meditation, known as breathwalking [37]. This technique involves the science of combining specific patterns of deeper breathing synchronized with the pace of your walking steps with directed, meditative attention to create a peak, mental state.

A small study in chronic hepatitis patients (most of whom were overweight) found that breathwalking improved body composition, metabolic liver functions, insulin resistance parameters, and mood over a period of 6 months [38].

Breathing techniques are readily available for combination with other therapies being used for stress and obesity, such as visualization, hypnosis and guided imagery, affirmative self-talk, and mindfulness exercises. Breathing techniques can also develop, learned, or conditioned relaxation responses when the person is facing the stress of food cravings, emotional eating, and stressful food/eating situations at holiday feasts, social events, or "eating out," as well as to reinforce one's commitment to healthy choices for weight loss and healthy well-being in general.

Visualization, hypnosis, and guided imagery—although these methods vary in style—all involve using imagination with a state of absorption and focused intention. For our purposes, we can view them as one modality as their features are usually all present and operating together. This therapeutic technique uses a state of focused concentration to become absorbed in images and ideas designed to evoke the relaxation response, create changes in mental and physiological processes, and promote greater belief and expectation for achievement of healthy intentions.

The robustness of this mind–body modality (visualization, hypnosis, and guided imagery) has perhaps the widest scope of application among mind–body therapies for obesity [39–41]. For example, it can be applied to all of the following:

- Reinforcing intentions for making wise food choices
- Palliating changes and food preferences
- Creating motivation for greater physical activity
- Promoting a positive incentive for and liking of exercise
- Uncovering subconscious emotional obstacles and barriers for greater compliance, changing eating behaviors, discovering learned mental/emotional associations to food, and encouraging a commitment to weight-changing activities
- Developing a "love affair" for healthy foods and eating patterns and portion sizes
- Increasing self-esteem and self-confidence
- Reinforcing self-compassion and self-love that will soothe, protect, and support commitment to behavioral changes and emotional associations to food, eating, and exercise
- Ego-strengthening, which encourages greater respect of self and empowerment to be confident in achieving weight-loss goals and activities
- Creating stronger belief in specific expectations for achieving weight-loss outcomes, compliance, and success

*Meditation and Mindfulness*: There are many varieties of meditation. All forms of meditation, even "moving meditations," create a conditioning for greater inner peace, which, in turn, creates the relaxation responses that neutralize emotional and physiological stress response patterns. Moving meditation may involve walking meditation techniques as discussed above and elsewhere [42].

Tai Chi, qigong [43], and yoga [44] also work to create a peaceful balance in the mind–body–spirit. As noted earlier, one cannot be "feeling anxious or stressed" while experiencing the relaxation response or inner peace at the same time. Meditation, mindfulness techniques [45, 46], and mindfulness-based exercises (breathwalking, Tai Chi, qigong, yoga) all promote the relaxation response [47]. Mindfulness techniques for stress reduction would seem to hold the greatest potential among meditative modalities for application for both stress and obesity. There is new research to support this [48].

Learning and practicing mind–body techniques, in and of itself, is a positive step toward lifestyle change. When combined with wise nutritional choices, regular exercise, and stress reduction skills, individuals have a greater potential for achieving weight loss despite stress.

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# Chapter 29
# Acupuncture and Obesity

**Seung Min K. Lee and Sanghoon Lee**

**Abstract** This chapter outlines the overall traditional East Asian medicine (TEAM) point of view in approaching obesity along with easy explanations on the most popular types of acupuncture available for treatment. According to the principles of TEAM, obesity is a pathophysiological state of the body with many diverse functions going awry. It is induced by many different reasons and develops into many different forms according to each patient's bodily constitutions, characteristics, and lifestyle and therefore must be approached differently for each patient. Unlike conventional medicine where treatment is provided for all types of obese patients alike, TEAM is based on holistic views and consequently approaches the problem from a more fundamental level, with greater emphasis on individuality. Thus, here we have also placed utmost importance on guiding the reader step by step into the field of syndrome differentiation, which will then allow the practitioner to tailor acupuncture treatment for each patient so that it can assist conventional medicine in areas unreached. Then we have aimed to provide easy explanation on three most popular types of acupuncture treatment available: manual acupuncture along with a table summarizing the key acupuncture points used for each type of syndrome, electroacupuncture along with succinct explanations on the whole mechanism of actions, and finally auricular acupuncture which may be conveniently used for the young, old, acupuncture-naïve, and acupuncture-experienced all alike.

**Keywords** Traditional East Asian medicine (TEAM) • Traditional Korean medicine (TKM) • Traditional Chinese medicine (TCM) • Obesity • Manual acupuncture • Electroacupuncture • Auricular acupuncture

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**Key Points**

- According to the principles of traditional East Asian medicine (TEAM), obesity is a pathophysiological state of the body with many diverse functions going awry.
- Obesity is induced by many different reasons and develops into many different forms according to each patient's bodily constitutions, characteristics, and lifestyle and therefore must be approached differently for each patient.
- Unlike conventional medicine where treatment is provided for all types of obese patients alike, TEAM is based on holistic views and consequently approaches the problem from a more fundamental level, with greater emphasis on individuality.
- The three most popular types of acupuncture treatment available are manual acupuncture, electroacupuncture, and auricular acupuncture.
- Acupuncture therapy is an essential component of successful obesity management to restore balance of the organs and energy, achieve and maintain a reasonable body weight, redistribute fat masses for a better figure, and suppress appetite and reduce food intake.
- The mechanism of action for each type of acupuncture is different. Electroacupuncture regulates its effects through the release of different neurotransmitters, while auriculoacupuncture aids in weight control by activating the center in the brain to suppress the desire of food, by influencing the appetite signal of the digestive tract, and by its influence on obesity-related hormone peptides.
- Despite increasing evidence on acupuncture's efficacy in treating weight-related disorders, it is recommended for patients and doctors to use acupuncture in conjunction with behavioral modification, herbal medication, and other dietary, exercise, and conventional treatment programs for best results.

## Introduction

Acupuncture is a method of treatment mostly used in traditional East Asian medicine (TEAM) [1, 2], but it is gaining worldwide popularity. According to a national survey conducted in 2002, acupuncture rated the third most frequently used complementary and alternative medicine (CAM) therapy in the USA, along with yoga and meditation, with the highest use among women, Asians, persons of higher educational attainment and income, and those living in the western or northeastern USA [3–5]. Given the increasing popularity and availability of CAM therapy nationwide, these number of patients have risen compared to the last decade. However, when looking into the use of acupuncture by overweight and obese people alone, data analysis reveals that less than 5 % of the obese have experienced acupuncture and that more astonishingly, there was lower use of acupuncture with people of the higher body mass index (BMI) categories [6].

This is understandable in a sense that until now, the use of acupuncture to reduce body weight and improve obesity wasn't without its criticism and controversy. The whole mechanism behind its effectiveness was not fully understood, and overall, it lacked conclusive evidence due to systematic reviews that contradicted previous results. Yet in 2009, a systematic review and meta-analysis with more rigorous and detailed search criteria was conducted concluding that acupuncture may actually aid in improving outcomes for body weight, as well as for obesity compared to conventional medication alone [7]. Including a total of 29 randomized controlled trials (RCT) for its systematic review, searched among a total of 19 electronic databases that included English, Korean, Chinese, and Japanese studies without language barriers, and comprised of 3,013 individual cases, this was one of the largest reviews that were done up-to-date, and consequently, it led to similar studies that delved even deeper.

Another systematic review that was conducted in 2010 concluded that herbal medicine and/or acupuncture not only demonstrated greater reductions in body weight, BMI, waist circumference, and blood total cholesterol in comparison to mere lifestyle modification or no treatment at all but also showed fewer relapses of weight gain after termination of treatment compared to placebo or pharmacological drugs [8].

The use of acupuncture in the field of obesity is gaining more and more popularity as emerging evidences support its efficacy not only in reducing weight but also in treating medical conditions such as musculoskeletal pain [9, 10], osteoarthritis [11, 12], hypertension [13–15], diabetes [16], depression, and even anxiety [17, 18]. All of which are well-known complications of unhealthy weight gain.

In order to fully understand and successfully utilize acupuncture for obesity in practice, it is of utmost importance to first understand the yin and yang, five organ theories of traditional East Asian medicine (TEAM), and then the pathophysiology of obesity in the TEAM point of view. With that concept steadfastly held in mind, we can go on to discuss the different types of acupuncture treatment available for different types of obesity patterns, intermittently providing examples of modern research to help clarify its mechanism of action.

## How Does TEAM View Obesity?

So what are the main causes and problems that lead to obesity? In TEAM where almost all of the different types of diseases can be found in at least one of its ancient encyclopedias, obesity is a relatively untouched subject, and there is only a few mentioning in the *Inner Classic of the Yellow Emperor*[1], where it divides overweight patients into two types, depending on their bodily proportions of fat and muscles. It mentions that both types are a result of overeating heavy, rich, and sweet foods and that continuous consumption will lead to idiopathic thirst, urination, and eventually sudden loss of consciousness—currently postulated to be symptoms of diabetes and stroke. However, there is not much explanation on treatment.

Therefore, current day primary obesity has to be approached by applying basic TEAM principles of maintaining harmony and balance of the five vital organs[2] and taking into account the consequent problems that may arise when such system goes awry.

In TEAM, the five vital organs that maintain our everyday health are the Liver[3], Heart, Spleen, Lung, and Kidney. These five work in close cooperation to maintain homeostasis by either supporting or hindering each other's functions. In obesity, the Spleen plays a critical role, and to understand this mechanism, we have to first peer into the digestive system.

Once the food enters the body, the Spleen functions like the "energy/qi transformer," or the "dynamo" in a machine—to transform and collect worthy energy and essential materials from it. However, it needs help from another organ to do so and right below it, the Stomach, is the "burner" which helps to heat up and combust the food for the Spleen. Thus, the food that has been combusted from the Stomach is separated into either essential substances that are then collected by the Spleen and transported to the organs and extremities or wastes—which are sent to the Small or Large Intestines for excretion. Next to the Spleen and Stomach, the Liver acts as a "booster" to help spread the clean energy absorbed by the Spleen up and outward, while the Kidney resides below the whole combustion site to fuel all organs fundamentally.

Yet, this is a very idealistic case, assuming that all organs are operating in optimal condition. When a person starts to gain weight in a pathological manner, the root of most causes arises with the deficiency of qi/energy in the Spleen. Deficiency of Spleen qi may be induced either congenitally or by

[1] A classic Chinese text which was published between 100 and 200 BC, considered to be one of the first treatises on acupuncture. It is also called *Huangdi Neijing* in Chinese.

[2] The five organs are not to be mistaken or confused as the actual viscera in human anatomy, but more as a convenient means of tool to explain the very complex and interrelated system working in cooperation to regulate our bodily functions.

[3] Since the five organs mentioned in this chapter refer to the five vital organs in TEAM physiology and not the anatomical organ itself, capital letters are used to differentiate between the two.

actual unsparing, harmful use of the Spleen such as frequent binges and fasting. When our body's "energy transformer" is weakened, it not only becomes difficult to garner enough energy sources for our body but it also becomes difficult to spread it around. Hence, the body gets congested with slow-flowing traffic, and just like today's traffic congestion, all the essential substances get crammed failing to reach the place of its destination on time. The body will feel heavy and react like there is not enough energy, which is why most overweight people tend to feel more and more lethargic, with lower level of tolerance for hunger, and crave for snacks or junk food that provides fast energy. Truthfully, it is not that the person actually lacks the essential nutrients; it is that they lack the sufficient and efficient flow of open traffic to get the materials to their places.

When the deficiency of qi in the Spleen becomes chronic, and the transportation function decreases, this leads the Spleen to fail to move and transform water fluids efficiently as well, leading humid to gather and collect and to accumulate into symptoms of dampness and to even congeal into phlegm. When phlegm[4] is produced, a myriad of other problems arise with it, and at this stage, the patient feels fatigued, experiences lower immunity, frequently develops edema and chest oppression, and develops a lot of sputum in the Lungs. Since the patient is lethargic, it leads to less exercise, starting a vicious cycle of accumulation of more phlegm and eventually of fat. Therefore, the basic treatment principle for all the aforementioned problems is to balance and strengthen the Spleen, which will eventually help the body to stop craving food and also effectively get rid of humidity and phlegm from the body. The analogy between the flow of qi and the flow of traffic will work much better if you think of your body's energy transportation system as a system of canals.

With Spleen qi deficiency in the background, there are multiple factors that aggravate the situation. One is excessive heat in the Stomach. Too much heat combusts foods too fast, produces hunger, and leads the person to develop a propensity to overindulge. A person can naturally have a lot of innate heat compared to others, but it can also be kindled up by eating a lot of heat-producing foods such as hot, spicy, greasy, and oily foods. Two is Kidney qi deficiency on top of Spleen qi deficiency. As mentioned earlier, qi deficiency of the Spleen itself is already bad enough for the whole digestive system, but when Kidney lacks qi as well, the person develops cold symptoms around the body, cold and weak limbs and genitalia, lumbar soreness, and impotence.

It is also important to mention the functions of the Liver. The Liver functions like the "booster," but on the downside it is also very easily affected by emotions of anger or depression. In many obese patients, the Liver functions are depressed due to emotional distress. When the Liver is depressed, it fails to course and discharge nutrients, blood, and qi and, moreover, even suppresses the Spleen to induce "traffic congestion." This phenomenon is especially frequently seen in modern-day obese patients with psychiatric signs and symptoms. Modern obese patients almost always show symptoms of Liver qi stagnation as well, with a tendency for comfort eating, which aggravates existing symptoms of obesity [19].

## *Syndrome Differentiation*

No two obese patients are exactly the same in TEAM diagnosis. After close examination and history taking, the patient may have gained weight due to initial Spleen qi deficiency brought about by long-term consumption of junk food and sweets, and another patient may have become obese because of too much heat in the Stomach dramatically increasing the amount of food intake. They might even show symptoms caused by multiple factors, such as a prolonged stagnation of Liver qi oppressing the

[4] Phlegm is a general term for the viscous turbid pathological product that can accumulate in the body, causing a variety of diseases. It can also include retained fluid, the clear and watery pathological product due to disordered fluid metabolism.

transportation functions, congenital deficiency of Kidney energy, or even blood stasis caused by external factors but eventually also hindering qi flow. All these may act in conjunction or even as a vicious cycle, with one problem leading to the next and then causing further blockage around the body.

Therefore, it is necessary to tailor treatments according to the patient's unique pattern of dysfunction and to figure out the crucial problem by addressing his/her own history and metabolic reasons for being overweight. Table 29.1 provides a simple explanation of the most common types of syndromes seen in the clinic, along with the mechanisms of action, associated symptoms, and other features/cautions organized through a variety of TEAM literature, clinical series [20], and individual clinical observations.

## Use of Acupuncture for Obesity

Acupuncture therapy is an essential component of successful obesity management:

1. To restore balance of the organs and energy
2. To achieve and maintain a reasonable body weight
3. To redistribute fat masses for a better figure
4. To suppress appetite and reduce food intake

Starting from the most simple and common type of manual acupuncture, there are numerous different types of acupuncture that you may use to help treat obesity: electroacupuncture, auricular acupuncture, laser acupuncture, small scalpel-like needling, pharmacopuncture, magnetized needling, scalp acupuncture, thread-embedding acupuncture, and Saam acupuncture [21][5] just to name a few. However, most of them have little or mostly low-quality research literature available to enable the assessment and comparison between the needling methods. The following pages will only delve into the three most frequently used and researched acupuncture treatments: manual acupuncture, electroacupuncture, and auricular acupuncture.

### *Manual Acupuncture*

Manual acupuncture is the simple insertion of thin metallic needles at specific points on the body that can be manipulated manually by twirling, thrusting, rotating back and forth, and scraping. The acupuncture points are usually chosen along the meridians connected to the dysfunctional organ of interest or specifically for the acupuncture point's known effects in combination with other points for a synergistic effect. It is believed that such insertion of needles in specific points will help, correct, and rebalance the flow of qi flowing along the energy pathways—meridians. However, there are about 361 acupuncture points along with many more extra meridian points and new acupuncture points positioned throughout the body, and it is in the skill of the acupuncturist to choose the most appropriate one for inducing the desired effect.

Table 29.3 shows the ten most frequently used acupuncture points in the treatment of obesity that was analyzed in a literature research of 47 RCTs from Sui [8].

[5] Saam acupuncture was developed by a Korean monk in the late seventeenth century and it uses "a combination of five transporting points of the involved meridians" to calculate the four most efficient acupuncture points to resolve symptoms. Due to its high convenience and efficiency, it is widely used in Korea but unfortunately not well known abroad yet. The acupuncture points that may be used according to Saam acupuncture to treat obesity will be briefly introduced in Table 29.2.

**Table 29.1** TEAM syndrome differentiation of obesity

| Type of syndrome | Mechanism of action | Characteristics/clinical symptoms | Other features/cautions |
|---|---|---|---|
| Stomach heat + Spleen deficiency | – Due to overindulgence of heat-producing foods<br>– Due to heat in the intestines causing constipation and stagnation<br>– Stomach heat produces hunger and a tendency to overeat but Spleen vacuity fails to disperse and transform the essence of food | Corpulence, fullness of head, vertigo, body heaviness, lassitude, hyperphagia, thirst, preference for drinking water, constipation, red tongue proper, slightly yellow greasy tongue coating, and slippery and rapid pulse<br>In the clinic, these patients usually describe frequent problems in their overall digestive system. They are easily hungry but also get easily full and bloated after only a few bites<br>You can actually observe a fuller, distended upper belly accompanied with frequent constipation | Prolonged time in treatment may exacerbate symptoms into accumulation of heat in the intestines as well, leading to even more heat in the Stomach |
| Deficiency of Spleen qi | – Due to dietary irregularities<br>– Due to frequent binges and fasting | Corpulence, edema, tiredness, body heaviness, asthenia, hypoxemia, poor appetite, abdominal fullness, loose stool, pale tongue, proper, thin greasy tongue, and threadlike, slippery pulse<br>In the clinic, these patients have a very pale complexion, with pale lips, and are always feeling tired, especially in the morning. They cannot eat much and tend to have a very slow metabolism. The abdominal fullness experienced is usually subjective | Frequently produces dampness retention |
| Deficiency of Spleen, Kidney yang | – Due to congenital deficiency of Spleen, Kidney yang<br>– Excessive use of Spleen, Kidney yang | Corpulence, tiredness, asthenia, lumbar soreness and leg weakness, impotence, sensation of coldness in the genitalia, pale tongue, and deep, threadlike, and weak pulse<br>In the clinic, they are usually very similar in outer appearance to those with deficiency of Spleen qi. Yet, you know that they have Kidney yang deficiency if they suffer from symptoms of coldness as well. Their overall discomfort feels better when their Stomachs are warmed, as in a hot bath | |
| Stagnation of Liver qi | – Due to emotional distress | Corpulence, melancholy, irritability, hypochondriac, rib-side distension or abdominal distension and fullness, bitter taste, irregular menstruation, insomnia, dreaminess, white or thin greasy tongue coating, and thread and taut pulse<br>Usually very emotional, worrisome females or easily irritated males suffer from stagnation of Liver qi | |

(continued)

**Table 29.1** (continued)

| Type of syndrome | Mechanism of action | Characteristics/clinical symptoms | Other features/cautions |
|---|---|---|---|
| Blood stasis | – Due to stagnation of qi flow<br>– Can be also induced by stagnation of Liver qi | Stabbing pain in the chest, irregular menstruation, dark or purple tongue, and wiry or choppy pulse<br>Distension of the lower belly is observed along with coldness in the lower part of the body. These patients don't look very obese but have a high percentage of fat concentrated in the lower abdominal area. Frequently observed in female patients | |
| Phlegm | – Due to possible problems in the functions of the Lung, Spleen, or Kidney | Tiredness, dark circles under eye, profuse phlegm, chest oppression, formation of sputum, slimy tongue, and slippery bowstring pulse<br>The most frequently seen symptom in patients with obesity is phlegm. It may be a cause itself or a problem that arises as a complication. Dramatic improvement in symptoms can be seen when such patients start physical workouts | |

**Table 29.2** Selection of manual acupuncture points for different types of syndromes

| Type of syndrome | Acupuncture points[a] |
|---|---|
| Stomach hyperactivity + Spleen hypoactivity | SP4 (*Gongsun*), LI4 (*Hegu*), LI11 (*Quchi*), ST25 (*Tianshu*), ST34 (*Liangqiu*), ST36 (*Zusanli*), ST37 (*Shangjuxu*), ST40 (*Fenglong*), ST44 (*Neiting*), BL21(*Weishu*), BL27(*Xiaochangshu*)<br>Stomach-reducing Saam acupuncture set[b]: **GB41**(***Zulinqi***)⊕[c], **ST43**(***Xiangu***)⊕, **LI1**(***Shangyang***)⊖, **ST45**(***Lidui***)⊖ |
| Deficiency of Spleen qi | SP4 (*Gongsun*), SP6 (*Sanyinjiao*), SP9 (*Yinlingquan*), ST25 (*Tianshu*), ST34 (*Liangqiu*), ST36 (*Zusanli*), ST40 (*Fenglong*), CV6 (*Qihai*), CV12 (*Zhongwan*)<br>Spleen-reinforcing Saam acupuncture set: **HT8**(***Shaofu***)⊕, **SP2**(***Dadu***)⊕, **LR1**(***Dadun***)⊖, **SP1**(***Yinbai***)⊖ |
| Deficiency of Spleen, Kidney yang | CV3 (*Zhongji*), CV6 (*Qihai*), CV12 (*Zhongwan*), KI3(*Taixi*)<br>Kidney-reinforcing Saam acupuncture set: **LU8**(***Jingqu***)⊕, **KI7**(***Fuliu***)⊕, **SP3**(***Taibai***)⊖, **KI3**(***Taixi***)⊖ |
| Stagnation of Liver qi | SP10 (*Xuehai*), BL17(*Geshu*), BL18(*Ganshu*), BL19(*Danshu*), GB31(*Fengshi*)<br>Triple Energizer-reinforcing Saam acupuncture set: **GB41**(***Zulinqi***)⊕, **TE3**(***Zhongzhu***)⊕, **KI20**(***Futonggu***)⊖, **TE2**(***Yemen***)⊖ |
| Blood stasis | SP6 (*Sanyinjiao*), SP10 (*Xuehai*), BL17 (*Geshu*)<br>Triple Energizer-reinforcing Saam acupuncture set: **GB41**(***Zulinqi***)⊕, **TE3**(***Zhongzhu***)⊕, **KI20**(***Futonggu***)⊖, **TE2**(***Yemen***)⊖ |
| Phlegm | ST28 (*Shuidao*), ST38 (*Tiaokou*), ST40 (*Fenglong*), TE4 (*Yangchi*), CV6 (*Qihai*), CV9 (*Shuifen*), CV12 (*Zhongwan*)<br>Spleen-reinforcing Saam acupuncture group: **HT8**(***Shaofu***)⊕, **SP2**(***Dadu***)⊕, **LR1**(***Dadun***)⊖, **SP1**(***Yinbai***)⊖ |

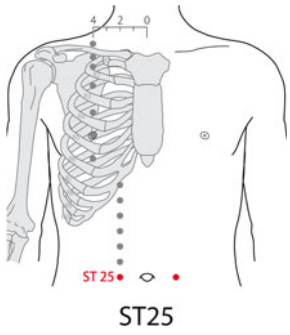
*BL* denotes the Bladder meridian, *CV* conception vessel meridian, *GB* Gall Bladder meridian, *KI* Kidney meridian, *LI* Large Intestine meridian, *SP* Spleen meridian, *ST* Stomach meridian, *TE* Triple Energizer meridian

[a]Acupuncture point SP4 refers to the 4th point of the Spleen meridian and the names in *italics* are its Chinese name

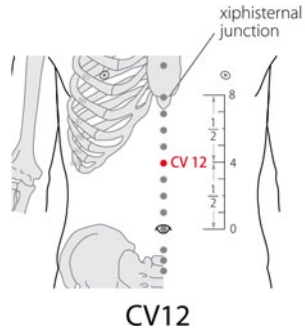
[b]Stomach-reducing Saam acupuncture set is a group of four acupuncture points typed in bold that helps to harmonize the dysfunction of the Stomach

[c]⊕ means that the acupuncture point needs to be reinforced. Likewise, ⊖ means that the acupuncture point needs to be reduced/sedated

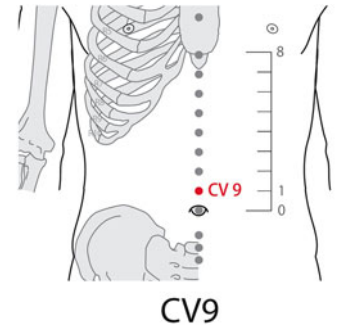
**Table 29.3** Point name and location of ten most frequently used acupuncture points in the treatment of obesity



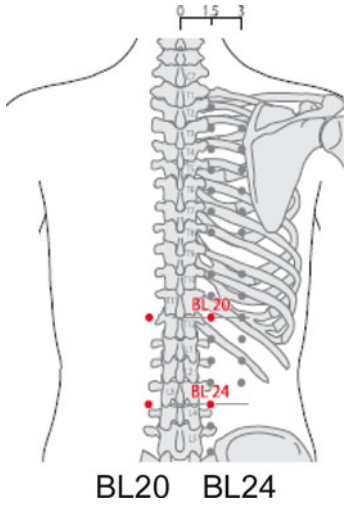

ST25 (*Tianshu*)[a]: On the upper abdomen, 2 B-cun[b] lateral to the center of the umbilicus



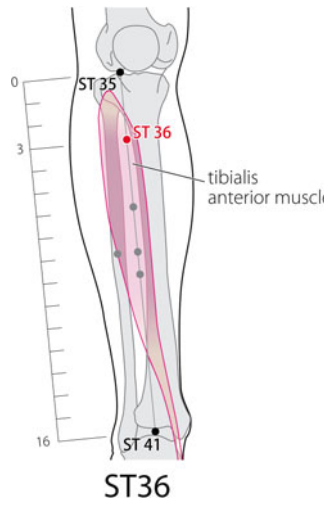

CV12 (*Zhongwan*): On the upper abdomen, 4 B-cun superior to the center of the umbilicus, on the anterior median line



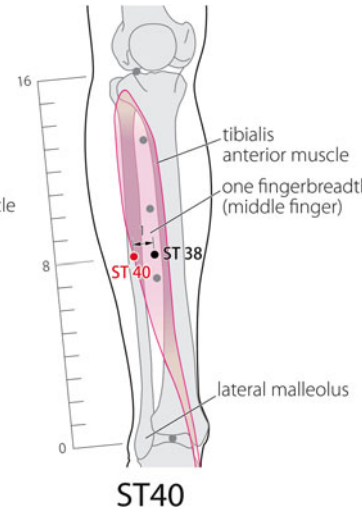

CV9 (*Shuifen*): On the upper abdomen, 1 B-cun superior to the center of the umbilicus, on the anterior median line




BL20 (*Pishu*), BL24 (*Qihai*): In the upper back and lumber region, at the same level as the inferior border of the spinous process of the 11th thoracic vertebra (T11), and the third lumbar vertebra (L3), 1.5 B-cun lateral to the posterior median line



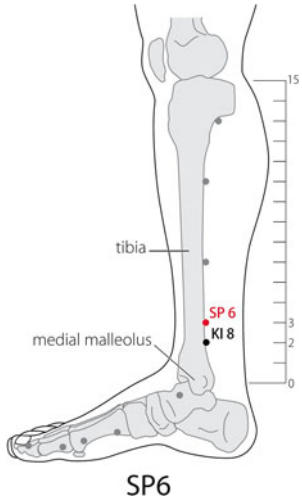

ST36 (*Zusanli*): On the anterior aspect of the leg, on the line connecting ST35 with ST41, 3 B-cun inferior to ST35



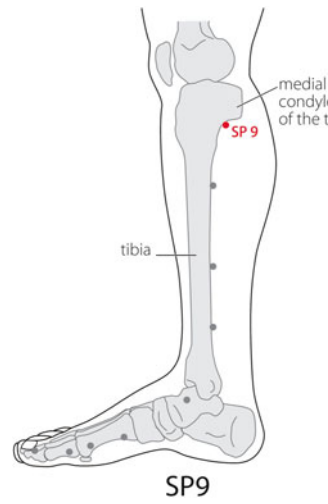

ST40 (*Fenglong*): On the anterolateral aspect of the leg, lateral border of the tibialis anterior muscle, 8 B-cun superior to the prominence of the lateral malleolus

(continued)

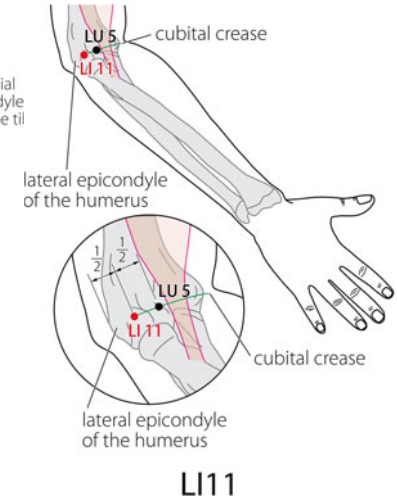
**Table 29.3** (continued)




SP6 (*Sanyinjiao*): On the tibial aspect of the leg, posterior to the medial border of the tibia, 3 B-cun superior to the prominence of the medial malleolus




SP9 (*Yinlingquan*): On the tibial aspect of the leg, in the depression between the inferior border of the medial condyle of the tibia and the medial border of the tibia




LI11 (*Quchi*): On the lateral aspect of the elbow, at the midpoint of the line connecting LU5 with the lateral epicondyle of the humerus

*BL* denotes the Bladder meridian, *CV* conception vessel meridian, *LI* Large Intestine meridian, *SP* Spleen meridian, *ST* Stomach meridian

[a]Acupuncture point ST25 refers to the 25th point of the Stomach meridian and the names in *italics* are its Chinese name

[b]"Cun" is a measurement terminology used traditionally to locate acupuncture points in proportion to the patient's body. When used alone, it usually refers to middle-finger cun, which is equivalent to the width of the interphalangeal joint of the patient's middle finger when it is flexed and is usually used to locate points on the lower limbs. B-cun, or bone (skeletal) measurement cun, refers to the proportional bone (skeletal) measurement method used to locate acupuncture points on the body. This method uses landmarks on the body surface, primarily joints, to measure the length and width of various parts of the body. This method divides the distance between two points of particular joints into equal portions and each portion equals to one B-cun. The pictures and standard location of acupuncture points are reprinted with kind permission of WHO [22]

## *Electroacupuncture*

Electroacupuncture is the stimulation of acupuncture points by passing electric currents between acupuncture needles for a set amount of time. Although its wide applicability and reliable curative effects has made it one of the most frequently used tools in TEAM for treating obesity as well as one of the most studied, the underlying mechanisms and the optimal modality for clinical practice are still under debate. However, most of the clinical researches up-to-date are helping to clarify how acupuncture exerts its effects through both systemic and also localized pathways, and thus, the method for use can be fairly summarized into the following.

First, electroacupuncture works through a variety of mechanisms. A review of literature conducted recently concludes that electroacupuncture brings about a significantly greater amount of weight loss than sham through its regulatory effects on neurotransmitters [23]. This is because during treatment, electric currents can be passed through in low (2 ~ 4 Hz) or high frequencies (100 ~ 120 Hz), and interestingly, different frequencies have shown to selectively induce the release of different neuropeptides [24].

Met-enkephalins and beta-endorphins are released in low frequencies (2 Hz) whereas dynorphins are known to be released in frequencies that are higher, such as 100 Hz [25]. The release of serotonins has also been observed, and all these work in conjunction to suppress appetite, cravings for food, depression, and even pain [26–28].

Because of such idiosyncratic characteristics of electroacupuncture, when managing pain—another popular area of application—it is recommended to alternate between the two frequencies for optimal results.

Then what about for obesity? A recent animal study showed that low-frequency electroacupuncture was more effective in reducing food intake compared to the use of high frequency and that treatment in 2 Hz resulted in downregulation of the orexigenic peptides in Neuropeptide Y [29]. In another study, low-frequency electroacupuncture showed positive effects on insulin resistance as well [30, 31]. In relation to the regulation of leptin, both frequencies had a beneficial effect on its resistance [32] whereas in lipid metabolism, high-frequency electroacupuncture (100 Hz) produced a reduction of plasma level of total cholesterol and triglyceride and increased serum leptin level more effectively than that of low frequency [33]. Thus, in obesity patients also, best results may be produced by alternating between the two frequencies.

Other than the central regulatory effects [34], it is also postulated that electroacupuncture can act directly on the peripheral and abdominal fat cells as well. For a long time, reduction of the fat cells in the immediate area of electroacupuncture treatment has been observed and several explanations have been offered: one, that the passing of electricity into the muscles produces heat in the affected area leading to increased blood flow; two, that the electric currents stimulate the nerve endings to release catecholamines; and three, that electroacupuncture stimulates the lipolytic receptor in human fat cells, namely, beta-2-adrenoreceptor (BAR-2). All three help to explain the phenomena of how electroacupuncture may facilitate the breakdown of fat cells and how it may redistribute it when applied in coordination with appropriately targeted physical exercise [35–38]. In addition, another recent study also observed that the increase in plasma endorphin levels can contribute to the lysing of fat cells as well [39].

To apply electroacupuncture, 6–12 acupuncture points are selected and tailored to the patient's symptoms. Most of them are situated in the abdomen or trunk area, to allow deep insertion of needles and sufficient passing of electricity. Stainless steel acupuncture needles are inserted to a minimum depth of 1 cm to a maximum of around 6 cm depending on the area of stimulation, and the needles are connected to an electric stimulator. The frequency is manipulated as wanted (ranging from 2 to 100 Hz), to a slightly painful intensity lasting for 20–40 min. There are reports of electroacupuncture being stimulated for an hour, but as far as we know, there is no proven evidence that the longer means the better.

It is important to note that, however, there are contraindications for electroacupuncture. When selecting acupuncture points, the two points should not cross the midline of the body, meaning that electricity should not pass through the body horizontally, and people with electric Heart pacemakers should avoid this treatment.

## *Auricular Acupuncture*

Auricular acupuncture is the application of needles into acupoints located in the ear. Since the ear is an extremely delicate organ, abundant with nerves and blood vessels, it is usually needled with tiny (0.2 cm) stainless steel auricular needles made into a thumbtack form that may be fixed with skin tape to keep them in place. For treatment of obesity, usually 4–7 auricular acupuncture points on one side of the ear are selected in accordance with the patient's symptoms, and the auricular acupuncture

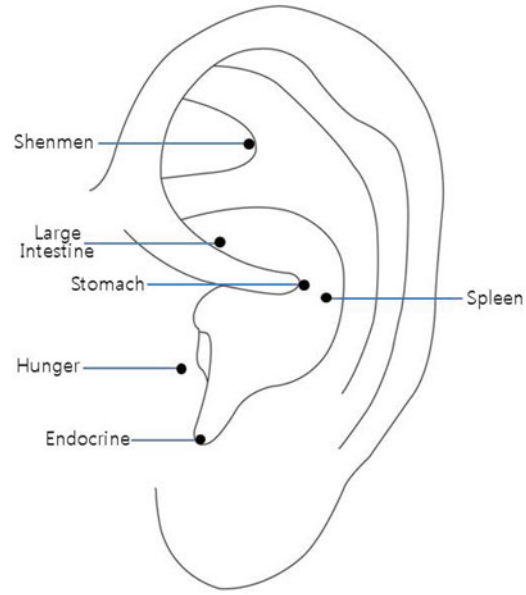



**Fig. 29.1** Popular auricular points for treatment of obesity

needles are inserted using forceps, fixed with ventilation tapes, and retained for approximately 3 days. The aforementioned process is repeated on the other side of the ear after 1–3 days until deemed unnecessary.

When applied appropriately and in hygienic settings, auricular acupuncture is absent of adverse effects and does not hinder the patient from the activities of daily living. Such convenience accounts for its high popularity as a treatment modality. However, it is not only the convenience factor that makes auricular acupuncture a popular form of treatment but also its effectiveness in treating it. Through much research, it is hypothesized that auricular acupuncture aids in weight control by helping to regulate and reduce food intake through the activation of the satiety center [40], by influencing the appetite signal from the gastrointestinal tract [41], and by its influence on obesity-related hormone peptides such as ghrelin [42].

Popular points for treatment of obesity by auricular acupuncture [8] are shown below (Fig. 29.1).

*Hunger point*: located on the middle point between the center of the tragus and infratragus apex
*Shenmen point*: located at the bifurcating point between superior and inferior antihelix crus and the lateral 1/3 of the triangular fossa
*Endocrine point*: located at the base of the cavum conchae, in the intertragic notch
*Stomach point*: located around the area where the helix crus terminates
*Spleen point*: located at the lateral and superior aspect of the cavum conchae
*Large Intestine point*: located at the superior aspect of the helix crus, top 1/3

## Conclusion

It is important to note that despite increasing evidence on acupuncture's efficacy in treating weight-related disorders, the main aim of its treatment is focused not on reducing excessive fat but more on restoring internal balance so that the body can manage to control itself once again. Therefore, it is recommended for patients and doctors to use acupuncture in conjunction with behavioral modification, herbal medication, and other dietary, exercise, and conventional treatment programs for best results.

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# Chapter 30
# Eating Disorders

**Carolyn Coker Ross**

**Abstract** Eating disorders such as anorexia, bulimia, and binge eating disorder include individuals who are both underweight and overweight or obese. These disorders share some commonalities with other causes of weight issues including that dieting is a known trigger for the development of all the eating disorders. Other common issues between obese individuals and those with eating disorders include body dissatisfaction, a history of weight-related teasing, and the influence of media and culture on the desire to be thin. Eating disorders have the highest mortality of any psychiatric disorder, and those who do not die from their disorder often experience many medical, psychological, and social consequences that have a serious impact on their lives. An integrative approach to treating eating disorders offers many advantages when used in conjunction with conventional therapies to reduce medical sequelae and improve overall cognitive and behavioral functioning.

**Keywords** Eating disorders • Anorexia • Bulimia • Binge eating disorder

### Key Points

- Eating disorders such as anorexia, bulimia, and binge eating disorder include individuals who are both underweight and overweight or obese.
- Eating disorders share some commonalities with other causes of weight issues including that dieting is a known trigger for the development of all the eating disorders.
- Other common issues between obese individuals and those with eating disorders include body dissatisfaction, a history of weight-related teasing, and the influence of media and culture on the desire to be thin.
- Eating disorders have the highest mortality of any psychiatric disorder and those who do not die from their disorder often experience many medical, psychological, and social consequences that have a serious impact on their lives.
- An integrative approach to treating eating disorders offers many advantages when used in conjunction with conventional therapies to reduce medical sequelae and improve overall cognitive and behavioral functioning.

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Eating disorders and obesity represent a spectrum of disorders that affect a large number of children, adolescents, and adults. Currently, the DSM includes criteria for the diagnosis of anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), and eating disorder not otherwise specified (ED-NOS). Males with eating disorders may strive for the thin ideal but can also be affected by muscle dysmorphic disorder characterized by an extreme desire to become more muscular [1]. Weight-related issues are not uncommon in individuals with BN, BED and ED-NOS. Between 40 and 60 % of those diagnosed with one eating disorder will cross over to another eating disorder during their lifetime [2].

The incidence of eating disorders continues to increase. In a large national study, the lifetime prevalence of AN was 0.9, 1.5 % for BN, and 3.5 % for BED in women. Women are three times more likely to develop anorexia or bulimia than men, although the incidence of these disorders in men is increasing as well [3]. Approximately one in four preadolescent cases of anorexia occurs in boys [4]. BED is more prevalent than both anorexia and bulimia combined. Sixty percent of those with BED are female and 40 % are male.

## Criteria for Diagnosis of Eating Disorders

Currently there are diagnostic criteria in the DSM-V for anorexia, bulimia, BED, and ED-NOS.

### *Anorexia Nervosa*

Anorexia nervosa is defined by the inability to maintain body weight at or above 85 % of ideal weight. Anorexics are often emaciated and have very disturbed eating behaviors, such as self-starvation. Individuals with anorexia have an extreme fear of gaining weight and of becoming fat. They also suffer with a distorted body image—seeing themselves as fat even when they are underweight. The criteria also include loss of three consecutive menstrual cycles. Men are affected with anorexia nervosa but eating disorders among men are underreported and most men never receive treatment. A 2003 Harvard study reported that the lifetime prevalence of anorexia is 0.3 % for men and 0.9 % for women [3]. The majority of individuals with anorexia are diagnosed in adolescence or young adulthood. Anorexia nervosa has the highest mortality rate of any psychiatric disorder. There is an estimated 10 % mortality in anorexics that have a 10-year history of the disease [5].

### *Bulimia Nervosa*

Bulimia is associated with recurrent episodes of binge eating which is defined as eating a large quantity of food in a short period of time. The binge is followed by purging behaviors such as vomiting; fasting; the use of diet pills, diuretics, and laxatives; and compulsive exercise. Individuals with bulimia are usually normal weight or slightly overweight. One of the hallmarks of bulimia is that their self-evaluation is often influenced by their weight, shape, or body image. It is estimated that 1.5 % of women and 0.5 % of men are diagnosed with bulimia during their lifetime [3].

### *Binge Eating Disorder*

BED affects 3.5 % of women and 2 % of men over their lifetimes. The criteria for BED are focused on the primary behavior—recurrent episodes of binging without compensatory purging behaviors.

Individuals with BED experience lack of control over their binge behavior. They also may experience emotional distress and disgust over their behaviors. They often eat in isolation because of embarrassment over how much they are eating [3]. The majority of those with BED are overweight or obese [3].

### *Eating Disorder Not Otherwise Specified*

ED-NOS is a category that includes people with night eating syndrome and all those who do not meet the strict criteria for anorexia, bulimia, or BED. They may have any combination of behaviors from any of the other eating disorders and weight may range from underweight to obese.

## Medical Complications of Eating Disorders

Table 30.1 offers a listing of the medical complications associated with eating disorders. Most individuals with eating disorders do not present asking for help with their anorexia, for example, but many are seen in various physicians' offices with complications of their eating disorder. For example, someone with anorexia may be referred to a gastroenterologist for treatment of irritable bowel syndrome or be seen in the emergency room for dehydration.

## Causes of Eating Disorders

Obesity and eating disorders share similar characteristics and risk factors including a history of dieting, the use of and exposure to the media promoting an ideal body type and size, body image issues, and weight-related teasing.

### *Dieting*

Many individuals with eating disorders are overweight or obese. The desire to lose weight can lead to the development of an eating disorder which can begin with dieting. Often dieting is followed by more extreme measures to lose weight (purging, diet pills, compulsive exercise, and diuretics) [6]. Dieting has been promoted as the solution to the obesity epidemic; however, dieting has been shown in prospective studies not to be effective in preventing obesity. For example, over the past 30 years in the USA, the percentage of calories from fat has decreased while the rates of obesity have increased [7]. Not only has being on a diet been shown to be correlated with BMI (body mass index) in children and teens but also is the most important predictor of new eating disorders [8]. In a study on adolescents, Boutelle et al. [9] found that overweight teens were more likely than their normal weight peers to engage in unhealthy weight control behaviors, including vomiting and laxative use. In another study on adolescents, those who engaged in dieting gained more weight over a 3-year period than nondieters and were more likely to develop binge-eating behavior [10, 11].

Studies show that the majority of individuals with eating disorders report dieting is what initiated their eating disorder behaviors [12]. Dieting therefore promotes the development of both eating disorders and obesity.

**Table 30.1** Medical risks and complications of eating disorders

| | Anorexia nervosa | Bulimia nervosa | Binge eating disorder |
|---|---|---|---|
| Cardiac | [a]Nonspecific ST-T wave changes, prolongation of QT interval, severe bradycardia, orthostatic blood pressure changes, peripheral edema, hypoproteinemia, cardiomyopathy, mitral valve prolapse | Low voltage, prolonged QT interval, bradycardia, cardiomegaly (from ipecac toxicity) | Stroke, high blood pressure, heart disease (secondary to obesity) |
| Pulmonary | If purging type, same as for BN | Aspiration pneumonia, pneumothorax, subcutaneous emphysema, rib fractures | Sleep apnea |
| Skin and teeth | [a]Lanugo (fine baby hair on face, forearms) | Salivary gland enlargement, loss of dental enamel due to purging, dental caries | None |
| Gynecologic | Amenorrhea | Abnormal menses | Polycystic ovarian syndrome, elevated androgens |
| Hematologic | Leukopenia | Hypochloremia, hypokalemia or metabolic acidosis (from vomiting, laxatives, diuretics), elevated amylase from vomiting | |
| Gastrointestinal | Constipation, gastroparesis, malabsorptive disorders | Bloating, fullness, GERD, abdominal pain, esophagitis, gastric rupture | Constipation, GERD |
| Metabolic and orthopedic | Hypoglycemia, hyperlipidemia, loss of bone mineral density<br>Sick euthyroid syndrome (normal TSH, decreased T3 and increased reverse T3)<br>Hypokalemia, hypophosphatemia | Hyperlipidemia, hypoglycemia (if restricting), elevated amylase | Hyperlipidemia, metabolic syndrome, increased risk for diabetes if obese, hyperglycemia, insulin resistance |

[a]Complications are related to starvation

*Source*: Zwaan, M., and J. E. Mitchell. 1993. Medical complications of anorexia nervosa and bulimia nervosa. In *Medical issues and the eating disorders: The interface,* eds. A. S. Kaplan and P. E. Garfinkel, 60–100. New York: Brunner/Mazel, Inc.

On a deeper level, dieting causes a separation from body cues of hunger and satiety. This separation of mind from body leads to overeating without being responsive to body cues and also leads to body image distortion and other forms of body image issues. Dietary restraint is a model used to explain the "diet mentality" common to both eating disorders and obesity. Individuals with both obesity and eating disorders restrict what they eat based on what they think they should or should not be eating. Dieting results in disinhibited overeating which leads to weight gain, further promoting the cycle of restraint alternating with overeating and binging [13]. Someone who begins with an eating disorder or obesity young in life, as most of these patients do, sees the body as their adversary, not their ally, and tends to operate on the assumption that the body can be molded into a thin ideal despite its genetic blueprint.

### *Body Dissatisfaction*

Body dissatisfaction has been consistently shown to be a risk factor for the development of eating disorders [14]. Body dissatisfaction influences the development of eating disorders by leading to exaggerated dieting methods to attain the thin ideal which of itself increases the risk for eating disorders. Body image issues also contribute to depression and anxiety, which may increase binging and purging behaviors. Finally, body dissatisfaction may directly increase the risk for eating disorders [15–17]. Poor body image is also associated with lower levels of physical activity in female and male adolescents [18]. While body dissatisfaction is present in both eating disorders and obesity, treatment of obesity does not generally address this issue, as do interventions for eating disorders. Treatments for obesity can certainly benefit from interventions aimed at body dissatisfaction due to its link to frequent dieting, binging, decreased physical activity, and mood (an influence on emotional eating) [19].

### *Media Influence*

More young people spend time watching TV or engaging in other media activities than ever before in our history [20]. The Fiji study demonstrated a marked increase in body image issues, weight and body shape preoccupation, and purging behaviors to control weight only 3 years after the introduction of Western television to a rural community in western Fiji [21]. Other studies have pointed to the influence of media on weight issues and the risk for development of eating disorders. The current cultural ideal of thinness for women and lean, muscular bodies for men pressures individuals to conform by whatever means necessary. Because this ideal is not possible for the vast majority of men and women, internalization of this ideal can lead to body dissatisfaction that then leads to disordered eating and an increased risk for eating disorders [22–24]. Field et al. reported that girls who tried to look like females in the media were twice as likely to report purging 1 year later than those who did not. As for obesity, the influence of the media increases body dissatisfaction and also the risk for disordered eating and subthreshold or actual eating disorders.

### *Weight-Related Teasing*

Studies have shown a significant correlation between weight-related teasing and the development of disordered eating including purging, binging, and restricting behaviors [18]. In a study of 1,902 young adults with a mean age of 25, weight-related teasing or comments made by family members and a significant other were associated with disordered eating in males and females [25]. This relationship did not just exist for younger individuals. In another study in middle-aged women, weight-related teasing along with menopausal status and aging anxiety also influenced disordered eating in this population [26].

## Integrative Medicine Approach to Eating Disorders

Integrative medicine therapies for eating disorders are distinct from conventional, medical-model therapies in a number of ways. Integrative medicine offers a whole-person approach, views food as the first and best medicine for eating disorder patients, and combines therapies that address the body,

**Table 30.2** Dosages of nutritional therapies

| Nutrient | Dosage |
|---|---|
| Omega-3 fatty acids | 1–3 g of combined EPA and DHA |
| Folate | 400–1,000 μg/day |
| B6 | 1.5 mg/day up to 100 mg/day |
| Niacin | 14 mg/day |
| B12 | 2.4 μg/day |

mind, and spirit. Botanical and nutritional treatments for mood and anxiety disorders, sleep, and digestion offer important alternatives to prescription medications.

Food is the best medicine for all of the eating disorders no matter whether underweight or normal or obese. Nutritional deficits are prominent in anorexia nervosa and include deficits in B vitamins, calcium, copper, essential fatty acids (EFA), glutathione, iron, magnesium, and zinc [27]. Zinc deficiency has also been found in significant numbers of bulimic patients [28].

## *Nutritional Therapies (Table 30.2)*

Studies by researcher Ancel Keys demonstrated the effect of starvation on behavior, mood, and physiology [29]. There are also demonstrated deficiencies in specific nutrients that affect energy, mood, and cognition. These deficiencies include the B vitamins, iron, vitamins A and C, and the EFA [30–32]. Nutritional deficiencies can also contribute to co-occurring disorders such as anxiety and depression and may exacerbate eating disorder behaviors.

### Essential Fatty Acids

The levels of EFAs are decreased in eating disorder patients with weight loss and are associated with higher risk for depression and other co-occurring disorders [33]. Omega-3 fatty acids have been studied in the treatment of major depression and bipolar disorder that are comorbid in eating disorder patients. Consumption of fish in the diet has been shown to reduce suicide risk and symptoms of depression and bipolar disorder [34, 35]. Supplementation with omega-3 fatty acids in anorexics with depression did not improve the effectiveness of the antidepressant, fluoxetine [36].

### B Vitamins

B vitamins offer protection from oxidative stress, convert glucose from food into energy in the brain cells, and are crucial in the manufacture of neurotransmitters in the brain. Deficiencies in B vitamins have been identified in patients with eating disorders and depression and have been implicated in poor response to antidepressant medication [37, 38]. Vitamin B12 may also reduce fracture risk in anorexics by increasing bone mineral density [39].

### Vitamin D

Vitamin D is important for bone health especially in patients with anorexia nervosa. Recent studies demonstrate a role for vitamin D in supporting the immune system and the prevention and treatment of depression [40].

Individuals with anorexia and bulimia may be deficient in vitamin D due to dietary restraint. Obese eating disorder patients may have deficient circulating vitamin D because of sequestration of this vitamin in fatty tissue [41].

### Amino Acids

The National Institute on Drug Abuse (NIDA) has identified a neurobiological overlap between addiction and eating disorders. For example, the hormone orexin fosters cravings for both food and drugs in animal studies [42]. Another research into the pleasure or reward cascade in the brain shows that there may be dysfunction in this mechanism due to genetic variants particularly in individuals with addictions, including eating disorders. This phenomenon has been called chronic abstinence syndrome or brain reward deficiency. Drugs of abuse including alcohol, cocaine, heroin, nicotine, marijuana, and sugar all cause activation of the reward system prompting the release of dopamine which reduces cravings. Drug use can reduce the amount of dopamine receptors in the brain. As well, individuals who have genetic variants that reduce dopamine (D2) receptor efficacy are at higher risk for multiple addictive, impulsive, and compulsive behaviors including drug and alcohol addiction, ADHD, Tourette's syndrome, autism, chronic violence, PTSD, schizoid/avoidant conduct disorder, and antisocial behavior. Researcher Kenneth Blum has coined the term "reward deficiency syndrome (RDS)" or chronic abstinence syndrome to describe this condition [43]. Individuals with RDS are therefore not able to produce enough of the neurotransmitters that help them feel good and function better. Studies have documented abnormalities in neurotransmitter levels in individuals with eating disorders that are associated with eating disorder behaviors, mood, and anxiety disorders [44, 45].

Production of neurotransmitters in the brain is dependent on certain vitamins, minerals, and micronutrients. Amino acids are the building blocks of protein and are the substrates for the production of neurotransmitters in the brain. Research studies have shown that the use of amino acids may help increase levels of neurotransmitters and reduce behaviors associated with eating disorders. For example, administration of L-tryptophan and 5-hydroxytryptophan (5-HTP), both precursors for serotonin, doubles the production of serotonin in the brain [46]. In studies on individuals with bulimia nervosa, acute tryptophan depletion resulted in an increase in caloric intake and mood irritability [47]. Tryptophan depletion was also associated with increases in body image concerns and subject's loss of control over eating [48]. Adding tryptophan to the diet reduced bulimic behaviors.

Amino acid therapies include the use of amino acids to reduce cravings, treat mood and anxiety disorders, and improve eating disorder behaviors (Table 30.3):

1. *5-HTP and L-tryptophan*—reduce symptoms of depression in over 60 % of patients and have been shown to be more effective than placebo and as effective as some prescription antidepressants [46].
2. *Phenylalanine (PA) and tyrosine (Tyr)*—PA is a precursor to Tyr, which is a precursor to dopamine. Both act as antidepressants. Tyrosine is also an adaptogen, helping reduce physical signs of stress [49].
3. *A mixture of three amino acids* has been shown to reduce cravings, weight regain, and binging behaviors in people who lost weight on the Optifast program, when followed for 2 years [50].

### Zinc

Zinc has been extensively found to be deficient in individuals with eating disorders [51, 52] and has been well studied in research [53]. Zinc has also been found to be deficient in chronic dieters. Symptoms of zinc deficiency include many of the symptoms associated with eating disorders,

**Table 30.3** Symptoms associated with chronic abstinence syndrome and the amino acid therapies used to treat these symptoms

| Chronic abstinence syndrome | Amino acids |
|---|---|
| Anxiety, stress | GABA, taurine, tryptophan |
| Low energy, apathy | L-tyrosine |
| Poor concentration, memory, brain fog | L-tyrosine |
| Hypersensitivity | D- or L-phenylalanine |
| Insomnia | L-tryptophan, 5-HTP, GABA, taurine |
| Cravings | L-glutamine, GABA, tryptophan |
| Depression, anhedonia | L-tyrosine |

particularly AN, including dermatitis, weight loss, loss of appetite, amenorrhea, and depression [54]. Underweight anorexics may be diagnosed with protein-energy malnutrition that affects the small intestinal mucosal absorptive capacity leading to decreased zinc absorption [55]. Zinc deficiency can in turn cause an altered epithelial barrier and may result in diarrhea which worsens malabsorption [55]. Studies further demonstrate that zinc supplementation during weight restoration in malnutrition and eating disorders is useful in increasing body mass index [56].

## Outcomes

The prognosis for individuals is variable. Bulimia and BED have an average duration of 8 years each. For anorexia and bulimia, 50 % recover, 30 % improve to some degree, and 20 % will continue to be chronically ill, some of whom will die from their disease [3]. Relapse rates after treatment are 35 % for anorexia and 31 % for bulimia. The highest risk for relapse from anorexia is 6–17 months after treatment and 6 months for bulimics. Relapse rates for ED-NOS are 42 % (which in these studies included BED) [57–59].

## Conclusion

Eating disorders share many common risk factors with obesity including media exposure, weight-related teasing, a history of dieting, and body image dissatisfaction. Nutritional deficiencies and protein-energy malnutrition are caused by eating disorder behaviors and may explain many of the symptoms associated with eating disorders. As well, nutritional deficits can have a dramatic impact on brain function, especially on the production of neurotransmitters that govern mood and behavior. Integrative medicine offers a whole-person approach to treating eating disorders and can play an important role along with conventional medical care.

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# Chapter 31
# Religious, Cultural, and Social Aspects of Eating

**Tina Colaizzo-Anas**

**Abstract** What, when, and how much we eat is the culminating behavior that makes up food intake patterns which can be influenced by religion, cultural context, and social milieu. Such influences are channeled by family, friends, faith communities, media, work environment, entertainment venues, etc. Effective counseling for weight management is dependent on an in-depth knowledge and understanding of and sensitivity to religious diversity/multiculturalism, with social intelligence. Practitioners must have skills to make positive accommodations to address diversity in religion, cultural heritage, and social context to affect positive outcomes. The richness of diversity of the American people offers many opportunities for the practitioner in weight management to partner with their clients and patients to make permanent healthy lifestyle changes. An expanding critical mass of evidenced-based research indicates that making cultural accommodations to weight management interventions has the potential to dramatically improve outcomes. Practitioners have a professional responsibility to assess their cultural competence and develop action plans to strengthen knowledge and skills in areas needing improvement. Many online resources are available that can assist the practitioner in assessing cultural competence. Opportunities exist for research to refine our understanding of how to make cultural adaptations to weight management interventions most effectively. As the American demographic changes, practitioners will be challenged increasingly to address the religious, cultural, and social needs of their patients.

**Keywords** Cultural food practices • Religious food practices • Fasting • Cultural competence • Multiculturalism • Weight management

### Key Points

- What, when, and how much we eat is the culminating behavior that makes up food intake patterns which can be influenced by religion, cultural context, and social milieu.
- Effective counseling for weight management is dependent on an in-depth knowledge and understanding of and sensitivity to religious diversity/multiculturalism, with social intelligence.
- The richness of diversity of the American people offers many opportunities for the practitioner in weight management to partner with their clients and patients to make permanent healthy lifestyle changes.

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- An expanding critical mass of evidence-based research indicates that making cultural accommodations to weight management interventions has the potential to dramatically improve outcomes.
- Many online resources are available that can assist the practitioner in assessing cultural competence.
- As the American demographic changes, practitioners will be challenged increasingly to address the religious, cultural, and social needs of their patients.

What, when, and how much we eat is the culminating behavior that makes up food intake patterns that can be influenced by religion, cultural context, and social milieu. Such influences are channeled by family, friends, faith communities, media, work environment, entertainment venues, etc. [1]. Effective counseling for weight management is dependent on an in-depth knowledge, understanding of, and sensitivity to religious diversity/multiculturalism, with social intelligence. Practitioners must have skills to make positive accommodations to address diversity in religion, cultural heritage, and social context to affect positive outcomes. For the remainder of this chapter, these factors will be referred to as RCS.

Not only is sensitivity to RCS vital for successful weight management interventions, but a keen recognition of the dynamic nature of the rapidly changing US demographic is important. The most recent US census data indicates that Hispanic and Asian ethnic groups are growing at a fast pace, largely due to immigration. In fact, more than 50 % of the growth in the US population between 2000 and 2010 is attributed to an increase in the Hispanic population estimated to total 50.5 million. Black or African-Americans number 38.9 million. In 2010, 5 % of census respondents identified themselves as Asian, 14.7 million people. The Asian population grew faster than any other race group (Table 31.1) [2].

With immigration comes the challenge of adapting to American culture. The process of adopting American dietary practices is gradual and is influenced by many environmental factors [3]. Often the shift to the American diet results in food intakes that are low in fruits and vegetables and high in fat. Dietitians must assess where in the continuum of acculturation a patient's dietary practices fall in order to employ successful nutrition education and counseling strategies. Opportunities to reinforce positive cultural food practices should be embraced. Gradually, with rapport building and respect, dietary interventions may be implemented including interventions for weight management [3]. The Academy of Nutrition and Dietetics *Nutrition Care Manual* offers many suggestions for acceptable healthy adaptations of cultural food practices for a variety of ethnic groups [4, 5].

Yia Yia's Acculturation to a Healthy American Diet

A 73-year-old Greek Yia Yia (grandmother) with diabetes immigrated to the USA to live with her son and his family. Yia Yia loved to cook and she started preparing souvlaki (seasoned beef), pastitsio (macaroni and beef casserole), moussaka (eggplant casserole), fried zucchini, spanakopita (spinach and filo dough pie), and baklava (a nut-filled filo pastry with syrup) on a weekly basis. While this fare was exquisitely delicious, it posed a challenge for the family who were controlling their intake of calories and cholesterol.

Yia Yia gradually accepted the suggestion to use part-skim mozzarella rather than feta cheese in her spanakopita.

Another challenge was for the family to witness Yia Yia's diet. She ate no fruit or what she perceived to be "high-sugar" vegetables. Over time Yia Yia gradually accepted one kiwi and one apple per day, i.e., when she saw that her a.m. finger sticks could be controlled when eating them. She accepted whole grain bread when she learned that it helped her blood sugar level.

**Table 31.1** Population by Hispanic or Latino origin and by race for the USA: 2000 and 2010

| Hispanic or Latino origin and race | 2000 | | 2010 | | Change, 2000–2010 | |
|---|---|---|---|---|---|---|
| | Number | % of total population | Number | % of total population | Number | % of total population |
| *Total population* | 281,421,906 | 100.00 | 308,745,538 | 100.00 | 27,323,632 | 9.7 |
| Hispanic or Latino | 35,305,818 | 12.5 | 50,477,594 | 16.3 | 15,171,776 | 43.0 |
| Not Hispanic or Latino | 246,116,088 | 87.5 | 258,267,944 | 83.7 | 12,151,856 | 4.9 |
| White alone | 194,552,774 | 69.1 | 196,817,552 | 63.7 | 2,264,778 | 1.2 |
| *Race* | | | | | | |
| *Total population* | 281,421,906 | 100.00 | 308,745,538 | 100.00 | 27,323,632 | 9.7 |
| One race | 274,595,678 | 97.6 | 299,736,465 | 97.1 | 25,140,787 | 9.2 |
| White | 211,460,626 | 75.1 | 223,553,265 | 72.4 | 12,092,639 | 5.7 |
| Black or African-American | 34,658,190 | 12.3 | 38,929,319 | 12.6 | 4,271,129 | 12.3 |
| American Indian and Alaska Native | 2,475,956 | 0.9 | 2,932,248 | 0.9 | 456,292 | 18.4 |
| Asian | 10,242,998 | 3.6 | 14,674,252 | 4.8 | 4,431,254 | 43.3 |
| Native Hawaiian and other Pacific Islander | 398,835 | 0.1 | 540,013 | 0.2 | 141,178 | 35.4 |
| Some other race | 15,359,073 | 5.5 | 19,107,368 | 6.2 | 3,748,295 | 24.4 |
| Two or more races[a] | 6,826,228 | 2.4 | 9,009,073 | 2.9 | 2,182,845 | 32.0 |

*Sources*: US Census Bureau, *Census 2000 Redistricting Data (Public Law 94–171) Summary File*, Tables PL1 and PL2, and *2010 Census Redistricting Data*

For information on confidentiality protection, nonsampling error, and definitions, see www.census.gov/prod/cen2010/doc/pl94-171.pdf

[a]In Census 2000, an error in data processing resulted in an overstatement of the "Two or more races" population by about one million people (about 15 %) nationally, which almost entirely affected race combinations involving "Some other race." Therefore, data users should assess observed changes in the "Two or more races" population and race combinations involving "Some other race" between Census 2000 and the 2010 Census with caution. Changes in specific race combinations not involving "Some other race", such as White *and* Black or African-American or White *and* Asian, generally should be more comparable

## Social Influences Affecting Food Patterns

To explore RCS influences further, one may consider that food choices are often made as a function of factors such as age, gender, occupation, lifestyle, and family history, in addition to cultural background. Social influences also include economic and environmental aspects. Food attitudes are forged early in childhood and are further shaped by interactions with the people that we encounter as we grow. For example, the heralded family meal has been shown repeatedly to have a lasting positive influence on food intake quality both during adolescence [6] and into young adulthood [7]. Despite this, outside influences can threaten the quality of food choices. The food choices of teenagers can be strongly influenced by peer pressure. Social factors continue to bare influence when women go to college [8]. Freshman women attribute the infamous "freshman 15" weight gain to newly found food independence, social comparison with peers, and continued influence of friends and family [8].

Cultural and Ethnic Food and Nutrition Education Materials: A Resource List for Educators
www.nal.usda.gov/fnic/pubs/bibs/gen/ethnic.pdf

In studying the social influences of eating patterns of young adults, Oygard and Klepp [9] found that the strongest social influence on eating patterns was the perceived eating norms of a partner. These authors went on to suggest eating patterns may be shaped by social influences throughout life [9]. A major challenge to making quality food choices in young adulthood is the decision to eat dinner with others or to eat "on the run." In a cross-sectional study of 1687 young adults, Larson et al. [10] found that 35 % of males and 42 % of females reported not having enough time to eat with others. These authors found that young adults who ate dinner with others had significantly higher fruit, vegetable, and dark-green and orange vegetable intakes. Conversely, young adults who reported eating on the run reported significantly higher intakes of soft drinks, fast food, total fat, and saturated fat. Interestingly, young adults living with parents or in rented apartments may be considered an at risk group because they eat fewer meals and have poorer dietary intakes compared to those living on campus [11]. By the time we are adults, our food preferences are limited to approximately 100 items that amount to 75 % of the food we consume [12].

While RCS continue to influence the foods that the elderly choose, these influences may be weakened by restrictions related to disease and decreases in sensitivity to taste [12]. Social situation can be a strong influence on food choices. For example, when men retire, significant weight loss has been demonstrated 18 months after retirement. This result occurred despite spending more time at breakfast and lunch and eating out more and having guests more frequently [13].

## Culture and Food Practices

The dictionary definition of culture is "The sum of attitudes, customs, and beliefs that distinguishes one group of people from another" [14]. Arising from cultural heritage are people's attitudes, customs, and beliefs about food. Ethnicity is defined as "identity with or membership in a particular racial, national, or cultural group and observance of that group's customs, beliefs, and language" [15]. Ethnic practices may dictate how food is prepared and when and how often food is eaten. Ethnic or religious customs may inform menu planning for religious rituals or social events [16]. Food often serves purposes beyond nourishing the body. While food provides a means for expressing devotion to culture [16], sometimes it is used as a means of self-expression or for fostering relationships. Food can be used to cultivate friendships, to exercise creative activity, or to be used as a reward for achievement [12]. See Table 31.2 for snapshots of cultural food practices of a sampling of American ethnic groups.

## Professional Cultural Competence

When considering the magnitude of the influence culture plays on human behavior, professionals may capitalize on many opportunities to garner rapport with their clients and to foster mutual respect while optimizing the potential for positive health outcomes. To these ends, Campinha-Bacote [17] and others have proposed a model of professional cultural competence that is defined as a process that includes cultural awareness (the professional's awareness of their personal attitudes, values, and beliefs), cultural knowledge, cultural skill in providing health care, skill in engaging in encounters in which culturally appropriate client and practitioner responses are elicited, and finally, a desire to seek greater cultural competence.

**Table 31.2** Cultural food patterns

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|---|---|
| Chinese | Common foods: low milk intake; frequent tofu, green vegetables, and fish with small bones; rice, grains, legumes; pork, hot peppers, fresh produce, soup, tea |
| | Seasonings: monosodium glutamate (MSG), soy sauces |
| | Method of food preparation: stir-fry, deep fat frying, steaming; preserved, pickled, dried, salted, fermented, or cured ingredients; dried, preserved, and salted foods [51] |
| | Diet pattern: "hot" and "cold" foods during pregnancy |
| | Diet-related condition: commonly lactose intolerance |
| | See also for common Asian foods: http://oldwayspt.org/resources/heritage-pyramids/asian-diet-pyramid/asian-diet-foods |
| Korean | Common foods: steamed rice, vegetables, soup, kimchi (pickled and fermented vegetables), fresh fruit, dried anchovies, and soy or soy products (tofu) [52] |
| | Method of food preparation: broiled or roasted meat or fish; seasoned fried beef |
| | Nutrient composition: high CHO, vitamins A and C, lower total fat, cholesterol, and saturated fat |
| | Diet-related condition: commonly lactose intolerance |
| Hispanic/Latino (varies according to country of origin—Mexico, Cuba, Puerto Rico, Central and South American countries) | Common foods: milk is rare; cheese as additive; chili peppers, mangos, avocados; corn or flour tortilla; beans and rice |
| | Nutrient composition: high in sugar and saturated fat (lard) |
| | Food patterns: fruits and vegetables may be viewed as luxuries; snacking with higher levels of acculturation |
| | Common diet-related diseases/conditions: obesity, type 2 diabetes, cardiovascular disease, dental caries |
| Asian Indian | Common foods: lentils, legumes; in some families, eggs, fish, shrimp, and milk; yogurt, combination foods: biryani (grain, meat), samosas (grain, vegetable, meat, fat), kheer (rice pudding), curry (meat, vegetable); bananas |
| | Food patterns/practices: often lacking in portion control; meals are made up with rice or rotis (wheat), lentils or chicken, fish, or shrimp along with vegetables and yogurt [53] |
| | Diet-related diseases/conditions: lower rate of colorectal, prostate, and lung cancers (although rising) than Western countries; high rates of oral and esophageal cancer in India; high incidence of diabetes |
| Mediterranean food pattern [54] | Common foods: high consumption of olive oil, fish, poultry, eggs; breads, fruits, unrefined cereals, vegetables; beans, legumes; low intakes of meat; moderate intakes of yogurt, cheeses, wine |
| | Lifestyle: physically active |
| | Diet-related conditions: Protective against cardiovascular disease [55] |
| Middle Eastern | Common foods: no pork; lamb, beef, yogurt, cheese, olive oil; Muslim food habits |
| | Diet-related condition: commonly lactose intolerance |
| Native American (varies according to the tribal heritage) [56] | Common foods: fried foods, fried bread, corn, mutton, goat (American Indians); seafood, game (Alaskan natives) |
| | Food practices: high emphasis on food as part of religious and social celebrations |
| | Diet-related diseases/conditions: obesity, type 2 diabetes |
| African American (regional variations in food patterns among the African diaspora from West and Central Africa, South America, the Caribbean, the American South) | Common foods: collard greens, kale, green beans, bananas, rice, potatoes, catfish, beef, salt pork, ham hocks, cornbread, biscuits, rice pudding, cakes, fruit and nut pies: soul foods include pastries, fried chicken, collards [4] |
| | Food practices: deep frying, stewing, and roasting, barbeque [4]; common flavorings include curries, peppers, coconuts, fresh herbs |
| | Diet-related diseases/conditions: diabetes, obesity, hypertension. See also: http://oldwayspt.org/resources/heritage-pyramids/african-diet-pyramid/african-heritage-foods |

Adapted from Escott-Stump S, 2008 [57] unless otherwise indicated

The National Center for Cultural Competence at Georgetown University offers a free online "Cultural Competence Health Practitioner Assessment (CCHPA)" [18]. The CCHPA uses six subscales to evaluate cultural competence including:

*Values and Belief Systems*: practitioner knowledge of cultural groups' traditional health practices, healthcare-seeking behavior, religious perspectives, and more.
*Cultural Aspects of Epidemiology*: practitioner knowledge of factors that contribute to culture-specific disease risk—including protective factors and health disparity.
*Clinical Decision Making*: the subscale that explores practitioner knowledge of cultural health beliefs and ability to utilize this knowledge in health assessments, diagnosis, and treatment decisions.
*Life Cycle Events*: a subscale that assesses practitioner knowledge and skill in addressing implications of culturally specific life cycle practices.
*Cross-Cultural Communication*: a subscale that assesses practitioners' knowledge and communication skills adapted for cross-cultural communication.

The CCHPA provides immediate feedback to practitioners on their online assessment. The assessment is accompanied by suggestions for resources to boost the practitioner's cultural competence within each domain.

## Cultural Attitudes About Health Care and Implications for Weight Management

Some diseases affect certain ethnic groups disproportionately. For example, the age-adjusted prevalence of diabetes is 33.5 % in American Indians living in southern Arizona. The prevalence of diabetes is 18 % higher among Asian-Americans, 66 % higher among Hispanics, and 77 % higher among non-Hispanic blacks compared to non-Hispanic white adults [19].

Attitudes, beliefs, and values can strongly influence patients' healthcare decision making particularly when enlisting professional help for health care. Such influences may underlie decisions regarding treatment of the sick, deciding whom to consult when sick, and how both patients and health practitioners perceive their roles [16]. Accordingly, these influences may suggest implications for accepting weight management interventions. Positive patient outcomes may be harnessed when the healthcare professional makes cultural accommodations. For example, culturally sensitive diabetes education interventions for Mexican-Americans have been shown to affect positively HbA1c, fasting blood sugar, and knowledge [20]. Similarly, in a meta-analysis of approximately 1,600 ethnic minority patients with type 2 diabetes who received culturally appropriate health education, HbA1c and knowledge scores improved [21].

One of the most successful interventions for disease prevention is the Diabetes Prevention Trial (DPP). The DPP demonstrated on a large scale that dramatic reductions in disease risk can result when lifestyle interventions are implemented with culturally appropriate adaptations. At least 45 % of the 3,200 participants enrolled in the DPP trial were from minority groups. An intent-to-treat analysis indicated a 58 % reduction in diabetes risk when a 7 % drop in body weight was the goal [22]. Diabetes incidence was reduced in all racial and ethnic groups. A 10-year follow-up study indicated that a 34 % reduction in risk was sustained without any change in the distribution of participants by ethnic origin [23].

While the success of culturally sensitive diet interventions have been well documented, the opposite is also true. For example, highly effective dietary interventions have been developed for the dietary control of high blood pressure, but their effectiveness has not always been shown to be as high in African-Americans compared to whites. In a recent secondary analysis of the Dietary Approaches

to Stop Hypertension (DASH) diet, African-Americans were found to be less compliant compared to whites. The variation in compliance was related to difficulty in limiting meat, sweets, and fat and eating less fruit. The diet intervention in this study did not include modifications to address the cultural food preferences and practices of African-Americans. No formalized strategies were employed to culturally adapt the intervention. Overall, compliance was the same in the DASH diet alone and the DASH diet plus weight management arms of the study [24].

The demographic group with the highest prevalence of obesity is African-American women (AAW). AAW seek out weight management programs infrequently and, when they do, have low success rates. The low rate of weight loss success has been shown to have negative effects on self-efficacy. The strongest motivators for losing weight among AAW were found to be (1) being diagnosed with a health issue, (2) appearance, and (3) saving on clothing costs [25]. These factors may be used to develop culturally sensitive messages for AAW weight management interventions. In addition to these factors, it is important to consider that the African-American community attaches high priority to religion and spirituality [26, 27]. Some researchers have cited the effectiveness of church-based interventions [28] and believe that these interventions must include spiritual components [29]; AAW churchgoers incorporate prayer, scripture, and gospel music in their efforts to make lifestyle changes [29, 30]. Programs in AAW churches benefit by utilizing trained lay health volunteers, social support, and family and community involvement [29]. While spiritual interventions may be helpful in planning weight management strategies for AAW, spiritual interventions without culturally sensitive messages may have limited effectiveness [31].

## Religion and Food Practices

All of the major world religions include food practices that must be considered for dietary planning. Some religions forbid certain foods. Others require abstinence from certain foods at certain times, usually in conjunction with religious feast days. Still others prescribe methods for how to slaughter animals for meat, for combining certain foods, and for where certain foods should be eaten. The goal of food practices varies from religion to religion. Some fast for health; others fast to deepen a relationship with God.

As Table 31.3 indicates, the meaning of fasting for many faith confessions is the cultivation of self-control which—in turn—has positive effects for the spiritual life. Substantial data on dietary intakes are available for the Greek Orthodox fast, the Daniel fast, and the Ramadan fast [32]. Studies of the Ramadan fast indicate that adherents either gain or lose weight, but may also have sleep disturbances, increased gastric acidity, and dehydration. The results are mixed, possibly related to heterogeneity in cultural practice [32–34]. The Daniel fast (Daniel 1:8–14), which is practiced by many Christians and Jews, involves ad libitum intake of fruits, nuts, seeds, vegetables, whole grains, and oil. All foods with preservatives, additives, sweeteners, flavorings, caffeine, and alcohol are prohibited. Body weight and fat have shown only nonsignificant declines, but total cholesterol, LDL-C, insulin, and CRP are lowered on the Daniel fast [35]. The Greek Orthodox fast often results in weight loss accompanied by decreases in total cholesterol, LDL cholesterol [32].

The Greek Orthodox fast involves a primarily vegan diet and applies to approximately 6 months of the year. According to the Greek Orthodox Archdiocesan website, “The primary aim of fasting is to make us conscious of our dependence upon God. If practiced seriously, the … . abstinence from food … . involves a considerable measure of real hunger, and also a feeling of tiredness and physical exhaustion … Abstinence leads, not merely-to this, but also to a sense of lightness, wakefulness, freedom and joy. Even if the fast proves debilitating at first, afterwards we find that it enables us … . to think more clearly, and to work more decisively. … . Most of us in the Western world habitually eat more than we need. Fasting liberates our body from the burden of excessive weight and makes it a

**Table 31.3** Food practices of the major world religions

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|---|---|
| Christianity: Roman Catholicism [58] | Fasting: One full meal per day; no snacking according to local custom and/or abstinence from meat; abstain from food and water 1 h before communion |
| | Fasting time and duration: during Lent (40 days before Easter, especially Ash Wednesday, the start of Lent, and Good Friday, the day Jesus Christ was crucified), on Fridays during Advent (the season before Christmas) |
| | Meaning of fasting: detachment from worldly desires or from what might be a "consumer attitude" in order to repent and become closer to God [59] |
| Christianity: Eastern Orthodox [58] | Fasting: abstain from meat, oil, wine, and all animal products including milk, eggs, butter, cheese, fish, but shellfish is permitted |
| | Fasting time and duration: every Wednesday and Friday; fasting is less strict if a feast day falls on a Wednesday or Friday, when fish, wine, and oil is permitted; two 40-day fasts: the Nativity fast is 40 days before the celebration of the birth of Jesus Christ and the Lenten fast is 40 days before the Resurrection of Jesus Christ (Pascha). A 2-week fasting period (August 1–14) precedes the Feast of the Dormition (the falling asleep of the Mother of God) and the period between the Feast of All Saints and the Feast of Sts. Peter and Paul (June 28) is designated as the Apostles' Fast. In total, Orthodox Christians fast approximately 6 months per year. A fasting calendar may be found at http://www.goarch.org/chapel |
| | Meaning of fasting: Controlling the desires of the body through fasting allows one's mind and soul to be more open to the guidance of the Holy Spirit, its liberating effect, for greater communion with God. During Great Lent, the meaning of fasting is deeper; it serves as an aid in repentance and transformation (see www.goarch.org/ourfaith/faithandlife/fasting.pdf) |
| Christianity: Protestantism [58] | Fasting: practiced by Mormons is the only Protestant faith confession that fasts; Mormons abstain from alcoholic beverages, hot drinks (coffee and tea), and caffeine-containing drinks. Consumption of meat is discouraged |
| | Food practices: Most Seventh-Day Adventists are lacto-ovo vegetarians; when meat is eaten, pork is omitted. Overeating and eating between meals are discouraged. Tea, coffee, alcoholic beverages, and strong seasonings (e.g., pepper and mustard) are not permitted or discouraged |
| | Meaning of fasting: for Mormons, a health code. Some Mormons fast 1 day per week and give their food money to the poor |
| Judaism | Fasting: complete fasting on feast days |
| | Fasting time and duration: sunset to sunset (Yom Kippur and Tisha b'An); sunrise to sunset on other feast days |
| | Meaning of fasting: to gain control over harmful bodily appetites |
| | Food practices: "keeping kosher" (often during Passover); refrain from eating pork, shellfish, certain fowl, and fish; include meat and fowl that are slaughtered in a prescribed manner (Kosher), unleavened bread during Passover; separate meat and dairy when manufactured or consumed; certain foods are associated with feast days; traditional foods during Passover (cheese blintz with sour cream, noodle kugel; traditional foods during Hanukkah include latkes and sour cream or apple sauce) |
| | See also http://www.myjewishlearning.com/daily_life/Kashrut.htm |
| Buddhism | Fasting: practice varies |
| | Fasting time and duration: days of new moon and full moon (varies) |
| | Meaning of fasting: a method of practicing self-control |
| | Food practices: customs vary, depending upon sect; follow ahimsa (nonviolence related to the infliction of pain on animals); lacto-ovo vegetarian; some eat fish; some eliminate beef only |
| | See also http://www.buddhanet.net/ |

(continued)

**Table 31.3** (continued)

| | |
|---|---|
| Hinduism | Fasting: not common but can vary from complete abstinence from food or restrict to fruit, simple foods vegetarianism, or avoidance of favorite foods |
| | Fasting time and duration: during holy days, new moon days, and on religious festivals |
| | Meaning of fasting: a way of staying close to God, to control earthly desires, and to foster peacefulness |
| | Food practices: a majority belonging to the Brahmin caste are lacto-vegetarians; adhere to ahimsa; beef is prohibited (the cow is considered sacred); devout Brahmins avoid alcohol, garlic, and onions; the Sikhs branch prohibit beef and alcohol and allow pork |
| | *Ayurveda* (*Asian Indian medicine*) *food practices*: |
| | Kasha foods, e.g., cereals and lentils, are cooked in water and are consumed in the home. Puce foods are cooked in ghee and milk and may be eaten outside of the house [5] |
| | Static foods (healthy foods): milk products (except cheese made with rennet), rice wheat, and legumes |
| | Raja sic foods (foods encouraging aggression): meats, eggs, rich or salty foods |
| | Tama sic foods (promote laziness or dullness): garlic, pickled foods, stale or rotten foods; alcohol |
| | See also http://www.hindunet.org/healthlifestyle/ |
| Islam | Fasting: all food and drink |
| | Fasting time and duration: from dawn to dusk during the month of Ramadan |
| | Meaning of fasting: remind Muslims of the need to be thankful and to remember the less fortunate [60] |
| | Food practices: eliminate "haram" foods which include pork, alcohol, carnivorous animals, or birds of prey, or foods containing by-products of the above (e.g., gelatin) |

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willing partner in the task of prayer, alert and responsive to the voice of the Spirit" (see http://www.goarch.org/ourfaith/ourfaith9199).

A main point is that Orthodox fasting has no spiritual value or can be harmful, if it is not combined with prayer. According to the Orthodox Study Bible, prayer is "communion with God through words of praise, thanksgiving, repentance, supplication, and intercession" [36].

The cultivation of self-control is the goal of many common behavioral weight management counseling strategies, e.g., stimulus control, self-monitoring, and cognitive restructuring. These common weight management strategies in combination with prayer and fasting may serve as effective religious accommodations. A Cochrane review on intercessory prayer for illness was recently published [37]. While intercessory prayer for obesity has not been studied, this investigation may offer insights for using prayer as an adjunct to weight management strategies. The authors of the Cochrane review used the following definition for intercessory prayer: Prayer is "petition to God on behalf of another who is in some kind of need." The objective of this Cochrane review was to evaluate the effects of intercessory prayer for people with ill health who were already receiving routine care. While some of the articles cited in the review documented positive effects of intercessory prayer [38], the authors' conclusion was that due to limitations of trials included in the review, further studies would be needed to draw firm conclusions about value of intercessory prayer. Some of the articles included in the review [37, 39] elicited a flurry of published comments [40, 41]. The major controversy that emerges when considering testing the hypothesis of prayer is the potential contradiction to the beliefs of faithful Christians and Jews who guard against "putting God to the test" [40].

The connection between weight management, prayer, and spiritual interventions is an approach that has already been established with Overeaters Anonymous (OA). OA is an international self-help organization that addresses compulsive overeating using the Twelve Steps and Twelve Traditions of OA. The 12-step program utilized by OA operates from the premise that compulsive overeating is beyond a person's power to overcome, and in order to overcome, one must surrender to a "Higher Power" [42].

A spiritual principle is associated with each of the Twelve Steps. These include honesty, hope, faith, courage, integrity, willingness, humility, self-discipline, love for others, perseverance, spiritual awareness, and service [43]. OA is organized into local chapters with meetings led by a chapter volunteer. Members make actions plans which may be coordinated with their healthcare provider. While no published studies evaluating the effectiveness of OA are available, a qualitative study was conducted to explore members' experiences with and perceptions of OA. Self-selected members who participated in focus groups indicated that OA was helpful to them, but they did not know why OA works [44]. It is an interesting thought to speculate that one reason OA may work is that it encourages members to be mindful of their food practices by making God more present through prayer. This mindfulness may provide ammunition against modern-day challenges of our "toxic" food environment, a term coined by Dr. Kelly Brownell, in his book, Food Fight: The Inside Story of the Food Industry [45]. Our "toxic food environment" bombards us unceasingly with messages tempting us to eat. The unrelenting temptation from media and advertising leads to overeating and consequently to overweight and obesity.

Fasting as an approach to weight management is commanding increased scientific attention. For example, alternate-day fasting (ADF) has been studied [32, 46, 47]. The duration of the longest studies of ADF has been 20 weeks, often limited by issues with compliance. While ADF has been shown to be safe, patients report hunger and irritability on fast days [47]. Feelings of hunger on fast days may be attenuated when ADF is modified to include some food intake, i.e., 25 % baseline energy intake, on fast days [48]. ADF can result in significant weight loss [32, 47, 48].

New data on the biochemical and physiological effects of fasting are being generated. One human study analyzed adipose tissue biopsies after a 72-h fast and found increased amounts of adipose tissue lipase triglyceride (ATGT) protein and decreased ATGT inhibitor GOS2 mRNA and protein [49]. ATGT removes the first fatty acid during lipolysis [50].

## Summary

The richness of diversity of the American people offers many opportunities for the practitioner in weight management to partner with their clients and patients to make permanent healthy lifestyle changes. An expanding critical mass of evidence-based research indicates that making cultural accommodations to weight management interventions has the potential to dramatically improve outcomes. Practitioners have a professional responsibility to assess their cultural competence and develop action plans to strengthen knowledge and skills in areas needing improvement. Many online resources are available that can assist the practitioner in assessing cultural competence. Opportunities exist for research to refine our understanding of how to make cultural adaptations to weight management interventions most effectively. As the American demographic changes, practitioners will be challenged increasingly to address the religious, cultural, and social needs of their patients.

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# Chapter 32
# Patient-Centered Strategies for Effective Weight Management

**Kathryn M. Kolasa**

**Abstract** Although the treatment of both adult and pediatric obesity in primary care is in its infancy, there is a growing base of evidence that patient-centered strategies, used by clinicians alone or in combination with other health-care professionals or community programs, can be effective. This paper presents, using the 5 As framework (Ask, Advise, Agree/Assess, Assist, and Arrange), behavioral strategies that assist patients making lifestyle changes for weight management.

**Keywords** Patient-centered strategies • 5 As framework • Weight management in primary care • Patient-centered medical home • Goal setting • Alternatives to clinic-based weight management • Motivational interviewing • Behavioral approaches • Technology

**Key Points**

- Although the treatment of both adult and pediatric obesity in primary care is in its infancy, there is a growing base of evidence that patient-centered strategies, used by clinicians alone or in combination with other health-care professionals or community programs, can be effective.
- The 5 As framework (Ask, Advise, Agree/Assess, Assist, and Arrange) provides behavioral strategies that assist patients making lifestyle changes for weight management.
- Primary care personnel can provide effective patient-centered weight management interventions such as motivational interviewing which is a patient-centered intervention based on social cognitive that has some but limited evidence of its success in achieving dietary and physical activity behavior changes and treating obesity.
- Although primary care obesity research is in its infancy, sufficient data are available to conclude that both conventional (calorie restricting) and behaviorally based approaches can lead to clinically significant weight loss in individuals.
- Challenges remain in preparing physicians and their offices to be aware of and adopt effective strategies as well as making weight management accessible and affordable to larger numbers of adults and children.
- The 5 As is one framework primary care physicians can use to deliver obesity counseling.
- There is great potential for community approaches and technology that are linked with primary care that has yet to be realized.

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Virtually all reports that call for comprehensive action to stop the obesity epidemic include a list of recommendations or strategies for different sectors. For example, the 2001 Surgeon General Report called for actions by (1) families and communities, (2) schools, (3) health care, (4) media and communication, and (5) worksite [1]. Interventions and activities are outlined for each setting to address the national obesity epidemic. Subsequently many states developed state plans that included more detailed strategies. The health-care community is called on to train providers in effective prevention and treatment techniques. State plans, like the one from North Carolina [2], call on the health-care community to be involved both in assisting individuals achieve and maintain a healthy weight and also in creating environments and policies that enable individuals to carry out their personal health prescriptions. The North Carolina plan calls for the establishment of policies and practices to offer counseling and behavioral interventions for adults identified as obese and would include strategies like US Preventive Services Task Force (USPSTF) recommendation that all adults are screened for obesity and those with a BMI > 30 kg/m$^2$ be offered or referred to an intensive multicomponent behavioral intervention [3]. The calls to action are needed because a variety of physician factors contribute to the gap between current practice and optimal management of adult and pediatric obesity in the United States. Those factors include but are not limited to lack of knowledge, satisfaction, and confidence in treating obesity; lack of time, reimbursement, resources, and support; and pessimism about patients' adherence to and efficacy of treatment [4–6]. Fortunately there is a growing evidence base of patient-centered strategies for effective weight management that clinicians can use alone or in combination with other health-care professionals or community program. Treatment of obesity in primary care is still in its infancy. Even so, Yanovski [7] in a commentary on obesity treatment in primary care suggested that more than a third of patients may respond to lifestyle counseling with a weight loss of up to 5 % of their baseline weight. While some are pessimistic about the efficacy of treatment, Wadden and coworkers report that weight loss does occur with lifestyle modification and even when followed by weight regain can be beneficial to long-term health [8]. Lifestyle or behavior counseling may not be sufficient for all obese individuals. Some patients will require additional treatment (e.g., medication or surgery) as an adjunct but not a replacement for lifestyle interventions [8].

The average weight loss individuals achieved, even in well-controlled clinical trials, is usually modest [9]. Even so, in most trials using conventional approaches like restricting calories or increasing physical activity, behavioral approaches, or a combination of approaches, many subjects achieve clinically meaningful long-term weight loss. The National Weight Control Registry [10] documents 1,000 of individuals who have lost significant amounts of weight (average >70 lb) and kept if off for long periods of time (average 6 years). So, it is clearly worth the effort to find strategies to assist more individuals in achieving sustainable weight loss, and patient-centered approaches are likely the key. The conventional approaches to weight management are detailed in other sections of this book. These approaches are appropriate and effective for some obese adults and children. This chapter will focus primarily on what is known about patient-centered strategies, especially behavioral strategies, that assist patients making lifestyle changes for weight management [11–17]. It will present these strategies using the 5 As framework recommended by the Centers for Medicare & Medicaid [15] (Fig. 32.1, Table 32.1).

## Patient-Centered Care

Patient-centered care and the patient-centered medical home emerged as a medical model in the 1970s. The Institute of Medicine [17] describes patient-centered care as providing care that is respectful of and responsive to the individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions. The patient-centered approach seeks understanding of the patient's world, finds common ground on what the problem is, and mutually agrees on management.

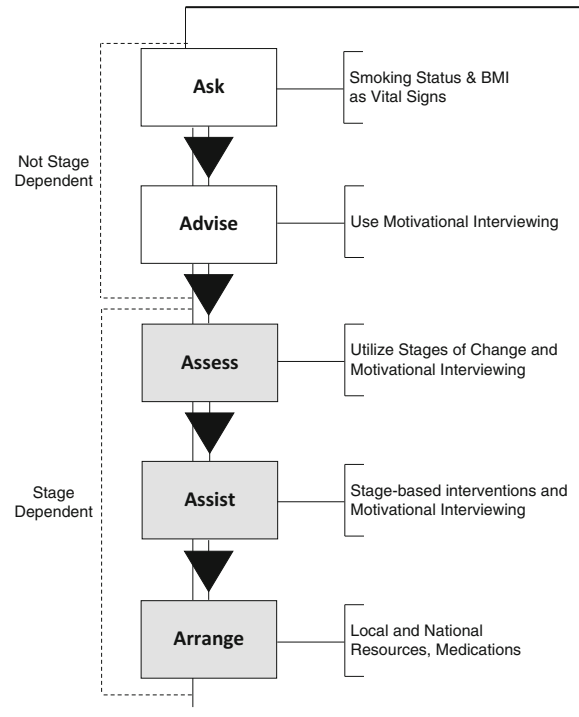


**Fig. 32.1** The 5 As framework and stages of change model. Reprinted from *Patient Education and Counseling*, development and evaluation of an instrument for assessing brief behavioral change interventions, 99–105, 2011, with permission from Elsevier

**Table 32.1** Approach for the identification, evaluation, and treatment of obesity

| | |
|---|---|
| Assess | 1. Severity of obesity with calculated BMI, measured waist circumference, and comorbidities |
| | 2. Food intake and physical activity in context of health risks and type of dietary approach patient might adhere to |
| | 3. Medications that affect weight or satiety |
| | 4. Readiness to change behavior and stages of change |
| Advise | 5. Diagnosis of overweight, obesity, severe obesity |
| | 6. Caloric deficit needed for weight loss |
| | 7. Different types of hypocaloric diets that lead to weight loss and ease of adherence |
| | 8. Appropriateness, cost-effectiveness of meal replacements, dietary supplements, over-the-counter weight aids, medications, surgery |
| | 9. Importance of self-monitoring |
| Agree | 10. If patient is not ready, promise to discuss at another visit |
| | 11. If patient is ready to change and is motivated, develop a treatment plan |
| | 12. If patient chooses diet, physical activity, and/or medication, set weight loss goal around 10 % from baseline |
| | 13. If patient is potential candidate for surgery, review |
| Assist | 14. Give patient copy of diet, physical activity guide, and behavior modification guide and identify method for self-monitoring (e.g., diary) |
| | 15. Provide web resources based on patient interest and needs |
| | 16. On follow-up, review food and activity diary |
| | 17. If the patient fails to achieve the first month goal, reassess |
| Arrange | 18. Follow-up appointments on schedule to meet patient needs |
| | 19. Referral to registered dietitian and/or behaviorist for in-depth one-on-one counseling and monitoring or weight management class |
| | 20. Refer to surgical program |
| | 21. Maintenance counseling to prevent relapse or weight regain |

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It seeks to enhance the relationship between the patient and the doctor. And it seeks to enhance prevention and health promotion [18]. A recent position statement from the American Diabetes Association and the European Association for the Study of Diabetes states there is good evidence to support the effectiveness of patient-centered care and that involving patients in health-care decision may enhance adherence to therapy [19]. Kirk and coworkers [20] reviewed lifestyle intervention studies and concluded that interventions should be designed for each patient or group of patients according to their risk factor status and the needs of the individual. Little and coworkers [21] found that patients do prefer this approach to care.

The term "medical home" was first used by the American Academy of Pediatrics in 1967 to describe the concept of a centralized source of care and record for children with special needs. For the treatment of pediatric obesity, the concept of family-centered care emerged soon thereafter. The recognition of patient-centered medical homes (pcmh) as a model for integrated health care has gained traction both in the health-care community and with the US government. This is considered a sound approach to organizing patient care that holds promise of improving the experiences of patients and staff involved in health care [22]. Since few primary care providers report gratification in counseling on diet and weight-related issues [4, 5, 23] and many patients feel they do not receive the support needed from their doctors for weight management, this is an important concept to pursue [4, 5, 23]. For recognition as a pcmh, a practice must have elements including access and communication, patient tracking and registry functions, care management, patient self-management support, electronic prescribing, test and referral tracking, performance reporting and improvement, and advanced electronic communications. A key element of the pcmh model is engaging patients and caregivers in their care. Both the prevention and treatment of obesity are opportunities for engagement [24].

There are several theories that support patient-centered counseling including but are not limited to the Consumer Information Processing Theory, Health Belief Model, Theory of Planned Behavior, Transtheoretical Model or Stages of Change Model, Social Cognitive Theory, Behavioral Self-Management, Health Belief Model, Goal Setting Theory, and Small Change Model [9, 25–27]. Each of these theories/models has strengths and limitations. Most of these theories gained prominence in substance abuse and smoking cessation work and are being adapted for defining strategies to change dietary and physical activity behaviors [9]. Health-care providers who understand the various theories will be better equipped to provide effective counseling to their patients.

## The 5 As Framework

The 5 As framework has been studied since the mid 1990s [15, 28–36]. In 2002, the Counseling and Behavioral Intervention Work Group of the USPSTF described each of the elements in the 5 As framework and then used it to report their findings about behavior counseling interventions [28]. In 2011, the Centers for Medicare & Medicaid [15] added coverage for screening and for intensive behavioral therapy for obesity (IBTO) and called for the counseling to be consistent with the 5 As [16, 31]. While researchers have used varying terms for the element, they typically stand for Ask, Advise, Agree/Assess, Assist, and Arrange (Fig. 32.1). This framework has been used for smoking cessation and thus is familiar to primary care providers but not generally applied to weight counseling. Gudzune et al. [35] engaged primary care physicians whose patients were enrolled in a weight loss trial in a focus group study to learn how physicians were communicating with their patients about weight loss. They found that many physicians, even without training, were using some patient-centered strategies in the counseling but that they could make improvements to enhance their effectiveness. Similar findings can be derived from Scott and coworkers' efforts examining ways physicians communicate with patients about weight management [37]. Several researchers suggest that training physicians in this type of counseling would improve obesity care [16, 31]. Alexander and coworkers [13] found that

83 % of physicians used at least one of the 5 As in encounters with obese adults but only about 5 % complete all five steps. Studying advice physicians give patients about fat and fiber to reduce cancer risk, Sciamanna and coworkers [38] found that physicians "asked" 42 %, "assessed" 34 %, "advised" 54 %, "assisted" 39 %, and "arranged" 22 % of the time, respectively. It's been suggested that physicians in a busy office practice may need to plan to complete the 5 As over a series of visits, although the effectiveness of doing so has not been studied. Some observers have suggested that the 5 As may be impractical for office-based practice if the implementation relies solely on the physician [33]. In team-based care, then, all members of the team need to be trained in using the framework for counseling. Taft and coworkers [36] demonstrated how dietitians might use of the 5 As in counseling children and families for obesity and cardiovascular risk reduction. Good examples of how to apply the 5 As to obesity management have been published [16, 36, 39]. Strayer and coworkers [34] took an additional step of describing how three behavioral change theories and strategies, the 5 As and Stages of Change or Transtheoretical Model (pre-contemplation, contemplation, preparation, action, or maintenance), can be combined for brief behavior change interventions (Fig. 32.1).

## Ask and Advise

In one how-to guide on delivering traditional obesity counseling using the 5 As framework [16], it is recommended that clinicians ask the patient's permission to discuss weight. "Ask" and "Advise," which are not stage dependent, are the constructs most often reported by the patient or documented in the chart [30, 31, 38]. Sciamanna and coworkers [38] noted that physicians who practice specific dietary behaviors like eating vegetables and fruits are more likely to "ask." So, the calls for physicians to be healthy role models are relevant to this discussion as well. Researchers report that clinicians often skip assessing the patient's readiness to change, yet it has been demonstrated that doing so helps identify the patients at advanced stages of behavior change for weight loss, diet, or exercise who would most benefit from counseling [40–42]. And while the USPSTF [43] concluded there was only small evidence to support initiating behavioral counseling in primary care settings to reduce cardiovascular disease, it did state clinicians could selectively counsel patients depending on factors including risk for disease and readiness to change. Perhaps clinicians should use brief tools to assess readiness since, earlier, Pignone and coworkers [44] concluded there was evidence that brief counseling of even unselected patients in primary care could produce small changes in intakes of fruits and vegetables and saturated fat although they were unsure of its impact on health. There are tools to guide the assessment of readiness [45]. It's been reported that knowing if a patient has been told to lose weight might also help identify patients that should receive behavioral counseling since they are more likely to be in a greater state of readiness [46]. When patients are in the pre-action stages of pre-contemplation, contemplation, and preparation, it is thought that the use of motivational interviewing (MI) [47], discussed later in this chapter, may be effective. As part of this step, a major theme is "motivating" patients to lose weight [35]. Other important issues to cover include praise and acknowledgment for weight loss success, the impact of weight loss on the patient's specific comorbidities, frustrations, and personal weight loss stories [35]. Efforts to improve patients' self esteem and self-efficacy for weight loss are part of this step, as well.

While there is only limited evidence demonstrating the effectiveness of using the Stages of Change Model for changing eating behaviors, it is clearly documented that a patient can be in different stages for different behaviors. They may, for example, be in the preparation stage to eat one more serving of fruit a day but in the pre-contemplation stage for reducing intake of sugar-sweetened beverages. The available evidence suggests that as an individual progresses successfully through stages of change for any food or beverage, his or her knowledge of food and nutrition and attitudes toward change improve.

Helping the patient identify the changes in their behavior that will most likely impact weight is critical at this stage. The Diabetes Prevention Program Lifestyle Manual at http://www.bsc.gwu.edu/dpp/index.htmlvdoc provides tools for implementation. In a patient-centered approach, even when the advice is the conventional calorie restriction, personalization of the advice to the patient's symptoms, values, and concerns of the patient will increase its likelihood of being successful. There are reports that patients given advice that leads to a caloric deficit may lose more weight than those given a specific calorie goal. For example, in one study, nurses were more successful in weight loss attempts if they did not use a specific diet regimen [48]. Tate and coworkers [49] demonstrated that making just one change, the replacement of caloric beverages with non-caloric beverages as a weight loss strategy, can lead to weight loss. Their participants averaged weight losses of 2–2.5 % over 6 months and suggested that adherence was better when the plan replaced beverages with non-caloric sweetened alternatives rather than just with water.

Since the 1990s there has been a movement toward the use of the non-dieting approach based on the premise that "diets don't work" [50, 51]. The available data suggest that "Healthy at Every Size" and other non-dieting efforts improve self esteem and body image; they don't result in weight loss [52]. By contrast recent studies of "small changes" and "mindfulness" are beginning to demonstrate that these approaches can lead to long-term changes in lifestyle. The small changes approach that is small reductions in conscious energy intake (100 cal per day) and increases in physical activity (2,000 steps per day) can lead to permanent weight loss at least in the group setting [9, 27]. While it would seem that this approach would work for at least some patients in the primary care setting, it is unclear what type of support is required to achieve and maintain weight loss.

Computer-tailored education is another strategy that has shown promise for identifying dietary behaviors such as increasing fruit and vegetable consumption and decreasing fat reduction that could assist a patient in weight loss without "counting calories"; however, the effect size is small [53, 54]. For clinicians embracing the small change model, using computer-tailored messages to may be an appropriate strategy for generating patient-centered prescriptions in the Assist step of 5 As. The first generation of computer-tailored education used patient kiosks or stand-alone computers to generate a report or pamphlet based on questions answered by the patient. The second generation (e.g., websites, e-mail) and third generation (mobile/remote) will be described later in this chapter.

## Agree/Assess

Goal setting is an important strategy in the Agree/Assess step of the 5 As. Goal setting has shown promise as a tool that can be successfully incorporated into weight reduction programs [55]. The clinician works collaboratively with the patient to determine if they will use a conventional, behavioral, or combination approach to weight management. Gudzune and coworkers [35] found physicians were able to partner with patients to achieve weight loss by helping patients realize they already have skills needed to lose weight, collaborating to set goals and plans, and establish a relationship with the patient as a foundation for further weight loss discussion. In the behavior approach the patient and clinician identify behavior and self-management goals, usually setting small goals, one at a time. Errickson and coworkers [26] use the SMALL mnemonic to describe patient-centered goals: *S*—self-guided and focused on behaviors that are negotiable; *M*—measurable so the patient knows the goal has been achieved; *A*—action-oriented and includes steps to make the goal a reality; *L*—linked to your life or within your lifestyle and matches challenges and strengths; and *L*—long term or something the patient can feel confident about maintaining. Small Change Model researchers acknowledge that one small change will not promote weight loss, but the accumulation of many small behavior changes that patients believe they can maintain over a lifetime could lead to gradual and significant

weight loss. The ASPIRE pilot demonstrated the potential for patients to sustain weight loss in this manner, over time [27].

There are several other mnemonics used to set goals including "SMART" and "WHAT." A SMART goal is a goal that is specific, measurable, achievable, realistic, and timely [56, 57]. Setting a SMART goal and assessing the patient's confidence in meeting this goal may be an effective way to conclude a patient-centered visit. This mnemonic stands for S—specific, significant, and stretching; *M*—measurable, meaningful, and motivational; *A*—agreed upon, attainable, achievable, acceptable, and action-oriented; *R*—realistic, relevant, reasonable, rewarding, and results-oriented; and *T*—time-based, timely, tangible, and trackable. For example, a patient after reviewing her dietary record and assessing the challenges she faces to following her weight management plan agrees to add at least one serving of non-starchy vegetables to her lunch on at least 5 days of the week to help improve satiety. The patient rates her confidence in her ability to meet this goal as a "9" on a "1–10" scale with "10" being "extremely confident." Constance and Sauter [58] write about inspiring and supporting behavior change using the "WHAT": *W*—what, when, and where the patient will; *H*—how much, many, and often; *A*—achievable and believable; and *T*—time frame for accomplishing the goal.

## Assist

This is the step where the patient receives the counseling. There are several tools, developed for conventional obesity counseling, that include elements of patient-centered counseling, available for use in primary care. The Nutrition Academic Award Program (www.nhlbi.nih.gov/funding/training/naa/index.htm) developed, tested, and shared useful tools including WAVE (Weight/Activity/Variety/Excess) and REAP (Rapid Eating and Activity Assessment for Patients) [59]. Many medical school nutrition curricula include instruction in the use of these tools for both assessment and counseling in the office setting. They are patient-centered tools when used to tailor the advice for the patient based on the dietary intake and physical activity reported by the patient. For efficiency, however, many counselors have prioritized the behaviors most often seen in their practice that contribute to weight management. For example, Schlair and coworkers [16] use the mnemonic "SERVE" to guide providing dietary advice that is evidence-based and most likely representative of behaviors of most overweight and obese Americans. They recommend counseling related to *S*—sugar-sweetened beverages; *E*—exercise habits; *R*—regularity of meals, especially breakfast and restaurant use; *V*—vegetable and fruit-rich diet; and *E*—eating less or portion size. These messages, however, need to be tailored to the individual if they are to be effective.

Several studies demonstrated that training physicians to provide brief, specific lifestyle strategies is effective in helping facilitate patients' behavior change [38, 46, 60–63]. Clinical tools that physicians can review and adopt are increasingly available. Examples include Obesity Provider Toolkits from the California Medical Association Foundation (www.thecmafoundation.org) and the Clinical Tools from North Carolina's *Eat Smart Move More* program (www.eatsmartmovemorenc.com). These kits reference evidence-based guidelines from organizations including but not limited to the National Heart Lung and blood Institute, the Academy of Nutrition and Dietetics (formerly the American Dietetic Association), the American College of Physician, the American Heart Association, and the American Academy of Pediatrics.

Physicians do complete the ASSIST step and at least sometimes work with their patients to handle the challenges that arise as part of weight counseling [35]. For example, they may work to temper expectations toward accomplishable goals, use standard messages to discuss weight loss, and reframe the discussion to focus on health rather than weight. But even those clinicians who employ patient-centered strategies do not use them all the time [36].

**Table 32.2** Staging and weight management for adults in primary care

| | |
|---|---|
| Stage 1 (Prevention Plus): counsel to prevent further weight gain (5–10 min) | • Give BMI assessment in context of chronic disease risks<br>• Give calorie goal<br>• Give consistent evidence-based food and beverage messages—regardless of BMI status of patient<br>• If overweight, give simple evidence-based strategies:<br>– Decrease sugar-sweetened beverage intake<br>– Decrease TV time to <2 h/day; none in bedroom<br>– Prepare/eat more meals at home<br>– Decrease portion sizes (100–500 cal)<br>– Increase physical activity 60 min/day (10,000 steps)—for weight loss need 90 min<br>– Increase fruits and vegetables intake to 9 per day<br>– Eat breakfast<br>– Sleep at least 6.5 h but no more than 9 h per day<br>– Monitor weight/keep food diary<br>– Refer to programs/dietitian |
| Stage 2 (Structured Weight Management): treatment to lost weight | • Calculate caloric need and set appropriate weight loss goal<br>• Counsel with evidence-based dietary approach. Be skilled in 1–2 plans (e.g., DASH, lower CHO or whole foods, plate approach for patients with diabetes)<br>• Follow up as frequency and intensity negotiated with patient<br>• Refer to registered dietitian (as appropriate) |
| Stage 3 (Comprehensive Multidisciplinary Intervention): treatment by colocated interprofessional team | • Same initial steps as Stage 2 but provided by most appropriate personnel for effort<br>• Measure rather than calculate energy needs<br>• Use as appropriate:<br>– Very low calorie (VLD)<br>– Over-the-counter medications/dietary supplements<br>– Prescription medications<br>– Trainer for physical activity<br>– Telephone/Internet/mobile device monitoring |

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Patients report physicians who do suggest weight loss do not provide specific enough strategies that they can act on [4, 63]. Too often physicians who embrace the concept of evidence-based practice for their specialty are either unaware or ignore the nutrition evidence when counseling patients about diet and physical activity [23]. Physicians need to determine the nutrition and obesity prevention and treatment messages they have time and skill to provide their patients. The Expert Committee for Childhood Obesity in Primary Care outlined stages for treatment: Stage 1 Prevention Plus where the pediatrician provides guidance on healthy eating and physical activity to improve BMI for overweight or obese patients and maintain BMI for those in normal range; Stage 2 Structured Weight Management where the pediatrician additional support from a dietitian or others delivers a specific plan for diet and physical activity, systematic monitoring, and planned reinforcement; Stage 3 Comprehensive Multidisciplinary Intervention where the pediatrician coordinates components, which might include a weight management center, commercial program, counseling, physical therapist, and others with structured behavior modification program and frequent monitoring; and Stage 4 Tertiary Care Intervention for patients who have been unsuccessful with other methods, a weight management center with a multidisciplinary team that might also employ medications, a very low-calorie diet, or bariatric surgery [63]. Table 32.2 depicts how this staging might be applied to adult weight management in primary care. Primary care offices that have only the resources to be Stage 1 or Stage 2 will provide

the best patient care may be handing the patient off to others with training or experience in weigh management or to worksite wellness programs. IBTO for patients with Medicare can be provided incident to a physician when provided in primary care [15]. Dietitians are among the health-care providers that have experience in delivering both behavioral and conventional obesity care. In 2012, the Family Medicine practice at East Carolina University (ECU) embraced the opportunity to provide IBTO. It designed a protocol that embeds the dietitian and a behaviorist in the practice of a group of family physicians with added certification in geriatrics. On collaboration continuum that ranges from minimal (level 1) to a close, fully integrated system (level 5), the ECU implementation has some elements of level 3 and some of level 4. The services, as required by CMS, are colocated. There is a shared electronic medical record and a basic appreciation for the role of each professional in treating the obese patient; communication is sometimes face to face; and there is shared influence. The model is more than collaborative but has not yet achieved the full status of integrative. With the current reimbursement structure, a fully integrative practice is unlikely. In this case, the primary care physician identifies the patients that would benefit from IBOT and, after a discussion with the dietitian, signs a contract to follow a weight management program of up to 20 visits starting with weekly visits and moving to less intensity.

Obesity management can be provided in different ways even within a single practice. For example, at ECU's Department of Family Medicine, a recognized National Committee for Quality Assurance (NCQA) Level 3, patient-centered medical home, physicians have varying skills and interests in personally counseling patients about weight management. Not all patients have access to IBTO, in part because of reimbursement issues. For its NCQA application the ECU practice chose three conditions to monitor: heart disease, stroke, and kidney disease. To ensure patient education for all patients with these conditions, the practice created a patient report card called "Stay Healthy—Know Your Numbers" that included providing the patient with his or her blood pressure, LDL, cholesterol, hemoglobin $A_1C$, and body mass index (BMI) (Fig. 32.2). The physicians work with their patient to set goals for each of that measure such as working toward a BMI less than 30 mm/kg$^2$. Among the behaviors that patients can choose to work on are seven nutrition goals. Handouts to match those goals are available. The same was done for exercise and other health goals. The physician assesses the patient's confidence in meeting the agreed upon goal(s) is assessed. Some of the physicians encourage their patients to use one of the resources and refer the patients to a registered dietitian that works within the practice. This process has led to increased referrals to the registered dietitian in Family Medicine as well as to ECU's Pediatric Healthy Weight Research and Treatment Center. As noted by Wadden and workers [64–66], the use of specialized personnel has financial and logistical consequences for primary care practices. Unfortunately, while ECU Family Medicine and many other Family Medicine residency programs have dietitians embedded in their programs for more than 30 years, little has been published on how integration affects provider and patient satisfaction, medical costs, and clinical outcomes [23].

The Pediatric Healthy Weight Research and Treatment Center at ECU is an example of Interprofessional practice. Since 2004, the Pediatric Healthy Weight Clinic (PHWC) has provided comprehensive, multidisciplinary weight evaluations and subsequent follow-up treatment for overweight and obese children and adolescents. Providers include two physicians who rotate clinical time, and licensed registered dietitian and one master's level family therapy intern. In a typical year about 300 new patients are evaluated in a half day session. About 600 follow-up visits are provided. Some patients, especially those who would have to travel long distances, are returned to their primary care provider with a treatment plan. All providers work from an integrated care model where care is shared among all providers with a high level of collaboration before, during, and after visits [67]. Treatment plans are grounded in biopsychosocial constructs and are formulated with each team member's involvement as well as the families, thereby establishing the PHWC as a stage three or comprehensive multidisciplinary intervention. The physician spends approximately an hour with each patient at the initial visit, gathering relevant family and medical history information and providing a thorough

**My Numbers**

**My Blood Pressure:** _____ **Date:** _____
High blood pressure damages your arteries and puts too much stress on your heart.

**My LDL Cholesterol:** _____ **Date:** _____
Cholesterol is like fat in your blood. High LDL "bad cholesterol" can clog your arteries.

**My A1C:** _____ **Date:** _____
The A1C shows your average blood sugar control over the past 3 months.

**My Weight :** _____ **My BMI:** _____
**Date:** _____
BMI is a measure of body fat based on your height and weight.

**My Goals**

**My blood pressure goal:**
☐ **<130/80** ☐ **<140/90**
☐ **Other** _____

**My LDL cholesterol goal is:**
☐ **<70** ☐ **< 100** ☐ **< 130** ☐ **< 160**
☐ **Other** _____

**My Diabetes goal:**
☐ **A1C < 7%** ☐ **A1C < 8%**
☐ **Other** _____

**My BMI/weight goals:**
☐ **BMI ≤ 19-25** ☐ **BMI ≤** _____
☐ **5% weight loss target:** _____

## ECU Physicians and YOU:
### Working together to lower your risk of heart disease, stroke and kidney disease

**My Nutrition Goals**

☐ Eat more fruits and vegetables.
☐ Cut back on sugary foods and drinks.
☐ Choose low -or no -fat dairy products.
☐ Choose lean meats that are not fried.
☐ Eat non-fried fish at least 2 days a week.
☐ Eat more whole -grain foods and foods that contain dietary fiber.
☐ Do not add salt to your food. Use a salt substitute, such as Mrs. Dash.
☐ _____
☐ _____

**Handouts Given**

☐ DASH
☐ Diabetes DASH
☐ Whole foods DASH
☐ Nutrition Survival Skills for Diabetes
☐ _____
☐ _____

**Fig. 32.2** Stay healthy—know your numbers

**My Exercise Goals**

- ☐ Increase my steps by 500 each day.
- ☐ Walk for 30 minutes at least 3-5 days each week.
- ☐ Strength exercises at least 2 days each week.
- ☐ _____
- ☐ _____

**Handouts Given**

- ☐ 10,000 Steps
- ☐ Exercise at home.
- ☐ Chair Exercises
- ☐ _____
- ☐ _____
- ☐ _____

**Other Health Goals**

- ☐ Stop all tobacco products.
- ☐ Take all my medications every day.
- ☐ Bring all my medications and supplements to every visit for a bottle check.
- ☐ Keep all my appointments.
- ☐ Monitor my blood sugar at home _____ times a day.
- ☐ Monitor my blood pressure at home _____ times a day.
- ☐ Check my weight daily (Heart Failure)

**Handouts Given**

- ☐ Stop Smoking
- ☐ Blood Glucose Log
- ☐ Blood Pressure Log
- ☐ Monitoring Blood Pressure
- ☐ Daily Weight Log for HF
- ☐ Monitoring Heart Failure Symptoms
- ☐ _____
- ☐ _____

**Resources for reaching my goals:** **Reason:**

- ☐ Nutrition/Pharmacotherapy _____
- ☐ Social Work/Behavior Therapy _____
- ☐ ViQuest/Greenville Aquatics _____
- ☐ Other: _____ _____

I feel I can do this: Yes _____ Somewhat _____ No _____

I was given a copy of this agreement for my records.

We agree to work together toward reaching these goals that can lead to better health.

Patient: _____ Provider: _____

Date _____

**Fig. 32.2** (continued)

medical exam. The dietitian uses a standardized medical nutrition therapy protocol to assess the patient's food environment, eating habits, and calorie needs. In addition, the dietitian uses indirect calorimetry to determine energy needs and tailor dietary advice for pediatric patients. The PHWC was one of the first clinics to offer this service to pediatric patients. The medical family therapist is present for each initial evaluation and provides appropriate follow-up and referrals for families needing

mental health services. A fully operational pediatric dental clinic, embedded in the PHWC, provides evaluation and treatment for obese and other chronically ill children. A continuing collaboration with the ECU Physical Therapy (PT) Department aims to understand and mitigate the effects of obesity on gait and joint function in overweight adolescents. Referrals are made to the PT Department as needed based on the initial evaluation. Regular follow-up appointments with the pediatrician and dietitian are scheduled, typically at least every 3 months, and are shorter in duration. Nursing staff track height, weight, BMI, and blood pressure. The physician plots BMI percentile and assesses physical activity behaviors as part of the medical visit. The medical family therapist evaluates quality of life and depression to ensure the patient's mental health needs are being addressed during the course of treatment. The dietitian provides ongoing support and evaluation of progress related to nutrition. The dietitian as part of this integrative care model has demonstrated the ability to aid overweight youth and their families in making behavior changes that positively impacted their weight status [68].

When the potential for reimbursement (from both Blue Cross Blue Shield of North Carolina and NC Medicaid) for nutritional counseling of obese youth by primary care providers and registered dietitians became a reality, IN4Kids was initiated [69]. Silberberg and coworkers studied the model of collaborative care and co-located services issue in eight pediatric and family medicine practices [69]. This IN4Kids program was built on the successes Henes and coworkers [68] had in demonstrating that a dietitian in a pediatric practice could aid overweight youth and their families in making behavior changes that positively impacted the child's weight status. Silberberg and coworkers [69] included a study of the cost-effectiveness of embedding a dietitian in the pediatric practice. They found that the rate of referral of obese children to the dietitian varied among practices but that only about one-fifth of the patients eligible for the service were actually referred to the dietitian, too few to be cost effective. Interestingly, the physicians and staff in those practices agreed that having a registered dietitian in their practice greatly improved weight management of its patients. Their work [69] encourages primary care practices, dietitians, and patient advocates to think through and address the preconditions for successful treatment of overweight in children and integration of dietitians into primary care.

In 2012, the ECU Family Medicine practice embraced the opportunity to provide IBTO to Medicare patients. The practice designed a protocol that co-locates a dietitian and a family medical therapy counselor in the practice of a group of geriatricians. The geriatricians and the counselors have developed an appreciation for the role of each in treating obesity in this population. On collaboration continuum that ranges from minimal (level 1) to a close, fully integrated system (level 5), this ECU service has elements of level 3 and 4 and will hopefully provide cost-effective care.

Tsai and Wadden [70] note that research on the management of obesity in primary care is in its infancy. They call for further research on different models of managing obesity in primary care practice. They [70] conclude that primary care providers alone cannot be expected to provide care to all the individuals who need it.

It is beyond the scope of this chapter to explore the other models being tested but a few studies are offered as examples of other personnel such as medical assistants and coaches that might provide face-to-face counseling in primary care. Greaney and coworkers [71] conducted the "Be Fit Be Well" study in a community health center. The program was designed to overcome the barrier of provider limited time. Participants received personalized tailored behavior change prescription with the doctor's signature. The prescription targeted changing specific obesogenic behaviors that would create an energy deficit and promote weight loss. While there has been significant research demonstrating the effectiveness of tailored messaging [53], this approach has not been widely adopted in primary care as of yet. The best way to integrated tailored messaging into a busy ambulatory practice is not known. Additionally, as Sciamana and coworkers found, the clinician runs the risk of patient dissatisfaction if the patient receives a tailored plan and the physician does not review it with them [38]. Although the effect size is small, using tailored messages as part of small change model may be an effective strategy. Ma and coworkers [72] demonstrated successful adaptation of the Diabetes Prevention Program

into primary care. Intervention delivery aided by technology is discussed later in this chapter. Until reimbursement issues are addressed, wide scale adoption is not likely.

In a study where medical assistants in primary care were part of the intervention delivery, about 20 % of the patients did achieve a 5 % weight loss [65, 66]. The researchers concluded that patients may need a more intensive treatment when initiating weight loss and/or they may need care from professionals with more specialized training in obesity management.

## Arrange

At the Arrange step, the clinician and patient plan subsequent contact or referral to programs. It is important for the clinicians to be aware of and arrange for patients to participate in community-based programs since primary care-based counseling is not effective for all [70]. Alexander et al. [13] found that those who complete the Arrange step had patients with more weight loss. Jay and coworkers [73] found that the more of the 5 As patients reported receiving, the greater their motivation to lose weight and intention to change their diet. If the clinician does not assist and arrange, a patient ready to change may not receive tools needed to make the change.

Fisner and colleagues [74] make suggestions for improving practitioners' awareness of community care such as developing and distributing localized leaflets. Jolly and coworkers [75] found that commercial programs can be less expensive and more effective than primary care for the treatment of obesity. Methods for delivering cost-effective community treatment, linked to primary care, are needed. In one study of stepped care, researchers found that altering the program at 3-month intervals to match the weight loss of the participants resulted in clinically significant weight loss at a lower cost than a conventional structured program [76]. A discussion of group weight management programs is beyond the scope of this chapter; however, it's important for physicians to be aware of the effectiveness of the various programs and match the patient to the program that might work best for them.

*Alternative Delivery of Weight Loss Interventions*: Professionally delivered, face-to-face behavioral weight loss treatment is considered by many to be the state-of-the-art approach for nonmedical treatment of moderate overweight and obesity [77]. Researchers have clearly demonstrated that comprehensive lifestyle interventions delivered in this manner can lead to clinically significant and sustainable weight loss [65, 66]. These programs are typically offered in research programs or at academic health centers, thereby limiting the number of people who can be served. Researchers and program administrators are seeking methods of disseminating weight loss interventions through different modes such as telephone and Internet, making it easier and more convenient for patients [7, 78]. Additionally, consumers have expressed a desire for alternatives to clinic-based weight management interventions.

A growing body of evidence supports the utility of the Internet as a platform for the delivery of weight loss interventions [79–82]. Experimentation is ongoing to determine what components work best for which individuals (e.g., traditional caloric restriction or behavioral strategies, self-monitoring, amount of human contact, linked to primary care or linked to non-clinical settings). It is beyond the scope of this chapter to provide a comprehensive review of this body work but a few examples are offered. Hersey and coworkers [80] found a cognitive behavioral approach to weight loss can be effectively delivered through a web-based or telephonic counseling mode. Johnson and colleagues [22] demonstrated the effectiveness of tailored home-based, transtheoretically based multiple interventions for weight management.

Even though these modes of delivery are feasible, the typical weight loss experienced by participants is usually less than in face-to-face encounters [81]. Even so, many believe technology holds promise [20, 81–84]. For example, Radcliff and coworkers [84] demonstrated that patients living in rural areas receiving counseling on the telephone had similar outcomes to those who had a

face-to-face encounter in a 12-month extended-care lifestyle maintenance program after an initial 6-month weight loss program, at a lower cost. Bennett and coworkers [85] described a unique behavioral intervention that relied very little on the provider in community health center. They used tailored behavior change goals, self-monitoring, and skill training, available via a website or interactive voice response: 18 telephone counseling sessions by trained coaches; and 12 optional support sessions and links with community resources. The effort produced modest weight loss and improved blood pressure control in a high risk, socioeconomically disadvantaged patient population. Retention is a concern for these types of programs and so efforts to reduce dropout as well as improve outcomes are under way. Remote coaching, for example, supported by mobile technology and financial incentives, holds promise to improve diet and activity [83]. As one might expect at this time, the results of studies are mixed. In one pilot, text messaging had no effect on the weight of the participants but was thought to have a role in promoting adherence to lifestyle changes [86].

It would be easy to link an affordable program like Eat Smart, Move More, Weigh Less, North Carolina (ESMMWL, NC) to the office setting. The program has been delivered in physician offices, in community and worksite settings, and through real-time Internet [87]. This 15-week program, delivered through an existing infrastructure of cooperative extension service consumer science agents and public health educators, informs, empowers, and motivates participants to live mindfully as they make choices about eating behaviors and physical activity. Although no specific reduced calorie diet plan is provided, participants are asked to set a weight loss goal of no more than two pounds per week. The curriculum is based on evidence-based strategies for healthy eating, and physical activity uses the theory of planned behavior and incorporates acceptance strategies such as living mindfully. The evidence-based strategies include eating fewer calories, eating more fruits and vegetables and whole grains, eating breakfast regularly, controlling portion sizes, eating more meals at home, drinking fewer calorie-containing beverages, keeping a food/physical activity record, increasing physical activity, and watching less television. In the test of the program performance in the community setting where 1,162 individuals completed the program, most (87 %) of the completers lost weight, averaging 8.4 lb. They reported changes in confidence to change eating behaviors and physical activity. In the test of performance as a worksite wellness program that included an incentive for completing the program, 1,341 (141 sites) had significant reductions in their BMI and waist circumference and increased significantly their confidence in eating healthfully and being physically active. Almost all participants reported being more mindful of what and how much they ate, being more mindful of how much daily physical activity they got, and eating fewer calories.

While this network of instructors allows for wide dissemination of ESMMWL NC through an existing infrastructure that keeps the price to participants affordable, the program developers wanted to test the performance delivering the program to an even wider audience using real-time, online synchronous, distance-education technology. Health educators and dietitians are the instructors and are skilled in using online teaching platforms to deliver the program. The platform used is Elluminate Live! [88] which has interactive features such as chat box, polling, “raise hand,” “emoticons,” “green check,” or “red cancel” which the instructors use to add interactivity during the sessions. It is hoped that this approach will address some of the reasons Internet programs have high dropout rates. Results from the first 250 participants to complete the program were positive and similar to weight, blood pressure, and healthy eating and physical activity behavior outcomes obtained in the face-to-face programs described earlier. This type of program became available to individuals regardless of their location at eatsmartmovemoreweighless.com. Efforts are under way to encourage physicians to refer patients to this program and additional efforts to obtain reimbursement from third-party payers for completion of the program. The program developers believe that this type of program can be effective for individuals with moderate obesity. However, Blackburn [81], in an editorial, expressed great optimism for the potential of mobile technologies to deliver intensive medical treatment of severe obesity, which includes lifestyle interventions when used along with very low-calorie diets. Riley [82],

too, believes that technology may impact individuals with multiple risks for chronic disease but suggests it remains to be seen if these advances will improve outcomes, reduce costs, or both.

Participants in programs such as Weight Watchers have been shown to have greater weight loss than in some primary care-based programs [89]. Some primary care providers recognize their offices are not structured in a way that they can provide weight loss counseling, and therefore, they refer patients to programs like Weight Watchers, especially if the patients do not have insurance or other access to registered dietitians for one-on-one counseling. Interestingly, while many obesity researchers are exploring behavioral therapies, a clinical trial of the Weight Watchers program found no benefit to adding a brief behavioral treatment to its standard program [89]. For patients that find the Weight Watchers approach effective, the key ingredients may be buddying up and group counseling. On the other hand, the ESMMWL NC face-to-face group counseling program, which did encourage buddying, too, found the behavioral approach, rather than a conventional dieting approach, led to success for the majority of its participants [51, 87]. This reminds us, as does the work by Gokee et al. [90] that found young people don't respond to conventional approaches, that a single approach will not meet the needs of all individuals. More research is needed to see what will work with various groups and to understand the barriers patients face in participating in community care [91].

## Additional Thoughts on the 5 As

A joint statement from several councils of the American Heart Association [33] described tools and strategies they believed were practical in busy ambulatory care settings. They categorized the strategies as (1) appropriate ways of discussing body weight with patients, including readiness to change; (2) approaches that involve multidisciplinary collaboration among health-care professionals; and (3) strategies that make use of information technology to deliver weight management programs. These strategies can all be incorporated into the 5 As framework.

Both researchers and clinicians need for greater understanding of the challenges of behavior change and all the factors that play a role (e.g., readiness for change, motivation, ability, confidence, peer and family influence, awareness of habits, support, environment, resources, access). For example, there are few reports on what works in minority nonwhite groups [95], although those that are published do support the effectiveness of a variety of dietary and lifestyle-based weight loss approaches. Mexican Americans and African Americans have been shown to benefit from culturally tailored treatment, but little is known about the response of Asians to different weight management approaches [92].

There is a need for greater understanding of the process of changing eating behaviors. It is well known that gaining nutrition knowledge to change behaviors is insufficient to guarantee behavior change. It appears that awareness of risks related to current behaviors is not sufficient to sustain long-term eating and physical activity behavior change for most adults. More needs to be known about how comprehending the benefits of behavior change and substituting alternatives for current behaviors affect weight management. There are data that describe the value in enlisting social support, rewarding self, and making a commitment to healthy eating and weight management, but even for these process factors, more needs to be known to use for effective weight management counseling.

## Motivational Interviewing

Motivational interviewing (MI) is a patient-centered intervention based on social cognitive theory. This is a non-confrontational/partnership approach that may be more difficult to practice than busy clinicians are willing or able to do. It involves expressing empathy, doing reflective listening,

developing discrepancies, creating a gap between current behavior and goals and cultivating motivation for change, rolling with resistance, while inviting the patient to consider a new perspective and supporting self-efficacy [47, 93, 94]. There is some but limited evidence of its success in achieving dietary and physical activity behavior changes and treating obesity [95–101]. In a small observational study, use of motivational interviewing techniques during weight loss discussions predicted patient weight loss [95]. DiLillo and West [100] provide an overview of motivational interviewing specific to weight loss and weight maintenance. They acknowledge that weight management is a new application for MI, especially when delivered by health-care providers to promote weight loss. They describe the work that shows the addition of MI to behavioral weight loss programs may have added benefit but also acknowledge that the feasibility and effectiveness of incorporating into real world settings needs study [100, 101].

Anshel and coworkers [102] demonstrated that using motivational interviewing techniques with male police officers resulted in weight loss and adherence to lifestyle changes. In their study, officers created an action plan that included a time management schedule that created a structure for at least three exercise sessions per week, desirable eating habits, and other changes in routines to impact weight and lipid levels. These approaches are patient-centered because the patients self-monitor the food and activity. Patients set their own goals, usually one at a time.

McDoniel and coworkers [103] sought to enhance MI with technology but found the treatment programs both with and without technology were successful for completers. We need to understand more fully how to help participants "complete." Since studies demonstrate conflicting results, they raise the question about the amount training and experience needed to ensure MI skill development that improves counseling interactions. In one study [104] the relationships of five MI techniques in 320 encounters were observed. In encounters that averaged between 19.4 and 23.0 min, the duration of the talk about weight was 3.3 min. During that time motivational interviewing spirit was present only 12 % of the time and empathetic statements were present only 6 % of the time. Open-ended questions were present and reflections were present 38 % of the time, each. Rohrer and coworkers [105] suggest that physicians and dietitians, even when trained, may not be able to deliver MI related to weight management with fidelity. They suggest that a health coach might be the appropriate team member to do so. However, for pediatric patients, Schwartz and coworkers [106] found it feasible for a pediatrician and a dietitian in office-based practice to use MI although they both felt they needed more training. Even so, patient satisfaction was high. The use of MI in office-based practice for effective weight management deserves further study. Schwartz [107] provides a description of the spirit, principles, and tools, including a script demonstrating how to talk with families about eating behaviors. Many busy clinicians are skeptical that more than the spirit of MI will be broadly incorporated into practice since the rather straightforward 5 As approach has yet to be widely adopted in a busy ambulatory setting.

Recognizing that time constraints may hamper the busy clinician from using the classic MI approach for weight management, the use of the mnemonic FRAMES developed for substance abuse has been suggested [108]: *F*—feedback or discussing the results of a readiness to change assessment; *R*—discussing personal responsibility; *A*—advice or giving professional recommendations for initial behavior change; *M*—menu or discussing a list of options; *E*—empathy or stating an understanding of the patient's stated and unstated responses; and *S*—self-efficacy or promoting an optimism that the patient "can do it."

Regardless of the behavioral approach to counseling take, it is generally accepted that nagging, preaching, talking and not listening, telling the patient what to do, labeling the patient noncompliant, and getting engaged in a power struggle are not patient-centered and will not motivate a patient to manage their weight.

## Clinical Care and the Socioecological Model

It is important to place the interaction between physician and patient in the context of the socio-ecological model. The Center for Disease Control's Division of Nutrition, Physical Activity, and Obesity (www.cdc.gov/) has funded many states to address the problems of obesity and other chronic diseases in efforts coordinated with multiple partners. The CDC's program is intended to improve the health of Americans by changing environments where people live, work, learn, pray, and play. Action to change environments and policies to support healthy eating and physical activity is happening in states even without CDC funding. Physicians should become aware of, support, implement as appropriate, and build on the recommendations for their locale. The North Carolina state plan [2] includes a section specific for health-care providers noting that they can be powerful advocates and should work for healthy eating environments including vending in health-care worksites (e.g., hospitals, clinics). As community leaders, physicians should advocate for healthy eating environments for all sectors of their community and facilities for physical activity. In their own clinical environments, health-care providers can build on the work done by community-based coalitions that have identified evidence-based strategies appropriate for their own locale.

## Conclusion

Primary care personnel can provide effective patient-centered weight management interventions. Although primary care obesity research is in its infancy, sufficient data are available to conclude that both conventional (calorie restricting) and behaviorally based approaches can lead to clinically significant weight loss in individuals. Challenges remain in preparing physicians and their offices to be aware of and adopt effective strategies as well as making weight management accessible and affordable to larger numbers of adults and children. The 5 As is one framework primary care physicians can use to deliver obesity counseling. There is great potential for community approaches and technology that are linked with primary care that has yet to be realized.

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# Appendix: Helpful Websites

## Calculators

**Body Mass Index Calculators:**

- Centers for Disease Control and Prevention: www.cdc.gov/nccdphp/dnpa/bmi
- National Heart, Lung, and Blood Institute: www.nhlbsupport.com/bmi

**Energy Requirement Calculators:**

- USDA: http://fnic.nal.usda.gov/dietary-guidance/interactive-tools/calculators-and-counters

**GrowthCharts:**

- http://www.pdacortex.com/STAT_Growth_Charts_Download.htm
- http://www.healthychildren.org/english/tips-tools/pages/default.aspx#growth-charts

## Fitness and Exercise

- http://www.fitness.gov/

## Food Intake and Exercise Tracking

- Calories-Count: www.caloriescount.com
- Calorie King: www.calorieking.com
- FitDay: www.fitday.com
- Self Nutrition Data: http://nutritiondata.self.com/
- SUPERTRACKER: https://www.supertracker.usda.gov/
- MY Fitness Pal: http://www.myfitnesspal.com/food/calorie-chart-nutrition-facts
- Shape Up America: http://www.shapeup.org/index.html

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## General Information

**Academy of Nutrition and Dietetics:**

- Website: www.eatright.org
- Evidence Analysis Library: www.andevidencelibrary.com
- Adult Weight Management Evidence-Based Nutrition Practice Guidelines: http://www.andevidencelibrary.com/topic.cfm?cat=2801
- Evidence-based publications and toolkits: www.andevidencelibrary.com/store.cfm (access limited to registered users)

## Government Websites

- Centers for Disease Control and Prevention: Overweight and Obesity: www.cdc.gov/obesity/index.html
- Dietary Reference Intakes: www.fnic.nal.usda.gov
- Institute of Medicine: www.iom.edu
- MedlinePlus: www.medlineplus.gov
- Nutrition.gov WeightManagement: www.nutrition.gov/nal_display/index.php?info_center=11&tax_level=1&tax_subject=390
- Portion Distortion: http://hp2010.nhlbihin.net/portion/
- USDA food and Nutrition Information Center: http://fnic.nal.usda.gov/
- Weight Control Information Network: http://win.niddk.nih.gov/index.htm

## Other

- Obesity Society: www.obesity.org
- WebMD Weight Loss Clinic: www.weightloss.webmd.com

## Interviewing and Patient Education

- Motivational Interviewing: www.motivationalinterview.org
- Nasco Nutrition Teaching Aids: www.eNasco.com
- Menu Planning: http://hp2010.nhlbihin.net/menuplanner/menu.cgi

## Integrative and Functional Medicine Resources

- American College for the Advancement of Medicine www.acam.org
- Dietitians in Integrative and Functional Medicine www.IntegrativeRD.org
- National Center for Complementary and Alternative Medicine http://nccam.nih.gov
- The American Board of Integrative Medicine http://www.abpsus.org/integrative-medicine

- The American Board of Integrative and Holistic Medicine http://integrativeholisticdoctors.org/
- The Bravewell Collaborative http://www.bravewell.org/current_projects/consortium/
- The Center for Mind-Body Medicine http://www.cmbm.org/
- The Institute for Functional Medicine www.functionalmedicine.org
- *The Consortium of Academic Health Centers for Integrative Medicine http://www.bravewell.org/current_projects/consortium/

*Forty-five leading medical schools in North America currently belong to the Consortium of Academic Health Centers for Integrative Medicine:

**Albert Einstein College of Medicine of Yeshiva University**
Continuum Center for Health and Healing
Roberta Lee, MD, Medical Director

**University of Alberta**
Complementary and Alternative Research and Education
Sunita Vohra, MD, MSc, Director

**University of Arizona**
Program for Integrative Medicine
Victoria Maizes, MD, Executive Director

**Boston University School of Medicine**
Program in Integrative Cross Cultural Care
Robert Saper, MD

**University of Calgary**
Canadian Institute of Natural and Integrative Medicine
Badri G. Rickhi, MD, Director

**University of California, Irvine**
Susan Samueli Center for Integrative Medicine
John Longhurst, MD, Director

**University of California, Los Angeles**
Collaborative Centers for Integrative Medicine
Emeran Mayer, MD, Professor of Medicine, Physiology and Psychiatry

**University of California, San Francisco**
Osher Center for Integrative Medicine
Margaret Chesney, PhD, Director

**University of Illinois at Chicago School of Medicine**
Keith Block, MD

**University of Chicago Pritzker School of Medicine**
North Shore University Health System
Leslie Mendoza Temple, MD, Director

**University of Cincinnati School of Medicine**
Michelle Zimmer, MD

**University of Colorado at Denver School of Medicine**
The Center for Integrative Medicine
Lisa Corbin, MD, Medical Director

**Columbia University**
Richard and Hinda Rosenthal Center for Complementary and Alternative Medicine
Fredi Kronenberg, PhD, Director

**University of Connecticut Health Center**
Programs in Complementary and Integrative Medicine
Mary Guerrera, MD, FAAFP, Director

**Duke University**
Duke Integrative Medicine
Adam Pearlman, MD, Director

**George Washington University**
Center for Integrative Medicine
John C. Pan, MD, Director

**Georgetown University**
School of Medicine, Kaplan Clinic
Aviad Haramati, PhD, Director of Education, Department of Physiology and Biophysics

**Harvard University**
Osher Institute
David Eisenberg, MD, Director, Division for Research and Education in Complementary and Integrative Medical Therapies

**University of Hawaii at Manoa**
Program in Integrative Medicine
Roseanne Harrigan, Ed.D, Director

**Johns Hopkins University School of Medicine**
Anastasia Rowland-Seymour, MD
Gerard E. Mullin, MD, Director of Integrative GI Nutrition Services
The Johns Hopkins Center for Integrative Medicine and Digestive Health
Linda A. Lee, MD, Director

**University of Kansas**
Program in Integrative Medicine
Jeanne Drisko, MD

**Laval University**
Integrated Approach in Prevention
Sylvie Dondin, MD

**University of Maryland**
Center for Integrative Medicine
Brian M. Berman, MD, Director

**University of Massachusetts**
Center for Mindfulness
Saki Santorelli, PhD, Director

**Mayo Clinic College of Medicine**
Brent A. Bauer, MD, Director, Complementary and Integrative Medicine Program

**McMaster University**
Family Practice Centre of Integrative Health and Healing
Esther Konigsberg, MD

**University of Michigan**
Integrative Medicine
Sara L. Warber, MD, Co-Director, Integrative Medicine Program/Co-Director, Complementary & Alternative Medicine Research Center

**University of Minnesota**
Center for Spirituality and Healing
Mary Jo Kreitzer, PhD, RN, Director

**University of Medicine and Dentistry of New Jersey**
Institute for Complementary & Alternative Medicine
Adam Perlman, MD, MPH, Executive Director

**University of New Mexico**
Health Science Center
Arti Prasad, MD, Director

**University of North Carolina at Chapel Hill**
Program on Integrative Medicine
Susan Gaylord, PhD

**Northwestern University Feinberg School of Medicine**
Northwestern Memorial Physician's Group Center for Integrative Medicine
Melinda Ring, MD, FACP

**The Ohio State University**
Center for Integrative Medicine
Glen Aukerman, MD, DABHM

**Oregon Health and Science University**
Women's Primary Care and Integrative Medicine Center for Women's Health
Anne Nedrow, MD, Director

**University of Pennsylvania**
Office of Complementary Therapies
Alfred Fishman, MD, Director

**University of Pittsburgh**
Center for Integrative Medicine
Ronald Glick, MD, Medical Director

**Stanford University**
Stanford Center for Integrative Medicine
Emily Ratner, MD

**University of Texas Medical Branch**
UTMB Integrative Health Care
Victor Sierpina, MD, Associate Professor, Department of Family Medicine

**Thomas Jefferson University**
Jefferson Myrna Brind Center for Integrative Medicine
Daniel Monti, MD

**Vanderbilt University**
Vanderbilt Center for Integrative Health
Roy Elam, MD

**University of Vermont**
Program in Integrative Medicine
Philip Trabulsy, MD

**Wake Forest University**
Holistic and Integrative Medicine
Kathi Kemper, MD

**University of Washington**
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