Treatment of the Obese Patient

Second Edition

Robert F. Kushner
Daniel H. Bessesen
Editors

Springer

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Preface to Second Edition

Since the publication of the first edition of *Treatment of the Obese Patient*, the US population prevalence rates for obesity in youth and adults have appeared to level off but remain unacceptably high, signifying the ongoing challenge of tackling obesity as a public health problem. Clinically, the recognition of obesity as a disease by the American Medical Association and other organizations has brought increased focus on the need to provide a range of medical interventions to advance obesity treatment and prevention. Scientifically, multiple advances have occurred that deepen our understanding of appetite regulation and the pathophysiology of obesity and its associated complications. These challenges and progress in knowledge of the complexity of obesity have prompted us to edit a second edition of this book.

Continuing what we believe is the practical format of the first edition, we chose to retain the two major sections for the book: Part I addresses physiology and pathophysiology while Part II focuses on clinical management. Part I has been fully expanded to ten chapters to capture the exciting developments in the science of obesity. Only two of these chapters, Neuroregulation of body weight (Chap. 1) and Gut hormones and the regulation of body weight (Chap. 3) provide updates from the first edition. The other eight chapters are entirely new and the topics covered were chosen to update readers on the latest advancements in the fundamental aspects of obesity and its complications. Chapter 2 reviews the hedonic neural pathway responsible for reward, reinforcement, and impulsivity. The critical importance of the perinatal period in development of obesity is addressed in Chap. 4. Three new exciting areas of obesity research that have evolved over that past 5 years, the importance of the gut microbiome, the role of brown adipose tissue, and the impact of restricted sleep time, are fully covered in Chaps. 5, 6, and 8, respectively. In Chap. 7 we turn our attention to the physiological adaptations that occur with weight loss and make weight maintenance difficult for our patients. Finally, the last two chapters in Part I address two topics that are particularly relevant to the practicing clinician, the pathophysiology of nonalcoholic fatty liver disease (Chap. 9) and the metabolic mechanisms of bariatric surgery (Chap. 10).

Part II has been reduced to 11 chapters that cover the most important aspects of clinical care of the patient with obesity. This section begins with recent advancements in the epidemiology of obesity (Chap. 11) following by a chapter on the assessment of the obese patient (Chap. 12). All subsequent chapters systematically and thoroughly review each component of treatment,

beginning with lifestyle management therapies, followed by pharmacotherapy and bariatric surgery. Behavioral strategies are addressed in Chap. 13, while dietary approaches and physical activity are covered in Chaps. 14 and 15, respectively. Recent advancements in pharmacotherapy and medications on the horizon are considered in Chap. 16. Newer surgical approaches and clinical outcomes are discussed in Chap. 17 while management of micronutrient deficiencies that occur following bariatric surgery are addressed in Chap. 18. The last three chapters of the section include treatment of obesity in the primary care clinic (Chap. 19) and the assessment and treatment of the child or adolescent with obesity (Chaps. 20 and 21).

We hope you will find the second edition of *Treatment of the Obese Patient* as useful and informative as the first edition. Whether you are a researcher in the field or a clinician who cares for overweight and obese patients, this edition is intended to be a valuable resource to keep you up to date in this rapidly evolving and exciting area of medicine.

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Part I

Physiology and Pathophysiology

Neuroregulation of Appetite

1

Ofer Reizes, Stephen C. Benoit,
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Introduction

Body weight (or more accurately body adiposity) is a tightly regulated variable. To maintain body fat stores over long periods of time, caloric intake must precisely match expenditure. Such a process relies on the complex interactions of many different physiological systems. As an example, one negative feedback system is comprised of hormonal signals derived from adipose tissue that inform the central nervous system (CNS) about the status of peripheral energy stores. These signals from adipose tissue or peripheral fat stores comprise one side of the hypothesized feedback loop. The receiving side of this regulatory system includes one or more central effectors that translate information about adiposity into appropriate subsequent ingestive behavior. When the system detects low levels of adiposity hormones, food intake increases while energy expenditure is decreased. On the other hand, in the presence of high adiposity signals, food intake is reduced and energy expenditure increased. In this way, the negative feedback system can maintain energy balance or body adiposity over long periods of time by signals in the CNS.

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The Dual-Centers Hypothesis

Historically, the conceptual framework which dominated thinking about the role played by the hypothalamus in the control of food intake was the Dual-Centers Hypothesis proposed by Stellar in a very influential article appearing in Psychological Review in 1954 [1]. In the same year that the discovery of leptin refocused attention on the role of the hypothalamus in energy balance, Psychological Review honored this article as one of the 10 most influential articles it had published in a century of publications. Stellar eloquently argued that the hypothalamus is the central neural structure involved in "motivation" generally and in the control of food intake more specifically. This control is divided into two conceptual categories controlled by two separate hypothalamic structures. The first category was "satiety" and was thought to be controlled by the ventromedial hypothalamus (VMH). The most important data that contributed to this hypothesis was that bilateral lesions of the VMH resulted in rats that ate more than controls and became obese. These lesioned rats were thought to have a defect in satiety and therefore the VMH was described as being a "satiety" center.

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Additionally, experimentally the lesion could be replicated by electrical stimulation of the VMH which also caused the animals to stop eating; i.e., these experiments demonstrated a role for the VMH in enhancing satiety. In contrast to the VMH, the lateral hypothalamic area (LHA) was thought to be the "hunger" nucleus as lesions of the LHA resulted in rats that under-ate and lost body weight. Additionally, electrical stimulation of the LHA caused eating in sated animals. Therefore, the VMH was thought to be the satiety center and the LHA was considered the hunger center. This characterization of the brain called the Dual-Centers Hypothesis was the dominant conceptualization of how the CNS controlled food intake for almost 30 years.

CNS Regulation of Food Intake

CNS regulation of food intake was originally thought controlled by the VMH and the LHA, however several challenges were made to this early hypothesis. The first was a realization that there are limitations to our understanding of the neurocircuitry using the lesions as an experimental approach to understanding CNS function. Conclusions made about larger lesion studies were difficult to interpret because lesions usually destroyed all fibers in the nuclei, not just those fibers of specific interest. An additional problem was that there are consequences of the lesion not directly tested. For example, although lesions of the VMH result in hyperphagia and obesity in rats, they also result in rapid and dramatic increases in insulin secretion from pancreatic β-cells [2]. Indeed, exogenous peripheral insulin administration results in increased food intake and repeated administration can result in rapid weight gain [3]. Therefore, in addition to regulating "satiety" the VMH also appears to have an important role in the regulation of insulin secretion [2]. Other studies support the idea that the VMH has roles in regulating functions other than "satiety." In particular, later data indicated that it was not cell bodies in the VMH but rather fibers running from the PVN to the brainstem that were critical for the effect of VMH lesions on insulin secretion [4, 5]. So while the changes in insulin secretion were potentially responsible for the effects of VMH lesions on food intake and body weight, this control of insulin secretion may not be directly mediated by the VMH.

Another challenge to the Dual-Centers Hypothesis came from work out of Grill's lab. He focused on transection of the neuraxis at different levels by utilizing the chronic decerebrate rat. The chronic decerebrate rat has a complete transection of the neuraxis at the mesodiencephalic junction that isolates the caudal brainstem, severing all neural input from more rostral structures like the hypothalamus. Hence, neither the VMH nor LHA (nor any other hypothalamic nuclei for that matter) could exert direct influence on the motor neurons in the brainstem critical for executing ingestive behavior [6]. Despite a complete loss of neural input from the hypothalamus, the chronic decerebrate animal has the ability to engage in consummatory behavior and to adjust that behavior in response to both external and internal stimuli. Chronic decerebrate rats respond appropriately to taste stimuli [6–9]. More importantly, chronic decerebrate rats demonstrate satiety and the size of the meals is influenced in the same manner as a normal rat [6, 8]. The caudal brainstem is therefore sufficient to integrate internal regulatory signals that limit meal size into ongoing ingestive behavior independent of the hunger and satiety centers of the hypothalamus. These data suggest that there are several regions in the CNS which mediate the control of food intake and that no single brain area constitutes either a "hunger" or "satiety" center.

CNS Regulation by Adiposity Signals and Effector Pathways

These challenges to the Dual-Centers Hypothesis led to new models for understanding the role of the hypothalamus in the control of food intake. Other research has focused on emphasizing factors and signaling pathways that control long-term energy balance. Adult mammals typically match their caloric intake to their caloric expenditure in a remarkably accurate fashion.

In the 1950s Gordon Kennedy postulated animals could regulate their energy balance by monitoring the major form of energy storage in the body, adipose mass [10]. When caloric intake exceeds caloric expenditure, fat stores are expanded and when caloric expenditure exceeds caloric intake, fat stores are reduced. In other words, if the size of the adipose mass could be monitored, energy intake and energy expenditure could be adjusted to keep adipose mass constant and thereby keep the energy equation balanced over long periods of time.

There are at least two peripherally derived hormones that provide key afferent information to the CNS for body weight regulation. Leptin, a peptide hormone secreted from adipocytes in proportion to fat mass, has received tremendous attention during the last two decades since its discovery. Considerable evidence has been generated that implicates leptin as one of the body's adiposity signals [11–14]. Leptin levels in the blood correlate directly with body fat, and peripheral or central administration of leptin reduces food intake and increases energy expenditure.

Importantly, leptin levels are better correlated with subcutaneous fat than with visceral fat in humans, such that the reliability of leptin as an adiposity signal varies with the distribution of body fat. There is a sexual dimorphism with respect to how body fat is distributed. Males tend to have more body fat located in the visceral adipose depot, whereas females tend to have more fat in the subcutaneous depot. Because females tend to have more subcutaneous fat than males, on the average, leptin is therefore a better correlate of total adiposity in females than in males [15]. Further, when energy balance is suddenly changed (for example, if an individual has been fasting for a day), plasma leptin levels decrease far more than body adiposity over the short term [16–18]. Hence, although much has been written about leptin as an adiposity signal, it does not account for all actions required by such a signal, suggesting that others may exist. One candidate is the pancreatic hormone, insulin.

Insulin is well known for its role in regulating glucose homeostasis, however an often under discussed role of insulin is as an adiposity signal. Plasma insulin levels also directly correlate with adiposity, and where leptin is a better correlate of subcutaneous adiposity, insulin correlates better with visceral adiposity [19–22]. Moreover, when energy balance changes, there are changes in plasma insulin that closely follow changes in energy homeostasis [23]. Therefore, both leptin and insulin can be considered adiposity signals, each indicating something different to the brain; insulin is a correlate of visceral adiposity and leptin is a correlate of subcutaneous adiposity and together or separately, they function as signals of changes of metabolic status.

The Control of Energy Intake

Food intake in mammals including humans occurs in distinct bouts or meals, and the number and size of meals over the course of a day comprises the meal pattern. Food intake is thought to be regulated by signals from the gut, brain stem, and hypothalamus. Most humans are quite habitual in that they eat approximately the same number of meals, and at the same time each day [24, 25]. Factors or signals that control when meals occur are different than those that control when they end; i.e., different factors control meal onset and meal size [25, 26]. Historically, meal onset was thought to be a reflexive response to a reduction in the amount or availability of some parameter related to energy. Changes in glucose levels were posited to stimulate meals in a hypothesis that was referred to as the glucostatic theory. This theory put forth the idea that a reduction of glucose utilization by sensor cells in the hypothalamus of the brain caused the sensation of "hunger" and a tendency to start a meal [27, 28]. An additional hypothesis was generated about what stimulates "hunger" and this was associated with changes in fuel, either from changes in body heat, upon fat utilization by the liver, or upon the generation of adenosine triphosphate (ATP) and other energy-rich molecules by cells in the liver and/or brain [29–32].

Food intake may be stimulated for reasons other than simple changes in energy substrates. An alternative hypothesis for meal generation is

that most meals are initiated at times that are convenient or habitual, and thus based upon social or learned factors as opposed to fluxes of energy within the body [33]. In this schema, the regulatory control over food intake is exerted on how much food is consumed once a meal is started rather than on when the meal occurs [34, 35]. Therefore individuals have flexibility over their individualized meal patterns and this is influenced by their environment and lifestyle. Hence, there are factors and signals that are regulatory controls which determine meal size, and this is generally equated with the phenomenon of satiety or fullness [26].

Satiety

Meal size is considered to be regulated. There is an initiation cue and a cessation cue that signals the completion of the meal. If meal size is controlled by signals that arise from the brain and gut, then the individual must have a means of measuring reliably how much food has been eaten; i.e., the number of calories consumed, or perhaps the precise relative amounts of carbohydrates, lipids and proteins, and/or other food-related parameters. Consumption must be monitored as the meal progresses so the person knows when to say "I'm full" and put down the fork [26]. Some parameters or signals might provide important feedback during an ongoing meal. These signals may be in the form of vision, smell, or taste to gauge the amount of energy consumed. However, several types of experiments have found that any such input is minimal at best.

To determine whether the gut conveys a signal to end the meal, animals have been experimentally implanted with a gastric fistula [36]. When the fistula is closed, swallowed food enters the stomach, is processed normally and moves into the duodenum. When the fistula is open, swallowed food enters the stomach and then exits the body via the fistula in a process called sham eating. In both instances the visual, olfactory, and taste inputs are the same, but the amount eaten varies considerably. When the fistula is closed (representing what happens in a normal meal), animals eat normal-sized meals; when the fistula is open (representing the experimental condition, or sham eating), animals continue eating for long intervals and consume very large meals [36–38]. Hence, whatever signals an individual uses to gauge how many calories have been consumed must arise no more proximally than the distal stomach and/or small intestine.

As ingested food interacts with the stomach and intestine, it elicits the secretion of an array of gut peptides and other signals that function to coordinate and optimize the digestive process. In 1973 Gibbs and Smith and their colleagues reported that the gut peptide, cholecystokinin (CCK), acts as a satiety signal, suggesting that this peptide may regulate the size of meals. When purified or synthetic CCK is administered to rats or humans prior to a meal, it dose-dependently reduced the size of that meal [39–43]. In further support of a role of endogenous CCK in eliciting satiety is indicated by the observation that the administration of specific CCK-1 receptor antagonists prior to a meal causes increased meal size in animals and humans [44–47] and reduces the subjective feeling of satiety in humans [44].

Endogenous factors that reduce the size of meals are considered satiety signals, and there are several different gut peptides that normally contribute to reductions in meal size and number [48, 49]. Besides CCK, gastrin releasing peptide (GRP) [50], neuromedin B [51], enterostatin [52, 53], somatostatin [54], glucagon-like peptide-1 (GLP-1) [55, 56], apolipoprotein A-IV [57], and peptide YY(3-36) [PYY3-36] [58] are all peptides secreted from the gastrointestinal system that have been reported to reduce meal size when administered systemically. In addition, amylin [59, 60] and glucagon [61, 62] secreted from pancreatic islets during meals also have this property.

These peptides signal the central nervous system via multiple mechanisms but all contribute to the phenomenon of satiety. The mechanism thought to be used by most is to activate receptors on vagal afferent fibers passing to the hindbrain (e.g., CCK [63–65], glucagon [66, 67]), or else to stimulate the hindbrain directly at sites with a

relaxed blood–brain barrier (e.g., amylin [68, 69]). Signals from different peptides, as well as signals related to stomach distension, are thought to be integrated either within the vagal fibers themselves or else in the hindbrain as they generate an overall signal that ultimately causes the individual to stop eating [70–73].

In summary, when food is eaten, it interacts with receptors lining the stomach and intestine, causing the release of peptides and other factors that coordinate the process of digestion with the particular food being consumed. Some of the peptides provide a signal to the nervous system, and as the integrated signal accumulates, it ultimately creates the sensation of fullness and contributes to cessation of eating.

An important and generally unanswered question concerns whether molecules and pathways that signal satiety have therapeutic potential to treat obesity. Thus, if satiety signals reduce individual meals (e.g., by administering CCK prior to each meal), individuals may adjust by increasing how often they eat and maintaining total daily intake essentially constant [74, 75]. CCK and the other gut-derived satiety signals have very short half-lives, on the order of one or a few minutes. Of note, rats with a genetic ablation of functional CCK-1 receptors gradually become obese over their lifetimes [76]. Hence, long-acting analogs of the satiety signals may have efficacy in causing weight loss. This is an area of considerable research activity at present.

Integration of Adiposity Signals

The information about total body fat derived from insulin and leptin must be integrated with satiety signals as well as with other signals related to factors including learning, the social situation, stress, and other factors, for the control system to be maximally efficient. Although the nature of these interactions is not well understood, several generalizations or conclusions can be made. For one, the negative feedback circuits related to body fat and meal ingestion can easily be overridden by situational events. As an example, even though satiety signals might indicate that no more food should be eaten during an ongoing meal, the sight, smell, and perceived palatability of an offered dessert can stimulate further intake. Likewise, even though an individual is severely underweight and food is available, the influence of stressors can preclude significant ingestion. Because of these kinds of interactions, trying to relate food intake within an individual meal to recent energy expenditure or to fat stores is futile, at least in the short term. Rather, the influence of homeostatic signals becomes apparent only when intake is considered over longer intervals. That is, if homeostatic signals predominated, a relatively large intake in one meal should be compensated by reduced intake in the subsequent meal. However, detailed analyses have revealed that such compensation, if it occurs at all, is only apparent when intervals of one or more days are considered in humans [77, 78]. This phenomenon was initially demonstrated in a rigorous experiment using rabbits, where weekly intake correlated better with recent energy expenditure than did intake after 1 or 3 days [79].

Homeostatic controls of food intake act by changing the sensitivity to satiety signals. The adiposity signals of insulin and leptin alter sensitivity to CCK. Hence, when an individual has gained excess weight, more insulin and leptin stimulate the brain, and this in turn renders CCK more effective at reducing meal size [80–84]. This association continues until the individual or animal becomes obese, and resistant to the adiposity signals of leptin and insulin.

The feeding circuitry is integrated. As discussed above, satiety signals that influence meal size interact with vagal afferent fibers that continue into the hindbrain [85, 86] where meal size is ultimately determined [87]. At the same time, the hypothalamic arcuate nucleus receives adiposity signals (leptin and insulin) as well as information related to ongoing meals from the hindbrain. Through integration of these multiple signals, metabolism and ingestion are monitored [11–14, 88].

Importantly, leptin and insulin fill distinct niches in the endocrine system. Although leptin

has been implicated in several systemic processes, such as angiogenesis, the primary role of leptin appears to be as a negative feedback adiposity signal that acts in the brain to suppress food intake and net catabolic effector [22, 89, 90]. Consistent with this, animals lacking leptin or functional leptin receptors are grossly obese. Insulin (as previously mentioned), in contrast, has a primary action in the periphery to regulate blood glucose and stimulate glucose uptake by most tissues. Analogous to leptin, however, deficits in insulin signaling are also associated with hyperphagia in humans, and animals that lack normal insulin signaling in the brain are also obese [22, 89–92].

The potential for redundancy between leptin and insulin has been highlighted by studies in which leptin and insulin have been found to share both intracellular and neuronal signaling pathways. The melanocortin system has long been thought to mediate the central actions of leptin (see Melanocortin discussion), though recent studies indicate insulin stimulates the expression of the melanocortin agonist precursor peptide pro-opiomelanocortin (POMC) in fasted rats and insulin-induced hypophagia is blocked by a nonspecific melanocortin receptor antagonist [93–98]. Furthermore, phosphatidylinositol-3-OH kinase (PI(3)K), an intracellular mediator of insulin signaling [99], appears to play a crucial role in the leptin-induced anorexia signal transduction pathway as well [99]. Leptin functionally enhances or "sensitizes" some actions of insulin. The underlying molecular mechanisms for the insulin-sensitizing effects of leptin are unclear, and studies are conflicting regarding the effect of leptin on insulin-stimulated signal transduction. While the long form of the leptin receptor has the capacity to activate the JAK/STAT3 [100, 101] and mitogen activated protein kinase (MAPK) pathways, leptin is also able to stimulate tyrosine phosphorylation of insulin receptor substrate (IRS-1) [101], and to increase transcription of fos, and jun [102]. Finally, recent research demonstrates that at least some dietary fats may inhibit leptin and insulin signaling cascades by acting directly on these neurons [103].

Central Signals Related to Energy Homeostasis

Neural circuits in the brain that control energy homeostasis can be subdivided into those that receive sensory information (afferent circuits), those that integrate the information, and those that control motor, autonomic, and endocrine responses (efferent circuits). Peptides such as insulin, leptin, and CCK, e.g., adiposity and satiety signals, are afferent signals that influence food intake. Additional more direct metabolic signals arise within the brain itself and also influence food intake, and these are discussed below.

Substrates such as glucose and/or fatty acids are utilized in most cells in the body and can be stored or metabolized to release energy. As oxygen combines with these substrates in the mitochondria of the cell, water and carbon dioxide are produced, and the substrate's potential energy is transferred into molecules such as adenosine triphosphate (ATP) that can be used as needed to power cellular processes. Most cells in the body have complex means of maintaining adequate ATP generation because they are able to oxidize either glucose or fatty acids. Hence, if one or the other substrate becomes low, enzymatic changes occur to increase the ability of the cell rapidly to take up and oxidize the alternate fuel. Compromising the formation of ATP disabled cells, and when it occurs in the brain, generates a signal that leads to increased eating [32, 104–106].

It has been posited that specific cells/neurons in the brain function as fuel sensors and thereby generate signals that interact with other neuronal systems to regulate energy homeostasis [32, 106]. The brain is sensitive to changes in glucose utilization because neurons primarily use glucose for energy. Recently, it has been demonstrated that in addition to sensing changes in glucose levels, the brain also responds to and uses fatty acids as sensors to influence food intake.

When energy substrates are abundant, most cells throughout the body have the ability to synthesize fatty acids from acetyl CoA (TCA cycle intermediate) and malonyl CoA via the cellular

enzyme, fatty acid synthase (FAS). When FAS activity is inhibited locally in the brain by the drug C75, animals eat less food and over the course of a few days, selectively lose body fat [107–109]. One interpretation of these findings is that there are some hypothalamic cells that have the ability to sense changes in fatty acids, and these are the critical populations of cells that are responsible for energy homeostasis [110]. The anorexic activity of C75 appears to require brain carbohydrate metabolism [111], further supporting a critical role of key hypothalamic cells in the regulation of energy homeostasis. Consistent with this idea is the observation that increases in either carbohydrate or long-chain fatty acid availability locally in the arcuate nucleus leads to reduced food intake and signals are sent to the liver to reduce the secretion of energy-rich fuels into the blood [112]. These findings further support the concept that some brain neurons can utilize either glucose or lipids for energy and hence function as overall energy sensors [31, 32, 113].

These nutrient sensing cells in the brain have begun to be more fully characterized. As previously mentioned, there are glucose sensing neurons/cells, and these appear to contain receptors and enzymes that are consistent with another type of cell that senses changes in glucose, the pancreatic β cells. Like β cells, certain populations of neurons and glia detect changes in glucose levels and generate signals that influence metabolism and behavior [114, 115]. In further support of an integrated system, there is evidence that the same or proximally close neurons contain receptors for leptin and insulin. What can be imagined from the current findings is that the brain is a critical "nutrient sensing" organ, there is a population of neurons that collectively samples different classes of energy-rich molecules (i.e., glucose and fatty acids) as well as hormones whose levels reflect adiposity throughout the body (i.e., insulin and leptin). These same neurons appear also to be sensitive to the myriad neuropeptides known to be important regulators of energy homeostasis [32], which will be described more fully below.

Anabolic Effector Systems

Neuropeptide Y

Neuropeptide Y (NPY) is one of the most potent stimulators of food intake [116–118], and NPY is proposed to be an anabolic effector that induces positive energy balance. NPY is a highly expressed peptide in the mammalian CNS [119, 120], and is well conserved across species. Hypothalamic NPY neurons are found primarily in the arcuate (ARC) and dorsomedial nuclei, and in neurons in the paraventricular nucleus (PVN) [121–126]. Endogenous release of NPY is regulated by energy balance. Specifically, in the arcuate, food deprivation, food restriction, or exercise-induced negative energy balance, each results in upregulation of NPY mRNA in the ARC and increased NPY protein. Repeated administration of NPY results in sustained hyperphagia and rapid body weight gain [127, 128]. The response of the NPY system to negative energy balance is mediated, at least in part, by the fall in both insulin and leptin that accompany negative energy balance. Central insulin or central/peripheral leptin infusion attenuates the effect of negative energy balance and reduced NPY mRNA levels in the ARC [129–132].

The ARC NPY system has received the most experimental attention. However, there is also evidence that implicates the dorsal medial hypothalamus (DMH) NPY system in the regulation of food intake. The role of NPY in the DMH in regulation of body weight is most evident in several genetic murine obesity models, such as in tubby and agouti *lethal yellow* mice, where these animals are hyperphagic, yet have no elevations in ARC NPY mRNA, but do have elevations in DMH NPY mRNA [133–135]. Rats that do not make a specific receptor for the classic gut-satiety factor, cholecystokinin (CCK) have elevated body fat mass [136], with elevated NPY mRNA in the DMH but not the ARC. There is growing evidence that points to the hypothesis that there are multiple inputs that determine NPY activity in both the ARC and DMH.

There has been considerable controversy about the importance of the NPY system because

mice with a targeted deletion of the NPY gene do not show a dramatic phenotype in terms of their regulation of energy balance [137]. Interestingly, when NPY-deficient mice are crossed with obese ob/ob mice, the resultant mice with both NPY and leptin deficiency weigh less than ob/ob mice which have an intact NPY system indicating that the NPY system contributes significantly to the obesity of ob/ob mice [138]. This is consistent with data showing elevated NPY levels in the hypothalamus of ob/ob mice. However, a number of other murine models of obesity have no apparent difference when crossed with NPY-deficient mice [139]. Thus one conclusion that could be reached from experiments on NPY-deficient mice suggests that NPY's importance may not be as great as the physiological evidence has indicated. Alternatively, NPY-deficient mice may compensate by changes in other pathways in the absence of NPY signaling [140, 141].

A critical role of NPY neurons in the arcuate nucleus was demonstrated specific ablation of these neurons in embryonic and adult mice. Bruning and colleagues induced targeted expression of a toxin receptor to neurons expressing AgRP [142]. NPY and AgRP (discussed in Melanocortin section) are co-expressed in a subset of arcuate nuclei. These are the critical NPY/AgRP neurons that are believed to mediate many of the effects of leptin and insulin on food intake. Using this technique, the investigators were able to induce cell death specifically in these neurons at a specific time in development [142]. In contrast to the embryonic deletion of these neurons, mice with adult targeted deletion of the NPY/AgRP neurons stopped eating and lost significant amounts of body adiposity. Indeed, the embryonic ablation of these neurons is consistent with ablation of the individual NPY and AgRP neuropeptides. This elegant study confirms the important role of these cells in the normal regulation of energy balance. While compelling, the data point to the importance of the neurons as opposed to the neuropeptides, NPY and AgRP themselves [142].

There are several NPY receptors that are critical for the physiological effects observed following NPY administration. Both the Y1 and Y5 receptors have significant expression in areas of the hypothalamus that are sensitive to the orexigenic effects of NPY. However, both pharmacological [143–148] and transgenic approaches to assessing the relative contributions of Y1 and Y5 receptors have resulted in conflicting data. There remains some speculation for the existence of an unidentified NPY receptor that contributes significantly to the feeding response [149]. Over the years, the NPY receptors have attracted significant interest by the biotechnology and pharmaceutical industry [150]. Despite this investment, NPY antagonists have to date failed to show significant efficacy in preclinical obesity models [151]. So, it is unlikely that we will see NPY pharmacological agents in the clinic in the near future.

Melanin Concentrating Hormone

As previously described, the lateral hypothalamic area (LHA) is an area critical for the regulation of food intake and fluid intake and was first reviewed in Stellar's original papers in the 1940s and 1950s. There are at least two peptides released from the LHA that appear to mediate these effects. The first is melanin concentrating hormone (MCH) and the second is orexin (see Hypocretin-orexin section). MCH regulates food intake and its expression is increased in obese ob/ob mice [152]. When MCH is delivered into the ventricular system it potently increases food intake [153, 154] and water intake [155]. Unlike NPY, repeated administration of MCH does not result in increased body weight [156]. Importantly, mice with targeted deletion of MCH have reduced food intake and decreased body weight and adiposity [157], unlike the NPY null mice. Recent evidence indicates that MCH is potently regulated by estrogen and may be an important component of mediating the effects of estrogen on food intake and energy balance [158]. Because there are MCH projections and receptors which are broadly distributed throughout the neuroaxis, and the fact that the MCH knockout animal is lean, it is likely that MCH has

a significant role in the regulation of food intake. Several MCH antagonists have been described in the literature and all appear to reduce body weight, food intake, and fat mass [159, 160].

Hypocretin-Orexin

"Hypocretins" [161] or "orexins" [162] are two names given to the same peptide. Hypocretin is the name more commonly used in sleep/wake cycle research, while orexin is more commonly used in food intake research. The orexins are comprised of two peptides (ORX-A and ORX-B) and two receptors, and while the cell bodies are located in close proximity to MCH-expressing neurons in the LHA, the two systems do not co-localize to any significant extent [163]. Considerable evidence indicates that central administration of ORX-A increases food intake [164, 165]. Like MCH, orexins have a broad distribution pattern and a variety of evidence links the ORX system directly to the control of arousal [166, 167].

In further support that the CNS is an integrated system, the LHA is positioned to receive information about nutrients and information concerning the levels of adiposity signals which are transmitted to the LHA via projections from the ARC. There are significant hypothalamic connections between the ARC, the PVN, and the LHA. Projections from the ARC synapse on both MCH and ORX neurons in the LHA [168]. NPY and melanocortin neurons from the ARC interact in a specific way with MCH and the ORX neurons in the LHA [164, 165, 169, 170] suggesting that this brain region is important in energy homeostasis. Additionally, ORX mRNA in the LHA is inhibited by leptin [162] and increased by decreased glucose utilization [171]. Finally recent data have demonstrated that orexin signals affect dopaminergic neurons in the ventral tegmental area (VTA) and likely increase hedonic or reward-based feeding. We also found that orexin may further modulate the activity of dopaminergic outputs by acting on the paraventricular thalamic nucleus (PVT) [172].

Ghrelin

Ghrelin is the endogenous ligand for the growth hormone secretagogue receptor [173, 174]. Endocrine cells of the stomach secrete ghrelin, and consistent with its role as an anabolic effector, centrally and peripherally administered ghrelin results in increased food intake in both rats [175, 176] and humans [177]. Ghrelin infusions result in dramatic obesity, and circulating ghrelin levels are increased during fasting and rapidly decline after nutrients are provided to the stomach [173, 174] (for review see: [178]). Ghrelin binds to the growth hormone secretagogue receptor which is found in the arcuate nucleus of the hypothalamus. NPY producing cells in the ARC are critical mediators of the effects of ghrelin [179–182]. Clinical evidence points to elevated levels of ghrelin in weight-reduced patients [183], with the notable exception of patients who have been successfully treated for obesity by gastric bypass where circulating ghrelin levels are low [184]. Finally, new data have demonstrated that the acylation of ghrelin is accomplished by the enzyme ghrelin O-acyltransferase (GOAT) and that its biological activities are dependent on the presence of this enzyme [185–187].

As previously discussed, there are numerous peptides secreted from the stomach and intestines that influence food intake. Gastrointestinal signals are thought to be released to restrain the consumption of excess calories and to minimize the increase of post-prandial blood glucose [34]. Gastrointestinal signals reduce meal size and provide signals as to the complexity of macronutrients consumed. The fact that only one gastrointestinal peptide stimulates food intake speaks to the importance of limiting meal size in the overall regulation of energy homeostasis. The ghrelin signaling pathway has received much publicity in the media and attention by pharmaceutical companies [188]. The data suggest that ghrelin antagonists may be potent inhibitors of food intake and good weight loss agents [189]. Indeed, several studies indicate that antagonists may be potent food intake inhibitors in lean rodents, though evidence in high-fat fed diet-induced obese rodents is lacking [190]. Finally, like orexin, it is now

clear that ghrelin also acts on the VTA to modulate reward and hedonic-based feeding and that GOAT is required for this action [186].

Catabolic Effector Systems

Catabolic systems are those that are activated during positive energy balance. These systems oppose those previously described which are activated during negative energy balance. When animals or humans consume calories in excess of requirements, body weight is gained. Additionally, if animals are forced to consume calories in excess of their needs, voluntary food intake drops to near zero and the animals gain body weight [191, 192]. These data provide further evidence that body weight is tightly regulated. Hence animals not only have potent regulatory responses to being in negative energy balance, but they also possess regulatory responses to being in positive energy balance. Catabolic systems are defined here as those that are activated during positive energy balance and which act to reduce energy intake and/or to increase energy expenditure and thereby restore energy stores to its defended levels.

Cocaine-Amphetamine-Related Transcript

Cocaine-Amphetamine-Related Transcript (CART) [193] was first identified as a gene whose expression is regulated by cocaine and amphetamine. CART is expressed in many of the POMC-expressing neurons in the ARC. CART expression is reduced during negative energy balance and is stimulated by leptin [194]. Exogenous administration of CART peptide fragments into the ventricular system potently reduces food intake [194–196] and ventricular administration of antibodies to CART produce significant increases in intake, implicating a role for endogenous CART in the inhibition of food intake [194]. However, at these same doses, CART also produces a number of other behavioral actions that make its exact role in the control of food intake unclear [197]. CART is a very prevalent peptide and its distinct role in the regulation of food intake and body weight is further confounded by data indicating that when delivered specifically into the arcuate nucleus, CART actually produces an increase in food intake [198].

Corticotropin Releasing Hormone and Urocortin

Corticotropin releasing hormone (CRH) is synthesized in the PVN and LHA and is negatively regulated by levels of glucocorticoids. CRH is a key controller of the hypothalamic pituitary axis (HPA) that regulates glucocorticoid secretion from the adrenal gland. Administration of CRH into the ventricular system potently reduces food intake, increases energy expenditure, and reduces body weight [199, 200]. As previously mentioned, when animals are overfed, they voluntarily reduced their food intake and CRH mRNA in the PVN is also potently increased [192]. The role of CRH in the regulation of food intake and body is complex due to the presence of a binding protein within the CNS and evidence that inhibition of this binding protein results in decreased food intake [201].

Urocortin is a second peptide in the CRH family. Urocortin administration reduces food intake but unlike what occurs following CRH, reductions in food intake are not associated with other aversive effects [202]. Urocortin is produced by neurons in the caudal brainstem with prominent projections to the PVN [203]. Given the central importance of the CRH system to activity of the HPA axis, the important role of peripheral glucocorticoids in controlling metabolic processes, and the inverse relationship between peripheral leptin and glucocorticoid levels, unraveling the complicated relationship of the CRH/urocortin systems in control of energy balance remains a critical but elusive goal. For a more thorough review of the CRH system and energy balance, see [204, 205].

Proglucagon-Derived Peptides

Pre-proglucagon is a peptide made both in the periphery and in the CNS. Pre-proglucagon encodes two peptides that have been shown to possess central activity: glucagon-like-peptide 1 (GLP-1) and glucagon-like-peptide 2 (GLP-2). Both peptides are made in the L-cells of the distal intestine and have well-described functions in the periphery with GLP-1 critical for enhancing nutrient-induced insulin secretion [206] and GLP-2 playing an important role in maintenance of the gut mucosa [207]. Pre-proglucagon is also made in a distinct population of neurons in the nucleus of the solitary tract with prominent projections to the PVN and DMH [208, 209] as well as to the spinal cord. Pre-proglucagon neurons appear to be targets of leptin, since peripheral leptin administration induces fos expression, a marker of neuronal activation, [210, 211]. Both GLP-1 and GLP-2 have distinct receptors with the GLP-1 receptor found predominantly in the PVN and the GLP-2 receptor in the DMH. When administered into the ventricular system, GLP-1 produces a profound reduction in food intake and antagonists to the GLP-1 receptor increase food intake [212, 213]. However, exogenous GLP-1 administration is also associated with a number of symptoms of visceral illness [214, 215], and GLP-1 receptor antagonists can block the visceral illness effects of the toxin LiCl [216, 217]. GLP-2 administration is associated with a less potent anorexic response but one that appears not to be accompanied by the symptoms of visceral illness associated with GLP-1 [218]. The interaction of these two co-secreted peptides is yet to be determined. GLP-1 is discussed in more detail in the chapter in this volume on gut peptides.

Serotonin

Serotonin has been implicated in body weight and food intake regulation based on animal and human studies [219]. Serotonin affects feeding behavior by promoting satiation and also appears to play a role in modulating carbohydrate intake [220]. The activity of serotonin is observed in several hypothalamic nuclei in the medial hypothalamus, notably the PVN, VMH, suprachiasmatic nucleus, and LHA [221]. There are at least 14 serotonin receptor subtypes, but the receptor subtypes implicated in feeding include $5HT_{1A}$, $5HT_{1B}$, $5HT_{2C}$, $5HT_{1D}$, $5HT_{2A}$, and $5HT_3$ [222]. Importantly, enhancement or stimulation of serotonergic activity leads to decreased food intake, while attenuation or inhibition of serotonergic activity leads to increased food intake. Indeed, clinical evidence for the importance of the serotonergic system derives from the highly efficacious drugs dexfenfluramine and fenfluramine [219]. Both were dual acting 5HT reuptake and 5HT releasing agents that were potent satiety drugs used as obesity therapeutics. They were withdrawn from the clinic due to untoward effects on the heart valve perhaps related to their activity at peripheral $5HT_{2B}$ receptor stimulation. Newer serotonergic agonists (including lorcaserin discussed in the chapter in this volume on pharmacotherapy of obesity) are being developed to selectively stimulate the $5HT_{2C}$ receptor subtype [223]. In fact, $5HT_{2C}$ null mice are obese and hyperphagic [224]. Finally, recent data shows that serotonergic signaling, specifically $5HT_{2C}$ receptors, requires melanocortinergic signaling to inhibit feeding [225].

CNTF

Ciliary Neurotrophic Factor (CNTF) is a neuronal survival factor shown to induce weight loss in rodents and humans [226, 227]. CNTF leads to a reduction in food intake and body weight apparently via activating pathways that mimic leptin, though unlike leptin, CNTF is active in leptin-resistant diet-induced obese mice [228]. Interestingly, CNTF-treated rodents and humans lose weight and maintain the reduced body weight for a long period after cessation of treatment. The implication of these observations is that CNTF resets the body weight "set point," or changes the weight the body defends. But the reason was not understood, though data from the Flier Laboratory sheds light on a potential mechanism for the maintenance of the weight

loss [229]. Flier and colleagues showed that CNTF induces neuronal cell proliferation in hypothalamic feeding centers. The new cells show functional leptin responsiveness. The data provide an explanation for the prolonged weight loss maintenance but do not explain how CNTF induces satiety and leads to weight loss. Initial data in rodents appeared to indicate that CNTF somehow suppresses the appetite enhancing neuropeptide NPY [230].

Melanocortins

The action of leptin and possibly insulin on feeding behavior is transduced by the melanocortin signaling pathway in the hypothalamus [231]. The arcuate nuclei in the hypothalamus contain two distinct populations of neurons that highly express the leptin receptor. These neurons are the pro-opiomelanocortin (POMC) and agouti-related protein (AgRP)/NPY neurons, which project onto neurons in the paraventricular and lateral hypothalamic area known to express the melanocortin receptors. The POMC containing neurons secrete the melanocortin agonist αMSH, while the AgRP/NPY containing neurons secrete the melanocortin antagonist AgRP. Leptin appears to reciprocally regulate these nuclei. Low leptin levels lead to increased expression of AgRP and reduced expression of POMC and αMSH. In contrast, high leptin levels lead to increased expression of POMC and reduced expression of AgRP.

The importance of the melanocortin signaling pathway in feeding behavior and body weight was originally uncovered by mouse fanciers characterizing coat color phenotypes in the mouse [232]. One of these mutations, named agouti *lethal yellow*, had a yellow coat color and was obese. The details of this unusual mutation were elucidated as well as its relevance to human obesity. The signaling system involves the melanocortin receptor and two functionally opposing ligands, an agonist derived from the POMC peptide and an antagonist, AgRP [233, 234]. Inactivating mutations in the receptor as well as the activating ligand, αMSH, lead to hyperphagia and obesity in both rodents and humans [235–237]. Likewise, overexpression of the antagonist, AgRP, also leads to obesity in rodents [94].

There are five mammalian melanocortin receptor subtypes involved in diverse physiological processes such as feeding behavior, energy balance, pigmentation, and stress response [238, 239]. The melanocortin-3 and -4 receptors (MC3R, MC4R) are expressed in the brain and implicated in body weight and feeding behavior regulation. The MC1R is expressed in the skin and implicated in skin and hair pigmentation. The MC2R is expressed in the adrenal gland and implicated in the stress response, part of the hypothalamic pituitary adrenal (HPA) axis. Finally, the MC5R is ubiquitously expressed in the periphery and implicated in sebaceous gland physiology.

The melanocortin receptors and particularly the MC4R have attracted significant attention from the pharmaceutical industry [240]. Indeed, pharmacological validation for the role of the melanocortin receptors in feeding behavior derives based on the peptide nonspecific melanocortin agonist melanotan II (MTII) [241, 242]. Rodent and human studies with MTII indicate that melanocortin agonism leads to reduced food intake. The melanocortin receptors are involved in a variety of physiological processes, thus identifying a selective agonist has been quite complicated. Despite significant biotechnology and pharmaceutical interest, pharmacological modulators of MC4R are not likely to appear in the clinic in the near future.

Reward

Recently, increasing attention has been devoted to extra-hypothalamic controls of food intake. Given the exquisite complexity and redundancy of the negative feedback biological system, it has become obvious that at times animals and humans consume food for reasons other than energy needs. While this work is described in detail elsewhere (e.g., [243]), we note here that areas of the brain that underlie reward and reinforcement

(so called "pleasure centers") are likely responsible for at least some of the hyperphagia that leads to obesity. In particular, the ventral tegmental area (VTA) and the nucleus accumbens are known to underlie eating associated with palatability [244–247]), often independent of energy needs. In fact, we recently demonstrated distinct effects of leptin at VTA and LHA sites [248]. Further, additional evidence suggests crosstalk between the hypothalamus and midbrain dopaminergic system that may increase the reward or reinforcement associated with palatable foods in times of negative energy balance. Much remains to be studied, however it seems clear that these systems greatly increase the complexity of CNS controls over food intake and contribute to the development of obesity in a calorie-rich environment.

Summary

The research and topics presented in this review are by no means the whole of work into the CNS regulation of food intake and appetite. In fact, there are rich areas of investigation over which we have only been able to briefly mention. The important conclusion from all of this work is, however, that the regulation system and specifically the CNS control of this regulation, is diverse and yet exquisitely integrated. From signals arising in the gastrointestinal tract, to hormones that convey adiposity information, to the multiple nuclei in the brain that receive and coordinate the behavioral response, each part of the system represents not an independent entity, but rather an important piece of a complex whole.

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Reward, Reinforcement, and Impulsivity in Obesity

2

Antonio Verdejo-Garcia

Abbreviations

BMI	Body Mass Index
SR	Sensitivity to reward
SP	Sensitivity to punishment
GNG	Go/No-Go
IGT	Iowa Gambling Task
BOLD	Blood-Oxygen-Level-Dependent Signal
dlPFC	Dorsolateral prefrontal cortex
mPFC	Medial prefrontal cortex
ACC	Anterior cingulate cortex
Hippocamp.	Hippocampus
Operc.	Operculum
NS	Nonsignificant

Introduction

Societal changes in food production, marketing, and availability have moved eating behavior outside purely homeostatic motives, raising awareness about the relevance of reward, reinforcement, and impulse control systems in regulating food intake [1]. In plentiful environments, where the appeal and size of food products is maximized and exploited, individual differences in reward sensitivity and impulsivity are likely to predict food preferences and food consumption [2]. Moreover, dietary patterns deeply entrenched in current societies (e.g. high-fat and high-calorie diets) have shown to detrimentally impact brain systems involved in reinforcement sensitivity and impulse control [3]. Partly as result of these changes, the prevalence of obesity has sharply increased in recent decades [4]. In response to this challenge, the scientific community has multiplied efforts to understand the contribution of reinforcement and impulse control systems to the risk, progression, and treatment of obesity.

Neuroscientific findings have stressed the relevance of four interrelated brain systems involved in processing food value and regulating food consumption [1]: (1) the hypothalamus, involved in regulating energy intake and maintaining homeostasis; (2) the striatum/limbic system, involved in coding the reward value of available reinforcers and ensuing activation of the impulsive system (approach or avoidance behavior); (3) the somatosensory/interoception system, involved in ongoing mapping of homeostatic signals and subsequent moderation of reward-impulsive and goal-driven systems; and (4) the ventromedial and dorsolateral prefrontal cortical systems, involved in goal-oriented self-regulation of behavior. The hypothalamus has been thoroughly characterized as the main regulator of basic metabolic processes [5] but it also feeds back to brain systems involved in food reward coding, interoception, and self-regulation/decision-making [1, 5]. The striatum/limbic system encompasses brain regions sensitive to

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stimulus-driven behavioral approach or inhibition: the ventral striatum and the amygdala, respectively. These regions represent the hedonic value of food (ventral striatum, amygdala), track the outcome value of food-related reinforcement (hippocampus, extended amygdala), and orchestrate motor responses during approach-avoidance learning (dorsal striatum, cerebellum) [6, 7]. The somatosensory/interoceptive system is essential to link perceived homeostatic signals with motivational states and reward predictions [8, 9]. The insula and the frontal operculum are additionally involved in updating and monitoring cognitive control systems involved in self-regulation [10]. Finally, the prefrontal system computes the relative value of food reinforcers, based both on their basic attributes (e.g. palatability) and more abstract long-term goals (e.g. healthy eating, dieting), and guides behavior accordingly [6]. The balance between ventromedial and dorsolateral prefrontal cortices serves to weigh the rewarding attributes vs. the anticipated outcomes and their consistency with goals [6], whereas ventrolateral prefrontal regions are particularly relevant to performance monitoring and response control [10].

Over the last decade, neuroscientific research has revealed several mechanisms by which dispositional differences or adaptations in the function of these systems can contribute to the risk and progression of obesity. Specifically, there is evidence to support: (1) that individual differences in reward responsivity and impulsivity are associated with the risk for weight gain and obesity [11, 12]; (2) that high-fat diets and excessive adiposity impair efficient communication between peripheral homeostatic regulators (e.g. insulin, leptin) and central reinforcement nuclei (e.g. striatum, insula) [13, 14]; and (3) that dysfunctional reinforcement functioning can ultimately "hijack" top–down inhibitory control and decision-making systems relevant to the self-regulation of eating in the context of lifestyle goals or treatment commitment [15]. There is also ongoing discussion on (4) parallels between obesity and addiction, mainly based on these overlapping deficits in reward and inhibitory control systems [16, 17]. However, this overlap seems to fit better with specific patterns of overeating (e.g. binge eating) [18, 19] than with the typical obesity phenotype [20, 21]. Therefore, in this chapter, I will discuss evidence hinting to the first three notions, taking a multimodal approach that will address findings from personality, neuropsychology, and brain imaging studies. The theoretical advantage of personality studies is the reliable measurement of stable dispositions purportedly associated with vulnerability to obesity [12, 22]. Complementarily, neuropsychological tools provide more accurate estimations of the current function (and malleability) of specific cognitive processes, including reward prediction and reinforcement value, impulsive action, and decision-making (i.e. impulsive choice) [23, 24]. Finally, neuroimaging studies offer insight about the brain underpinnings of trait and cognitive measures, as well as about the dynamic interplay between different brain systems, or between hormonal signaling and brain systems relevant to obesity [25]. The evidence provided by these multimodal assessments will be discussed in the framework of maturational stages, differentiating findings from pediatric/adolescent populations vs. adult populations. This distinction is based on evidences showing that brain maturational processes impact trait and cognitive aspects of reward sensitivity and impulsivity [26], and that obesity is better characterized as a dynamic process in which predisposing traits (e.g. child hypersensitivity to reward) may turn to opposite states as the condition evolves (e.g., hyporesponsivity to reward in adult chronic populations) [5]. To avoid further confounders, I will only review evidence directly related to obesity, leaving aside related conditions such as binge eating disorder, or relevant comorbidities like diabetes or hypertension. Moreover, I will focus on studies lacking pre- and post-prandial manipulations, in order to attain a more uniform account of long-lasting (vs. transient) alterations associated with the condition.

Assessment Tools: Multidimensionality and Convergence of Personality, Cognition, and Neuroimaging

During this chapter I will review evidence from self-reported personality questionnaires, neuropsychological tests, and neuroimaging tools that

have been applied to the study of sensitivity to reward and impulsivity in the context of obesity. These varied tools provide different but complementary insights into reward processing and impulsivity constructs, which I discuss in this section prior to description of the specific findings from these studies.

Self-reported personality questionnaires assess general dispositional traits of the individual: how the individual would typically behave in a given situation, or to what extent the subject agrees or disagrees with particular statements. Conversely, neuropsychological tests are designed to provide objective "current state" indices of behavioral performance linked to the function of specific cognitive systems and processes. Both personality and neuropsychological measures are often used in combination with different neuroimaging techniques. Structural neuroimaging tools (e.g. Magnetic Resonance Imaging, MRI) serve to quantify gray and white matter, total or regional brain volumes through different statistical approaches [27]. Resting-state functional connectivity is useful to characterize synchronized activation of large-scale inter-connected brain systems [28]. In the obesity literature, both of these measures have been successfully correlated with personality traits or performance on neuropsychological tests [25, 29]. However, the more widely used approach is that of functional neuroimaging (with PET or functional MRI) which measures regional brain activity (or neurotransmitter activity) during actual performance on specific cognitive tasks. This latter approach offers the opportunity of characterizing the neural underpinnings of normal (or abnormal) responsivity and function of reward sensitivity and impulse control systems and processes [30, 31] and I will mainly rely on this evidence to describe the brain underpinnings of these processes.

Several questionnaire measures have been developed based on major personality theories. For the purpose of this chapter, I will focus on three main personality models and measures: the Gray's behavioral inhibition and behavioral approach systems model [32], which is typically measured with the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) [33]; the Costa and McRae Five-Factor model, which is measured with the NEO-PI inventory [34]; and the UPPS pathways model, which is measured with the UPPS-P scale [35]. Gray's model defines two dimensions of personality that represent the sensitivity of two neuropsychological systems involved on motivated response towards environmental stimuli. The behavioral inhibition system is sensitive to environmental stimuli signaling potential punishment or non-reward, therefore inhibiting behaviors associated with perceived threat. Conversely, the behavioral activation system is sensitive to environmental stimuli signaling potential reward or non-punishment, resulting in behavioral activation linked to the prospect of reinforcement. The SPSRQ assesses the differential sensitivity of these systems, with high sensitivity to reward scores representing increased sensitivity of the behavioral activation system, and high sensitivity to punishment scores representing increased sensitivity of the behavioral inhibition system.

The Five-factor model defines five broad personality dimensions (factors) that represent different constellations of traits: Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. In this chapter I will address three of these factors, since they encompass specific facets of impulsive personality [34]. Conscientiousness represents the tendency to orientate behavior according to long-term goals, such that low conscientiousness comprises poor deliberation and low self-regulation. Extraversion represents proneness to seek novel stimulation and experiences, including exciting things linked to potential harm. Similarly, neuroticism represents increased sensitivity to negative emotions, including proneness to trigger impulsive responses when under these feelings. Obesity has been mainly associated with low conscientiousness and high neuroticism, whereas there is mixed evidence hinting to both high and low extraversion.

Building on the Five-factor model and on factor analysis of an array of well-validated measures tapping on impulsive traits, Whiteside and Lynam [35] originally developed the UPPS model and scale. This model defines impulsivity as a behavioral outcome that can be potentially triggered through different personality pathways.

They originally proposed four different pathways: negative urgency, representing the tendency to succumb to strong impulses under the influence of negative emotions; lack of perseverance, representing difficulty to stay through tasks until completion, especially when they are long, boring, or difficult; lack of premeditation, representing the tendency to act without sufficient regard of potential consequences; and sensation seeking, representing proneness to engage in novel, exciting activities that can be risky or not [35]. A fifth dimension of positive urgency (the tendency to succumb to strong impulses under the influence of positive emotions) was later added to the scale and model to represent a positive emotionality pathway to impulsive behavior [36]. The dimensions of lack of perseverance and premeditation stems from the Five-factor dimension of conscientiousness, whereas negative urgency stems from neuroticism, and sensation seeking from extraversion [35].

All of these scales have demonstrated sound psychometric properties and validity. However, it is worth noting that there are a number of well-known caveats inherent to the self-report methodology. Some of these caveats are particularly relevant for obese populations. For example, individuals with obesity are at higher risk of social marginalization and may therefore be more susceptible to social desirability biases. Furthermore, similar to other impulsive populations, individuals with obesity are purportedly more prone to exhibit a careless approach to questionnaires themselves.

In contrast to self-report (which primarily addresses stable and broad domains) neurocognitive measures are designed to obtain precise estimations of the current function of cognitive processes, and to relate the function of these processes to that of relevant brain systems. In the framework of sensitivity to reward and impulsivity, four major families of measures have been put forward. Sensitivity to reward can be measured with (1) cue-related attention/motivation tests, and (2) relative reinforcement value tests. Impulsivity can be measured with (3) response inhibition tests, and (4) impulsive choice tests including delay discounting and decision-making tasks [22, 37].

Cue-related attention/motivation can be evoked through different probes. These probes include attentional bias tests (e.g. Dot Probe), measuring the strength of the attentional engagement toward (or the difficulty to disengage from) spatial locations formerly paired with incentive cues (i.e. food stimuli); and cue-delayed incentive tasks (e.g. Monetary Incentive Delay), measuring degree of responsivity to cues associated with prospective rewards [38]. The dependent measures of these tests include behavioral reaction times, eye-tracking based time estimations of attention allocation, and cue-related physiological and brain activations. Conversely, relative reinforcement value procedures measure the amount of time or effort invested on particular reinforcers (e.g. food procurement) relative to other competitive options (e.g. reading magazines). Both types of tasks engage the dorsomedial prefrontal–ventral striatal brain circuit typically involved in stimulus-driven motivation [39].

With regard to impulsivity, response inhibition tests are based on the ability or difficulty to suppress an automated (prepotent) response. Some of these tests stress the ability to suppress perception or attention-based primed responses (e.g. similar to target "non-target stimuli" in Continuous Performance tests, or the reading response in the Stroop test), whereas other measures stress the ability to suppress a previously reinforced or a previously initiated motor response, such as in Go/No-Go and Stop-Signal tasks respectively [40]. Both types of tests seem to engage overlapping brain circuits encompassing ventrolateral and dorsolateral prefrontal cortices, and dorsal striatal regions [41, 42]. Within the impulsive choice family, measures of delay discounting define impulsivity in terms of choice preference for a small reward available immediately (or after a short delay) over a larger reward available at some point in the future [43, 44]. Decision-making measures involve choices between a safe option and a more risky option that offers a "superficially appealing" gain. These measures

include the Iowa Gambling Task [45] and the Risky Gains Task [46]. Impulsivity can be indexed by selection of the highly rewarding option despite the clear potential for negative outcomes. A separate aspect of the decision-making process is reflection impulsivity, which represents the tendency to gather and evaluate sufficient information before making complex decisions [47]. This aspect can be measured with specific probes (e.g. the Information Sampling Task) or through indirect indices of planning time and increased errors in Maze tasks (Austin or Porteus Maze tests) and Tower tasks (Tower of Hanoi or Tower of London tests) [37]. The latter are based on the assumption that poor reflection at the planning/pre-decisional stage will reduce the accuracy of the eventual decision [48]. Delay discounting and decision-making tests engage overlapping brain systems that encompass the midbrain and striatum, the insula, and the medial orbitofrontal cortex [49].

There is a classic controversy in the literature concerning notable mismatch between results from self-report and neurocognitive measures of impulsivity. The different targets of these complementary approaches (trait vs. state, general dispositions vs. specific operations) partly explain this mismatch. Recent studies have traced tentative links between trait measures of premeditation and perseverance and cognitive measures of response inhibition, and there is also evidence of correspondence between emotional dispositions to impulsivity (positive and negative urgency) and medial orbitofrontal brain regions involved in decision-making. However, readers must be aware of the existence of frequent disparities in reconciling findings from these approaches.

Reward and Punishment Sensitivity

In this section, I review available evidence on sensitivity to reward and punishment in overweight and obesity populations, across personality, neuropsychological and neuroimaging methodologies relevant to these constructs. I initially review evidence obtained in pediatric populations (children and adolescents), to then move to adult populations. In those instances in which systematic or meta-analytic reviews are available, I primarily draw my conclusions from the findings from these studies. In addition, I consider case-control studies providing detailed biometric descriptions of the clinical populations and utilizing well-validated measures and statistical control.

Adolescents

Personality Measures

Trait sensitivity to reward is regarded as a vulnerability marker for obesity, due to positive associations with overeating and increased BMI in children of 6- to 13-years-old [50]. During mid-adolescence (12- to 17-years-old) there is also a significant association between sensitivity to reward and poor premeditation and sensation seeking traits, which may promote external eating patterns [51]. However, the association between sensitivity to reward and BMI in child and adolescent populations (10- to 15-years-old) seems to be nonlinear: there is a positive correlation between sensitivity to reward and BMI in normal weight and overweight children/adolescents, but there is a negative correlation between sensitivity to reward and BMI in obese children/adolescents [52]. Considering that sensitivity to reward emerges early in life and promotes BMI gain, and that this positive association turns negative along the BMI continuum, the data seems to support a dynamic vulnerability model [11], by which hypersensitivity to reward originally fosters weight gain to then being detrimentally impacted by fat accumulation. Considerably less is known about sensitivity to punishment, but available evidence indicates that conjointly increased sensitivity to punishment and reward is particularly associated with excess weight problems in adolescence [53].

Cognitive Measures

With regard to attentional bias towards food cues, there is no consistent behavioral evidence of this

phenomenon in children or adolescents, although neuroimaging studies have shown suggestive findings that I discuss in the following section. In relative reinforcement value tasks, children and adolescents with greater BMI levels exhibit faster rates of motivated responses associated with actual food rewards relative to competitive reinforcers [54]. Furthermore, the relative reinforcing value of food prospectively predicts BMI gain across one year [55].

Neuroimaging

Structural neuroimaging studies have demonstrated that in adolescents who are overweight or obese, there is a positive correlation between gray matter in somatosensory cortices (SII, parietal operculum) and sensitivity to reward, whereas the directionality of this association is negative in normal weight peers [29]. Functional neuroimaging studies have further shown that adolescents who are overweight or obese exhibit increased functional activation of anterior cingulate, frontal/rolandic operculum, and somatosensory regions (insula and parietal operculum) during anticipation of highly palatable food, coupled with increased activation of the frontal/rolandic operculum regions during the intake of highly palatable food [56]. During attentional bias towards food visual cues, adolescents with excess weight also exhibit increased activation of the insula and the frontal operculum [57]. Moreover, during attentional orientation towards and passive observation of visual food cues, adolescents with higher BMI show increased activation of dorsolateral and ventrolateral prefrontal regions, which purportedly reflects food-evoked attentional "hijacking" [57, 58]. Increased ventrolateral activation toward cues prospectively predicts BMI gain [57]. Therefore, current evidence indicates that both trait sensitivity to reward and state sensitivity to actual food reward are associated with abnormal function of brain somatosensory regions, while observation of food stimuli hyper-engages attention/executive control regions.

Interim Conclusion and Future Directions

Concerning reward/punishment sensitivity, obesity in adolescent populations is associated with BMI-related reductions in trait sensitivity to reward, higher explicit motivation towards food reinforcement, atypically increased positive association between brain somatosensory regions volume and activation and reward excitability, and increased involvement of brain attentional control regions during presentation of food stimuli.

Adults

Personality Measures

Similar to the case in children and adolescents, the association between sensitivity to reward and BMI in adults is non-linear: there is a positive correlation between sensitivity to reward and BMI in normal weight and overweight adults, but there is a negative correlation between sensitivity to reward and BMI in moderate to morbidly obese adults (BMIs~>35) [59]. Interestingly, both overweight and obesity have been associated with increased sensitivity to punishment [60]. Therefore, the reward/punishment profile of moderate to morbidly obese adults is better characterized by reduced sensitivity to reward and increased sensitivity to punishment. It is worth mentioning that these temperamental traits are regarded to be genetically mediated, such that there is particular interest on dopamine and opioid receptor genes implicated in both reward processing, and in the pathogenesis of obesity [22]. There is evidence showing that individuals with excess weight and binge eating disorders carrying gene variants associated with decreased dopamine D2 receptor availability (*DRD2/ANKK1 Taq1A* A1 carriers) are characterized by increased sensitivity to reward relative to individuals with excess weight and binge eating disorder not carrying the "high risk" A1 allele [61]. Moreover, it has been shown that the rare *G118 variant* of the *mu* opioid receptor gene (*OPRM1*), associated

with gain of hedonic function, is overexpressed in excess weight individuals with binge eating disorder compared to excess weight individuals who do not binge [62]. However, the association between dopamine or opioid gene polymorphisms and BMI has not been supported by larger epidemiological studies [63]. Therefore, while it is plausible that dopamine and opioid gene variants mediate individual differences on sensitivity to reward and eating habits, its relevance to obesity has not yet been solidly established.

Cognitive Measures

A systematic review of available evidence has shown that obese populations consistently and robustly demonstrate increased sensitivity to food in relative reinforcement value tasks [22]. Moreover, it has been shown that the relative reinforcement value of food is a significant predictor of BMI, and this association is moderated by disinhibited dieting [64]. There is no evidence to support an increased motivational/attentional bias towards food rewards on implicit association tests [65]. However, this motivational/attentional bias has been observed in individuals with excess weight and binge eating disorder when utilizing fine-grained eye-tracking tools measuring orientation of attention towards food images, and difficulty to disengage attention from the spatial locations associated with those images [66, 67].

Neuroimaging

Cue-reactivity functional neuroimaging studies have demonstrated that obese individuals exhibit significantly increased activation in medial prefrontal/anterior cingulate cortex, striatum, insula, and hippocampal regions during visual processing and anticipation of high vs. low rewarding food [68, 69]. Interestingly, a similar pattern of hyperactivations has been observed in obese individuals relative to normal weight controls during anticipation of monetary rewards [20]. Moreover, individuals with obesity show increased effective connectivity between the caudate nucleus and amygdala and insular regions during visual processing of high- vs. low-calorie food [70]. Importantly, the strength of functional activation in the anterior cingulate, insula, and caudate regions is prospectively associated with lower long-term weight loss following a lifestyle weight management intervention [71].

Interim Conclusion and Future Directions

Concerning reward/punishment sensitivity, obesity in adult populations is associated with increased trait sensitivity to punishment, decreased trait sensitivity to reward, increased explicit (but not implicit) motivation towards food-related reinforcement, and hyperactivation and hyperconnectivity of brain reward systems during anticipation of high-calorie food and money.

Impulsivity

In this section, I review available evidence on impulsivity in overweight and obese populations, across personality, neuropsychological and neuroimaging methodologies. I will first review evidence obtained in pediatric populations (children and adolescents), and then move to adult populations. In those instances where systematic or meta-analytic reviews are available, I will ground my discussion on the findings from these analyses. In addition, I primarily review case-control studies providing detailed biometric descriptions of the clinical populations and utilizing well-validated measures and statistical control.

Adolescents

Personality Measures

Meta-analytic evidence has shown small clinically nonsignificant effect sizes for questionnaire measures of impulsivity in pediatric populations [24]. Nonetheless, it has been shown that increases in BMI are significantly associated with elevations of negative urgency [51]. These findings indicate that impulsive personality is not

a major characteristic of adolescents with excess weight; however, higher levels of adiposity are linked to elevations in negative urgency. These elevations in negative urgency are malleable and relevant to treatment outcome, in the sense that the adolescents who reduce urgency levels to a greater extent also achieve greater reductions in BMI during multicomponent interventions (including dieting, physical activity, and psychological interventions) [23].

Cognitive Measures

Meta-analytic evidence has shown moderate to large effect sizes for motor and decision-making measures of impulsivity in pediatric populations [24]. Specifically, adolescents with obesity are characterized by lower vigilance and poorer response inhibition on motor impulsivity measures (e.g. Go/No-Go or Stop Signal), preference for high immediate rewards at the expense of larger delayed punishments on gambling tasks, and preference for immediate rewards over larger delayed rewards on delay discounting measures [24, 72, 73]. Noteworthy, steeper rates of delay discounting are associated with steeper gains in BMI over time [74]. Conversely, obesity is not associated with significant alterations on attentional impulsivity or reflection impulsivity in adolescents.

Neuroimaging

Structural neuroimaging studies have linked higher BMI with decreased orbitofrontal gray matter, mid-cingulate cortex gray and white matter, and body of corpus callosum white matter [75–77], both relevant to increased trait impulsivity and response disinhibition [78, 79]. Conversely, BMI levels have been positively associated with white matter volumes in rolandic operculum, mid-temporal bundles, dorsal striatum and splenium [77, 80] which are relevant systems for sensory/emotional memories and habits. Functional imaging of motor impulsivity during a Go/No-Go task has shown that in obese individuals BMI negatively correlates with activation of dorsolateral and ventrolateral prefrontal cortices and frontal operculum/anterior insular regions during inhibition trials [81]. Risky decision-making in an impulsive choice task is associated with decreased anterior insular and increased midbrain activation in overweight and obese adolescents [82].

Interim Conclusion and Future Directions

Concerning impulsivity, obesity in adolescent populations is associated with BMI-related elevations in trait negative urgency, significant cognitive deficits on response inhibition and decision-making, structural alterations in orbitofrontal, mid-temporal and dorsal striatal regions, and abnormal activations of the anterior insula during response control and risky decisions.

Adults

Personality Measures

Evidence summarized in a systematic review has mapped personality findings to the Five-Factor Model, concluding that obesity is characterized by increased neuroticism and decreased conscientiousness [22]. This notion is in fitting with findings obtained with the multidimensional UPPS-P scale, demonstrating that obesity is specifically linked to elevations in negative urgency and lack of perseverance [59]. Higher neuroticism and negative urgency reflect negative emotion-driven impulsive behavior, as manifested by obesity-related elevations in specific measures of emotional eating [5]. Similarly, *lack of* conscientiousness, or perseverance, as manifested in ADHD-like symptoms has been associated with both emotional eating and external eating [12], both triggered by affective or environmental cues in the absence of hunger.

Cognitive Measures

Evidence from systematic reviews has shown that obesity is associated with significantly poorer performance on measures of motor impulsivity (e.g. Stop Signal, Hayling test), delay discounting

(particularly when food is involved) and risk-taking [22, 83]. There is also evidence showing that obese individuals have deficits in solving maze planning tasks involving components of reflection impulsivity [22, 83]. There is however no consistent evidence about obesity-related deficits on attentional impulsivity or decision-making tests involving uncertainty about punishment [22, 83, 84].

Neuroimaging

Structural neuroimaging studies have demonstrated that obese individuals have reduced gray matter in the dorsolateral prefrontal cortex, frontal operculum and dorsal striatum [27], key brain regions for response inhibition. It has been shown that in female obese individuals BMI negatively correlates with activation of response control specialized regions, including the supplementary motor area, the insula, and the inferior parietal lobe during the "stop" trials of the Stop-signal task [85]. Comparatively less is known about functional brain alterations associated with impulsive decision-making. However, there is longitudinal evidence showing that decreased activation in dorsolateral and ventrolateral prefrontal cortices and inferior parietal lobe regions during delay discounting predict weight gain across 1–3 years in obese female individuals [86].

Interim Conclusion and Future Directions

Concerning impulsivity, obesity in adult populations is associated with negative urgency and lack of conscientiousness/perseverance traits, response inhibition deficits, and decreased frontostriatal gray matter coupled with decreased activation in dorsolateral and ventrolateral prefrontal cortices and inferior parietal regions during impulsivity tasks, which prospectively predicts weight gain. Most imaging evidence stems from studies on obese female populations, but preliminary evidence suggests significant sex-related differences in structural measures and brain-behavior associations [87]. Therefore, a closer look to sex differences is warranted to allow generalization of findings.

Concluding Remarks

The research on reward processing and impulsivity in obesity has been increasing exponentially during the last decade, and is expected to continue to grow over the coming years. Current findings have used a range of methods, and the field is in need of further multimodal and longitudinal studies addressing questions of causality and progression of illness. Notwithstanding these limitations, some points have been well-established across different methodologies and age cohorts. This evidence is summarized in Table 2.1, which provides a snapshot of findings across personality, neuropsychological and neuroimaging measures across pediatric and adult populations. Based on the evidence that I have reviewed in this chapter, it can be concluded that obesity (customarily defined as BMI levels above 30 kg/m^2) is characterized by dispositionally lower sensitivity to reward (reward deficiency), coupled with *higher* responsivity to food rewards, response disinhibition, and steeper discounting of delayed rewards, all of which are longitudinally associated with weight gain. These deficits are also manifested as dysfunctions in neural systems involved on somatosensory processing (insula/frontal operculum), reward seeking (striatum, extended amygdala, cerebellum), stimulus-oriented attention (dorsolateral prefrontal cortex), and decision-making (orbitofrontal cortex). More research is needed on the negative affective pathway to reward seeking and impulsivity, since both sensitivity to punishment and negative urgency (the tendency to make impulsive acts under negative affect) are elevated in populations with obesity. Critically, more research is warranted to address the dynamic association between reward processing, impulsivity and obesity, since both variables are purportedly involved in vulnerability to weight gain, but there is growing evidence on mechanistic pathways by which unhealthy diets and adiposity have a detrimental impact on these characteristics.

Table 2.1 Summary of findings from self-report personality questionnaires, neuropsychological tests and neuroimaging tools that have been applied to the study of sensitivity to reward and impulsivity in the context of obesity

	Personality			Neuropsychological tests				Brain systems		
	SR/SP	Neuroticism	Conscient.	Cue-induced attention	Reinforce. value	Response inhibition	Impulsive choice	Interoception	Reward	Cognitive control
Children/ Adolescents	↓ SR	↑ Urgency with ↑ BMI	NS	NS	↑ Food reinforcing value	↓ Motor Inhibition: (Stop Signal & GNG)	↑ Delay discounting ↑ Preference Reward/Risk choices (IGT)	↑ Correlation Gray matter SII and SR ↑ BOLD SII, Insula, Frontal Oper. & ACC during Food Anticipation ↓ BOLD Insula during Impulsive Choice	↑ Gray matter Hippocamp. ↑ BOLD Midbrain during Impulsive Choice	↑ BOLD activation of dlPFC during Food Visual Cues
Adults	↓ SR ↑ SP	↑ Urgency	↑ Lack of perseverance	NS Reaction Times ↑ Eye-tracked Attention to Food ↑ BOLD signal during Money Anticipation	↑ Food reinforcing value	↓ Motor Inhibition (Stop Signal) ↓ Primed Words Inhibition (Hayling Test)	↑ Delay discounting NS Preference Reward/Risk choices (IGT) ↓ Reflection (Maze Tests)	↓ Gray matter Frontal Operculum ↓ Connectivity Insula	↓ Gray matter Dorsal Striatum & Cerebellum ↑ BOLD mPFC, Striatum & Hippocampus during Food (& Money) Anticipation	↓ Gray matter Dorsolateral Prefrontal Cortex ↓ BOLD Anterior Insula on Stop Signal

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Gut Peptides

3

Tannaz Vakilgilani, Sagen Zac-Varghese, and Stephen R. Bloom

Introduction

Appetite and body weight are tightly regulated by appetite centres within the brainstem and hypothalamus. For weight to remain constant, energy intake and energy expenditure should be balanced. Information regarding energy intake is relayed to hypothalamic and brainstem nuclei via hormonal and neuronal signals from the gastrointestinal tract (GIT). Entero-endocrine cells throughout the GIT release gut hormones. These gut hormones exert diverse physiological functions including gut motility, acid secretion, appetite control and regulation of food intake. The release of gut hormones from entero-endocrine cells is stimulated by the presence of nutrients within the gut lumen and also by the enteric nervous system. We are recently beginning to understand how the diverse population of entero-endocrine cells function and signal to regulate appetite via both paracrine and endocrine means.

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Several gut hormones produced by the intestine and pancreas have been shown to inhibit food intake (anorexigenic) (Table 3.1). These include peptide tyrosine tyrosine 3-36 (PYY_{3-36}), pancreatic polypeptide (PP), cholecystokinin (CCK), oxyntomodulin (OXM), and glucagon-like peptide-1 (GLP-1). Ghrelin produced in the stomach is the only gut hormone known to stimulate feeding (orexigenic).

This chapter discusses the pathophysiological roles of orexigenic and anorexigenic gut hormones in the regulation of food intake.

The Hypothalamic Circuitry

The hypothalamus contains several nuclei involved in appetite regulation including the lateral nuclei, ventromedial (VMN), dorsomedial (DMN), paraventricular (PVN), perifornical and arcuate nuclei (ARC). Anatomically it is in close proximity to the brainstem, amygdala and higher brain centres that are involved in appetite control.

The ARC, positioned at the base of the hypothalamus with an "incomplete" blood–brain barrier, is directly exposed to factors in the systemic circulation such as gut hormones. It contains two subsets of neurons: orexigenic neurons containing neuropeptide Y (NPY) and agouti-related peptide (AgRP), and anorexigenic neurons containing pro-opiomelanocortin (POMC) (Fig. 3.1). The latter is a precursor of α-melanocyte-stimulating hormone (α-MSH), and cocaine- and amphetamine-regulated transcript (CART).

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Table 3.1 Anorexigenic and orexigenic gut hormones

Peptide	Sites of synthesis	Stimulus	Actions	Mediation of action	Molecular forms
Anorexigenic OXM	L cells of distal ileum and colon Pancreas CNS	Meal Calorie content Fat	Inhibits food intake Inhibits gastric acid secretion Inhibits gastric motility Reduces pancreatic enzyme secretion	GLP-1 receptor Glucagon receptor Suppression of ghrelin	–
GLP-1	L cells of distal small ileum, colon Pancreas CNS	Meal	Incretin effect on insulin secretion Suppresses glucagon release Promotes pancreatic β-cell growth Inhibits food intake Delays gastric emptying Inhibits gastric secretion Inhibits lipase secretion	GLP-1 receptor	GLP-17-36 GLP 17-37
PYY3-36	L cells of distal ileum, colon, rectum CNS	Meal Fat and protein Calorie content CCK, Gastric acid, Bile acid, Bombesin, IGF-1	Inhibits food intake Reduces gastric motility Inhibits gallbladder secretion Inhibits pancreatic secretion	Y2 receptor Inhibits NPY	PYY 1-36 PYY 3-36
PP	PP cells in islets of Langerhans CNS		Inhibits pancreatic enzyme secretion Inhibits food intake Gall bladder relaxation	Y4 receptors	-
CCK	I cells of duodenum, jejunum; CNS Enteric nerve ending	Food ingestion, protein, fat	Stimulates gall bladder contraction Stimulates pancreatic exocrine secretion Delays gastric emptying Inhibits gastric acid secretion Reduces food intake Increases satiety Stimulates bowel motility	CCK A CCK B	Multiple Intestinal CCK-33, CCK-8
Orexigenic Ghrelin	Stomach small bowel colon Hypothalamus	Fasting	Promote GH release Increases food intake Promotes gastric motility Promotes PP release	GHS receptor	–

CCK cholecystokinin, *CNS* central nervous system, *GHS* growth hormone secretagogue, *GLP-1* glucagon-like peptide-1, *PP* pancreatic polypeptide, *PYY* peptide YY

α-MSH produces its anorexigenic effects mainly via melanocortin receptors (MCR). Of the five identified MCRs, MC3 and MC4 receptors, present in high density in the PVN, have been shown to be important in the regulation of food intake [1]. α-MSH is a natural endogenous agonist, while AgRP is an endogenous antagonist of the MC3/MC4 receptors [2]. Disruption of the MCR pathway has been shown to be associated with extreme obesity [3]. In fact, transgenic animals lacking the POMC gene, having MC4 receptor mutations or overexpressing AgRP, have been shown to be hyperphagic and obese [3, 4]. In humans, MC4 receptor mutations have been shown to be the most common known cause of single gene (monogenic) obesity [5, 6]. On the other hand, NPY with a shorter half-life compared to AgRP is proposed to exert its effect via Y receptors, subtypes of which have been described (Y1–Y6) (discussed below) [7–10].

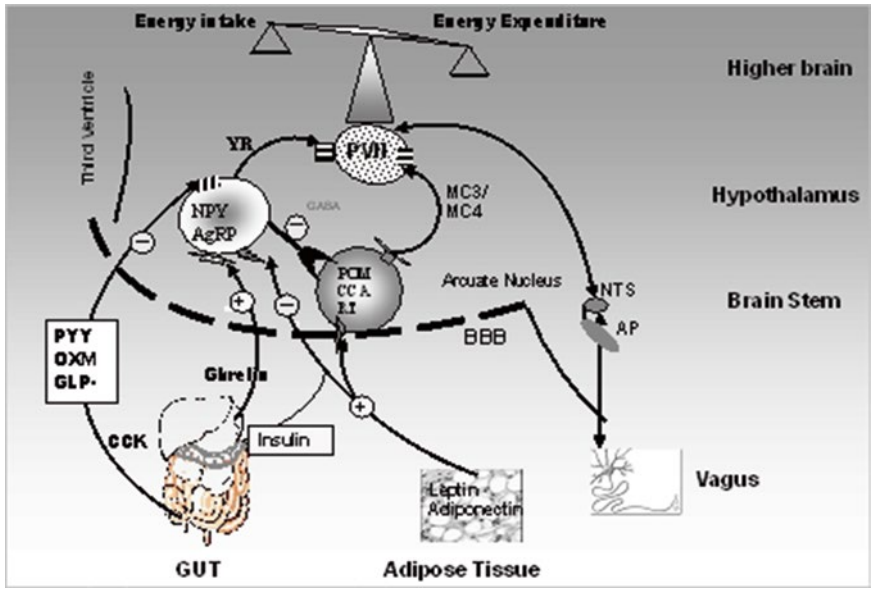

Fig. 3.1 Gut peptide regulation of appetite. Schematic diagram of the gut–brain, gut–gut and gut–adipose tissue interactions. *MC3/MC4 R* melanocortin 3 and 4 receptors, *YR* Y receptors, *NPY/AgRP* neuropeptide Y and agouti-related peptide neurones in the arcuate nucleus in the hypothalamus, *POMC/CART* pro-opiomelanocortin and cocaine-amphetamine regulated peptide, *PVN* paraventricular nuclei, *NTS* nucleus tractus solitarius, *AP* area postrema, *BBB* blood–brain barrier

NPY has a higher affinity to Y1 and Y5 receptors. These are available in high abundance in the NTS from which NPY neurons project to the PVN.

Neuron projections from the ARC extend to the PVN and DMN (Fig. 3.1). Activated neuronal pathways in the PVN signal to the nucleus tractus solitarius (NTS), which also integrates signals from the sympathetic and vagal afferent fibres. The PVN also coordinates input from melanin-concentrating hormone (MCH) producing neurons in the lateral hypothalamus and other brain areas such as the area postrema (AP), regions of the brainstem, and the amygdala that impact food intake. The latter has some areas, which increase feeding and other areas, which inhibit feeding. It is worth noting that areas in the brainstem and amygdala control the mechanics of feeding including salivation, liking, chewing and swallowing. Destruction of these areas would thus cause the animal to lose its recognition for the type and/or quality of food.

The dorsal vagal complex (DVC) comprises the dorsal motor nucleus of vagus (DVN), the AP and the NTS. The DVC is an important part of the brainstem, which transfers peripheral signals from the gut to the hypothalamus via afferent vagal nerves. Mechanoreceptors and chemoreceptors in the GIT activate vagal afferent nerves and these assemble in the NTS. Ultimately, neuronal signals in the NTS conduct signals to hypothalamus. Ascending and descending neuronal projections between the brainstem and hypothalamus are important in the control of food intake [11].

Insulin and glucagon from the pancreas, leptin from adipose tissue and gut hormones (PYY_{3-36}, GLP-1, CCK, and OXM) from the GIT are known anorexigenic hormones. They directly inhibit NPY/AgRP secreting neurons and stimulate POMC/CART neurons in the ARC [12]. Reciprocal to this is the orexigenic gut hormone ghrelin. Ghrelin stimulates NPY/AgRP neurons and inhibits its POMC/CART neurons, thereby promoting meal initiation and food intake. While leptin and insulin are known to be long-term regulators of adiposity and energy expenditure, gut hormones are short-lived signals controlling food intake.

Anorexigenic Gut Peptides

PP-Fold Family of Peptides

The PP-fold family of peptides include PYY and PP from the gut and NPY from the central nervous system. These peptides are structurally similar being 36 amino acid peptides containing several tyrosine residues. They are characterised by a specific tertiary structure known as the PP-fold and they become biologically active following COOH-terminal amidation. PP-fold peptides appear to exert their effects through the Y receptors (Y1, 2, 4 and 5) which are classified according to their affinity to PYY, PP and NPY fragments and analogues [7] (Table 3.2). They are all seven transmembrane domain receptors that inhibit adenylate cyclase by coupling to G proteins. The Y1 receptor also increases intracellular calcium and the Y2 receptor regulates calcium and potassium channels. Y1–Y5 are present centrally in the brain, and peripherally in the intestine, pancreas, heart, muscle and blood vessels. They have diverse functions including stimulations/suppression of appetite, reduced intestinal secretion, vasoconstriction and analgesia. Table 3.1 summarises the distribution and functions of these receptors.

PYY

PYY was first isolated from porcine intestine [13]. It is produced by entero-endocrine L cells throughout the intestine, but predominantly in the ileum and colon [14, 15]. PYY is co-localised and co-secreted with GLP-1 in response to nutritional stimuli. PYY is released into the circulation 15 min following food ingestion. Once in the circulation, the native PYY_{1-36} undergoes N-terminal truncation by the action of dipeptidyl peptidase IV (DPPIV) to produce the 34 amino acid form, PYY_{3-36} [16]. This is the active circulating form of PYY. Post-prandial plasma levels of PYY_{3-36} plateau after 1–2 h, but remain elevated for up to 6 h.

PYY_{3-36} is released into the circulation in proportion to the number of calories ingested [17]. Meal composition has also been shown to affect PYY release. Higher plasma levels of PYY are achieved after isocaloric meals of fat compared

Table 3.2 The affinity, distribution and actions of the known Y receptor superfamily

Receptor	High affinity peptide	Low affinity peptide	Distribution	Proposed actions
Y1	NPY, PYY	PP	Cortex DRG Amygdala Hypothalamus Blood vessels	Analgesia Anxiolysis ↑ appetite Vasoconstriction
Y2 (Pre-synaptic)	NPY, PYY, PYY (3-36)	PP	Hypothalamus DRG Hippocampus Intestine	Anorexia Analgesia ↑ Memory ↓ secretion
Y4	PP,NPY (2-36), NPY (3-36), PYY, NPY/PYY	NPY/PYY fragments PYY (3-36)	Hypothalamus Amygdala Thalamus Intestine, pancreas, heart, muscle	↑ Appetite
Y5	NPY, PYY, NPY (2-36), NPY (3-36), PYY (3-36), NPY/PYY	NPY/PYY fragments	Hypothalamus Thalamus NTS	↑ appetite ↑ ACTH
Y6 (mouse)	PP, NPY/PYY	C-terminal NPY fragments	Intestine Spleen	
Y6	A truncated non-functional receptor in man produced by deletion in sixth TM domain			Heart, muscle, intestine, spleen

DRG dorsal root ganglion, *NTS* nucleus tractus solitarius

with that of proteins and carbohydrates [18, 19]. Recent studies in rodents and in man revealed that protein had the most influential effect on PYY release [20], followed by fat and then carbohydrate [21]. Short chain fatty acid (SCFA) infusion into the colon also stimulate PYY release [22] through GPR43 and GPR41 (SCFA receptors) co-expressed on the L-cell apical surface [23, 24]. A number of other factors have been shown to stimulate PYY release including CCK, gastric acid, bile acids, insulin like growth factor-1 (IGF-1), bombesin and calcitonin gene-related peptide (CGRP). Neural signals, such as vagal stimuli, have also been implicated [25, 26]. Evidence to support the latter is the increase in PYY levels in response to the presence of food in the duodenum, before its arrival to the L cells in the ileum. In contrast, release of the peptide is inhibited during fasting [9, 27], and by GLP-1 [28].

PYY Actions

PYY delays gastric emptying and reduces gastric acid and pancreatic secretions [29]. This inhibitory effect is mediated by the stimulation of Y1, Y2 and Y4 receptors on enterocytes and neurons [30, 31]. Infusion of PYY_{3-36} to healthy volunteers reduces the gut transit [22] probably by its effect on PYY binding sites in the DVC. PYY also affects central appetite regulation [29] and enhances energy expenditure [32, 33].

The peripheral administration of PYY reduces appetite in mice and in man [8, 27]. In mice, administration of PYY_{3-36} peripherally was shown to acutely reduce food intake. This reduction in food intake continued on chronic peripheral administration of the peptide resulting in reduced weight gain [8]. PYY_{3-36} has also been shown to inhibit food intake in man. A single infusion of PYY_{3-36} causes a 30 % and 31 % reduction in food intake in a free-choice meal 2 h post infusion [8, 27] in both obese and lean individuals. Subjective hunger ratings were also reduced with the reduction in calorie intake without changes in gastric emptying [27]. The appetite reducing effect of PYY_{3-36} persisted for 24 h in both lean and obese subjects, despite PYY_{3-36} levels retuning to basal levels, which implies that PYY_{3-36} may be an important physiological postprandial satiety signal. This supports the findings in the animal studies and suggests that, unlike leptin, PYY resistance [9, 18] seems unlikely.

Insulin sensitivity has been found to be improved by PYY_{3-36}. In animal models of diabetes, long-term peripheral administration of PYY3-36 has been shown to improve glycaemic control as a consequence of reduced food intake, body weight and visceral fat [34].

Mechanism of Action

PYY_{1-36} binds to Y1, Y2 and Y5 receptors; however, PYY_{3-36} binds selectively to Y2 receptors. Y2Rs are mainly located in the CNS [35, 36]. The anorexigenic effect of PYY_{3-36} is absent in Y2 receptor knockout mice [8, 9] and was shown to be completely blocked by Y2 receptor antagonist [37, 38]. Peripheral administration of PYY3-36 has been shown to cause c-fos activation in the ARC [8] demonstrating the ability of peripheral PYY_{3-36} to activate neurons in this hypothalamic nucleus.

NPY neurons inhibit POMC neurons via GABA mediation. Therefore, inhibition of the NPY neurons results in a reciprocal activation of POMC neurons and induces appetite suppression [39]. However, the anorectic effects of peripheral PYY_{3-36} were retained in POMC knockout mice raising questions about the importance of melanocortin peptides for the action of PYY_{3-36}. In support of this, MC4R knockout and agouti mice are shown to be sensitive to the anorectic effects of peripherally administered PYY_{3-36} [40]. These findings support the notion that PYY may exert its effect through multiple pathways. Therefore, it is tempting to propose that although Y1 and Y5 receptors have lower affinities for PYY, they might override the actions of Y2 receptors when they are exposed directly to increasing amounts of PYY. This might be the reason for the contrasting actions of PYY when injected to different parts of the brain. The reduction in the orexigenic effects of centrally administered PYY in both Y1 and Y5 receptor knockout mice [41] further supports this hypothesis. In addition, the AP appears to be yet another brain region through which PYY_{3-36} exerts its effect. In rats, ablation of the AP results in an increase in the acute anorectic effects of PYY_{3-36} [42].

PYY Levels in Normal Physiology and Disease

Obese people have relatively lower basal levels of PYY_{3-36} and have an attenuated surge in PYY3-36 following a meal. This might explain their impaired satiety and greater food intake [43]. They also have lower fasting PYY levels compared with lean subjects [44]. PYY levels are subject to diurnal variation. Levels are higher during sleep (in non-shift workers). Levels are also elevated in cachetic conditions such as cardiac cachexia [45], chronic kidney disease (CKD) [46] and hepatic cirrhosis. In patients with diabetic gastroparesis, there are an increased number of colon cells expressing PYY. This may be the cause of the reduction in gastric emptying and the abnormal gut transit time [47]. PYY may also mediate weight loss following gastric bypass surgery. In wild-type mice, weight reduction following bariatric surgery is associated with increased PYY expression and fasting PYY levels [48]. In contrast, bariatric surgery in PYY KO mice was not associated with weight loss acutely.

PP

PP is produced by PP cells (F cells) within the pancreatic islets [49–51]. It is also expressed sporadically throughout the GIT [30]. Circulating PP levels are subject to diurnal variation being lowest in the early hours of the morning and highest in the evening. Its circulatory half-life is seven minutes [52]. PP is released in response to meal ingestion in proportion to size and caloric content of the meal. The release of the peptide is biphasic, though increasing with consecutive meals [53]. Once in the circulation PP levels remain elevated up to 6 h.

Circulating levels of PP are increased by adrenergic stimulation, ghrelin, motilin and secretin [54–56], and are reduced by somatostatin [57]. Vagal tone also appears to regulate PP release both post-prandially and throughout the day. Propantheline (an anti-muscarinic agent) has been shown to block both the diurnal and the post-prandial levels of PP by 60 %. The latter is shown to be abolished by vagotomy [47].

PP has an inverse relationship with body mass index (BMI) with higher levels in anorectic compared to obese subjects [58, 59]. Transgenic mice, with overexpression of PP, have reduced food intake and lower lean body mass [49]. However, obese animal models show lower sensitivity to the effects of PP compared with the high sensitivity observed in lean animals. Peripheral administration of PP reduces food intake, gastric emptying and also increases energy expenditure through the vagus nerve in mice [51, 60, 61]. In patients with Prader-Willi syndrome, intravenous infusion of PP was shown to reduce food intake [62]. Infusion of PP for 90 min to healthy volunteers reduces food intake acutely and also reduces food intake by 25 % 24 h following infusion [63, 64].

It is thought that PP exerts its anorectic effects via the ARC. PP also signals through Y4 receptors in the vagus nerve [51, 65]. Peripheral PP administration leads to c-fos expression in the brainstem, amygdala and hypothalamus [66]. Manganese-enhanced magnetic resonance imaging (MEMRI) in fasted mice following peripheral administration of PP demonstrates reduced signal intensity in the ARC, VMH and PVN, which correlates with reduced food intake [67]. Other postulated mechanisms for the anorectic effects of PP are via the NPY and orexin pathways and through suppression of ghrelin secretion and vagal neurons. Both NPY protein and mRNA expression are reduced following peripheral PP administration and PP has reduced effects following vagotomy.

PP agonists would be attractive as potential agents for obesity treatment. In 2011, PP 1420, an analogue of PP was developed and used in a phase 1 trial study to assess its tolerability; the results were encouraging and further trials are currently being undertaken [68].

Cholecystokinin (CCK)

CCK was the first hormone recognised to be involved in appetite regulation [69]. It is produced primarily by the I cells in the duodenum

and jejunum and to a lesser extent in the ilial mucosa. It is also produced in the brain and by enteric nerve endings where it acts as a neurotransmitter [70]. There are various types of CCK with different lengths. CCK-58, CCK-39, CCK-33 and CCK-8 have all been found in man [71]. The biologically active form of CCK shares a sequence (carboxy-terminus) homology with gastrin [70]. CCK is released post-prandially following exposure of I cells to free long chain fatty acids and amino acids [72, 73]. The cellular pathway, which leads to CCK production, has become clearer in recent years. I cells express GPR40 (a G-protein-coupled receptor), which induces CCK release in response to long-chain fatty acids [74]. It is also recognised that amino acids have a direct effect on I cells by activating calcium sensing receptors (CaSR), which will stimulate CCK secretion [75].

CCK is a known satiety peptide; it slows gastric emptying and inhibits gastric acid secretion, but stimulates intestinal motility, gall bladder contraction, and increases pancreatic exocrine secretion. CCK is known to inhibit food intake in man and in rodents [76]. However the duration of its action is short, with a half-life of only 1–2 min. Therefore, no anorectic effect is observed if CCK is administered more than 15 min before meal intake [77]. Additionally, chronic administration of CCK reduces food intake and increases meal frequency. Consequently, long-term administration does not appear to have any effects on body weight [78]. This suggests that CCK is a short-term inhibitor of food intake.

Mechanism of Action

CCK-1R and CCK-2R belong to the class 1 G-protein-coupled family. CCK activates phospholipase C following binding to these receptors, and this leads to intracellular calcium release [79]. Structurally, there is 48 % similarity in sequence between these receptors [80]. CCK-1R identifies the N-terminal heptapeptide and CCK-2R recognises the N-terminal tetrapeptide, which is similar in CCK and gastrin. This results in greater affinity of CCK-1R to CCK compared to gastrin, whereas CCK-2R has identical binding affinities to both peptides [81]. CCK-1R is the main receptor which modulates food intake and satiety. There are two forms of CCK-1R: high affinity/low capacity and low affinity/high capacity [82]. In mice activation of low and high affinity CCK-1Rs are required to induce satiety, however in rats only the low-affinity CCK-1R activation appears to be important to cause satiety [83]. Pancreas, gall bladder, stomach, kidney, lung and vagus nerve are the main sites that express CCK-1Rs [84]. CCK-1Rs are also present in the brainstem, the hypothalamus; the SON, PVN and DMN, substania nigra, ventral tegmental area and nucleus accumbens [85–87]. There is a high concentration of CCK-2Rs in CNS, however they have a limited peripheral expression in stomach and uterus [84].

Selective CCK-1R agonists cause a reduction of food intake [88]. Although CCK-2R knockout mice are hyperphagic and 28 % heavier than wild-type mice [89], activation and deactivation of this receptor has not revealed any alteration in food intake [90, 91].

The exact role of CCK in inhibition of food intake via the vagus nerve is still unclear. It has been shown that CCK can change gene expression within vagal neurons. Vagal expression of the cannabinoid receptor CB1, melanin-concentrating hormone (MCH) and its receptor MCHR-1 is abolished by activation of CCK-1Rs [92, 93]. It is also recognised that CCK enhances the expression of the Y2 receptor [94], and CART [95] on vagal afferent neurons.

Peripheral administration of CCK, at doses sufficient to inhibit food intake, has been shown to induce synthesis of c-fos in the brainstem, NTS and the dorsal vagal nucleus [96]. Vagotomy blocks the effect of CCK on food intake indicating neuronal requirement for the mediation of CCK action to the CNS [97]. In obesity, because of the decreased electrical excitability, vagal afferent neurons display resistance to the effect of CCK [98].

The Proglucagon Gene Products

Proglucagon is a prohormone containing 160 amino acids with a 20-amino acid signal sequence

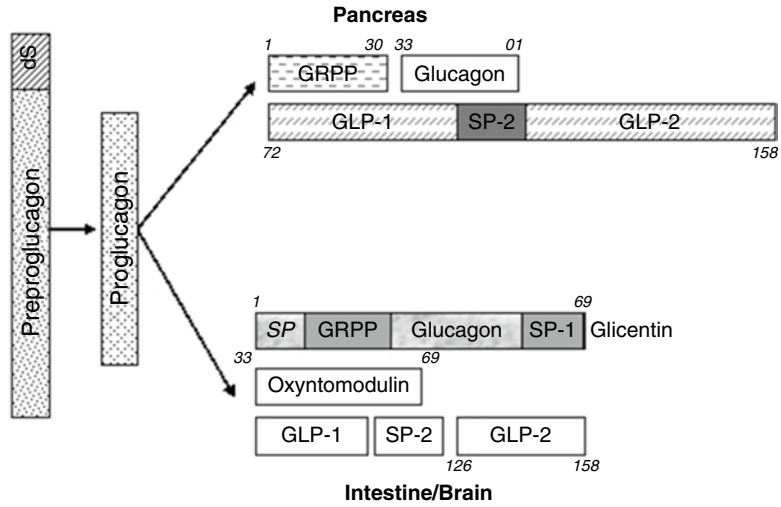

Fig. 3.2 Preproglucagon products. *GRPP* glicentin-related pancreatic polypeptide, *GLP-1* glucagon-like peptide-1 (7-36), *GLP-2* glucagon-Like peptide-2, *SP-1* spacer peptide-1, *SP-2* spacer peptide-2, *S* signal peptide

at the N-terminal end [99]. The preproglucagon gene is expressed in alpha cells within the pancreas, entero-endocrine L cells within the intestine and the NTS in the brainstem [100]. Prohormone convertases 1/3 and 2 convert proglucagon to a number of biologically active fragments. Specifically, in the CNS and L cells OXM and GLP-1 and GLP-2 are produced [101] and in the pancreas, glucagon is produced [102] (Fig. 3.2).

Oxyntomodulin (OXM)

OXM is a 37-amino acid peptide produced in the L cells of the intestine along with GLP-1 and GLP-2 [103, 104]. OXM shows diurnal variation with low levels early in the morning and higher levels in the evening [105]. It is released in proportion to food ingestion and calorie intake [103]. Increased plasma levels of OXM have been shown to inhibit gastric acid secretion and motility in both humans and rodents. OXM also stimulates intestinal glucose uptake and decreases pancreatic enzyme secretion in rats. It also causes insulin release via either direct stimulation of β-cell GLP-1R and glucagon receptors (GCGR) or activation of GLP-1Rs on sensory nerves [106, 107].

Administration of either OXM or OXM analogues results in weight loss in obese rats, mice and humans by inhibition of food intake and increases in energy expenditure [108–110].

No specific OXM receptor has been identified. However, OXM is an agonist for both the GLP-1R and the GCGR [101, 111, 112]. OXM reduces food intake by activating GLP-1Rs [113, 114]. Recent studies suggest that OXM exerts its stimulatory effect on energy expenditure via GCGR activation [115, 116] and its glucoregulatory action mostly via GLP-1Rs [117].

Exendin$_{9\text{-}39}$, which acts as a GLP-1 antagonist, can block the actions of both GLP-1 and OXM [18]. GLP-1Rs are present in the NTS and the ARC in addition to its widespread presence peripherally in the GIT, lung, pancreas and heart. Interestingly, exendin$_{9\text{-}39}$ administration into the ARC abolishes the peripheral effects of OXM but not those of GLP-1 [114]. This suggests an ARC site of action for OXM, while GLP-1 acts via the brainstem. Further evidence suggests different neuronal activation patterns between OXM and GLP-1. OXM has a lower affinity (twofold) to GLP-1 receptors compared to GLP-1 [118]. Activation of the neuronal c-fos expression in the ARC, but not in the brainstem region, was observed following intraperitoneal (IP) administration of OXM and exendin$_{9\text{-}39}$ [108, 112, 119, 120]. This pattern of activation is different from that seen following GLP-1 administration [114].

An OXM analogue, selective for GLP-1Rs, has a 100-fold lower effect on liver glycogenolysis.

Chronic administration of this analogue to obese mice revealed that weight loss, lipid lowering and anti-hyperglycaemic effects were reduced compared to native OXM. These data support the potential role of GCGR activation by OXM in inducing weight loss [115].

OXM simultaneously activates GCGRs and GLP-1Rs and these have contradictory effects on glucose homeostasis. However, the overall effect is that OXM ameliorates glucose tolerance [117, 121]. In rodents studied with a pancreatic clamp, intrahypothalamic glucagon inhibits liver glycogenolysis and consequently opposes the effects of circulating glucagon to increase liver glucose production. This suggests that activation of GCGR in the CNS following OXM administration in animals may improve glucose metabolism [122].

An additional mechanism whereby OXM may exert its effect on appetite is via suppression of ghrelin. In rodents and humans, peripheral administration of OXM results in a reduction of circulating ghrelin levels by 20 % [114] and 44 % [120] respectively. Human studies on the effects of OXM on appetite control appear to be promising and indicate a novel potential role that OXM or OXM agonists may have as anti-obesity therapeutic agents [108].

Glucagon-Like Peptide-1 (GLP-1)

GLP-1 is secreted from the L cells in response to food intake [123, 124]. Two biologically active potent forms (GLP-$1_{7\text{-}37}$ and GLP-$1_{7\text{-}36}$) have been identified, which undergo rapid inactivation and cleavage by dipeptidyl peptidase IV (DPP IV). As a result GLP-1 has a very short circulatory half-life of 1–2 min. Both isoforms have the same potency but GLP-$1_{7\text{-}36}$ is the main circulatory form in man [125].

GLP-1 levels fall with fasting and rise postprandially. In expectation of food, GLP-1 levels have been found to rise in animals [126]. It has been also shown that eating slowly enhances GLP-1 and PYY levels following food intake [127]. Patients with type 2 diabetes have lower post-prandial GLP-1 levels as compared to controls [128]. Recent studies have shown that activation of prostaglandin E receptor 4, free fatty acid 1 and osteocalcin triggers GLP-1 secretion in mice [129–131].

GLP-1 Actions

GLP-1 exerts its effects via a range of different pathways. It acts as a regulatory peptide in appetite control, it enhances satiety [132] and consequently suppresses food intake [133, 134]. Similar to glucose-dependent insulinotropic peptide (GIP), GLP-1 is an incretin hormone that triggers greater insulin secretion following an oral glucose load as compared to an intravenous glucose infusion [135].

GLP-1 stimulates β-cell proliferation, promotes islet cell neogenesis and reduces β-cell apoptosis in rodents [135, 136]. It also stimulates insulin release in the presence of glucose [137], inhibits glucagon secretion [138] and reduces gastric emptying which results in the reduced transient rate of nutrients to small bowel leading to a decrease in glycaemic excursions following food ingestion [139].

GLP-1 induces adenyl cyclase activity and consequently cAMP production via GLP-1R activation. GLP-1Rs have been identified in both glial and neuronal cell types, in the hypothalamus, striatum, brainstem, substantia nigra and subventricular zone [140–142]. There is a higher volume of GLP-1R mRNA in ARC, PVN and SON [143]. GLP-1 and leptin are present in the nodose ganglion cells and the congruent action of these two peptides stimulates the vagus nerve. This suggests that synergism of these hormones might occur at the level of the vagus nerve resulting in inhibition of food intake [144]. The role of the vagus nerve in mediating GLP-1 action is further demonstrated by the attenuation of GLP-1's inhibitory effect on food intake following total truncal vagotomy [25]. GLP-1 results in c-fos expression in the brainstem [114]. Peripheral injection of GLP-1 resulted in intensified c-fos expression in the ARC, whilst ICV administration enhanced c-fos expression in the PVN, NTS and AP [25, 145].

Central administration of GLP-1 in rodents has been shown to inhibit food intake, which, if continued, results in weight loss [133]. Peripheral administration causes reduced food intake in rodents and man in a dose-dependent manner [134, 146–149].

Subcutaneous injections of GLP-1 in obese human subjects over 5 days were shown to cause

a 15 % reduction in calorie intake [150] and 0.5 kg weight loss. Though low levels have been shown in obese subjects, levels normalise after weight loss [134]. The anorectic effects of GLP-1 have been shown to be preserved in obesity [150]. Vilsboll and colleagues have shown that GLP-1R agonists cause an average weight reduction of 2.9 kg in overweight and obese people with or without type 2 diabetes [151].

Both intravenous and subcutaneous infusions have been shown to improve blood glucose levels in poorly controlled diabetics. HbA1c was shown to be reduced by 1.3 % over a 6-week period of subcutaneous infusion of GLP-1 in addition to a 2 kg weight loss [152].

GLP-1 levels increase following Roux-en-Y bypass, which could be one of the reasons for glucose normalisation post-surgery in patients with type 2 diabetes [153].

The collective actions of GLP-1 resulting in inhibition of food intake, reductions in weight, glucose dependant reductions in blood glucose levels, and improvements in diabetes control, make it an excellent candidate for the treatment of diabetes. Its therapeutic application is of immense importance in diabetic patients who are increasingly overweight and suffer from drug-related hypoglycaemia.

Orexigenic Gut Peptides

Ghrelin

Ghrelin, the endogenous ligand for the growth hormone secretagogue receptor [154] (later called ghrelin receptor GRLN-R), is a 28-amino acid peptide which is a product of preproghrelin peptide modification by prohormone convertase (PC) 1/3 [155]. Ghrelin requires acylation with medium-chain fatty acids (MCFAs) at the serine 3 residue by ghrelin O-acyltransferase (GOAT) to convert it to its active form [156]. Proghrelin is octanolated by GOAT prior to its entrance into the golgi apparatus where it is cleaved by PC 1/3 [157]. Desacyl-ghrelin, which is an unacylated peptide and lacks the fatty acid chain is present at higher levels in the circulation than acyl ghrelin. It was primarily believed to be inactive, as it does not appear to activate GRLN-R, however further studies suggest that it does have an active role [158, 159]. Ghrelin is secreted from oxyntic endocrine cells in the stomach and to a lesser extent from cells in the small and large intestine named X/A cells in rats and P/D_1 cells in humans [160]. Two known morphological types of X/A cells, closed-type and open type are located in the stomach and distal gut respectively [161]. It has been shown that circulating levels of ghrelin are reduced significantly following gastrectomy [162]. There is evidence for ghrelin expression in other tissues including the hypothalamus, pancreas, lungs, ovaries and testes. In the hypothalamus, ghrelin expression has been shown in the ARC adjacent to the orexigenic neurons; however, its physiological role here needs to be established [163, 164]. Circulating levels change throughout the day in relation to meals; increasing during fasting, peaking just before food intake and decreasing post-prandially [165–167]. Similarly, GOAT expression and circulatory levels are increased with fasting [168]. Ghrelin reaches trough levels 60–120 min after food intake. As with other peptides, levels are subject to diurnal variations being high in the night and declining in the early hours of the morning along with leptin levels. The post-prandial decline of ghrelin is proportional to calorie intake and nutrient sensing but not stomach volume. In keeping with this, glucose, but not water/saline, infusion into the stomach causes suppression of ghrelin levels [169]. The effect of glucose on ghrelin is independent of insulin action. Further studies in man have shown that carbohydrate and to a lesser extent fat reduces ghrelin levels in normal [170] and type-1 diabetic patients [171]. While leptin, GHRH, testosterone, thyroid hormone and parasympathetic activity up-regulate ghrelin; insulin, somatostatin, growth hormone and $PYY_{3\text{-}36}$ result in its down-regulation.

Ghrelin Action

Ghrelin has various biological actions including regulation of food intake, energy homeostasis and

GIT motility. Since its discovery, accumulating evidence supports its orexigenic effects and its role in the regulation of body weight. In both animal and human studies, ghrelin has been shown to contribute to signalling pre-prandial hunger and meal initiation [160, 162]. Acute administration of ghrelin increases food intake in animals and obese and lean humans [172–174], while chronic administration results in hyperphagia and obesity in animals [175]. Central administration of ghrelin, by direct injection into the ICV or ARC, stimulates food intake and can be inhibited by GRLN-R antagonists [176]. This suggests that ghrelin is an endogenous regulator of food intake. GRLN-R knockout mice did not have enhanced food intake following exogenous ghrelin administration [177]. In humans; following intravenous ghrelin administration, though short lived, appetite and food intake increases by 28 % in normal volunteers [178]. However, satiety is not changed post-prandially following ghrelin administration [178]. In a recent study, participants exposed to food pictures during an intravenous ghrelin infusion had increased activation in the amygdala, orbitofrontal cortex, anterior insula and striatum as measured by functional MRI [179].

Mechanism of Action

Evidence demonstrates that ghrelin exerts its effects mainly via the orexigenic peptides NPY/AgRP in the hypothalamus. Central injection of ghrelin increases NPY/AgRP gene expression and blocks the anorexic actions of leptin. NPY/AgRP antibodies or NPY Y1 receptor antagonists abolish ghrelin-induced feeding but ghrelin antibodies do not inhibit NPY-induced feeding. Electrophysiological studies have shown that ghrelin activates NPY neurons and inhibits POMC with the former being post-synaptic and the latter a pre-synaptic effect. Peripheral administration of ghrelin also results in c-fos expression primarily in the ARC. This suggests that ghrelin might reach the ARC through the incomplete blood–brain barrier at the base of the hypothalamus. In keeping with this idea, animals with a damaged ARC show no increase in feeding after ghrelin administration. Ghrelin neurons are expressed elsewhere in the brain. An increase in c-fos activation following central ghrelin administration has been shown in the PVN, DMN, lateral hypothalamus and in the AP and NTS in the brainstem [180, 181]. Central ghrelin neurons also terminate on orexin-containing neurons in the lateral hypothalamus [182] which have been shown to be stimulated following ICV ghrelin injection.

Despite the evidence supporting its orexigenic effect, central ghrelin action does not appear to be the only factor involved in meal initiation and promotion of food intake. Recently, ghrelin infusions in six men and one woman with previous complete truncal vagotomy had no effect on food intake [183]. This suggests that intact vagal nerve is required for ghrelin's stimulatory effect on food intake.

Ghrelin in Physiology and Disease

In addition to calorie intake and meal composition, ghrelin levels appear to be influenced by the nutritional status of the individual. In transgenic mice with increased levels of bioactive ghrelin in their stomach, a high fat diet suppresses the hyperphagic effect of ghrelin [184]. The basal level is shown to be reduced in chronic obesity with an attenuated post-prandial response [170]. The latter may explain persistent eating habits in obese patients. The level of ghrelin is increased during fasting, cachexia [185], in states of malnutrition and in patients with anorexia nervosa [186]. An increased circulating level of ghrelin has been documented in patients with Prader-Willi syndrome compared to obese controls [187]. Ghrelin levels are reduced after a Roux-en Y gastric bypass, but not other forms of anti-obesity surgery, despite massive weight loss [188]. One explanation might be that the surgery involves the removal of the ghrelin secreting part of the stomach [188, 189], although the real mechanism is still unknown. However, in addition to the mechanical restriction due to reduced stomach size and hence reduced meal portions, it has been hypothesized that the decreased ghrelin levels seen in these patients contributes to their maintained weight loss.

Gut Hormone Synergism and/or Antagonism

From the previous sections, it is evident that multiple factors are involved in the regulation of food intake and energy homeostasis and gut hormones appear to play a central role. Here, we propose three different interactive processes (Fig. 3.1):
Gut–Brain interactions
Gut–Gut interactions
Gut–Adipose interactions

Gut–Brain Interactions

Gut peptides increase/reduce food intake via the appetite centres in the brain. This can be through specific known or even yet unknown receptors, direct effects from the circulation and/or through neuronal activation outside the blood–brain barrier. Peripheral and central administration of both the orexigenic and anorexigenic gut peptides results in c-fos activation (neuronal activation) in the ARC. Suppression/activation of NPY neurons and NPY mRNA expression and the reciprocal effect in POMC neurons following gut peptide administration is associated with altered feeding control. Several receptors that are involved in mediating the actions of gut peptides in the hypothalamus and brain stem have now been identified (Table 3.2). In support of this, receptor knockout animals have defective food intake and body weight. Similarly, defects in MC4 receptors have been described in human forms of obesity. However, the central effect of these gut peptides is abolished in vagotomised animals, indicating the importance of neural pathways in connecting gut signals to the hypothalamus and other appetite centres in the brain.

Gut–Gut Interactions

Three mechanisms appear to be involved here. Firstly, the effect of nutrients on the release of gut peptides; secondly, the synergistic and antagonistic actions of gut peptides on each other; and thirdly, the effects of gut peptides on gastric emptying and gut motility.

In addition to external cues, following food ingestion, various factors affect the release and circulating levels of gut peptides and thereby their effect on the appetite centres in the brain. Nutrients sensed within the gut [18] influence PYY, PP, OXM and GLP-1 release while stomach distension influences the release of PP and CCK, which indicates the effects of chemoreceptors. A higher calorie intake results in a more sustained release of PYY and consequently a reduction in calorie intake in the subsequent 12–24 h. Reciprocal to this ghrelin is suppressed post-prandially in proportion to meal energy content assisting further in promoting satiety and meal termination.

Gut hormones appear to act both synergistically and antagonistically with each other. Interestingly, increasing evidence suggests that whichever way they work they appear to complement each other to promote satiety. Co-administration of PYY_{3-36} and PP reduces food intake in an accumulative way both in humans and in rodents [190, 191]. PYY_{3-36} and OXM co-administration can have an additive anorectic effect in overweight and obese humans [192]. Exendin, a GLP-1 receptor agonist, and PYY act synergistically, but through different mechanisms to reduce food intake [193]. CCK is well known to produce early satiety [77], but the meal to meal duration is longer than what can be explained by CCK levels. Therefore, it is in order to suggest a

(continued)

Gut–Gut Interactions (continued)

sequential release and suppression of gut hormones to sustain the diurnal pattern of food intake. For example ghrelin peaks before food ingestion and is suppressed post-prandially, during which CCK, one of the earliest peptides released, promotes early satiety. While persistence of PYY_{3-36} and OXM level prevents the animal (human) from continuous eating and reduces subsequent calorie intake in the following 12–24 h [27, 120]. In contrast, GLP-1 has been shown to suppress PYY_{3-36} [28], however, the short half-life of GLP-1 in circulation might yet be another explanation for the persistent release of PYY. Similarly, OXM has been suggested to exert its anorexigenic effect, at least partly, through the suppression of ghrelin. To some extent, this may explain the suppression of ghrelin post-prandially in addition to its suppression by nutrient sensing in the gut.

Another action of gut peptides, PYY, OXM and PP is the reduction of gastric motility. This causes delay of gastric emptying, and consequently leads to the persistence of food/nutrients in the gut. The latter may produce a satiating effect through, three mechanisms: (1) activation of chemoreceptors, (2) activation of the vagal afferents, and (3) persistence release of PYY and OXM.

Gut–Adipose Interaction

Gut hormones have been shown to interact with long-term signals from adipose tissue. GLP-1 is known to improve insulin sensitivity and thereby glycaemic control. In rodents, peripheral administration of PYY_{3-36} for 4 weeks resulted in improved glycaemic control and reduced body weight and visceral fat [188]. Wynne et al. [108] showed a significant reduction in leptin and an increase in adiponectin, markers of adiposity, associated with reduced body weight in 14 patients who had subcutaneous OXM injections for 4 weeks.

Conclusion

Obesity is a global health problem that has become a real challenge for health care systems due to its associated high morbidity and mortality rate. Despite the large volume of research in complex signalling pathways between gut and brain, no pharmacological treatment has yet been developed that can produce the considerable weight loss seen following bariatric surgery. However, bariatric surgery has its own hazards and its use is limited to morbidly obese individuals. Bariatric surgery results in an alteration of the gut hormone profile that may actually be responsible for persistent weight loss. Finding a pharmacological treatment for obesity will be a major breakthrough. The decision to eat or not and/or alterations in energy expenditure are central to the dilemma of increased body adiposity.

Gut peptides are secreted from the gastrointestinal tract either before or after each meal. They can act in synergism or antagonistically to each other, but in a sequential manner and in concert with neural and long-term signals from adipose tissue. Recent advances in establishing their identification, characterisation and their increasingly recognised effect on appetite and gastrointestinal motility has contributed tremendously to our understanding of the central regulation of appetite and energy homeostasis. Gut hormone-based therapy already exists in current clinical practice. We are now entering a new era for discovering longer acting synthetic gut hormones and their combination therapy as a novel obesity treatment.

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Critical Importance of the Perinatal Period in the Development of Obesity

4

Peter R. Baker II and Jacob E. Friedman

Introduction

As the adult and childhood obesity epidemic becomes ever more widespread, attention has turned to the early origins of obesity in hopes of finding potential causes and suitable interventions. Recent research in maternal–fetal health has shed light on an aspect of obesity previously overlooked, but clearly fundamental in the origins of obesity and related diseases. In arguably the most crucial time of human development, the time spent in utero, humans are inextricably attached and exposed to the maternal environment. The perinatal period from conception to 1 year of life where infants triple their fat mass is a period of profound metabolic changes that are directly influenced by the mother's nutritional and metabolic status. While we had assumed that the maternal–placental–fetal interface was homeostatic, well regulated, and relatively unchanging from pregnancy to pregnancy, it is now increasingly evident that each system has its own independent physiology and metabolism, and that each trimester has the ability to profoundly alter the trajectory of developing infant metabolic systems.

For this reason research has turned to the maternal effects of obesity on fetal development as a critically important factor in the origins of intergenerational obesity, particularly in children. The central hypothesis lies in the notion that when pregnancy is combined with pre-existing obesity, this results in a developmental program of epigenetically induced metabolic dysregulation in tissues and cells from the brain, skeletal muscle, immune system, adipose tissue, pancreas, and liver. This dysregulation persists postnatally, and predisposes the offspring to early onset obesity and obesity-related sequelae. Thus, metabolic programming of intergenerational obesity, due to early life exposures both during gestation and postnatally may be passed on from generation to generation, and have the potential to multiply exponentially on a population-based level.

Here, we discuss the current state of knowledge on how maternal obesity alters placental and thereby fetal metabolic regulation. We discuss the consequences of excess maternal fuels, inflammation, and oxidative stress associated with obesity and insulin resistance, and how these may combine to affect fetal development on a cellular and molecular level to change appetite, mitochondria, and fuel storage. Efforts to interrupt this transgenerational cycle are important from a public health perspective. A successful intervention would benefit the child, the mother, her future pregnancies, and subsequent generations.

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We also examine potential targets for intervention using nutritional and pharmaceutical-based therapies.

The Combination of Obesity and Pregnancy: A Metabolic Recipe for Excess Infant Growth

Obesity in Pregnancy: Insulin Resistance and Altered Fuel Metabolism

Depending on ethnicity, current estimates are that obesity and overweight effect up to two-third of all US women of reproductive age (NHANES data 2012). Women entering pregnancy who are obese and insulin-resistant already carry cause for concern, but the effects of pregnancy on insulin sensitivity and gestational weight gain compound these untoward effects, thus exposing the growing fetus to excess fuels, hormone changes (adiponectin, leptin, insulin), and inflammatory cytokines. In the fed state, insulin resistance increases LDL cholesterol, VLDL-derived lipids, and changes in both circulating and local inflammatory mediators. In the fasting state, insulin resistance is associated with excess lipids in the serum as free fatty acids and triglycerides associated with lipoproteins (VLDL and LDL), all of which are known to adversely affect placental health and infant birth weight [1–5]. In addition to elevated lipids, growing evidence also suggests that insulin resistance is associated with elevation of plasma branched chain amino acid levels (BCAA, including valine, leucine, and isoleucine) [6]. The role of disordered BCAA metabolism may, by some accounts, lie in adipose tissue and is associated with further increased rates of lipolysis and insulin resistance in this tissue [7]. This, in turn, may accelerate lipid availability and fuel transfer when combined with the normal metabolic changes that occur during pregnancy.

In association with increased rates of lipolysis of triglyceride stores from adipose tissue that occurs naturally in late pregnancy, there is normally a significant increase of fatty acid oxidation in skeletal muscle, but the pathways for fatty acid oxidation may be suppressed by obesity resulting in excessive maternal insulin resistance [8, 9]. Although the exact mechanisms are still unclear, key metabolic regulatory genes (including the PPAR and SIRT families) contribute to reduced fatty acid oxidation in skeletal muscle, causing mitochondrial dysfunction and accumulation of medium chain acylcarnitines esters and corresponding impaired ability to use long and medium chain fatty acids for energy [8]. The resulting decrease in mitochondrial energy production is further exacerbated by reduced glucose transport into skeletal muscle and adipose tissue, believed to be caused by placental hormones interfering with insulin signaling [10]. Further, in the liver fatty acid oxidation is also impaired with excess free fatty acids and trigylcerides stored in vesicles resulting in fatty liver and hepatic inflammation, presumably via lipotoxicity. This inflammation likely contributes to hepatic insulin resistance as well as reduced suppression of hepatic glucose production, seen in obese and GDM subjects during late pregnancy [11, 12]. Placental hormones responsible for decreased glucose transport in skeletal muscle also contribute to hepatic insulin resistance by interfering with insulin signaling [13, 14].

Increases in biomarkers of oxidative stress and reduced mitochondrial activity have been reported in maternal skeletal muscle during obesity [15]. Mechanisms underlying these mitochondrial abnormalities are not completely understood, however it is well documented that mitochondrial function is abnormal on multiple levels in obese as compared to normal weight individuals. It is clear that the combination of increased fuels and reduced expression of antioxidant enzymes like manganese superoxide dismutase (MnSOD) in skeletal muscle and adipose tissue results in increased reactive oxygen species (ROS) and inflammation [15]. This appears to magnify insulin resistance even further in obese individuals during pregnancy.

Inflammatory Changes and its Effect on the Placenta and Fetus

The innate and adaptive immune systems also play a significant role in provoking maternal insulin resistance when combined with obesity. Mitochondrial dysfunction and ROS production is coupled with cytokine release (e.g. TNF-α), adaptive immune cell activation (e.g. CD8+ T cells) [16], and immune cell invasion into tissues (e.g. macrophage infiltration of adipocytes) [17]. Evidence also suggests that inflammatory genes are upregulated in adipose tissue [18] and skeletal muscle [19] of obese women early in gestation, suggesting that local tissue inflammation may play a major role in insulin resistance during pregnancy. Further, recent results suggest that alterations in the immune system may be due to restructuring of the maternal gut microbiome as pregnancy advances [20]. Evidence for direct metabolic influence and a downstream effect(s) of mucosal immune responses both contribute to the exacerbation of metabolic derangement and inflammation in obesity [21–23].

Women who enter pregnancy in the obese state (with all its metabolic sequelae) experience the natural insulin resistance of pregnancy which then further impacts the development of the placenta and fetal metabolic systems. Insulin resistance increases or sometimes goes unchanged in the first trimester, but worsens in all women particularly during the third trimester, especially when gestational diabetes (defined as glucose intolerance first recognized in pregnancy) is diagnosed. In the early first and second trimester the mother may actually be more sensitive to insulin than she is in the nonpregnant state leading to increased lipid storage and adiposity [24]. While this anabolic lipid storage is more profound in nonobese women, likely due to their underlying insulin sensitivity, storage of higher amounts of fuels in the obese mother exacerbates an already deranged metabolism. The effects on fetal development, specifically on the placenta and at an epigenetic level in the developing fetus, is largely unknown. It is clear though that infants born to women with visceral adiposity who have greater insulin resistance in the first trimester are at risk for increased neonatal birth weight [25].

The increase in lipid catabolism in late pregnancy results in a decrease in skeletal muscle insulin sensitivity (−50 %) that serves to allow glucose to reach the rapidly growing fetus. The peak use of amino acids and glucose by the fetus occurs at 22–26 weeks, while lipid transport into the fetus accelerates in the third trimester [26]. Maternal fatty acid oxidation normally increases in late pregnancy [27, 28]. In obesity however, genes involved in inflammation and fatty acid lipolysis are more highly upregulated in maternal adipose tissue, resulting in greater mobilization of glycerol and free fatty acids to mother and the developing fetus. This is coupled with an increase in liver VLDL triglyceride production which is sustained by high estrogen levels [29]. Physiologically, this catabolic process was thought to allow the mother to utilize fatty acids in muscle and glycerol (a gluconeogenic substrate in the liver) to be used preferentially over ingested glucose and amino acids. However, the latter two molecules are used preferentially in the fetus, and are transported actively across the placenta.

The effects of an earlier shift to a catabolic state [30] in obese versus non-obese mothers, coupled with the maternal state of insulin resistance and preferential transport of fatty acids to the fetal side of the placenta, exposes the fetus of the obese mother to much larger amounts of fatty acids at an earlier time in gestation than in nonobese individuals. In the placenta, during the third trimester, gene expression of lipid transport-associated genes is increased by ~65 %, while glucose only increases by 9 % [31]. Add to this the fact that the fetus does not readily oxidize fatty acids due to low carnitine palmitoyl transferase enzyme activity, the result is the fatty acids delivered to the fetus are stored as adipose tissue or used in anabolism. Active fatty acid transport from the mother to the fetus creates a preferentially (and exponentially) higher concentration of fat on the fetal side of the placenta especially in the last 10 weeks of gestation [26, 32–34]. It is thought that this overload of lipids, specifically in the third trimester, may trigger placental inflammation and results in

exposure to cytokines in the fetus along with a predisposition to macrosomia [35]. In a nonhuman primate model obese mothers on high fat diet with excess hyperinsulinemia show reduced uterine and fetal blood flow, suggestive of fetal hypoxia [36]. Further, 13 of 36 cytokines examined were significantly upregulated in the umbilical circulation (but not in the mother's circulation) from these insulin-resistant dams on HF diet. As fetal and placental hypoxia can stimulate the production of cytokines, these findings suggest that high maternal insulin resistance may trigger fetal/placental hypoxia that in turn increases circulating inflammatory cytokines in the fetus. This is consistent with reported human data showing increased inflammation in cord blood of infants born to obese mothers [37], and in sheep fetuses from mothers exposed to over-feeding [38]. While organ/tissue development, particularly the placenta is markedly different in rodents and other species compared to humans and nonhuman primates, studies show that lowering placental inflammation in a transgenic obese mouse model prevented subsequent development of inflammation and nonalcoholic fatty liver disease (NAFLD) that was otherwise seen in the wild-type offspring [39]. This is further supported by a recent study demonstrating increased and persistent levels of inflammation in micropremies (<28 weeks gestation) born to obese mothers, for up to 2 weeks postnatally [40]. This suggests an exaggerated and prolonged inflammatory state in the third trimester and beyond. Taken together, these results suggest a model whereby excess maternal insulin resistance results in exposure to hypoxia/inflammatory stimuli in the fetus during gestation in addition to lipid overload may be a critical driver of fetal developmental programming of juvenile obesity and its sequelae.

Obesity in Pregnancy: Impact on Fetal Metabolic Systems

The effects of changes in circulating fuels on fetal development can be dramatic. Along with obesity, gestational diabetes is on the rise given the prevalence of obesity (BMI > 30) in women of reproductive age approaches 30 %. Both pregestational and gestational (after 16 weeks gestational age) diabetes have damaging effects, with the former being more detrimental than the latter. During the critical period of organogenesis and limb formation in the first trimester the teratogenic effects of pregestational diabetes are well established, and include cardiac malformation [41], neural tube defects, and cranial-caudal regression [42, 43]. The mechanisms are still poorly understood, but are thought to involve multiple factors including high, fluctuating insulin levels, high amounts of circulating fatty acids, overproduction of reactive oxygen species, and direct, dose-dependent, toxic effect of hyperglycemia [44].

While there are known effects of hyperglycemia on fetal development, the effects of obesity can be more subtle but with equally lasting influences on the offspring. The incidence rate of macrosomia (infant birth wt >90 percentile) has increased to roughly 20 % of all births, the majority of which are born to normoglycemic mothers. A maternal body mass index (BMI) of >30 kg/m^2 has been associated with isolated first trimester pregnancy loss by a factor of 1.2 and recurrent pregnancy loss by a factor of 3.5 as compared to pregnancies occurring in normal weight mothers, even in the absence of co-morbid conditions like polycystic ovary syndrome [45]. Conversely, maternal weight loss is associated with a decreased rate of fetal loss [46]. Throughout gestation, the effects of overnutrition alone are transmitted from mother to fetus, and the insulin resistance on the maternal side of the placenta is transmitted to the fetal side. The most obvious effect of high glucose is macrosomia. Even in the absence of diabetes however, there is still risk for macrosomia in the infant of an obese, normoglycemic mother [47, 48]. Emerging data points to the effects of triglycerides in fetal overgrowth, as infants of normoglycemic obese mothers have been shown to have more adipose tissue mass [30] for the same birth weight. Likewise, in the absence of macrosomia, infants of obese mothers can demonstrate increased adiposity at birth, may have fatty liver, and are at future risk for onset of metabolic syndrome as early as 6 years of age. Proinflammatory cytokines in the amniotic fluid of obese versus nonobese women suggest the

underlying inflammatory nature of obesity in pregnancy may be transmitted to the fetus. The full impact this state has on fetal development is unknown, however there are known adverse developmental effects of inflammation on the fetal lung [49], immune system [50], liver [39, 51], and the central nervous system [52].

New Factors Involved in the Development of Maternal Insulin Resistance

The Microbiome

New studies indicate that the maternal gut microbiome may be an important source of maternal insulin resistance and inflammation, and these effects may be passed on to the newborn infant. There is a wide variety of bacterial species that colonize the gut of the obese mother that can shift both her metabolism and alter the initial colonization of the newborn infant. The communication between the host and its gut microbiota can affect stress–response signaling and other metabolic hormones and biochemical pathways in the host that may affect the retention of energy and developmental trajectory of body weight [53]. Obese pregnant women demonstrate evidence for doubling of plasma endotoxin levels as compared to pregnant women with normal BMI [54], suggesting translocation of bacteria or bacterial products across the intestinal mucosa, that may contribute to systemic and placental inflammation and insulin resistance [55, 56]. Recently, Koren et al. showed that pregnancy is accompanied by alterations of the gut microbiome, which, in turn, create a positive-feedback loop sustaining conditions seen in the metabolic syndrome [20]. These changes in microbes when transplanted into sterile mice increase serum insulin levels, inflammation, and fat deposition, but these effects were only seen when human maternal stool was transferred during the third trimester, and were absent when the same obese mother's stool was transferred in the first trimester [20]. This indicates a powerful effect of maternal gut microbiota on the development of obesity and insulin resistance in the host in late pregnancy. Further, it suggests that the gut microtia changes throughout the course of human pregnancy, much like the time-ordered changes in insulin sensitivity. Although some of these women had gestational diabetes mellitus (GDM) and BMIs were variable, there was no characterization or description of the specific impact of GDM or obesity on the maternal or infant microbiome, or effects described on infant body weight or adiposity.

A recent observational study analyzed the fecal microbiota of 50 pregnant women, classified as normal weight ($n=34$) or overweight ($n=16$), to determine if there was a correlation with maternal body weight, gestational weight gain, and serum biochemical variables at 24 week of pregnancy [57]. The numbers of *Bifidobacterium* spp. and Bacteroides were low, whereas the numbers of staphylococci and enterobacteria (including *Escherichia coli*) were high in overweight compared with normal-weight pregnant women. In addition, *E. coli* was more abundant (1 logarithmic unit) in women with excessive weight gain than in women with normal weight gain during pregnancy. Moreover, maternal *E. coli* loads were positively correlated with infants' birth weight, which suggested the transfer of maternal features to the newborn [57]. Again, no maternal metabolic measures or fetal/infant data were reported in this study. Another study recently showed an association between high Bacteroides and excessive weight gain during pregnancy [58]. Further studies are required to define the mechanisms by which intestinal bacteria influence a mother's physiology and to define how such effects might contribute to infant microbiome development, weight gain, adiposity, inflammation, and feeding behaviors from in utero exposure.

Development of the Infant Microbiome and Weight Gain/ Inflammation

The enteric microbiome is a unique physiological ecosystem recently implicated in both humans and mice as a potential primary mediator of metabolism and obesity. The postnatal assembly of the human microbiota begins at birth and plays an important role in resistance to pathogen invasion,

immune stimulation, and other important developmental cues early in life [59]. Vaginally delivered infants clearly receive a strong input of vaginal and possibly other urogenital microbiota as they pass through and exit the birth canal [60, 61], whereas infants delivered by Cesarean section (c-section) display reduced colonization of bacteria early in development [62, 63]. The effects of delivery mode can persist for months and may have consequences for infant health; infants delivered by c-section tend to be at higher risk for obesity, and at greater risk for some immune-mediated diseases [64, 65]. Further, the metabolic communication between the host and its gut microbiota can affect stress–response signaling and other metabolic and biochemical pathways that may in turn effect the developmental trajectory of body weight [53]. Alterations in intestinal microbial composition in the first year of life may last throughout childhood, and may contribute to the development of obesity [66, 67] and other health outcomes, although the mechanisms remain obscure. As one possible mechanism, inflammation likely reduces the abundance of other bacteria that compete with the proinflammatory pathogens and alter the native microbiota effectively promoting organisms that may increase the ability of some microbes to extract otherwise indigestible dietary polysaccharides [68]. Alternatively, enteroendocrine cells of the gut secrete a variety of metabolically related peptides all known to be connected to food intake, lipid storage, and energy homeostasis and can be activated by microbial metabolites expressed by enteroendocrine cells [53, 69]. Overall, the mode of delivery has a significant impact on microbial composition early in life. Additional factors, including early infantile exposures like breast feeding (including bacteria within the milk and on the mother's skin) and exposure to probiotics and antibiotics likely also play a role.

First Foods: Breast Milk and Infant Formula Affect Obesity

Rapid and excess weight gain during the first 6 months of life has consistently been identified as a predictor of later obesity, even among breast fed infants [70–74]. In general, breastfeeding is associated with protection against rapid infant gain and later obesity [75–78]. The mechanisms responsible are not known but likely involve the delivery of bioactive components that regulate infant appetite, metabolism, and weight/adiposity gain [79]. Maternal obesity may cause alterations in these bioactive components in human milk. Animal data suggest that the milk of obese or diabetic mothers may impart deleterious programming effects to offspring, potentially via alterations in milk fat composition, adipokine, and cytokine content. Murine pups born to lean dams that were suckled by an obese dam exhibit increased adiposity and reduced insulin sensitivity after weaning [80]. When pups born to lean dams were cross-fostered to diet-induced obese dams, these offspring displayed increased body weight, a nonalcoholic fatty liver disease phenotype, and increased inflammatory cytokines IL-6 and TNF-α by 3 months of age [81]. Control pups cross-fostered by gestational diabetic dams exhibit hypothalamic malprogramming in the arcuate nucleus postweaning that may cause a dysregulation of appetite, food intake, and body weight [82]. Epidemiological data from humans are less conclusive. Exclusive breastfeeding at 2–4 weeks among gestational diabetic (GDM) women was associated with an increased relative infant body weight [83]. However, in 5 and 16 year old offspring of GDM mothers, breast-feeding was protective against obesity in offspring [84]. However, maternal BMI factored into that relationship and obese mothers needed to breastfeed longer to impart protection to offspring [84]. The effects of lactation on infants born to mothers with type 2 diabetes (who are most often overweight/obese) have not been systematically studied.

Evidence in rodent models indicates a link between a maternal high fat diet and upregulation of obesigenic genes (including PPARa and IGF2) in offspring [85]. This has also played out in human studies, where intervention in fatty acid composition in the maternal diet. Supplementation with n-3 long chain polyunsaturated fatty acids (LCPUFA) not only influenced breast milk fatty acid composition by reducing the n-6 to n-3 LCPUFA ratio, but also led to decreased adiposity of offspring in the first year of life [86].

Epigenetic Mechanisms in Fetal Programming

Changes in body composition and morphology point to a more fundamental change in the way the fetus of the obese mother processes macronutrients. Evidence that high lipid exposure affects both epigenetic regulation and overall risk for obesity and related disorders in the offspring of obese mothers is mounting. The most basic mechanisms of embryonic development and cell differentiation are altered with lipid exposure. This is mainly accomplished through altering gene expression patterns in the offspring, however the mechanism by which metabolic factors impact DNA has remained elusive. Emerging evidence implicates the role of epigenetic (primarily methylation) modifications in fetal DNA, influenced by maternal environmental factors, in effecting altered fetal metabolism and later risk for development of obesity and metabolic syndrome in the child.

Epigenetics is defined as the modification of gene expression and activity without the modification of the primary DNA sequence. Several mechanisms exist, and have been shown to be influenced by nutritional status in the mother. The most common and well understood epigenetic mechanism is methylation, in which a methyl group is added to the CpG island near the promoter of a particular gene. The result is inactivation of that gene. In the 0–9 week gestational age embryo methylation patterns across the genome are much lower than in the >9 week gestational age fetus, with organogenesis and fetal growth heavily influenced by increasing methylation throughout gestation [87]. Many studies have demonstrated aberrant methylation patterns in nutrient-related conditions including fetal growth restriction and under nutrition [88–91]. These results demonstrate the importance of nutrient exposure in regulating primary fetal development, and suggest a possible role for overnutrition as a determinant of gene expression in utero. A second type of epigenetic regulation in the fetus is histone modification. This is a way of altering the chromatin structure or the post-translation gene products to alter transcription availability and enzyme activity respectively. Histone deacetlyases (or HDACs), in particular, have been implicated in the regulation of chromatin structure and thus gene expression in response to changes in nutrient exposure. Rodent models reveal alternate regulation of the transcription factor pancreatic duodenal homeobox 1 (Pdx1) in growth-restricted pregnancies [92]. Other studies highlight the role of acetylation in the expression of IGF1 and Glut4 in exposure to restricted fetal growth [93, 94]. In the nonhuman primate, maternal high fat diet exposure is associated with decreased n-3 fatty acids in maternal serum [95] as well as nonalcoholic fatty liver disease with increased hepatic apoptosis in the fetus [35, 95]. Fetuses have increased levels of hepatic histone H3K14 acetylation, which coincide with decreased HDAC1 gene expression, protein content, and activity [96, 97].

Effects of Macronutrient Dysregulation in the Obese Mother on Adiposity and Stem cell Function in the Offspring

Maternal overnutrition is typically accompanied by a Western, high fat diet. The combination of maternal obesity and increased fat intake during pregnancy effect the offspring on many levels. Behaviorally, in utero exposure leads to aberrant proliferation of orexogenic hypothalamic neurons [98], which in turn results in the upregulation of leptin production as well as an increased expression of POMC and NPY receptors (normally downregulated in the presence of high leptin levels) [99, 100]. This is found to persist despite weaning onto a higher fat diet, which should lower POMC and NPY receptor expression as a counter-regulatory mechanism. Instead, offspring are inclined to take in more food with less energy expenditure, and consequently developed obesity. This dysregulation, demonstrated in sheep models as well [101], combined with increased anxiety in the offspring of obese primates [102] implicates a significant role in brain development and imprinted behavior in transgenerational obesity.

Recent evidence based on lineage tracing in mice also suggests that major tissue-resident macrophage populations, including liver kupffer cells and peritoneal macrophages, are established prior to birth and maintain themselves subsequently during adulthood independent of replenishment by blood monocytes [103]. This suggests that fetal exposures associated with high maternal insulin resistance may prime these resident immune cells rendering them responsive to further stimulation as proinflammatory effector cells and/or differentiation into fibrotic macrophages following initial injury that may contribute to fatty acid storage or lipid oxidation in liver and other tissues postnatally. Mesenchymal stem cells, which differentiate into bone, muscle, or adipose tissue, preferentially differentiate into adipose with exposure to high amounts of fat. Adipogenic versus myogenic potential is regulated by several key enzyme, including NF-kB, PPAR-γ, and AMPK, which all favor adipogenesis and overproduction of adipogenic hormones including leptin and adiponectin [101]. This effect can be reproduced in vitro and in mouse models with the use of PPAR-γ agonists like rosiglitazone [104], and may help to explain how high fat exposure in utero can lead to increased adiposity in the newborn.

In other tissues, cellular function is altered dramatically in response to changes in nutrient load and content. Lipid exposure has been linked to increase fat deposition in the pancreas [105]. Pancreatic beta cell mass is diminished (with lower insulin secretion) in growth restriction and in excess (with higher insulin secretion) in obesity[106–108]. As mentioned above, this is attributed to epigenetic regulation of Pdx1 which persists into the adulthood for the offspring. Exposure to high amounts of lipid have also been shown to induce cell death [109], but upregulation of Pdx1 (as in obesity) is protective against this [110, 111]. The relationship between all of these phenomenon and increased susceptibility to type 2 diabetes in the offspring of obese mothers is still being investigated.

Animal models exposed to a maternal high fat diet have lasting effects (from the fetus through the adult offspring) in increased body weight, reduced insulin sensitivity, increased adiposity with reduced muscle mass, and increased lipid deposition in the liver [35, 112–114]. Even when the high fat diet source is removed from the offspring, there is a persistence of fat accumulation in the liver of adult offspring [115, 116]. In human studies, maternal obesity (pre-pregnancy and gestationally related obesity) is associated with increased risk for metabolic syndrome and obesity in offspring as early as 6 years of age [117, 118], with the strongest and most lasting effects associated with maternal obesity and weight gain in the first and second trimester [119]. This provides strong evidence for a lasting, imprinted affect following exposure to maternal overnutrition.

The evidence for fetal programming following exposure to a high fat diet in an already obese mother is overwhelming; however the mechanisms are still being delineated. Lipid exposure and subsequently induced inflammation is thought to have a regulatory effect on key lipid regulatory enzymes including those in the PPAR and LXR families [120]. Rodent models demonstrate increased lipogenesis with impaired mitochondrial function, coupled with the development of fatty liver [121]. In humans, de novo synthesis of lipids (and upregulation of associated genes including SREBP1, ACC, FAS, SCD1, and LXRa) is seen in exposure to a high fat diet. In the same study, there was a downregulation in fatty acid oxidation (CPT1 and PPARα) and mitochondrial oxidative capacity implicating a profound dysregulation of lipid handling in these subjects [122]. SIRT3, a ubiquitous and potent regulator of mitochondrial processes is found to be downregulated in the offspring of obese mothers [123]. This has been directly linked to downregulation of fatty acid oxidation and mitochondrial function via reversible lysine deacetylation, with evidence pointing to the involvement of multiple interrelated pathways within the mitochondria [124–127].

Very little is known about the dysregulation of metabolic pathways in the fetus, however it is clear that the major cellular target of metabolic dysregulation is the mitochondria. Whether mitochondrial

impairment is due to [128], or causes [129], aberrant lipid metabolism remains a question. In the presence of increased lipid load there is impairment of intra-mitochondrial fatty acid oxidation and electron transport chain activity, but also an increase in reactive oxygen species and a concomitant decrease in glutathione. This has been demonstrated in the mother, as well as in embryonic/fetal offspring using mouse models [130] in exposure to both fatty acids [131] and high amounts of protein [132] prior to conception, with mitochondrial dysfunction still evident in the embryo [133]. Taken together, this suggests a programmed mitochondrial dysfunction (both in oxidative capacity and lipid oxidation) induced by maternal obesity, perpetuated by high lipid exposure and overnutrition, which persists through the fetal period and into adulthood in offspring.

Interventions

Each period during development, before, during or after pregnancy, offers a potential target for intervention to interrupt the programming and transmission of obesity from mother to offspring. During pregnancy, dietary interventions could be employed to limit fetal exposure to high amounts of lipid. The traditional dietary restrictions in a mother with gestational diabetes focus on limiting the amount of carbohydrate to protect the fetus from hyperglycemia and insulin resistance [134]. The findings above would suggest a better strategy might be the use of a lower fat diet with higher amounts of complex carbohydrates to maintain caloric balance [135, 136]. Dietary modifications for reducing gestational weight gain have also proven to be effective in treating gestational diabetes-related macrosomia and decreasing associated morbidity and mortality [137]. Further, modest improvements in childhood obesity have been associated with improved maternal weight and diabetes status early in pregnancy and during the postpartum period [138, 139]. It should be noted however that some studies have found this intervention to be ineffective [140]. The use of insulin in gestational diabetes has also been a mainstay of usual therapy. Early and aggressive treatment with exogenous insulin may serve to protect the fetus from maternal hyperglycemia and increased circulating free fatty acids as well [2]. Further decreasing exposure to high lipid levels, like triglycerides and VLDL, may be possible with niacin and omega-3 fatty acids (as found in cod liver oil) [34, 120]. While organ/tissue development, particularly the placenta is markedly different in rodents and other species compared to humans and NHP, we recently demonstrated that lowering placental inflammation in a transgenic obese mouse model prevented subsequent development of obesity and associated inflammation and NAFLD in the wild-type offspring [39]. Taken together, the results suggest that lowering maternal insulin resistance by preventing inflammation, or weight gain, or possibly exercise, could limit fuels and inflammatory stimuli in the fetus during gestation that may be a critical driver of subsequent juvenile obesity.

Direct modification of epigenetic changes may also be a powerful treatment approach for obese mothers. It is clear that epigenetic regulation, specifically via methylation and acetylation are dynamic processes that could change over time. Altering methylation by supplementation of folate, vitamin B12, choline, and other nutrients involved in methyl-donor generation could decrease obesity risk in the offspring of obese mothers and has been shown to be effective in mice [141–143]. Similarly, supplements that alter acetylation could also help in mitigating the effects of maternal obesity on her offspring. Resveratrol, a modulator of SIRT3, has been associated with improved mitochondrial function in obese nonhuman primates. Finally, altering inflammation with small molecules like taurine in the mother may also be a viable tool [144].

Postnatal therapy is also an option, including modification of the maternal and/or infant microbiome with anti- or probiotics. Finally, dietary modification in breast feeding mothers may alter the exposure of the infant to potential obesity-promoting molecules, such as leptin, insulin, or adiponectin that are transmitted to the infant in the breast milk.

Summary and Conclusions

The intrauterine environment is increasingly recognized as an important contributor to the rapidly rising incidence of juvenile obesity and associated metabolic disorders. Clinical and epidemiological studies have repeatedly shown a strong association between maternal BMI and childhood obesity and co-morbidities in offspring. However, not all obese women give birth to overweight infants and the intrauterine effects resulting from maternal obesity that trigger metabolic disease in the offspring are not well understood. While some obese women remain relatively normal metabolically, others show a pattern of genes, cytokines, and metabolic changes in maternal tissues and the placenta consistent with a metabolic syndrome that provokes a metabolic overload to the fetus during gestation. To date, there is ample evidence that maternal obesity leads to obesity in the child in a process that begins as early as the first trimester and plays out throughout the life of the offspring. For example, we recently discovered that human infants born to obese and gestational diabetic mothers have a >50 % increase in liver fat compared to infants of normal weight mothers, as demonstrated by MRI/MRS [145] suggesting that maternal obesity in humans contributes to hepatic fat storage in newborn infants. Whether this abnormality is reversible postnatally is unknown, but has very important clinical implications for understanding the pathophysiology of obesity, since multiple systems may be affected that prime the infant for subsequent inflammation, insulin resistance, and the progression of metabolic diseases such as CVD, diabetes, or NAFLD later in life. A variety of processes contribute to programming of the fetus including preferential differentiation of mesenchymal stem cells, alteration of DNA and enzymes epigenetically, and aberrant expression of some of the most basic and essential regulators of energy metabolism. The cause is also multifaceted, and centers around inflammation, insulin resistance, hyperglycemia, and hyperlipidemia, and possibly the microbiome of the obese mother. All of these are exacerbated by pregnancy, and the effects are likely transmitted across the placenta directly to the fetus. Peri- and postpartum exposures further may contribute to infant risk. The entire pregnancy as well as the early postnatal period are pivotal for breaking the cycle of maternal to infant obesity, but more studies are needed to support recommending specific treatments that could halt the transgenerational cycle of obesity.

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Gut Microbiome and Obesity

5

Harry J. Flint, Sylvia H. Duncan, and Petra Louis

Introduction

Interest in the role of the resident gut microbiota in human health and disease has increased rapidly over the past 10 years, including strong interest in the potential for our gut microbiota to influence weight gain and adiposity. Much of this interest was triggered by the hypothesis that the composition of the bacterial communities in our gut can influence 'energy harvest' from the diet [1] and by evidence for microbial influences on fat deposition [2]. As research has progressed, the interpretation of experimental data has often had to be refined, and many more interactions have emerged that suggest possible impacts of the microbial community on host physiology, energy intake and expenditure, as discussed in recent reviews [3–7] (Fig. 5.1). We will attempt here to give a brief overview of this rapidly developing field of research.

The ability to analyse gut microbial communities by non-cultural approaches, especially high-throughput sequencing, has led to a great deal of new information on the diversity and composition of the human colonic microbiota. Phylogenetic approaches based mainly on amplified 16S rRNA genes reveal that the two dominant bacterial phyla detected in faecal samples from healthy individuals are the Gram-negative Bacteroidetes and the Gram-positive Firmicutes, with Proteobacteria, Actinobacteria and Verrucomicrobia also represented. Although there is considerable inter-individual variation at the species level, 50–60 dominant species are present in most individuals [8–10]. It is not yet clear whether inter-individual variation in microbiota composition is continuous or semi-discrete, and evidence suggestive of different 'enterotypes' [11] within the human population is currently under debate. Communities dominated either by *Prevotella* spp. or *Bacteroides* spp. (both belonging to the Bacteroidetes phylum) have been reported from several large studies, but evidence for a third, Firmicutes-dominated, enterotype originally proposed by Arumugam et al. [11] appears less consistent [12, 13]. It now appears that diet may be a major factor driving such variation [12].

Impact of Diet on the Gut Microbiota

The main energy sources available to bacteria in the large intestine are non-digestible carbohydrates (plant cell wall polysaccharides and resistant starch) and host products, especially mucin.

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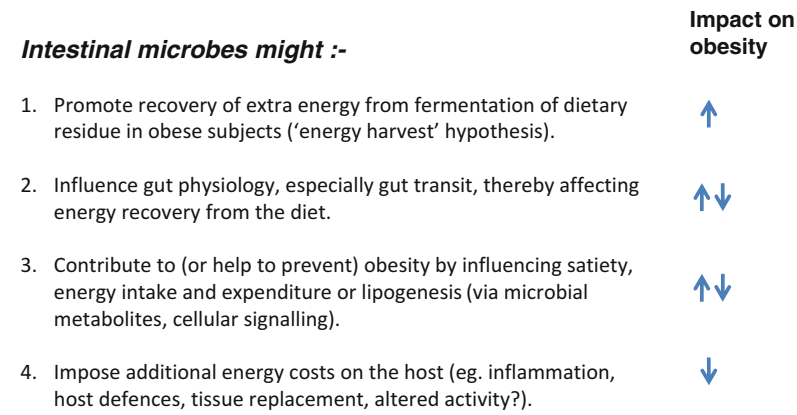

Fig. 5.1 Potential influence of intestinal microbiota on obesity in humans

There is clear evidence that gut microbiota composition changes with dietary intake. This can be seen in short-term dietary intervention studies, where the representation of certain groups in the faecal microbiota is reported to increase within a few days of switching to diets high in particular non-digestible carbohydrates such as resistant starch [9, 14]. There is also clear evidence from numerous studies for microbiota changes in response to prebiotics [15–18]. These short-term shifts are however strongly influenced by inter-individual variation, and individual variation apparently remains the main factor determining the overall composition of the microbial community despite the consistent response of specific 'diet-responsive' bacterial groups [9]. Broadly-based shifts in the gut microbial community have nevertheless been reported in groups of subjects who differ in habitual, long-term dietary intake. In particular, Wu et al. [12] reported higher proportions of Bacteroidetes in subjects consuming diets high in protein, and higher proportions of *Prevotella* in those consuming more fibre. A similar shift was seen in a group of African children compared with Italian children whose diets differed in fibre and protein intake [19].

In obese subjects, gut microbiota changes have also been shown to result from weight-loss diets. In obese male volunteers there was a significant decrease in the faecal populations of the *Roseburia*+*E. rectale* group of Firmicutes bacteria and in bifidobacteria within 4 weeks following a shift to weight-loss diets with high protein and decreased carbohydrate contents [20, 21]. The cross-over design showed clearly that this change was driven by the diet rather than by weight loss, since it was partially reversed when there was a shift to a second weight-loss diet containing a higher content of total carbohydrate [22]. In an earlier study, Ley et al. [23] reported an increase in % Bacteroidetes in obese subjects following 52-week weight-loss regimes. The initial % Bacteroidetes in these subjects was lower than in most other studies, as discussed below.

Evidence for Changes in Microbiota Composition in Obese Humans

An early report, based on sequencing of amplified 16S rRNA genes, indicated a much higher ratio of Firmicutes to Bacteroidetes in faecal samples from 12 obese humans than in two lean controls [23]. This appeared consistent with the higher Firmicutes:Bacteroidetes ratio seen in genetically obese mice compared with lean mice, leading to the proposal that the ratio of these two phyla within the gut microbiota might be a causative factor in obesity [1]. Subsequent studies using FISH microscopy however either did not detect a change in % Bacteroidetes with BMI [22] or indicated a slightly increased % Bacteroidetes [24] in obese subjects. Numerous studies have now been performed using quantitative PCR, high-throughput sequencing of 16S rRNA genes or metagenome sequencing to analyse the faecal microbiota

in obese subjects, leading to the conclusion that there is no consistent difference between lean, normal weight and obese subjects at the bacterial phylum level [4, 9, 25–27]. Some differences are however apparent at the genus and species levels [28] including between MZ twins who were discordant for BMI [29]. Given the impact of diet on microbiota composition at this level, discussed above, it seems likely that such differences will at least partially reflect differences on dietary intake between obese and normal-weight individuals. Yokota et al. [30] recently suggested that increased secretion of bile acids may contribute to alterations of the microbiota on high fat diets due to the antimicrobial activity of secondary bile acids. They demonstrated microbiota changes in line with those seen in several studies on high fat diets (i.e. an increase in Firmicutes at the expense of Bacteroidetes) after feeding rats increasing levels of cholic acid. There is also increasing evidence that type 2 diabetics show altered microbiota profiles when compared with healthy subjects, with a decreased representation of certain groups of Firmicutes and of bifidobacteria [31–34]. The increased incidence of metabolic syndrome and type 2 diabetes in obese subjects is therefore an important confounding factor when interpreting microbiota changes in the obese.

Recent work using metagenomic sequencing has shown that microbiota profiles in obese subjects can be distinguished as being of low (LGC), or high (HGC) gene count, reflecting high and low species diversity [28]. The LGC type tends to be dominated by the Gram-negative *Bacteroides* and may correspond to one of the 'enterotypes' proposed by Arumugam et al. [11]. Obese or overweight subjects, showing the LGC profile had significantly higher insulin resistance and fasting triglyceride levels, indicative of metabolic syndrome, compared with HGC individuals [28]. Moreover, obese LGC individuals showed more rapid past weight gain on average than obese HGC individuals. In a companion study, a 12-week intervention on weight-loss diets increased the gene count in the LGC group, while improving symptoms associated with metabolic syndrome in both groups [35]. The simplest interpretation of these findings is that gut microbiota composition in these subjects is largely driven by their dietary intake, although, conversely, consequences of changes in host physiology could also influence microbiota composition. A diet that is low in fibre and high in digestible carbohydrates, especially simple sugars, might account for the LGC profile (found in both obese and lean individuals) while at the same time promoting the development of metabolic syndrome.

In human studies it is usually not possible to distinguish between microbiota changes that are consequences of changes in diet and/or host physiology from any that might be contributing factors in obesity, adiposity and inflammation. However there is intriguing evidence, mainly from animal studies to suggest that individual bacteria could have more significant roles in influencing host nutrition, physiology and behaviour. A number of studies have shown that transfer of gut microbiota from obese humans, compared with non-obese donors, to germ-free mice results in increased weight gain and adiposity in the colonised mice. Most recently, this result has been reported for obese human twin pairs that were discordant for BMI with the microbiota from the obese twin promoting adiposity and weight gain when transferred into germ-free mice to a greater extent than the microbiota from the relatively lean twin [36]. Diet is likely to have driven the separation in the microbiota composition between the members of each twin pair, but the transfer experiments suggest that this altered composition is also contributing to adiposity and weight gain. Such effects require mechanistic explanations and some of the possibilities are considered below.

Potential for Microbiota Composition to Influence Energy Recovery from the Diet

The gut microbial community in the large intestine contributes to the overall 'energy harvest' from the diet by fermenting components that remain undigested by host enzymes in the small

intestine. Short-chain fatty acids produced by microbial fermentation are efficiently transported across the gut wall and used as energy sources, with butyrate being preferentially utilised by the gut epithelium. The over-riding factor that determines how much energy is delivered via microbial fermentation is the non-digestible carbohydrate (fibre) content of the diet, together with gut transit, which is of course influenced by fibre content [5, 37]. More rapid whole gut transit may lead to a greater fraction of dietary intake failing to be digested in the upper GI tract, thus increasing the substrate available for fermentation in the large intestine [38]. On the other hand, rapid transit also tends to decrease the extent of fibre degradation and the efficiency of SCFA absorption [37]. Faecal SCFA concentrations are reported to be higher in obese subjects [24, 39, 40] which seems most likely to reflect higher dietary intake.

The potential factor that has attracted most speculation is the species composition of the gut microbiota [25, 41]. It is therefore worth considering in more detail the mechanisms by which changes in microbiota composition might affect energy recovery from the diet by considering the following questions.

Does Microbiota Composition Influence the Rate and Extent of Substrate Fermentation in the Colon?

If certain 'keystone' species were required to initiate degradation of recalcitrant substrates, then their absence from the microbiota could have a major impact on the release of energy from dietary residue. An example of this phenomenon comes from the finding that, among 14 obese human volunteers, ingested RS3 starch remained largely unfermented only in two individuals who lacked ruminococci in their faeces [9]. Relatives of *R. bromii* appear to be particularly potent degraders of this type of starch by comparison with other amylolytic species [42]. It is currently unclear how common such deficiencies in 'keystone species' are within the general population, but their consequence would be to reduce energy gain.

Does Microbiota Composition Influence the Stoichiometry of Fermentation in the Gut?

In vitro experiments show clearly that perturbation of the microbial community composition, e.g. resulting from a pH change, can result in major shifts in the ratios of the major fermentation products [43]. While acetate, propionate and butyrate all supply energy to the host, they are utilised by different tissues and have different physiological consequences, as discussed further below. Deficiencies in butyrate-producing bacteria (which belong to the Firmicutes within the human colonic community) have now been reported in several disease states, including type 2 diabetes [34], and overall decreases in these bacteria are known to result in decreased butyrate production [20, 43].

Hydrogen utilisation plays a central role in anaerobic metabolism, and the consequences of variation in hydrogen utilising microbes have been the subject of much speculation. Methanogenic archaea occur in high numbers in approximately half of the population; some reports indicate that they are increased in obese subjects [40, 44] while others suggest the contrary [24]. It is possible that in the absence of methanogenesis more carbon would be diverted into SCFA and therefore to the host (Table 5.1); indeed this is one of the goals of attempting to inhibit methanogenesis in the rumen [45]. In the absence of inhibition, however, the equivalent amount of carbon may simply be released as CO_2 when methanogen populations are low. Another important group of hydrogen utilisers are acetogens, which have the ability to convert H_2 and CO_2 (or formate) to acetate. This introduces an additional non-dietary source of acetate carbon [46] but the contribution and degree of variability of this route for acetate synthesis in the human colon has not been fully established.

Table 5.1 Possible impacts of methanogenic archaea and methanogenesis upon 'energy harvest' from the diet

Consequence of methanogenic activity	Consequence for energy harvest
1. Net loss of carbon as CH_4	Decreased? [BUT without methanogenesis equivalent C may simply be lost as CO_2]
2. Increased efficiency of energy metabolism by H_2-producing bacteria	Increased? [BUT same increase will apply to acetogenic bacteria + H_2 producers?]
3. Methanogenic activity correlates with slow gut transit	Increased? Fibre degradation and SCFA absorption more efficient at slower transit times?

Another effect of hydrogen utilisation is to increase the growth efficiency of hydrogen-producing, substrate-degrading species [47]. As this is predicted to occur with both methanogens and acetogens it would be assumed to apply to any 'normal' gut microbial community, although there is some intriguing evidence that cellulolytic ruminococci may be dependent on the presence of methanogens within the microbiota [48]. If degradation of some dietary carbohydrates was increased in the presence of methanogens, this might tend to increase 'energy harvest' (Table 5.1).

Does Microbiota Composition Affect the Uptake of SCFA by the Gut Epithelium?

As already noted, gut transit is thought to have an important influence of SCFA uptake. Conversely, SCFA are themselves known to affect gut motility and transit via interactions with receptors that influence gut hormones, although these effects may differ in different regions of the intestine. This creates complex feedback loops whereby microbiota composition may influence absorption of fermentation products by the host. There is also intriguing evidence that methane may slow gut transit [49]; methanogens appear to be associated with slow gut transit [50] but whether this is because of their slow growth rate or their impact on gut motility is not known.

Potential for Microbiota to Influence Energy Expenditure and Adiposity

The intestinal microbiota influences host physiology beyond their direct actions in the gut (Fig. 5.2). Several possible routes of cross-talk exist between the microbes and host tissues, encompassing metabolic, immunological, endocrine and neural pathways [3, 51, 52], and the exact mechanisms of interaction are currently under extensive research. Another factor that has to be taken into consideration is the role host genetics play in determining the response to obesogenic diets as well as the composition of the microbiota. High heritability of gene-by-diet interactions has recently been demonstrated in a genome-wide association study in different mouse strains on a high fat/high sugar diet [53]. A parallel investigation of the gut microbiota revealed significant phylum-level shifts in response to diet across different genetic backgrounds, however, effects of the genetic background on the composition and plasticity of the microbiota were also evident. Only one of the genetic loci found to be associated with body fat, which include three amylase genes, was found to be associated with significant changes in microbiota composition, namely an enrichment of *Enterobacteriaceae* within the phylum Proteobacteria. In addition, three specific microbiota phylotypes showed a modest correlation with obesity traits. Intriguingly, *Akkermansia* displayed a negative correlation with body fat percentage despite the fact that this genus showed the strongest overall enrichment on the high fat/high sugar diet [53].

Some studies have found that energy balance could be profoundly influenced in animal models by the introduction of a single bacterial species. Administration of a purified probiotic strain of *Lactobacillus reuteri* led to the prevention of weight gain without significantly affecting the existing microbiota or calorie consumption in mice on a Western diet. The underlying effect appeared to be a modulation of the immune system towards a more anti-inflammatory tone, and

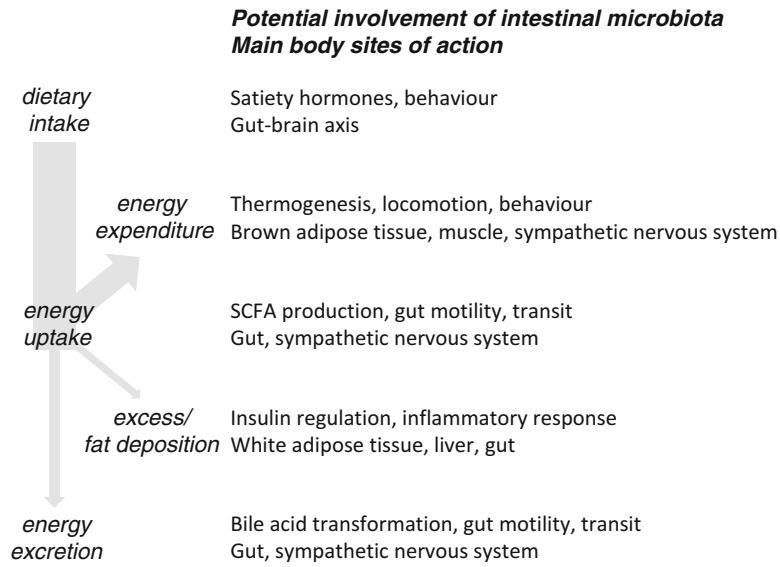

Fig. 5.2 Potential influences of intestinal microbiota on energy balance in humans

the phenotype was transferable to naïve hosts via purified $CD4^+$ T cells from animals consuming the probiotic [54].

Separately, it has been reported that *Akkermansia muciniphila* (which comprises 3–5 % of the colonic microbiota in healthy adults) abundance correlates inversely with body weight. This bacterium has a specialist role and derives its carbon and energy from the mucus layer lining the intestinal tract. In contrast to Parks et al. [53] who found an increase of *Akkermansia* on a high fat/high sugar diet (see above), Everard et al. [55] demonstrated that populations of this organism are diminished on high fat diets, which resulted in a reduction in the thickness of the mucus layer. Moreover, re-introduction of *A. muciniphila* by gavage to mice fed a high fat diet reduced body weight and improved body composition without changes in food intake. It also restored the mucus layer, decreased circulating lipopolysaccharide (LPS) levels and increased glucose tolerance compared to control animals gavaged with either PBS or killed cells [55]. Both studies found that the reduction in weight gain and body fat was achieved without a significant reduction in food intake, indicating that energy balance regulation was influenced via other factors, such as locomotor activity and heat production.

A direct link between obesity, glucose metabolism and low-grade inflammation has previously been demonstrated by subcutaneous administration of LPS, which led to insulin resistance and fat mass development in mice [56]. An intact gut barrier function is crucial in preventing LPS from crossing from the gut into the systemic circulation (increased plasma LPS levels have been termed metabolic endotoxemia), and the gut microbiota may influence gut permeability via actions on the mucus layer or regulatory effects on epithelial cells (e.g. tight junction protein expression) [57]. Bacterial signalling appears to involve the endocannabinoid system, endogenous bioactive lipids that regulate barrier function, as well as the enteroendocrine peptide glucagon-like peptide-2 [55].

Inflammation may be mediated by several bacterial products such as lipopeptides, LPS and flagellins that act as ligands for toll-like receptors (TLRs) 2, 4 and 5, whilst other TLRs detect nucleic acid motifs. In most cell types detection of these bacterial ligands evokes a potent inflammatory response inducing myeloid-differentiation factor 88 (MyD88) and NF-kappa B which results in a broad array of pro-inflammatory chemokines and cytokines. By contrast, recognition of these bacterial moieties by intestinal epithelial cells

has been reported to lead to enhancement of barrier function, and epithelial repair rather than overt inflammatory responses.

LPS is continuously released in the intestinal tract as a consequence of bacterial cell lysis and serum LPS was shown to be 76 % higher in type 2 diabetics compared to the control cohort and consumption of a high fat meal resulted in a 50 % higher endotoxin level [58]. High fat diets can increase absorption of LPS present in the cell walls of Gram-negative bacteria either by incorporation into chylomicrons or by increasing intestinal permeability [56]. LPS is a potent inflammatory mediator that signals in a TLR4-dependent manner and infusion of LPS can increase weight gain, adiposity, insulin resistance and liver triglycerides. Separately deletion of TLR5 in mice, which senses bacterial flagellin, results in an alteration in the composition of the gut microbiota and also to features of metabolic syndrome including insulin resistance, increased adiposity and blood pressure and increased cholesterol levels [59].

An important role of inflammation in the development of obesity is in line with the notion that germ-free animals are resistant to diet-induced obesity [60]. However, Fleissner et al. [61] demonstrated that this effect is dependent on the specific dietary ingredients of high fat diets and that germ-free mice are not generally protected against obesity by comparing different types of high-fat diet with equal macronutrient content. Furthermore, it has recently been shown that, in contrast to germ-free mice, germ-free rats did not exhibit decreased adiposity compared to their conventional counterparts, and alterations in host lipid metabolism differed between rats and mice [62]. Therefore, differences in host metabolism as well as morphological and physiological alterations of germ-free animals compared to conventional animals require careful consideration in the assessment of microbiota-mediated effects on adipogenesis.

Recently Upadhyay et al. [63] have linked effects of the microbiota in diet-induced obesity in mice to gut immunity by investigating mice deficient in lymphotoxin, which is involved in normal mucosal defence against pathogens. Lymphotoxin-deficient mice were resistant to diet-induced obesity and also showed changes in gut microbiota composition, particularly an increase in segmented filamentous bacteria. Germ-free animals receiving the microbiota from lymphotoxin-deficient animals remained lean, whereas cohousing of animals with lymphotoxin negative and positive genetic background lead to weight gain in the negative background, indicating transferability of the host phenotype via the microbiota. The authors postulate that changes in gut mucosal host immunity in response to diet influence the microbiota, which in turn affects systemic host physiology.

Microbes may also signal to the host via short-chain fatty acids, the major metabolic end products of fermentation by bacteria in the colon, via G-protein-coupled receptors GPR41 (or free fatty acid receptor (FFAR)3 and GPR43 (FFAR2). The dominant acids usually detected are acetate, propionate and butyrate, all of which activate FFAR2 and 3 with different potency [64]. The receptors are expressed in various tissues, including the gut, a range of immune cells and adipose tissue, but their prime site of action remains under study and there is some conflicting evidence in the literature with regard to their function [64]. Nevertheless, FFAR3 has recently been linked to activation of sympathetic neurons via SCFA, whereas ketone bodies acted as antagonists [65]. Thus SCFA may influence energy expenditure by affecting heart rate and thermogenesis via this route. FFAR2 knockout mice, on the other hand, were shown to develop obesity on a normal diet, whereas overexpression of FFAR2 in adipose tissue promoted a lean phenotype even on a high fat diet [66]. These effects were abolished when the animals were raised under germ-free conditions, indicating an involvement of the gut microbiota. On a molecular basis, the activation of FFAR2 suppressed insulin signalling specifically in white adipose tissue, with a consequent inhibition of fat accumulation, while promoting energy expenditure in other tissues [66].

Other effects of SCFA, such as increased expression and production of hormones involved in appetite regulation (glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) in the gut; leptin

in adipose tissue) may also be mediated by FFAR2 and 3. An involvement of FFAR2 in GLP-1 release from colonic L cells has been demonstrated in cell cultures as well as in vivo [67]. It remains to be established, however, how transferrable results from animal models are to humans, as it has been shown that there are differences between hosts with regard to the potency and selectivity of different SCFA on the receptors, as well as the receptor interaction with downstream effectors [64]. Regardless of the underlying mechanisms of action, there is also evidence for an anti-obesogenic effect for both propionate and butyrate when given orally [68, 69], and modulation of host energy balance through dietary stimulation of microbial SCFA production is an attractive concept to help tackle obesity. Prebiotic supplementation has been shown to be effective in reducing inflammation in animal models and increasing satiety in humans [7], but the complexity of the microbiota as well as the multitude of possible molecular routes for interaction with the host require further investigation before specific members of the microbiota or certain microbiota profiles can unequivocally be assigned a role in preventing or promoting obesity.

Impact of Antibiotics

Antimicrobials potentially alter microbiota composition [70] and epidemiological studies in humans have shown that antibiotic treatment during the first 6 months of life [71] may have an effect as this is a time when the host adipocytes are developing [72]. In young mice subtherapeutic levels of antibiotics were recently found to change gut microbiota composition and increase fat mass [73]. Additionally this study identified an increase in SCFA in the large intestine, suggested to reflect increased fermentation. On the other hand, Cani et al. [74] reported that treatment of obese and diabetic mice with antibiotics (ampicillin and neomycin) for a period of 4 weeks led to a reduction of metabolic endotoxemia, body weight and body fat. The impact of antibiotics is likely to depend critically on dosage, on the particular antibiotic/s used, and on events both in the small and large intestine [75] making generic interpretations difficult and probably unwise.

Conclusions

There is increasing evidence from studies with small animal models that the microbiota of the gut can influence adiposity and weight gain. Explanations for these effects appear to lie with the impact of microbial activities and metabolic output upon host physiology. Although the microbial fermentation of non-digestible dietary residue contributes energy to the host, the hypothesis that the gut microbiota of obese and lean individuals differ in the efficiency with which they retrieve energy from dietary residue ('energy harvest') remains unproven. On the other hand, small animal experiments indicate that adiposity and weight gain can be promoted by the transfer of 'obesogenic' microbiota into germ-free animals, with some evidence that individual species can play a role. Potential mechanisms include influences on food intake and satiety, energy expenditure and the control of pathways that influence inflammation pathways, glucose homeostasis and adipogenesis. It appears that these microbial factors can have an influence on human obesity, but their exact contribution has still to be fully assessed.

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Browning of Adipose Organ

6

Saverio Cinti

The Concept of Adipose Organ

Anatomical dissection allows isolation of several visible adipose depots from the bodies of small mammals [1–3]. These depots are located in two main anatomical sites: under the skin (subcutis) or into the trunk in contact with thoracic and abdominal viscera (Fig. 6.1). Small amounts of adipose tissue can be found in organs such as bone marrow, lymph nodes, pancreas, parathyroid glands, parotid glands, and thymus.

Subcutaneous Fat Depots

Two main subcutaneous depots are present in small mammals. The largest subcutaneous depot is localized in the anterior part of the body (anterior subcutaneous depot: *ASC*). In the posterior part of the body at the inguinal level is the simple, but large, posterior subcutaneous depot (*PSC*). In addition, minor subcutaneous depots are located in the limbs (*Lfat*).

ASC

Its shape and location is very complex: the more consistent and large part of it is localized in a deep fossa between the two scapulae (interscapular area). From this central core several elongated bilateral projections reach the neck and the upper limbs. Those projecting to the neck reach superficial and deep levels (cervical fat). The superficial parts can be subdivided into anterior and posterior. These last are located under nuchal muscles.

Two bilateral projections reach the upper limbs. Two are superficial and two are deeply located among the dorsal muscles. These last deep projections reach the axillae (axillary fat) and are continuous with thin and large dorsolateral prolongments.

PSC

This depot can be considered as a fascia that wraps around the origin of posterior limbs. Thus this fascia starts at the dorso-lumbar area and runs at the inguinal level to end at contralateral dorso-lumbar area. While passing at the pubis level, a large projection reaches the gluteal area. This depot is easy to distinguish as three bilateral areas: dorso-lumbar, inguinal, and gluteal areas. A large lymph node is usually found in a point that can be considered as the boundary between the inguinal and the dorsal area. In some cases, a second bilateral lymph node can be found at the level of the dorso-lumbar area.

Lfat

The limb fat depots are always small. They are located under the fascia that surround the limb, thus even if they can be considered subcutaneous depots it must be outlined that they have a close

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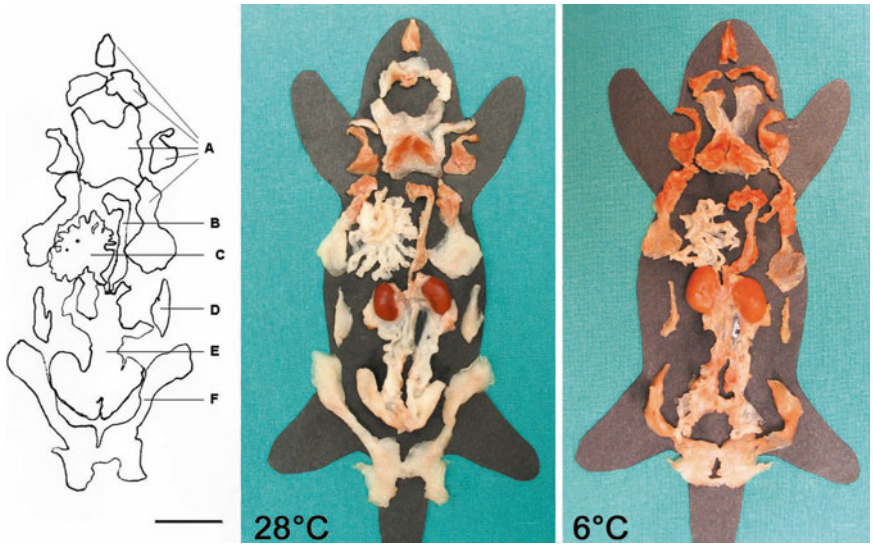

Fig. 6.1 Gross anatomy of the adipose organ of adult female 129Sv mice. The subcutaneous and visceral depots were dissected and positioned on a template of the mice to show their location in the organism. The mouse on the *left* was maintained under warm conditions (28 °C for 10 days) and the mouse on the *right* under cold conditions (6 °C for 10 days). Note the visually evident transformation of the color of the organ due to the increase of BAT and decrease of WAT contained in the organ. The organ is made up of two subcutaneous depots: A: anterior (deep cervical, superficial cervical, interscapular, subscapular, axillo-thoracic) and F: posterior (dorso-lumbar, inguinal, gluteal) and of several visceral depots: B: mediastinal, C: mesenteric, D: retroperitoneal, and E: abdomino-pelvic (perirenal, periovarian, parametrial, perivesical). Bar: 1 cm. Reproduced from Murano I, Zingaretti CM, Cinti S. The Adipose Organ of Sv129 mice contains a prevalence of brown adipocytes and shows plasticity after cold exposure. Adipocytes. 2005;1(2): 121-30 with permission

connection with muscles. In this respect their localization can be considered quite similar to those deep parts of the anterior subcutaneous depot described above (see below for histology implications). Two small depots are located per each limb: at the level of shoulder and elbow in the anterior limbs and at the level of tight and popliteal fossa in the posterior limbs.

Truncal (Visceral) Fat Depots

In the trunk of female mice there are two main depots: one is located into the thorax cavity between the lungs and one is located in the abdominal cavity with extension into the pelvis [4]. The first depot is therefore located in the mediastinum and we refer to it as mediastinic depot. The second occupies several areas in connection with abdomino-pelvic viscera and therefore we refer to it as abdomino-pelvic depot. Minor depots are located in extra-serosal areas of the trunk such as between the thoracic wall and the thoracic parietal pleura and between the abdominal wall and the parietal peritoneum. Other minor, but very important from clinical perspectives, depots are located into peritoneal folds: omentum and mesenteric depots.

The fat depots in male mice differ in the trunk. This location contains a large depot, called epididymal fat, which is entirely surrounded by peritoneal sheets in tight connection with the testis.

Histophysiology

The vast majority of the above described depots show a mixed composition of adipocytes. Thus, white and brown adipocytes are the normal parenchymal cells of most of the depots of the adipose organ [5].

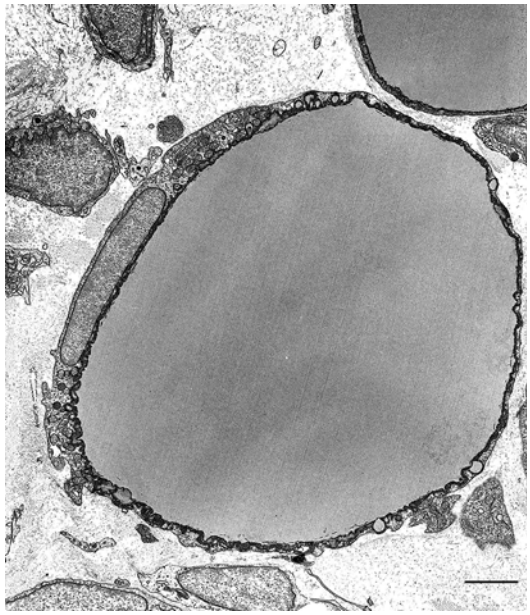

Fig. 6.2 Electron microscopy of unilocular white adipocyte from epididymal fat of three weeks old rat. Bar: 3 μm. Reproduced from Cinti S. The Adipose Organ. Milan: Kurtis; 1999 with permission from Editrice Kurtis

White adipocytes derive their name from the fact that they occupy the white parts of the adipose organ forming white adipose tissue (WAT) and contain lipids (adipocytes). They are large cells showing a spherical shape. Their size is variable from the largest epididymal or inguinal (70–80 μm in diameter, mice at 28 °C) to the smallest omental or mesenteric (40–50 μm, mice at 28 °C). About 90 % of their volume is occupied by a unique lipid vacuole (unilocular adipocytes) composed by triacylglycerides. Their nucleus has a crescent shape due to the need to adapt to the shape of the lipid droplet and cytoplasm is thin and poor of organelles (Fig. 6.2).

Brown adipocytes occupy the brown parts of the organ forming brown adipose tissue (BAT) and contain lipids (adipocytes). They are smaller cells (30–40 μm, mice at 28 °C) with polyhedral shape with roundish central nucleus and cytoplasm rich of numerous large characteristic mitochondria packed with cristae and several lipid droplets (multilocular adipocytes) composed by triacylglycerides (Fig. 6.3).

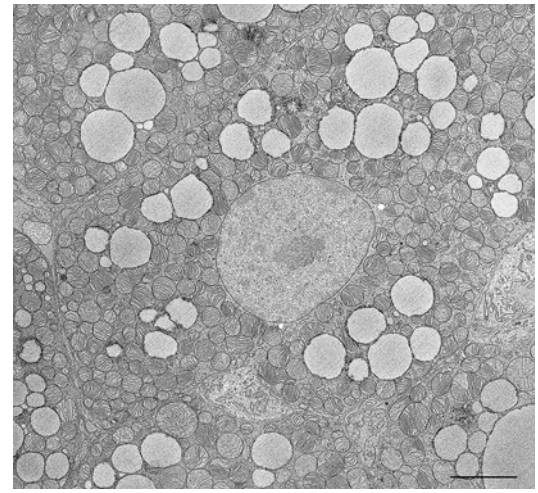

Fig. 6.3 Electron microscopy of multilocular brown adipocyte from interscapular fat of 10 days old rat. Note characteristic abundant mitochondria. Bar: 3 μm. Reproduced from Cinti S. The Adipose Organ. Milan: Kurtis; 1999 with permission from Editrice Kurtis

This different morphology accounts for their different function: white adipocytes store energy (triacylglycerides) in order to allow intervals between meals. Of note, sphere is the geometric shape allowing maximal volume in minimal space. Thus, most of the energetic needs of the organism during fasting are satisfied by fatty acids release of white adipocytes. White adipocytes are also endocrine cells because they release several hormones implicated in different metabolic pathways. The most important hormone released by white adipocytes is leptin [6]. Leptin signals the brain the amount of fat contained in the adipose organ. Low levels of this hormone induce hunger and behavioral changes to increase food intake.

Brown adipocytes burn energy (triacylglycerides) when animals are exposed to temperatures below thermoneutrality. The multilocularity favors a wide lipid-hyaloplasm interface allowing a massive disposal of fatty acids to be burned in the mitochondria [7]. Uncoupling protein 1 (UCP1) is uniquely expressed in the inner mitochondrial membrane of brown adipocytes and it is responsible for the main function of these cells [8]. In fact the enormous amount of fatty acids

burned in the mitochondria is uncoupled from ATP synthesis and dissipated as heat. The process is tightly regulated by the nervous system through the sympathetic neurons that directly reach brown adipocytes with noradrenergic synapses en passant. Norepinephrine activates specific β3 adrenoceptors that are responsible for the activation of the thermogenetic program of these adipocytes [9, 10]. Recently, a hormone produced by brown adipocytes has been identified: betatrophin. This hormone is important for pancreatic beta cells proliferation implying a direct activity of brown adipocytes in glucose metabolism [11]. Fibroblast growth factor 21 is also produced by brown adipocytes with an important role on glucose metabolism [12, 13].

White adipose tissue differs from brown adipose tissue not only for their parenchymal cells (white and brown adipocytes), but also for vascular and nerve supply that is much more dense in the brown parts of the adipose organ [14].

As visible in Fig. 6.1, in animals kept at room temperature BAT is present mainly in ASC, in mediastinic and perirenal depots. Microscopic quantitative analyses of the whole adipose organ performed in different strains revealed that small amounts of brown adipocytes are also present in most of the white-appearing fat depots [5]. Thus, in normal conditions, all white fat depots contain brown adipocytes and would be better defined as predominantly white fat depots. Pure white depots are rare (epididymal). Mediastinic fat is the only depot we found composed exclusively by brown adipocytes in Sv129 mice kept at 28 °C.

Interscapular BAT is usually referred as "pure" brown fat. This is not correct from an anatomical point of view because it is only a part of ASC that clearly shows white and brown parts (Fig. 6.1). Together with the parenchymal adipocytes several other cytotypes are present in the adipose organ: blood vessels cells, nerve cells, fibroblasts, macrophages, mast cells, and adipose stem cells [1].

The adipose organ is considered one of the most important mesenchymal stem cell reservoirs of the whole organism. A simple method to isolate mature adipocytes from the rest of the tissue was developed about 30 years ago [15]. Collagenase digestion followed by centrifugation allows separation of mature adipocytes (floating at the end of centrifugation) from the rest of the tissue generally referred as stroma-vascular fraction (SVF). SVF contains all lipid-free cells including adipose stem cells. When seeded in primary culture with adipogenic medium, they develop into mature adipocytes [16]. These cells can also be forced to develop into muscle cells, condrocytes, and osteocytes under appropriate culture conditions [17]. The adipose stem cell origin is debated. For many years, cells related to the capillary wall of adipose tissues have been regarded as possible adipose stem cells [16, 18] and we recently pointed to endothelial cells as the source for the development of both white and brown adipocyte precursors [19, 20]. A recent paper reached different conclusions [21], thus the question remains unsettled.

Adipose Organ of Pregnant and Lactating Mice

During pregnancy and lactation the two subcutaneous depots (ASC and PSC) undergo a process of mammary gland development [1, 22]. In female mice at birth, the epithelial ducts end in three bilateral nipples located in the ASC and two bilateral nipples end in the PSC. During the first three postnatal weeks ducts develop infiltrating the whole subcutaneous fat depots. Thus, in female mice the ASC and PSC correspond to the structures that develop into mammary glands during pregnancy and lactation (Fig. 6.4). Under the hormonal stimulus of pregnancy and lactation (mainly: progesterone and prolactin respectively) new mammary gland components appear as lobulo-alveolar structures (or simply alveoli). These are the most important components of the mammary gland because they are the site for production and secretion of milk. They occupy all ASC and PSC volume among ducts.

Fig. 6.4 Gross anatomy of the adipose organ of adult lactating female mouse. Note both subcutaneous depots are transformed into mammary glands. Bar: 1.5 cm. Reproduced from Cinti S. The Adipose Organ. Milan: Kurtis; 1999 with permission from Editrice Kurtis

Lobulo-alveolar cells are characterized by large amounts of cytoplasmic lipids (Fig. 6.5). Thus they are parenchymal cells of the adipose organ in pregnancy and lactation. We identified the epithelial cells forming mammary alveoli as pink adipocytes. In fact the term adipocyte is used for cells that are characterized by abundance of cytoplasmic lipids (as in white and brown adipocytes). Considering then that white and brown describes the colors of the part of the organ containing white and brown adipocytes, pink is the color of ASC and PSC during pregnancy. Thus, even if alveolar cells form epithelial glandular structures their definition as pink adipocytes seems to be appropriate.

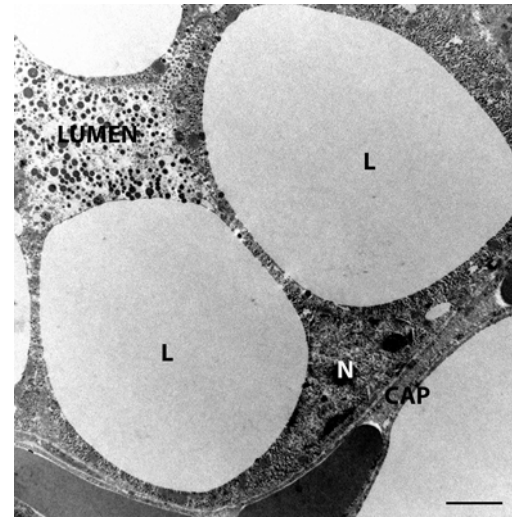

Fig. 6.5 Electron microscopy of pink adipocyte. Note the abundant cytoplasmic lipid droplets (L). Several dense milk granules are visible in the lumen of the alveolus formed by pink adipocytes. *N* nucleus of pink adipocyte, *CAP* capillary. Bar: 2.5 μm

Plasticity of Adipose Organ

The presence of three different parenchymal cytotypes in the adipose organ raises the question: why are three different cells with specific well different functions contained in the same organ? With this question in mind we studied the adipose organ in different physiologic conditions in which one of the specific functions was enhanced.

Cold

Brown adipocytes' main function is thermogenesis. Thus, cold exposure enhances the BAT activity. Looking at the gross anatomy of adipose organ of cold-exposed mice, we observed that most of the depots appearing as white in warm acclimated mice turned to a brownish color and most of brown areas became darker brown when animals were cold acclimated (Fig. 6.1).

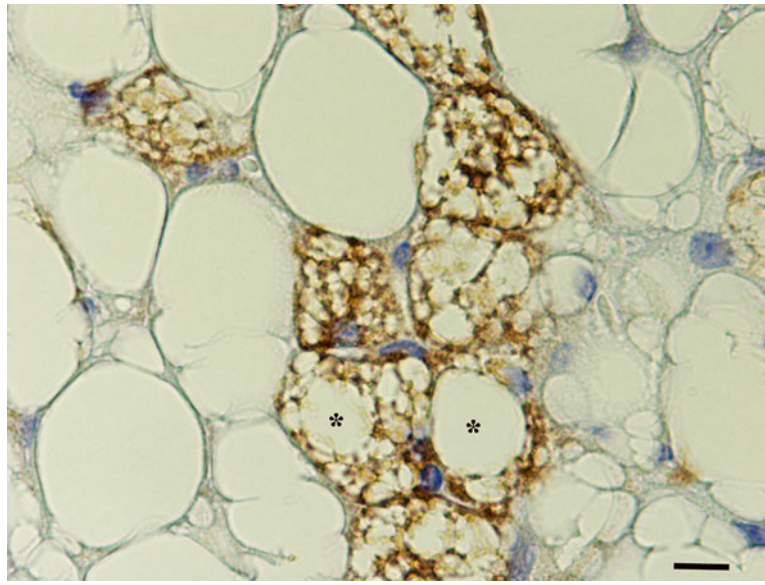

Fig. 6.6 Immunohistochemistry (UCP1) of subcutaneous fat of adult mouse exposed to cold (6 °C) for 5 days. UCP1 immunostained adipocytes (*brown*) are both multilocular and paucilocular (*Asterisk*). Bar: 18 μm. [4]

Histology, electron microscopy, morphometry, and immunohistochemistry studies comparing the adipose organ of warm acclimated (28 °C per 10 days) with that of cold acclimated (6 °C per 10 days) mice showed that this browning of the adipose organ is mainly due to a direct conversion of mature white adipocytes into metabolic active thermogenetic brown adipocytes [23–25]. Of note, we also found intermediate forms of adipocytes never described before: paucilocular adipocytes. These adipocytes have a morphology similar to that of unilocular white adipocytes, but are smaller and show many small lipid vacuoles surrounding a predominant central lipid droplet. These cells contain numerous mitochondria with a morphology that covers a complete spectrum between classic "white" mitochondria and classic "brown" mitochondria. Furthermore, some of these adipocytes are immunoreactive for the protein marker of brown adipocytes: UCP1 (Fig. 6.6). These cells, that are also present in the adipose organ of warm acclimated mice, always occupy mainly the boundaries between white and brown areas in any fat depot. In summary, we think that under the noradrenergic stimulus due to cold exposure part of the WAT of the adipose organ converts into thermogenetic BAT by direct transition at cellular level from a specific phenotype into a different phenotype [26, 27].

The key target for this phenomenon is the specific β3 adrenoceptor. Mice lacking this receptor have a very blunted phenomenon [28]. Sympathetic nervous system, activated by cold exposure, expands by branching its parenchymal fibers into the adipose organ and this is accompanied by white into brown conversion of adipocytes. In line with this observation, we found a positive correlation between parenchymal noradrenergic nerve fibers and the number of brown adipocytes in the adipose organ of two different strains of mice [3, 5, 29].

This white to brown plasticity of adipose organ is of paramount importance because mice lacking BAT or its function become massively obese in comparison to control mice with identical food intake and physical exercise [30, 31]. Furthermore, mice expressing UCP1 in white fat are obesity-resistant [32] and the obesity prone mice have reduced amount of BAT in comparison with obesity-resistant strains [5, 33].

BAT is also important to prevent diabetes and atherosclerosis. Removing the insulin receptor specifically in BAT induces hyperglycemia [34]. BAT explants regulates insulin sensitivity [35] and

BAT activity controls triglycerides clearance [36, 37]. Thus, BAT can be considered as an important organ to fight the metabolic syndrome [37].

The recent re-discovery of BAT in the adipose organ of adult humans [38–42] renewed the attraction of scientists to this tissue in view of the human health care possibilities. We found that adult humans have BAT with most of the characteristics found in mice, including morphology, UCP1 expression, high density of parenchymal noradrenergic fibers, and perivascular adipocyte precursors. In our case series of human adults, as well as in other studies, age, body mass index and insulin resistance correlate inversely with presence of BAT in the classic anatomical site for humans: the supraclavicular area [42]. Age-related disappearance of human BAT seems to spare supraclavicular more than interscapular BAT [43], thus suggesting that supraclavicular BAT in humans correspond to interscapular BAT in mice even if detailed studies of supraclavicular BAT in mice are lacking. On the other hand, PET images showing metabolically active BAT in humans seem to suggest that this depot is tightly connected with subclavian vessels in line with the idea that BAT areas of the adipose organ are linked to heart, aorta and its main branches: carotid, subclavian, intercostals, and renal vessels. This is clearly visible in PET images of cold acclimated humans and corresponds to PET images of patients suffering from pheocromocytomas (benign tumors secreting high levels of epinephrine and norepinephrine) before surgery [44]. Thus, human adipose organ seems to share many characteristics of murine adipose organ and allows the hope we could modulate the browning of human adipose organ in order to pervert or curb the metabolic syndrome affecting a very large percentage of humans in western countries.

Of note, we recently showed that even human omental WAT, that seems to be a pure white fat, can be converted into BAT under the peculiar noradrenergic stimulus of pheocromocytomas. We found that in all 12 adult patients studied, omental WAT undergo a remodeling process: half of them had a significant reduction of the adipocytes' size and half had a conversion of white adipocytes into UCP1 expressing brown adipocytes. Furthermore, this WAT to BAT transition was accompanied by a significant brown phenotype gene expression, and increased density of vessels and parenchymal noradrenergic fibers. Several UCP1 immunoreactive paucilocular adipocytes (we consider as morphologic-immunohistochemistry marker of direct WAT to BAT conversion, see above) were also found. Electron microscopy of paucilocular cells found in omentum of our case series of pheocromocytomas patients showed similar aspects of those found in fat of cold exposed mice: small lipid droplets at the periphery of a predominant central lipid droplet and numerous mitochondria with the white to brown morphology spectrum. We also found mitochondria with transitional characteristics: i.e. with white-like morphology at one extremity and brown-like morphology at the opposite extremity [45]. Similar mitochondria were described previously in adipocytes developed in vitro from the stroma-vascular fraction obtained from BAT, sampled from the axillary fat of a dead newborn [46]. Electron microscopy can distinguish perivascular adipocyte precursors [47, 48], thus it is possible to make quantitative analysis with this technique. Our quantitative electron microscopy showed that adipocyte precursors were not significantly increased in omentum of pheocromocytomas patients. In line with these results, the proliferative marker Ki67 was absent in nuclei of brown adipocytes confirming our previous murine data showing that noradrenergic stimuli do not induce proliferation of new adipocytes [45], consistent with results from other authors [49, 50]. All together, these data support the idea that brown adipocytes derive from a direct conversion of white adipocytes also in humans.

Beta adrenergic agonists are able to curb murine obesity [51–53] and drugs have been created in order to see if any therapeutic effect can be obtained to curb human obesity, however clinical trials were found to be unsuccessful [54, 55]. Nevertheless, several molecular mechanisms that overcome the beta adrenoceptors have been described recently (reviewed in [56]). Interestingly, physical activity seems to induce BAT activation and browning of WAT both in mice and humans [57–59].

Warmth and Obesity

When mice are exposed to warmth, a whitening effect is visible in the gross anatomy of the adipose organ [1]. Classic interscapular BAT changes the morphology of its brown adipocytes. They change gradually into white-like adipocytes. This morphologic transformation is accompanied by suppression of brown genes (such as UCP1) and activation of genes that are inactive in classic multilocular brown adipocytes (such as leptin and S-100b) [60, 61]. This transformation is also evident in beta-less mice (lacking all beta adrenoceptors). Beta-less mice are particularly prone to obesity and related disorders [31]. Genetically, obese mice have similar transformations of the adipose organ including brown to white transdifferentiation of interscapular BAT [62]. Thus, warm acclimation or chronic positivity of energy balance in absence of leptin or its receptor induces the opposite effect of cold exposure probably due to reduction of noradrenergic stimulus as suggested by knockout experiments described above. Chronic positive balance induces proliferation and development of new adipocytes and the adipose organ of obese humans can reach 60–70 % of the body weight (normal 15–20 %) [63, 64]. Thus the obese adipose organ is characterized by hypertrophy and hyperplasia of adipocytes.

Macrophage Infiltration

Two independent groups in the United States showed that the adipose organ of obese animals and humans is infiltrated by macrophages. This infiltration is correlated with the size of adipocytes and is strictly coincident with the appearance of insulin resistance. Cytokines, playing key roles in inducing insulin resistance, are expressed more by the stroma-vascular fraction of fat (including macrophages) than the floating fraction formed by mature adipocytes, thus implying the importance of macrophages infiltration in determining insulin resistance and subsequent type 2 diabetes [65, 66]. We showed that most of the macrophages that infiltrate fat are arranged to form characteristic figures that we identified as crown-like-structures (CLS) [67] (Fig. 6.7). These structures are formed by macrophages surrounding remnants of dead adipocytes. Such remnants, especially lipid droplets,

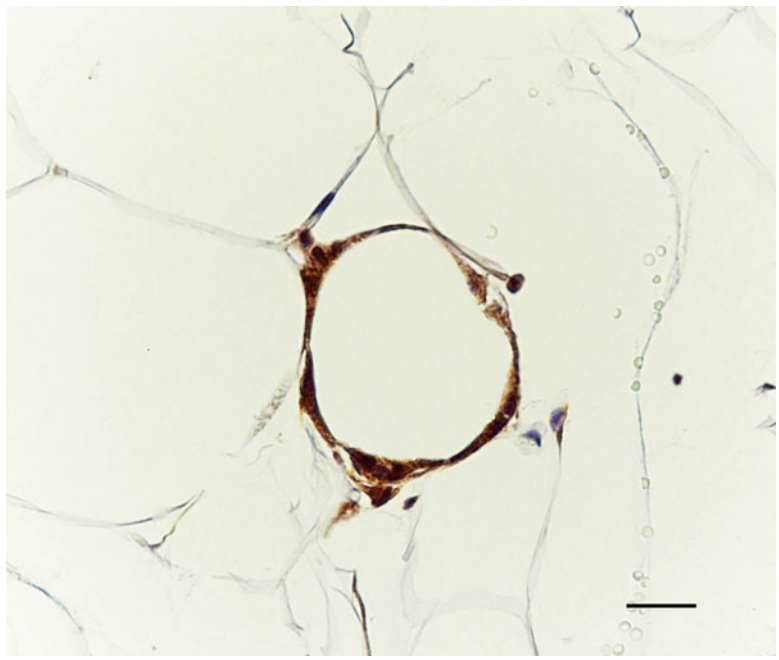

Fig. 6.7 Immunohistochemistry (F4/80) of white fat of obese mouse showing a crown-like structure (CLS). Bar: 35 μm

are large and require a long period of time for their reabsorption, thus inducing a chronic low grade inflammation similar to the reabsorption of foreign bodies. In fact, as in the classic foreign body reaction CLS can be also formed by syncytial giant multinucleated macrophages. In order to verify whether CLS are formed in correspondence of adipocyte debris we used a transgenic model where apoptotic death of adipocytes is specifically induced by administration of a dimerizer that activates the caspase 8 in adipocytes. In this model all dead adipocyte formed CLSs in line with our hypothesis [68]. The time course of fat histopathology in this model revealed that CLS appear in the adipose tissue after the death of adipocytes, demonstrating that death of adipocytes per se can be sufficient to attract macrophages and induce them to form CLS that characterize the chronic histopathology of fat in this model [68]. Hormone-sensitive lipase knockout mice are lean but their fat is characterized by hypertrophic adipocytes. In these animals, we found the same density of CLS as in fat of obese animals [67]. Of note, we found a positive correlation between the density of CLS and the size of adipocytes both in subcutaneous and visceral fat depots, but the density was lower in subcutaneous fat that showed larger adipocytes [69]. Thus, we raised the hypothesis that visceral adipocytes have a smaller death cell size (size triggering death) [27] in line with the more well-known morbigen role of visceral fat accumulation [70]. Both in mice and humans, we found an absence of CLS in hyperplastic obesity that is characterized by absence of metabolic complications. The positive correlation between size of adipocytes and insulin resistance has also been recently found in nonobese humans [71]. The plasticity of the adipose organ could be used for the treatment or prevention of type 2 diabetes and insulin resistance because the white to brown transformation implies the size reduction of unilocular white adipocytes as one of the first steps in the transdifferentiation pathway, suggesting that a "mild" transdifferentiation could be sufficient to reduce the size of adipocytes, induce mitochondria biogenesis and transform the histology of adipose tissue into a more healthy form.

Pregnancy and Lactation

During pregnancy and lactation, all subcutaneous depots of the adipose organ are transformed into mammary glands. Our morphologic studies of the transforming subcutaneous depot suggest that alveoli develop through two different modalities. The first occurs during the first half of pregnancy, where alveoli are formed by epithelial cells in which no cytoplasmic lipid droplets are still visible. The second one takes place during the second part of pregnancy, and is accompanied by a progressive reduction of subcutaneous fat. During this period, alveoli formed by epithelial cells containing an impressive amount of lipid droplets in the cytoplasm appear (Fig. 6.5). We propose to identify this cell type that appears in the adipose organ during pregnancy and lactation as pink adipocyte (see above). This new concept is reinforced by our original observations that pink adipocytes derive from a direct transformation of white adipocytes [72, 73]. As a matter of fact, our ultrastructural data support the possibility that in the second half of pregnancy subcutaneous adipocytes, likely under proper hormonal stimuli, acquire epithelial features, and aggregate together with other pink adipocytes and myoepithelial cells to form adipose-derived milk-secreting alveoli. In order to prove this striking transdifferentiation of adipocytes into milk-producing glands, and to establish whether the opposite process occurs during mammary gland involution, we adopted lineage tracing techniques that confirmed our hypothesis. The transdifferentiation of white adipocytes into alveolar cells (pink adipocytes) was also confirmed by explants experiments. In these experiments we showed that both adipose tissue, as well as isolated adipocytes from Rosa26 mice, when explanted into pregnant wild-type female mice gives rise to marked glands, reviewed in [56].

The Adipose Organ Theory: White–Brown–Pink Triangle

All data described above give a possible explanation to the question: why are three different cell types (white, brown, and pink adipocytes), with

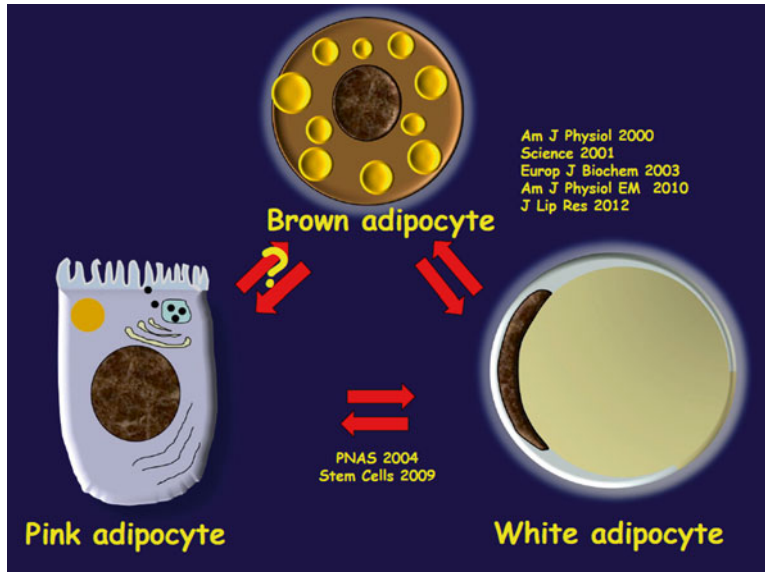

Fig. 6.8 Scheme showing the plastic triangle theory

three different functions, contained in the same organ? Considering all data together our answer is: because adipocytes are able to convert directly into different phenotypes. This direct conversion or transdifferentiation implies special genomic characteristics of this cell type that are able to reprogram physiologically and reversibly their genome in order to give rise to different cell types with different morphology and functions. In order to complete the triangle of adipocyte plasticity (see Fig. 6.8), reversible brown–pink transdifferentiation should be proved in future experiments.

Summary and Perspectives

In summary, all data from our and other's laboratories seem to suggest that adipocytes are a special cell type with plastic properties hitherto not described for parenchymal cells of other organs in mammals. This plasticity accounts for important physiologic properties, all linked to energy partitioning among vital functions for individual survival and species maintenance: thermogenesis, metabolic needs, and nutrition of pups.

Considering all similarities between mice and humans in anatomy and physiology of adipose organ, it is easy to understand the importance of dissecting molecular mechanisms underlying the plastic triangle of adipocytes. This may open new avenues for the future treatment of widely diffuse and important pathologies such as metabolic syndrome (white to brown) [74] or breast cancer (white and brown to pink) [75].

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Adaptive Responses to Weight Loss

7

Michael Rosenbaum and Rudolph L. Leibel

Introduction

Obesity has arguably become the single greatest health problem in the U.S. as reflected by its prevalence and its contributions to major, costly illnesses such as diabetes and cardiovascular disease [1, 2]. Sustaining weight loss over time is more difficult than the process of losing weight per se [3, 4]. This difficulty is reflected in the very high recidivism rate to obesity following otherwise successful weight loss [5]: only about one out of six adults who are overweight or obese are able to lose and sustain a 10 % or greater weight reduction for longer than 1–2 years [6]. In contrast to the prevailing view that the lack of success in long-term weight reduction is due to a lack of willpower on the part of obese individuals [7–10], studies of the metabolism and behaviors of lean and obese individuals attempting to sustain weight loss demonstrate that body weight is regulated. The difficulty in long-term weight reduction is the predictable biological consequence of CNS-mediated processes that occur as a result of decreased energy (fat) stores.

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Evidence that Body Weight Is Regulated

Genetics

Stored energy (fat) is important to reproductive efficiency and survival in circumstances of restricted access to food [11, 12]. The pressures of natural selection and predation have, therefore, likely favored enrichment of the human genome for alleles favoring energy ingestion and storage in service of reproductive integrity in the form of fertility and ability to breastfeed offspring [12–17]. The consequences of such evolutionary forces are more potent genetic/physiological mechanisms for defense of body fat than for preventing its accretion [11, 12, 14, 17]. The heritability of body fatness, meaning the fraction of the differences among individuals living in the same or similar environment that is attributable to genes, has been estimated at 30–80 % depending upon the strategy used [18–24], the age, gender, and ethnicity/race of the population studied, and the variable(s) used to define body fatness [21, 25]. These calculations are largely based on differences in concordance rates/correlations of phenotypes in monozygotic versus dizygotic twins or

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on studies of the resemblance of adoptees to their adoptive versus their biological parents [26–30]. Regardless of the approach employed, it is clear that the heritability of body fatness is comparable to that of height and is greater than that of many diseases such as schizophrenia and breast cancer [29]. The heritability of the somatic phenotype is conveyed by genetic effects on both energy intake and expenditure, with the predominant effect likely via the former [22–24, 31–33].

Long-Term Stability of Weight

In adults, there is a remarkable constancy of body weight and composition over long periods of time (the average American gains 0.5–1.5 kg/year or about 4,000 kcal of stored energy) [34–37], representing an approximately 0.4 % positive "error" relative to an annual total caloric intake of approximately 900,000–1,000,000 kcal [35, 36]. The tight "coupling" of energy intake and output necessary to achieve this constancy is evident when one considers that simply increasing or decreasing energy expenditure by 150 kcal/day (roughly a single 8 oz. glass of milk) without changing energy intake would result in a net energy imbalance of ~50,000 kcal (about 15 pounds of body weight) over 1 year.

Individuals Successful at Sustained Weight Loss

The responses of metabolic, neuroendocrine, behavioral, and autonomic physiological systems in the context of attempts to sustain weight loss demonstrate the potency and redundancy of the systems that favor regain of lost weight. Long-term studies of weight-reduced children and adults find that over 75 % of individuals attempting to sustain a 10 % or greater weight loss return to their previous weight percentiles within 1–2 years [3]. Most individuals successful at sustained weight loss report persistent conscious efforts to decrease energy intake and increase expenditure beyond the respective levels characterizing individuals who are "naturally" at the same weight [38–41]. The National Weight Control Registry follows a large (over 5,000 individuals) population of predominantly Caucasian females who have sustained a weight loss of more than 30 pounds for over 1 year (mean weight loss is ~30 kg sustained for 6 years representing an average ~25–35 % weight reduction) [39, 42]. Within this study population, individuals maintaining a reduced body weight consume an average of approximately 100–200 kcal/day less and exercise approximately 200–250 kcal/day more than individuals reported in the National Health and Nutrition Education Survey III (NHANES III) [39, 40, 43, 44]. In addition, the majority of successful long-term weight loss maintainers weigh themselves at least once a week, eat breakfast every day, watch < 10 h of television per week (vs. a national average of 28 h), and adhere to a low fat, low calorie diet [38–41, 44]. While there is some metabolic resistance to weight gain during overfeeding and to at least short-term maintenance of an elevated body weight, it is clear that resistance to maintenance of an experimentally elevated body weight is neither as potent nor as long-lasting as that related to maintenance of a reduced weight [11, 45–49].

Metabolic and Behavioral Consequences of Maintenance of Reduced Body Weight

As discussed above, long-term studies of weight-reduced children and adults indicate that over 75 % return to their previous weight percentiles [50] within 1–2 years, while studies of those successful at sustained weight loss indicate that the maintenance of a reduced fat mass will require a lifetime of meticulous attention to energy intake and expenditure [39, 41]. The responses of lean and obese individuals to experimental perturbations of body weight suggest that stored energy, particularly fat, is defended by central nervous system-mediated mechanisms that are qualitatively and quantitatively similar in lean and obese individuals. Regardless of the initial somatotype, there is potent "opposition" to the maintenance of reduced body weight (fat) that is achieved

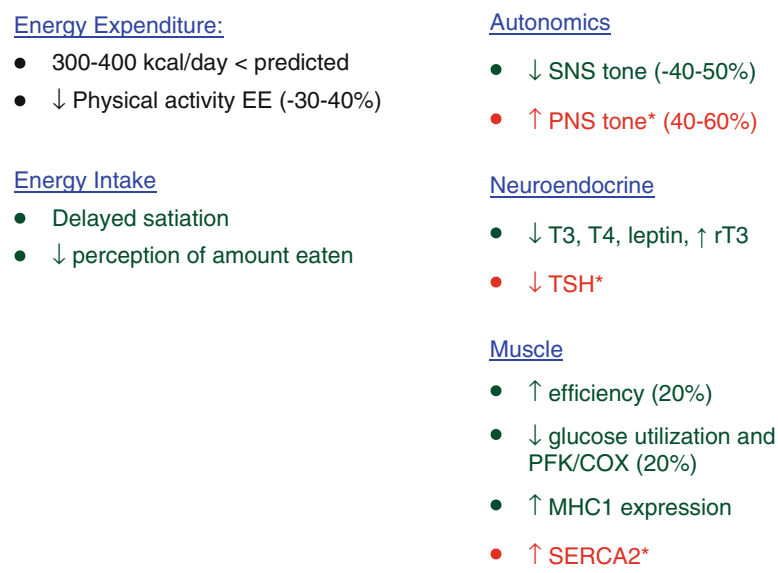

Fig. 7.1 Energy homeostatic systems that are significantly altered during maintenance of a 10 % or greater reduced body weight compared to the same subjects at usual weight. *Asterisk*—Not affected by leptin repletion [45, 46, 51–59]

by coordinated regulation of energy intake and expenditure mediated by signals emanating from adipose, gastrointestinal, and endocrine tissues, and integrated by the liver and the central nervous system (see Fig. 7.1). In-patient [51, 60] and out-patient [39, 50] studies indicate that the multi-system (metabolic, behavioral, neuroendocrine, and autonomic) opposition to sustained weight reduction produces a hypometabolic and hyperphagic state that does abate over time in most individuals. As discussed above, this regulatory system defends body fatness in service of reproductive integrity and survival and is the logical consequence of the environment in which most hominid evolution occurred. The components of this system are described below.

Energy Expenditure

Within the context of a highly controlled in-patient environment in which subjects are maintained at stable body weights by being fed a liquid formula before and after weight loss, we have found that maintenance of a 10 % or greater reduction in body weight in lean or obese individuals is accompanied by an approximate 20–25 % decline in 24-h energy expenditure (TEE) [45, 61]. This decrease in weight maintenance calories is 10–15 % below what is predicted solely on the basis of alterations in weight and body composition [45, 61]. Thus, a weight-reduced individual will require ~300–400 fewer calories per day to maintain the same body weight and level of physical activity as a never-obese individual of the same body weight and composition. The ~300–400 kcal magnitude of adaptive thermogenesis reported in in-patient studies of weight-reduced individuals [45] is remarkably similar to the changes in energy balance (increased physical activity and decreased energy intake) reported by subjects in the National Weight Control Registry [39]. This adaptive thermogenesis occurs regardless of whether the person is initially lean or obese [45]. It should be noted that this response is heterogeneous, for example, the range of decline in energy expenditure per unit of fat-free mass in 45 individuals studied before and after a 10 % weight loss ranged from −38 % to −6 % (unpublished data based on [45]). It should also be noted that while there is additional adaptive thermogenesis

following additional weight loss, it appears that the majority of the relative hypometabolism is induced early on in the weight loss process [62] and that the declines in energy expenditure following a weight loss of 10 % from usual weight are greater than those following additional weight loss from 10 % to 20 % below usual [45].

The necessity for these long-term changes in lifestyle is consistent with the observation that the reduction in 24-hour energy expenditure (TEE) persists in subjects who have sustained weight loss for extended periods of time (6 months–7 years) in circumstances of enforced caloric restriction in the biosphere 2 project [63] and lifestyle modification [64]. Analyses of data regarding energy expenditure in bariatric surgery patients are often confounded by the effects of the surgery on the co-morbidities and medications that preceded the procedure. That said, some studies have reported similar declines in energy expenditure following bariatric surgery to those seen following dietary weight reduction [65], while others have suggested that the effects weight loss via bariatric surgery on energy expenditure may be "blunted" compared to dietary weight loss [66–69].

TEE is the sum of resting energy expenditure (REE; cardiorespiratory work and the work of maintaining transmembrane ion gradients at rest; approximately 60 % of TEE), the thermic effect of feeding (TEF; the work of digestion; approximately 5–10 % of TEE), and non-resting energy expenditure (NREE, energy above resting that is expended in physical activity; approximately 30–40 % of TEE in sedentary individuals). Each of these components of TEE is differentially affected by weight reduction. There is no significant change in TEF (the fraction of the energy contained in food that is utilized to digest it) following weight loss [45]. REE per unit of metabolic mass has been reported to show no change [70–72] or a moderate decrease accounting for about 25–35 % of the decline in TEE beyond that predicted on the basis of body composition changes [45, 61, 73]. The variability in results probably reflects inter-study differences in multiple factors including degree and duration of weight stability before and after weight loss, ambient temperature, and changes in subject fitness and time spent in physical activity following weight loss [74]. In contrast, during dynamic weight loss there is little or no debate that REE is significantly lower (approximately 15–25 %) than at usual weight [45, 75–79]. Regardless of whether or not there are significant declines in REE following weight loss, NREE is clearly the compartment of energy expenditure that is most affected by changes in body weight [45, 76, 80, 81] consistent with the importance of physical exercise in the successful maintenance of reduced weight [39, 40].

The pre-eminence of NREE—accounting for over 70 % of the variance in the decline in TEE below predicted values in weight-reduced subjects [80, 82]—could be due to declines in the actual amount of physical activity or increased contractile efficiency of skeletal muscle, or both. In studies of rodents and of out-patient humans, maintenance of a reduced body weight is associated with no change or an increase, rather than decrease, in the amount of time spent in physical activity [45, 72, 76, 78, 83], supporting the view that skeletal muscle work efficiency is increased [80, 81] following weight loss. These effects are most evident at low levels of work/power (10–25 watts during bicycle ergometry) suggesting that some of the muscle-mediated opposition to reduced weight maintenance might be diminished by exercising at higher levels of power output [80, 84] or by engaging in exercises such as resistance training which favor increased expression of more powerful but less efficient myosin heavy chain isoforms (see below) [85, 86].

Studies of skeletal muscle chemomechanical efficiency (calories expended above resting per unit of power generated) in weight-reduced subjects indicate that maintenance of a reduced body weight is associated with an approximate 20 % increase in skeletal muscle work efficiency and an approximate 18 % relative increase in the fractional use of free fatty acids as fuel during low level exercise [52, 80], whether measured by bicycle ergometry or ^{31}P-NMR muscle spectroscopy [80]. These results are consistent with vastus lateralis muscle biopsies in which the ratio of glycolytic (phosphofructokinase, PFK) to oxidative (cytochrome oxidase) enzyme activities is significantly decreased and the expression of the more efficient myosin heavy

chain (MHC) and sarcoplasmic endoplasmic reticulum Ca^{2+}-dependent ATPase (SERCA) isoforms (MHCI and SERCA2) are significantly increased following weight loss [52, 53, 80]. The magnitude of these changes in muscle efficiency, biochemistry, and gene expression is potentially physiologically sufficient to account for the increased skeletal muscle efficiency and decreased utilization of glucose as fuel during low level exercise following weight loss [52, 53, 80].

Neuroendocrine Function

By virtue of its constituent neuronal outflow tracts to the ANS, neuroendocrine axes, and cortical tracts subserving food intake and energy expenditure, the hypothalamic pro-opiomelanocortin (POMC)-melanocortin-melanocortin 4 receptor (MC4R) pathway provides a central nexus for the integrated effects on energy intake and expenditure of hypoleptinemia or weight loss [87, 88]. Briefly, POMC is cleaved to alpha-melanocyte stimulating hormone (α-MSH) and beta-endorphin (β-EP) as well as other bioactive molecules. Alpha-MSH stimulates release of hypothalamic pro-TRH. β-EP inhibits the release of hypothalamic corticotropin releasing factor (CRF; an anorexiant neuropeptide). POMC expression is sensitive to ambient leptin concentrations and therefore is decreased in low leptin states, such as congenital leptin or leptin receptor deficiency or during and following weight loss [89, 90] with resultant expected increased activity of the hypothalamic–pituitary–adrenal (HPA) axis and decreased activity of the hypothalamic–pituitary–thyroid (HPT) axis. If the weight loss or hypoleptinemia is sufficiently severe, there is also a functionally significant decreased activity of the hypothalamic–pituitary–gonadal (HPG) axis resulting in infertility (and protection of the female from conceiving in times of undernutrition with neither the mother, the offspring, or their genes are likely to survive the pregnancy or early feeding period) [47].

The importance of the HPA axis in energy homeostasis is exemplified by the observation that the hyperphagic, hypometabolic (similar to weight-reduced humans), and hypercortisolemic phenotypes of leptin-deficient or leptin-resistant rodents are abolished by chemical or surgical adrenalectomy [91]. Hypercortisolemia results in loss of lean body mass and increased partitioning of stored calories to fat [88]. Studies of the HPA axis in which human subjects were assessed following various weight loss regimens have reported increases [92], decreases [93], and no change [94] in indices of cortisol production following weight loss. Discrepancies among such studies may reflect differences in subject populations regarding exercise, gender, age, or weight loss regimens, as well as the degree of weight stability at the time of study.

Thyroid hormone increases energy expenditure by increasing heart rate, blood pressure, muscle ATP consumption (largely by stimulating production of muscle ATPase and favoring expression of the less mechanically efficient more glycolytic myosin heavy chain II (MHCII) isoform) [53, 95]. The thyroid-hormone-deficient patient is hypotensive, bradycardic, and lethargic and tends to gain weight while the hyperthyroid patient is hypertensive and tachycardic and tends to lose weight [96, 97]. Both weight loss and the maintenance of a reduced body weight are associated with small but statistically significant decreases in circulating concentrations of triiodothyronine (T3) and increases in the circulating concentrations of its bioinactive enantiomer reverse T3 (rT3) [46, 51], suggesting that weight loss results in increased peripheral conversion of thyroxine (T4) to rT3 [46]. Thyroid releasing hormone (TRH)-stimulated pituitary thyroid stimulating hormone (TSH) release is not diminished either *during* caloric restriction [98] or *after* weight loss [99] in humans. However, as discussed above, low ambient leptin reduces POMC production in hypothalamic neurons resulting in decreased activity of hypothalamic pro-thyroid releasing hormone (pro-TRH) neurons in rats [100] as a result of decreased α-MSH [101]. Therefore, the decline in TSH during and after weight loss [46, 51] may reflect decreased production of TRH rather than decreased sensitivity of TSH neurons.

Autonomic Nervous System Function

The autonomic nervous system includes major outflow tracts linking afferent biochemical signals regarding energy stores and efferent tracts regulating energy homeostasis. Increased parasympathetic nervous system (PNS) tone slows heart rate and decreases resting energy expenditure. Sympathetic nervous system (SNS) tone modulates feeding behavior via effects on various gut peptides and transmission of nutrient-derived signals to the brainstem and also mediates the effects of cannabinoid receptor-1 activity [102, 103]. SNS tone also directly increases heart rate, and acts directly on the thyroid gland to increase secretion of thyroid hormone [48, 104] (24 h urinary norepinephrine excretion accounts for a significant proportion of the variance in energy expenditure and its subcomponents in weight stable subjects [46]).

The maintenance of a reduced body weight is associated with significant declines in SNS tone and increases in PNS tone [46, 48, 105] which may account for a significant fraction of the hypometabolic state through direct effects on skeletal muscle, and/or indirectly via effects on circulating concentrations of thyroid hormones [46, 106, 107]. Thus, weight-loss-mediated changes in autonomic nervous system activity may constitute a link between weight-loss-associated changes in energy and neuroendocrine homeostasis.

Brown Adipose Tissue

Brown adipose tissue (BAT) allows the uncoupling of mitochondrial substrate oxidation from ATP production and release some of the energy of fatty acid oxidation as heat [108]. BAT is a major contributor to adaptive thermogenesis in small mammals [109] via its role in both obligatory (maintenance of body temperature) and facultative (response to low ambient temperature) thermogenesis [110]. Physiologically, BAT activation and subsequent heat generation depend upon the integration of input from the SNS activation of adrenoreceptors (predominantly β_3) [111], with activation of at least one of the thyroid hormone receptor (TR) subtypes (TRα or TRβ) [110]. Since both SNS tone and circulating concentrations of bioactive thyroid hormones are reduced following weight loss (see above), it is possible that a significant fraction of the unexplained variance in energy expenditure following weight loss is attributable to changes in the BAT [112].

Recent advances in positive emission tomography (PET) scanning technology have allowed detailed imaging of BAT using uptake of 2-[^{18}F] fluoro-2-desoxy-glucose (FDG) and a hybrid scanner. Several groups have demonstrated the ability to detect BAT in healthy human beings with varying results as to whether thermal stimuli are necessary for its detection [113–115].

However, while BAT is a major contributor to adaptive thermogenesis in small mammals [109], and contributes to non-shivering thermogenesis in human infants, its thermogenic role in adult humans remains unclear. Previous studies showed a lack of a significant presence of BAT in humans except under extreme conditions of hypercatecholaminemia [116, 117] and, until recently, quantitative assessment of the contribution of BAT to total adaptive thermogenesis in humans has not been performed and was probably underestimated. Recent studies of cold-induced BAT thermogenesis in humans who were placed in a suit perfused with 18 °C water showed an activation of an average of ~168 ml of BAT (vs. no detectable BAT at room temperature of 25 °C) and an average increase in TEE of ~77 kcal/h (1,857 kcal/day, 11 kcal/ml BAT/day) [118]. Based on these data, the sustained activation of approximately 30 ml of BAT would be sufficient to reverse most of the adaptive thermogenesis that occurs during maintenance of reduced body weight [45]. Since no BAT activation was detected at room temperature, it is likely that whatever role BAT plays in human energy homeostasis beyond the neonatal period is likely to more evident in obligatory (metabolic) than in facultative (thermoregulatory) thermogenesis. Clothing, central heating, heated transportation ensure that in developed countries most individuals spend most of their time in thermoneutral

conditions, reducing the need for facultative thermogenesis and possibly contributing to the increasing prevalence of obesity [11, 119]. The recent identification of mechanisms that could potentially result in the "browning" of white adipose tissue (WAT), thus increasing energy expenditure by WAT, may provide a mechanism for increased functional importance of BAT-like cells in humans [120].

Energy Intake (See Table 7.1)

As discussed above, the long-term constancy of body weight despite large day-to-day variations in caloric intake and physical activity indicates that, at usual weight, energy intake and energy output are "coupled" and, over time, vary directly with each other thus maintaining a relative constancy body energy stores. If this coupling persisted following weight reduction then weight-reduced individuals would naturally eat less in response to the hypometabolic state induced following weight reduction. In this physiological scenario, it would be relatively easy for a weight-reduced person to comply with dietary recommendations to sustain weight loss even if the number of calories required to sustain the weight reduction were substantially lower than someone naturally at the same weight.

Unfortunately for those attempting to lose weight and to sustain the loss, this "coupling"—which reduces caloric intake in response to decreased energy expenditure—is disrupted during and following weight loss [121]. During dynamic weight loss, i.e., in a state of negative energy balance, and during maintenance of reduced body weight (i.e., a state of energy balance), human beings and rodents are both hungrier (willing to eat more often) and less satiated (willing to eat more per meal) [54, 122]. Briefly, during strict maintenance of a reduced body weight on a bland liquid formula diet with little or no hedonic value, functional magnetic resonance imaging (fMRI) studies of overweight or obese subjects before and after weight loss demonstrate increased blood oxygen level-dependent (BOLD) signaling in response to food in the orbitofrontal cortex and brain areas mediating reward [55]. They also demonstrate decreased BOLD signaling in response to food in the hypothalamus and in the pre-frontal cortex and brain areas

Table 7.1 Effects of weight loss and leptin on fMRI response to visual food cues

Brain areas more active in response to visual food cues at 10 % reduced weight (leptin-depleted) than in leptin-sufficient states (usual weight or weight-reduced but with leptin repletion)		Brain areas less active in response to visual food cues at 10 % reduced weight (leptin-depleted) than in leptin-sufficient states (usual weight or weight-reduced but with leptin repletion)	
Structure	Net function (Effect)	Structure	Net function (Effect)
Brainstem	↑ Signal processing (food recognition)	Hypothalamus	↓ Integration of leptin/humoral signaling
Globus pallidus	↑Food reward	Amygdala	↓ Response to sensory cues (feelings of fullness)
Insula	↑Food reward expectation	Cingulate	↓ Self-control and error recognition (dietary restraint)
Ventral striatum	↑ Food reward and motivation	Inferior parietal lobule	↓ Response based on experience (action based on previous knowledge)
Lingual and superior temporal gyri	↑ Affective response to high and low caloric density foods		
Net effect after weight loss	**↑ Food reward**	**Net effect after weight loss**	**↓ Food restraint**

The net effect of low leptin states is to decrease neural response in brain areas related to food reward and to decrease response to food in brain areas related to restraint [55]

mediating restraint. These changes in neural signaling in response to food following weight loss are consistent with the observation that before a liquid formula meal, these same weight stable subjects report feeling less full (hungrier, greater food reward expectation) and perceive themselves as having eaten less (despite ingesting the same 300 kcal 2 h before the study) and also perceive themselves as less satiated and having eaten less despite having increased their actual intake (diminished food restraint) following ad *libitum* formula consumption [54]. The simultaneous declines in both energy expenditure and satiety following weight loss conspire to create the optimal biological circumstance for weight regain [123]. Interestingly, studies of subjects in the National Weight Control Registry indicate that successful maintenance of reduced body weight is associated with extremely high levels of dietary restraint [124, 125]. Whether this trait was present prior to the initiation of weight loss, or is a learned response, is the subject of ongoing research.

The Role of Leptin (See Fig. 7.1)

A critical mediator of these reciprocal changes in energy intake and expenditure is the adipocyte-derived hormone leptin that circulates in weight-stable individuals in close direct proportion to fat mass [126]. Leptin-deficient humans and rodents demonstrate a hyperphagic/hypometabolic phenotype that is similar to that seen in weight-reduced humans, and leptin signaling affects many of the weight-reduced phenotypes discussed above [127]. Leptin suppresses food intake by promoting the production of anorexigenic hypothalamic neuropeptides (processed products of POMC) and reducing the expression of orexigens such as neuropeptide Y (NPY), agouti-related peptide (AgRP), and melanin concentrating hormone (MCH). Mice overexpressing the melanocortin 4 receptor (MC4R) antagonists, agouti signaling protein (ASP) or agouti-related peptide (AgRP) [128] are obese. Thus, decreased circulating leptin concentration as a result of reduced fat and/or negative energy balance mass has the net effect of stimulating food intake [88].

The hypothalamic POMC–melanocortin–MC4R pathway is highly sensitive to circulating leptin concentrations and POMC expression is decreased in low-leptin states [129, 130] (see above). Therefore, reduced ambient leptin induced by weight loss should be associated with decreased HPT and increased HPA axis activity by virtue of decreased levels of hypothalamic α-MSH and β-EP, respectively [129, 130]. Rodents and humans with hypomorphic mutations in *MC4R* [131], disruptions of POMC gene expression [132, 133] or of proneuropeptide (e.g., POMC, pro-ACTH, pro-TRH) processing by prohormone convertases [134, 135] are obese. The importance of leptin in mediating these effects is confirmed in the observation that fasting in rodents causes hypoleptinemia that is associated with increased arcuate and brainstem NPY and AgRP mRNA expression and decreased POMC mRNA in lean animals to a greater degree than in leptin-receptor-deficient animals [136, 137]. Once activated, γ-aminobutyric acid (GABA-ergic) outflow from NPY neurons suppresses leptin activation of POMC and anorexiant neurons, including melanocortin-4 receptors. Leptin is also clearly not the only peripheral signals to NPY and POMC neurons. Caloric restriction increases NPY expression and decreases POMC expression in the arcuate nucleus as well as increasing corticosterone production in the obese, leptin-resistant Zucker *fa/fa* rat [138].

The effects of exogenous leptin on energy homeostasis are dependent upon the nutritional environment in which it is applied. Administration of leptin to leptin-deficient rodents and humans in doses that restore circulating leptin concentrations to their physiological range increases energy expenditure [139], decreases energy intake, increases sympathetic nervous system activity [140], and normalizes hypothalamic–pituitary–adrenal, thyroid, and gonadal function [88, 129, 141]. Yet, in humans (lean or obese) and rodents who are not leptin-deficient, induction of even modest weight loss requires doses of leptin that produce plasma leptin concentrations over ten times normal [142, 143]. In contrast to the limited effects on energy homeostasis of leptin administration to humans who are either leptin-sufficient or in a state of dynamic weight

loss, leptin appears to have very potent effects on the hypometabolic, hyperphagic state that characterizes the weight-reduced and weight stable individual [54, 56, 141]. More specifically, we have found in short-term (5-week) studies that physiological leptin repletion following weight loss at least partially reverses the metabolic (decreased energy expenditure and increased skeletal muscle chemomechanical efficiency), neuroendocrine (decreased circulating concentrations of T3 and T4 but not TSH), and autonomic (decreased SNS but not increased PNS tone) [56]. In this sense, the weight-reduced state may be "perceived" by CNS elements relevant to energy homeostasis as a state of relative leptin deficiency. Pharmacotherapy designed to activate the leptin-signaling pathways may help weight-reduced individuals to sustain their weight loss [144]. It is likely that these agents will be effective at doses below those required for weight reduction per se.

Implications for Future Directions

Wing and Hill proposed that successful weight loss maintainers be defined as "individuals who have intentionally lost at least 10 % of their body weight and kept it off at least one year" [39]. No matter whether surgical, pharmacological, variations in diet caloric density or macronutrient content, or other behavioral methods are used to promote weight loss, it is apparent that for most individuals all or almost all of the weight loss occurs in the first 6–9 months of the intervention [145, 146]. While the amount of weight lost in this time period may vary (greatest with bypass bariatric surgery), the slope of the line relating subsequent weight regain to time after this initial weight loss period does not differ significantly among interventions [145, 147–149]. Approximately 15 years ago, McGuire et al. reported that only about 20 % of individuals who had attempted to lose weight were able to meet this goal of 10 % sustained weight loss [5].

These figures have not improved over the past decade and a half, despite the advent of multiple new weight loss and maintenance plans that are "guaranteed," and the approval, and often subsequent disapproval, of various weight loss medications [150–152]. Kraschnewski et al. [6] reported that only one out of six overweight or obese adults is able to sustain a weight loss of 10 % or greater. The Look AHEAD trial examined the efficacy of an intensive lifestyle intervention in overweight or obese adults with type 2 diabetes that consisted of an approximately 1,600 kcal/day diet, 175 min of moderately vigorous physical activity per week, and screening by a health professional weekly for 6 months, then three times per month for 6 months, and then monthly for a total of 4 years. Only 40 % of the initial subject population was able to lose >10 % of their initial weight and of those, only 40 % were able to sustain the weight loss. Thus, even with an intense intervention, the odds ratio was 3:2 against being able to lose at least 10 % body weight and 6:1 against being able to lose and maintain a 10 % or greater reduced weight. The resistance to efficacy from this extensive and expensive intervention reflects, in part, the potency of the biological opposition to sustained weight loss.

These observations suggest possible directions for future research. Further research into means of extending the period of actual weight loss would result in greater initial reduction in body weight and a higher percentage of individuals reaching a weight at which co-morbidities, or co-morbidity risks, are significantly reduced. Dynamic weight loss, which is a state of negative energy balance, should be seen as a state distinct from static weight maintenance which is a state of energy balance. Pharmacotherapies designed specifically for weight maintenance, probably affecting the leptin signaling pathway, should result in reversal of much of the weight-reduced phenotype and assist in maintenance of reduced body weight. Other therapies, whether diet, exercise, pharmacologically, or surgically based should be specifically designed to reverse the consequences of weight loss with a particular focus on decreasing skeletal muscle work efficiency and appetite. Interventions, such as leptin, that are less effective in promoting weight loss in humans may be very effective in promoting main-

tenance of reduced body weight. The metabolic and behavioral responses to weight maintenance are both heritable and heterogeneous [19, 31–33, 153]. It may be possible to identify certain behavioral and imaging phenotypes and genotypes as well as environmental factors that are predictive of the weight loss and maintenance of reduced weight in response to different types of interventions.

There is substantial evidence that these questions can be answered. The pharmaceutical industry is examining combination medications to address concerns regarding weight maintenance and prolonging of the weight loss period [144]. Analysis of feeding behavior in gastric bypass patients indicates a significant post-operative decline in food reward value compared to gastric banding patients which could reflect changes in molecular signaling by intestinal peptides, changes in the gut microbiome, or learned behaviors following this surgery [154]. Cluster analyses of individuals successful at keeping weight off has suggested that the age of onset of obesity may be negatively correlated with likelihood of successfully losing weight and sustaining weight loss by behavioral intervention [42]. Those individuals who have sustained weight loss by lifestyle changes demonstrate very high levels of food restraint (in contrast to most weight-reduced individuals) suggesting that pre-weight loss assessment of food restraint may be predictive of the response to lifestyle intervention [125].

Summary

The regulation of body weight is the result of the coordinate interactions of multiple systems that "conspire" to defend body energy (triglyceride) stores following weight loss by disproportionately decreasing energy expenditure and increasing the drive to consume calories. Attempts to sustain weight loss invoke adaptive responses involving the coordinate actions of metabolic, neuroendocrine, autonomic, and behavioral processes that "oppose" the maintenance of a reduced bodyweight. The multiplicity of systems regulating energy stores, and opposing the maintenance of a reduced body weight, illustrate that somatic chemical energy stores in general, and fat stores in particular, are actively "defended" by interlocking bioenergetic and neurobiological physiologies. Important inferences can be drawn for therapeutic strategies by recognizing obesity as a state in which the human body actively opposes the "cure" over long periods of time beyond the initial resolution of the obese phenotype.

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Shortened Sleep Time and Obesity

8

Plamen D. Penev

Introduction

Human sleep is an actively generated, periodically recurring, and reversible state of unconsciousness which includes alternating phases of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. The length of each NREM–REM cycle in humans is approximately 90 min and is repeated 4–6 times per night. The daily sequence of sleep and wakefulness is regulated by the interaction between homeostatic mechanisms and signals from the circadian timing system. Multiple heritable and non-heritable factors, such as age, sex, race/ethnicity, environmental (e.g. geographic latitude) and socioeconomic conditions (e.g. family structure, work schedules, poverty), physical health, and psychological wellbeing contribute to the between-subject variability in habitual sleep duration. On average, 7–8 h of nighttime sleep is needed to optimize human neurobehavioral performance [1].

Driven by the demands and opportunities of modern life, many people now sleep less than 6 h per night. In the clinic, this behavior most commonly presents as a diagnosis of insufficient sleep syndrome (ICSD-9, #307.49-4) and is receiving increased attention as a risk factor for obesity and related metabolic morbidity [2]. This chapter introduces the notion that extended wakefulness has increased metabolic cost, which triggers a set of neuroendocrine (e.g. increased hunger and reduced satiety), metabolic (e.g. lower resting metabolic rate), and behavioral (e.g. reduced daily activity) adaptations aimed at increasing food intake and conserving energy. Although this coordinated response may have evolved to offset the metabolic demands of sleeplessness in natural habitats with limited food availability, it can become maladaptive in a modern environment that allows many to overeat while maintaining a sedentary lifestyle without sufficient sleep.

Sleep and Energy Metabolism

The inherent complexity of the association between shortened sleep and obesity is highlighted by the existence of reciprocal connections between sleep–wake behavior and the systemic control of fuel availability. In order to facilitate adaptation and metabolic survival of the organism in diverse natural habitats, the demands of balancing energy intake and expenditure are linked to the timing, quantity, and quality of sleep. Accordingly, daily sleep quotas of various animal species factor in variables such as basal metabolic rate, caloric density and macronutrient composition of the usual diet, as well as the ease and safety of its procurement [3]. For example, weight gain in rodents kept in a safe environment

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with abundant food supply leads to more sleep, whereas food deprivation results in increased vigilance and sleep loss, presumably to help maximize food finding and bioenergetic survival. Conversely, sleep deprivation in ad lib fed rats results in negative energy balance and weight loss despite the presence of compensatory hyperphagia, demonstrating that sleep can play an important role in energy conservation, tissue maintenance, and metabolic survival in the face of environmental adversity. Observations in individuals with abnormal thyroid function or pathological or experimentally induced disruption of food intake also indicate that human sleep can be influenced by changes in energy metabolism and metabolic substrate availability [3].

Metabolic Cost of Human Sleep Loss

Sleep is a state of maximally reduced total energy expenditure as a result of sleep-imposed immobility and absent nutrition, which eliminates the energy cost of physical activity and food-related thermogenesis, along with a 20–30 % decrease in basal metabolic rate, since less energy is needed to support brain function, sympathetic activity, breathing, circulation, core body temperature, etc. during sleep [4]. Jung et al. quantified the energy that is conserved by young non-obese adults during 16 h of wakefulness and 8 h of nighttime sleep in a room calorimeter compared to a matching period of total sleep deprivation [5]. Total energy expenditure was 32 % higher during the 8-h period without sleep and the metabolic cost of sleep deprivation averaged an additional ~135 kcal over 24 h. Similar experiments showed that 5 days of insufficient sleep in a room calorimeter (the equivalent to a work week) also increased total daily energy expenditure by ~111 kcal/day [6]. Together, these results indicate that both total sleep deprivation and recurrent sleep insufficiency increase daily energy expenditure and support the importance of sleep in conserving a physiologically meaningful amount of energy. If such sleep-loss-related increase in energy demand was not offset by specific physiological adaptations (such as increased food intake, lower basal metabolic rate, reduced physical activity, etc.), then lack of sufficient sleep would be predicted to lead to weight loss. Carrying this argument further, chronic sleep insufficiency would result in increased 24-h energy expenditure sufficient to offset the positive "energy gap" and prevent weight gain in more than 90 % of the population in developed societies [7]. However, such simplistic reasoning is not consistent with available epidemiological and experimental data and fails to capture the complexity of the multiple physiological adaptations in the relationship between sleep loss and human energy metabolism. Numerous attempts to detect sleep-loss-related weight loss dating back to the earliest studies of total sleep deprivation in humans with sufficient access to food have produced negative results. Instead, a number of epidemiological studies have established an association between self-reported short sleep and increased body mass index or obesity [8].

Defense of Energy Homeostasis in Sleep-Deprived Humans

A robust system of neuroendocrine, metabolic, and behavioral defenses is activated when human energy expenditure exceeds the amount of energy intake. Changes include lower anorexigenic and higher orexigenic hormone concentrations to increase hunger, reduce satiety and stimulate food intake, combined with lower sympathetic tone, reduced resting metabolic rate, and decreased activity-related metabolic expenditure to conserve energy [9, 10]. These adaptations provide potent opposition to the threat of weight loss and depletion of body energy stores, and create ideal conditions for efficient retention of fat in both lean and obese individuals [9, 11]. From a clinical point of view, such increases in appetite and metabolic efficiency pose significant challenges to the success of therapies which combine caloric restriction and increased physical activity to ameliorate metabolic risk in obesity-prone individuals.

The changes in human energy metabolism in response to insufficient sleep share considerable

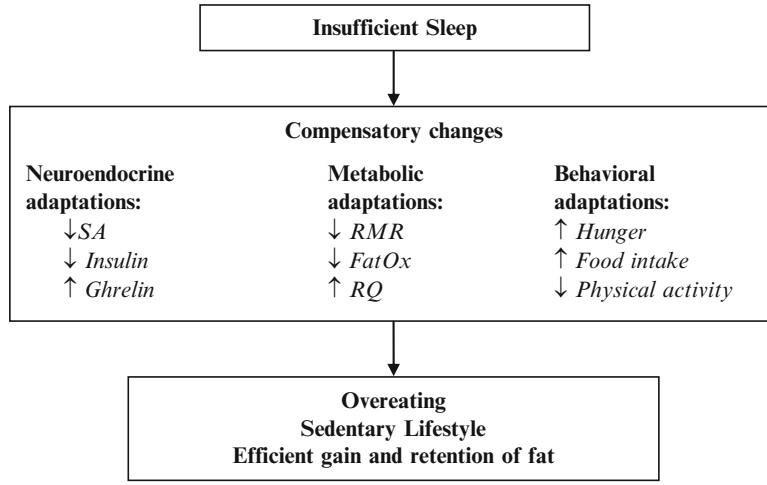

Fig. 8.1 Insufficient sleep triggers a set of neuroendocrine, metabolic, and behavioral adaptations aimed at increasing food intake and conserving energy. *SA* sympathetic activity, *RMR* resting metabolic rate under basal conditions, *FatOx* fraction of energy derived from fat oxidation, *RQ* respiratory quotient

similarity with the human metabolic adaptations to negative energy balance (Fig. 8.1) as illustrated by a study of overweight adults treated with a 14-day hypocaloric diet and varying amounts of daily sleep (caloric deficit of ~680 kcal/day and time-in-bed fixed at 5.5 vs. 8.5 h/night) on two separate occasions in random crossover fashion [12]. Participants lost ~1.0 BMI unit of body weight during each treatment, but lack of sufficient sleep reduced the amount of weight lost as fat by 55 %. Thus, subjects defended their energy balance more vigorously when they did not obtain enough sleep and energy-dense fat was conserved at the expense of 60 % greater loss of less-calorically dense and metabolically costly-to-maintain lean body mass. Other neuroendocrine, metabolic, and behavioral changes in response to sleep loss included enhanced hunger, higher orexigenic (ghrelin) and lower anorexigenic hormone (leptin, insulin) concentrations, signs of lower sympathetic activity, and decreased resting metabolic rate (independent of the changes in body composition) to conserve energy. Similarly, measurements obtained after a single night of total sleep deprivation in other studies indicate that the extra energy cost of additional wakefulness can lead to compensatory declines in morning resting metabolic rate [13] and energy expenditure during a subsequent night of recovery sleep [5]. Individuals exposed to recurrent sleep restriction in non-respiratory-chamber settings to allow greater freedom of movement and adaptation in daily physical activity also compensated for the extra energy cost of additional wakefulness and did not show a significant increase in 24-h energy expenditure measured by doubly labeled water [12, 14, 15].

Shortened Sleep and Obesity

The neuroendocrine, metabolic, and behavioral adaptations in response to insufficient sleep combined with an environment which offers abundant access to food and promotes inactivity can conspire to cause greater energy imbalance and lead to accelerated weight gain and obesity. This could result from increased food intake in excess of energy expenditure, reduced energy expenditure relative to food intake, or a combination of the two.

Increased Energy Intake

Early experiments in young men exposed to insufficient sleep and reduced caloric intake

found lower anorexigenic (leptin) and higher orexigenic (ghrelin) hormone concentrations in association with increased hunger and appetite [16], whereas reports of sleep-deprived volunteers who were given adequate or excess amounts of self-selected calories found either stimulatory or no independent effects of sleep loss on plasma leptin [17–21]. Additional experiments combining 2 weeks of sleep restriction with over- or underfeeding showed that sleep insufficiency did not affect the corresponding rise and fall in leptin, whereas ghrelin increased only in the presence of sleep loss and negative, but not positive, energy balance [12, 14]. These observations support the notion that the early reports of lower leptin and higher ghrelin concentrations reflected the ability of sleep loss to amplify the human neuroendocrine response to caloric restriction (Fig. 8.1), and that sleep-deprived humans have a more vigorous response to threats of negative energy balance [4]. In further agreement with this concept, St-Onge et al. exposed healthy men and women to 4 days with sleep opportunity of 4 vs. 9 h/night and caloric restriction (average daily deficit of ~400 kcal) [15]. When participants slept less during the 4-day period of caloric restriction, their ad lib energy intake on day 5 was ~300 kcal higher than that after the same caloric restriction with an extended sleep opportunity. If operational under long-term free-living conditions, this enhanced response to caloric restriction may undermine the success of dietary weight-loss therapy in individuals with insufficient sleep—a possibility which is consistent with data from early clinical trials and epidemiological observations [22–24].

Sleep-deprived humans also exhibit greater propensity to overeat when given unrestricted access to easily available calories. This increased food intake does not require alterations in circulating orexigenic and anorexigenic hormone concentrations [6, 14, 25] and has been attributed to multiple sleep-loss-related changes in the central mechanisms that regulate human eating behavior, such as altered neuronal responsivity to stimuli from the environment, digestive system, and peripheral metabolic networks; declines in dietary restraint; enhanced reward seeking and desire for calorie-dense foods; and increased motivation and food purchasing behavior [26–29]. Lack of sleep can also lead to excessive energy consumption as a result of longer exposure to environmental stimuli which promote overeating, as well as maladaptive changes in the circadian pattern and timing of daily food intake. Indeed, insufficient sleep has been associated with late night eating combined with irregular meal habits and more snacking between meals [14, 30–36].

In addition to energy, sleep also conserves carbohydrate. Higher respiratory quotient (RQ) measurements following sleep restriction [18] and repeated disruption of sleep [37] suggest that partial sleep loss is associated with use of a greater proportion of energy from carbohydrate. Sleep restriction also caused a shift in substrate utilization toward oxidation of relatively more carbohydrate in overweight and obese adults placed on a 2-week hypocaloric diet [12]. The modest decline in fasting blood glucose and improved insulin economy in this setting [38] resembled the human metabolic adaptation to reduced carbohydrate availability. These findings raise the possibility that increased use of carbohydrate in individuals with insufficient sleep may stimulate hunger and food intake at times of diminishing glucose availability at night and during the late postprandial period. Indeed, some studies suggest that higher RQ predicts future weight gain [31]. In addition, Chaput et al. observed that self-reported short sleepers have more relative hypoglycemia at the end of an oral glucose tolerance test, which also predicted future weight gain [39, 40].

Decreased Energy Expenditure

The apparent adaptation in 24-h energy expenditure in response to sleep loss indicates that the additional metabolic cost of extended wakefulness can also be offset by declines in resting (basal metabolic rate) and non-resting (activity-related) energy expenditure. Limited by the reliability of subjective recall and differences in study design and population, cross-sectional analyses of sleep and physical activity have given

inconsistent results showing either positive, negative, or no significant association between shortened sleep time and changes in physical activity. Few studies have directly tested the effects of sleep deprivation on the amount and intensity of daily activity outside of the limitations imposed by a room calorimeter. Roehrs et al. found a higher percentage of time spent in inactivity in laboratory settings after one night of total sleep deprivation [41]. Schmid et al. reported that overnight sleep restriction reduced the amount and intensity of free-living activity on the following day [17]. In contrast, Brondel et al. found that a night with restricted sleep was followed by a day with increased food intake and more movement [42], while Bosy-Westphal et al. and Calvin et al. did not find effects of sleep restriction and higher food intake on daily activity [18, 25]. Finally, St-Onge et al. studied healthy lean adults exposed to 5 nights with fixed time-in-bed (4.0 vs. 9.0 h/night) and inadvertent caloric restriction and reported lower percent time spent in very heavy and heavy physical activity and a trend for lower peak activity during the sleep-restricted condition [15]. Interpreting the results of these studies is challenging, since the impact of insufficient sleep on activity-related energy expenditure can differ as individuals adapt to recurrent exposure [43, 44] and brief interventions cannot capture the changes in physical activity of people who exercise only a few times a week. Similarly, the amount of daily activity can change considerably in response to positive or negative energy balance [9].

More recently, free-living activity counts and time spent in sedentary, light, moderate, and vigorous-intensity physical activities were measured by accelerometry in matching groups of participants with habitual sleep <6 vs. ≥6 h/night [45]. Compared to participants who slept ≥6 h/night, short sleepers had 27 % fewer daily activity counts, spent less time in moderate-plus-vigorous physical activity (−43 min/day), and were more sedentary (+69 min/day). To test whether insufficient sleep can be a causal factor for the reduced physical activity in short sleepers, 18 subjects completed 1 week of experimental sleep restriction in the laboratory (time-in-bed 5.5 h/night) and a matching period with 8.5-h nighttime sleep opportunity in randomized crossover fashion [46]. Participants received a carefully controlled weight-maintenance diet and those who exercised regularly were allowed to follow their usual exercise routines. Sleep restriction decreased daily activity by 31 % as participants spent 24 % less time engaged in moderate-plus-vigorous-intensity physical activity and became more sedentary. Importantly, most of the decrease in physical activity during the 5.5-h time-in-bed condition was seen in individuals with regular exercise habits (−39 % vs. −4 % decline in exercisers vs. non-exercisers): on average, they re-allocated 30 min of daily moderate-plus-vigorous-intensity activity to less intense light and sedentary behaviors when their sleep was curtailed. Estimates of energy balance in studies where habitual exercisers were exposed to 2 weeks of treatment with time-in-bed of 5.5 vs. 8.5 h/night suggest that insufficient sleep is accompanied by combined reduction in resting and activity-related energy expenditure of ~250 kcal/day—an amount equivalent to 60 min of moderate physical activity at 3.6 MET for the average study participant. The clinical significance of such reduced energy expenditure is readily apparent, since current guidelines recommend 1 h of daily moderate-intensity physical activity for the prevention of long-term weight gain.

Clinical Relevance

Reliance on a single question about habitual sleep in the clinic is problematic, since the answer can be influenced by co-existing depression, anxiety, sleep disorder or other health problems and reflect one or more aspects of participant's usual time-in-bed, perceived sleep duration, or subjective sleep quality. Emotional distress and complaints of poor sleep were important correlates of self-reported short sleep in the Penn State [47] and MONICA/KORA study cohorts [48]. Thus, psychological stress, anxiety, and depression accompanied by difficulty sleeping, overeating, and adoption of other unhealthy behaviors may be important contributors to the association between short sleep and obesity.

Obstructive sleep apnea can also confound the association of insufficient sleep and obesity. Besides loss of slow-wave and rapid-eye-movement sleep, this disorder involves recurrent hypoxia, frequent arousals, and nighttime hyperactivity of adrenal and sympathetic stress–response mechanisms with higher metabolic cost, which may lead to compensatory changes in daytime food intake and physical activity, and facilitate the retention of fat in affected individuals. Additional research is needed to characterize human energy balance and substrate metabolism in various sleep disorders.

It has been argued that the weight gain related to a 2-h reduction in daily sleep from 7 to 5 h/night "could be worked off in very much shorter periods of brisk walking" and that instead of trying to obtain sufficient sleep, overweight individuals should focus on "more effective methods for weight reduction, such as comparatively brief periods of exercise" [49]. However, engaging in more physical activity when sleep is insufficient may be easier said than done. As described above, compared to urban adults who sleep ≥6 h/night, those who habitually curtail their sleep were more sedentary, had decreased amounts of daily movement, and spent less time in activities with moderate and vigorous intensity [45]. A similar behavioral pattern was produced by experimental sleep restriction to 5.5 h/night [46], suggesting that insufficient sleep can undermine the maintenance of regular physical activity and its health benefits. In addition, treatment with a hypocaloric diet resulted in reduced energy expenditure, decreased loss of fat, and more hunger when time-in-bed was restricted to 5.5 h/night [12], and sleep-deprived individuals ate more when ad lib food intake resumed after a few days of caloric restriction [15]. Along with emerging observational and clinical trial data in free-living adults [22–24], these findings suggest that insufficient sleep can undermine the success of therapies combining reduced food intake and increased physical activity to decrease the metabolic risk of obesity-prone individuals. Although further experimental work is needed to understand the relationship between shortened sleep and obesity, it is now prudent to recommend that overweight and obese individuals attempting to reduce their caloric intake and increase their physical activity should obtain adequate sleep and seek effective treatment for any coexisting sleep disorders.

Summary

Sleep is a fundamental physiological state that has evolved over millions of years and plays a critical homeostatic role in most complex organisms. Epidemiological studies have demonstrated that restricted sleep time is a common side effect of living a modern life. Epidemiological studies have also linked shortened sleep time with the development of obesity and other metabolic disorders such as insulin resistance and type 2 diabetes. Experimental studies have shown that shortened sleep time has important effects on energy expenditure, food intake, and metabolism. An organizing hypothesis is that the increased metabolic demands of prolonged wakefulness result in adaptive responses in energy expenditure, food intake, and metabolism that promote a state of positive energy balance that offset the energy demands of sleeplessness. Recent research is beginning to unravel the basic mechanisms that underlie these responses. Although we do not yet have randomized controlled trials that define the optimal duration of sleep needed to promote weight loss and weight loss maintenance, it seems likely that assessing sleep patterns and promoting sleep sufficiency will become increasingly important in the evaluation and treatment of obese patients.

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Obesity and the Pathogenesis of Nonalcoholic Fatty Liver Disease

9

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Obesity is associated with altered physiological functions in almost all tissues and organ systems of the body. The liver in obese people is characterized by an accumulation of intrahepatic triglyceride (IHTG) known as steatosis, which is the central feature of nonalcoholic fatty liver disease (NAFLD). This can progress to steatohepatitis if inflammation and fibrosis are also present. NAFLD is an important public health problem because of its high prevalence, potential progression to severe liver disease, and strong link with important cardiometabolic risk factors [1]. NAFLD is associated with an increased risk for developing insulin resistance, type 2 diabetes, dyslipidemia (high plasma triglyceride and/or low plasma high density lipoprotein-cholesterol concentrations), and hypertension [2]. Here we attempt to provide a concise yet comprehensive assessment of the complex clinical and physiological interactions among NAFLD, obesity, and metabolic dysfunction, with a focus on the liver.

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Diagnosis and Prevalence of NAFLD

Steatosis has been traditionally defined by chemical means, when IHTG content exceeds 5 % of liver volume or liver weight [3], or by histological means, when 5 % of hepatocytes contain visible intracellular triglyceride [4, 5]. Both of these definitions require a liver biopsy for assessment. More recently, advances in imaging technology allowed the evaluation of IHTG content by using magnetic resonance spectroscopy (MRS) in large numbers of subjects [6, 7]. The results from one study in subjects who were considered to be at low-risk for NAFLD (individuals of normal weight with normal fasting serum glucose and alanine aminotransferase concentrations, and without diabetes mellitus) indicated an upper "normal" amount of IHTG of 5.6 % of liver volume, which represented the 95th percentile in this population [6]. Data from another study found the 95th percentile for IHTG content in young lean subjects with normal oral glucose tolerance was 3 % [7]. It is important to point out that none of the values proposed for the diagnosis of NAFLD are based on the relationship between IHTG and either metabolic or clinical outcomes. In fact, the relationship between multi-organ insulin sensitivity and IHTG content in obese subjects is linear, without evidence of an obvious threshold that can be used to define "normal" [8].

The prevalence of NAFLD increases with increasing body mass index (BMI) [9]. An analysis of liver histology from liver donors [10],

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automobile crash victims [11], autopsy findings [12], and clinical liver biopsies [13] suggests that the prevalence of steatosis and steatohepatitis are approximately 15 % and 3 %, respectively, in non-obese individuals, 65 % and 20 %, respectively, in persons with class I and II obesity (BMI 30.0–39.9 kg/m^2), and 85 % and 40 %, respectively, in extremely obese patients (BMI ≥40 kg/m^2). The relationship between BMI and NAFLD is influenced by racial/ethnic background and genetic variation [7, 14, 15].

Normal Liver Physiology

The liver serves as an intermediary between exogenous (dietary) and endogenous sources of energy and the various organs and tissues of the body that consume energy [16]. It ensures that a vast number of metabolic functions proceed either continuously or in biological rhythms (e.g., circadian), or vary according to specific states (fasting and feeding) and tissue energy requirements [17, 18]. From a metabolic point of view, the liver is the most versatile organ of the whole body. Hepatic tissue organization reflects this complex metabolic activity.

Hepatic Anatomy and Vasculature

The normal liver weighs between 1,000 and 2,400 g in healthy adults (typically 1.5 kg), and is heavier in men than women and in obese than lean subjects [19]. It has four lobes (left, right, caudate, and quadrate) and a highly branched vascular network consisting of a dual blood supply, from the hepatic artery which delivers oxygen-rich blood and the portal vein which drains the gastrointestinal tract and delivers nutrient-rich blood, and multiple venous outflow tracts through at least three distinct hepatic veins (right, middle, and left) which drain into the vena cava [20]. The liver parenchyma is organized into lobules which take the shape of polygonal prisms (typically, pentagonal or hexagonal in cross section), centered around a terminal branch of the hepatic vein (central vein). Hepatic arterioles and portal venules (along with bile ductiles, lymphatics, and sympathetic and parasympathetic nerve fibers) run together within the unique, honeycomb-like structure of the liver, forming the portal tracts at the corners between adjacent lobules [20, 21]. Hepatic lobules consist predominantly of liver cell plates or sheets (cords in cross section), one cell thick, made up of polyhedral hepatocytes.

Metabolic Zonation of Liver Parenchyma

The unique structure of the liver creates a specific pattern of blood circulation: blood from the hepatic artery and the portal vein arrives at the portal tract, spreads and mixes in the sinusoids and is drained by the central vein; hence its chemical composition changes along the liver cell plate. This creates concentration gradients for oxygen, hormones, and metabolic substrates and products [22–24]. Consequently, hepatocytes located upstream, near the portal tract (periportal zone), are exposed to a different blood microenvironment than those located downstream, near the central vein (perivenous zone). The different metabolic signal patterns for the periportal and the perivenous cells, together with innervation density and biomatrix gradients and perhaps also receptor density gradients, are thought to be responsible for the structural and functional heterogeneity observed across the liver parenchyma (metabolic zonation) [22–24]. This specialization of different hepatocyte populations is reflected in compartmentalized gene expression patterns and enables the liver to synthesize and degrade, in a highly regulated manner, a wide variety of molecules, including carbohydrates, lipids, amino acids and proteins, bile acids, and exogenous compounds [22–24].

With respect to carbohydrate metabolism, gluconeogenesis, glycogen degradation to glucose, glycogen formation from pyruvate, and glucose release take place in the periportal zone, whereas glycolysis, glycogen degradation to pyruvate,

glycogen formation from glucose, and glucose uptake take place in the perivenous zone [22–24]. Zonation of hepatic lipid metabolism is much less pronounced [23, 24]. There is evidence that cholesterol synthesis and β-oxidation of fatty acids are more prominent in periportal hepatocytes, whereas the capacity for de novo lipogenesis and fatty acid esterification into cellular and very low density lipoprotein (VLDL) lipids is greater in perivenous cells [23–26]. Still, gradients for intracellular triglyceride accumulation and VLDL-triglyceride and apolipoprotein B secretion are quite shallow and typically not observed, whether in the fasted or the fed state [25–27].

Hepatic Blood Flow and Oxygen Uptake

Under basal, resting conditions, approximately 100 ml of blood passes through 100 g of hepatic tissue every minute (i.e., 1.5 l/min through the whole liver), which represents 25–30 % of the cardiac output [28–31]. Out of the total amount of blood reaching the liver, 65–85 % is nutrient-rich blood supplied by the portal vein and 15–35 % is oxygen-rich blood supplied by the hepatic artery [30–32]. Oxygen consumption by the liver is substantial and varies between 2 and 7 ml/min per 100 g of tissue [33]. Hepatic artery and portal vein contribute approximately equally to hepatic oxygen supply [28]; the exact proportion depends not only on the hepatic arterial and portal venous blood flows, but also on the respective oxygen contents and fractional extractions [34]. Following ingestion of a mixed meal, blood flow and oxygen consumption in the splanchnic region (i.e., liver plus gut) are augmented for several hours (by 25–60 % above fasting values), accounting for approximately half of the postprandial increases in cardiac output and whole-body oxygen uptake [35–37]. Portal vein blood flow also increases considerably post-prandially (by 40–100 % above fasting values) to facilitate the transport of absorbed nutrients to the liver [38, 39].

Hepatic Energy Metabolism and Fuel Selection

Despite the fact that the liver makes up only a small portion (approximately 2.5 %) of total body weight [19], it accounts for a substantial fraction of cardiac output and oxygen consumption [28]. It is thus not surprising that it accounts for a disproportionately large amount of total resting energy expenditure, approximately 21 % in the reference man and woman [40]. This estimate is somewhat greater (25–33 %) when the splanchnic region is considered [41], and is nearly as much as the contribution from skeletal muscle and adipose tissue combined (22–26 % of total resting energy expenditure), which together make up for approximately 60 % of total body weight [40]. This means that the resting metabolic rate of the liver (200 kcal per kg of organ weight per day) is roughly 15 times greater than that of skeletal muscle (13 kcal per kg of organ weight per day) and about 45 times greater than that of adipose tissue (4.5 kcal per kg of organ weight per day) [40].

Hepatic energy needs can be explained by the various transport and secretory functions, synthesis and storage of macromolecules, metabolic interconversions, and substrate cycling. These energy requirements are met, for the most part, by the aerobic catabolism of various substrates, predominantly fatty acids and amino acids, but also lactate, ethanol, fructose and, to a lesser extent, glucose; the contribution of each substrate varies depending on availability and prandial state [16, 17, 42, 43]. Given that a large number of energy-demanding and energy-yielding biochemical reactions proceed simultaneously, it is nearly impossible to assess quantitatively the mixture of substrates being utilized by the liver in vivo; most data comes from in vitro experiments with perfused animal livers and isolated hepatocytes [42, 43]. It has been estimated that fatty acid and amino acid oxidation provide more than 90 % of basal hepatic energy requirements, whereas ureagenesis, futile substrate cycling, gluconeogenesis, and protein synthesis are the main energy-requiring

processes, maximally accounting for 35 %, 22 %, 19 %, and 11 %, respectively, of total hepatic energy expenditure [42].

Metabolic Dysfunction of the Liver in NAFLD

The liver performs a number of essential biochemical functions which are necessary for whole-body metabolic homeostasis [18]. For instance, it maintains plasma glucose concentration within a narrow range, by releasing glucose into the bloodstream in the post-absorptive state, and taking it up in the postprandial state. The liver is also central in normal lipid and lipoprotein metabolism, by taking up and synthesizing fatty acids, channeling them towards oxidative or esterification pathways, and secreting plasma lipoproteins. NAFLD has been associated with alterations in most of the liver's physiological metabolic functions.

Glucose Metabolism

During the post-absorptive state, when no exogenous carbohydrate is available, endogenous glucose production (>90 % of which comes from the liver) increases to maintain plasma glucose concentration [44]. Approximately 60 % of the glucose produced is taken up by the central nervous system and around 20 % is taken up by the splanchnic region (liver and gut), whereas the remainder is consumed by other glucose-utilizing tissues, e.g., red blood cells, skeletal muscle, and adipose tissue [45, 46]. The rise in endogenous glucose production during fasting is the result of accelerated gluconeogenesis (the formation of glucose from non-glucose precursors such as lactate, pyruvate, glucogenic amino acids, and glycerol) and glycogenolysis (the degradation of glycogen to glucose) in response to the low fasting insulin concentration and insulin/glucagon ratio [44, 47]. In healthy subjects, hepatic gluconeogenesis and glycogenolysis contribute approximately equally to basal endogenous glucose production [47, 48]. After a mixed meal, endogenous glucose production decreases as a result of the increasing insulin concentration and insulin/glucagon ratio [44]. Hepatic glucose production is very sensitive to changes in circulating insulin levels. Specifically, an increase in insulin concentration from 11 mU/l (basal) to only 37 mU/l causes a 70 % decline in hepatic glucose production, whereas at a plasma insulin concentration of 53 mU/l, hepatic glucose production is suppressed by almost 90 % [46]. Insulin inhibits hepatic glucose production predominantly by stimulating glycogen synthesis (direct pathway) and, to a lesser extent, by inhibiting proteolysis and lipolysis, thereby limiting the supply of gluconeogenic precursors (indirect pathway) [47]. Many studies have found that hepatic insulin resistance, i.e., diminished ability of circulating insulin to suppress hepatic glucose production, is directly related to IHTG content [49–52], independent of BMI, percent body fat, and visceral fat mass [49, 50, 52–54]. For example, individuals with NAFLD have approximately 35 % lower suppression of endogenous glucose production in response to insulin infusion compared to BMI- and body fat-matched control subjects [50].

Although the link between hepatic insulin resistance and NAFLD is well established, it is not known whether NAFLD causes or is a consequence of insulin resistance, or possibly both. Studies conducted in rodents have found that liver steatosis and hepatic insulin resistance can be induced after only a few days of high-fat feeding, before any change in systemic metabolic function and inflammation occurs and before the development of obesity [55, 56]. Excessive accumulation of intracellular lipid intermediates generated by fatty acid metabolism, particularly diacylglycerol (DAG) species, is considered a possible link between increased IHTG content and hepatic insulin resistance. DAG can in fact interfere with insulin action by activating protein kinase C and consequently disrupting normal insulin receptor function, which ultimately leads to impaired insulin-mediated suppression of hepatic glucose production [57]. A study in obese human subjects found that intrahepatic DAG content, but not ceramides or acylcarnitines (other derivates of fatty acid metabolism), is

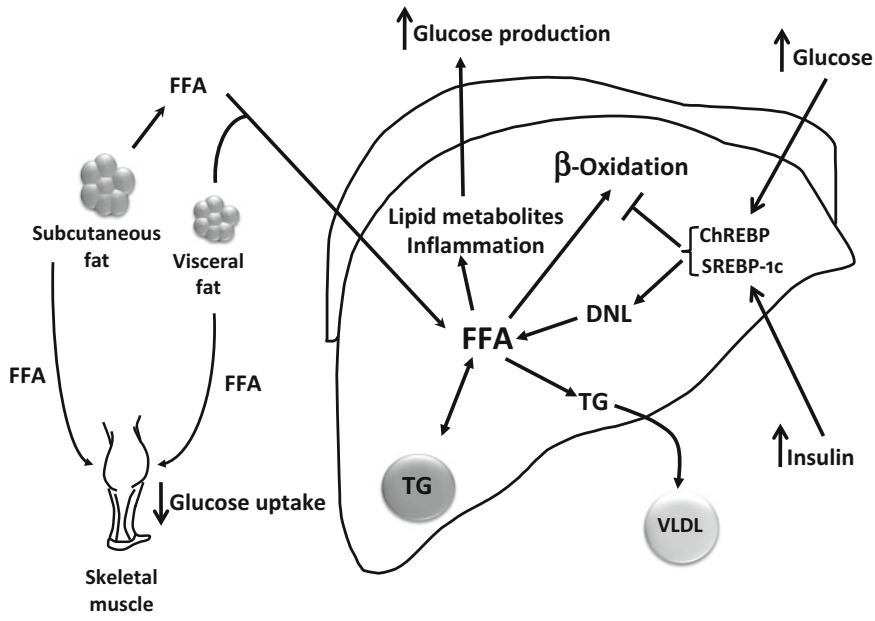

Fig. 9.1 Physiological interrelationships among fatty acid metabolism, insulin resistance, dyslipidemia, and intrahepatic triglyceride content in nonalcoholic fatty liver disease (NAFLD). The rate of release of free fatty acids (FFA) from adipose tissue and delivery to the liver and skeletal muscle is increased in obese persons with NAFLD, which results in an increase in hepatic and muscle FFA uptake. In addition, intrahepatic de novo lipogenesis (DNL) is greater in subjects with NAFLD which further contributes to the accumulation of intrahepatic triglyceride (IHTG). The production and secretion of triglyceride (TG) in very low density lipoproteins (VLDL) is increased in subjects with NAFLD, which provides a mechanism for removing IHTG; however, the rate of VLDL-TG secretion does not adequately compensate for the rate of IHTG production. Increased plasma glucose and insulin associated with NAFLD stimulate DNL and inhibit fatty acid oxidation (β-oxidation), by affecting sterol regulatory element binding protein (SREBP-1c) and carbohydrate responsive element binding protein (ChREBP). These metabolic processes lead to an increase in intracellular fatty acids that are not oxidized or exported in VLDL-TG, but instead are esterified to IHTG and stored within lipid droplets. Certain lipid intermediates of fatty acid metabolism and activation of specific inflammatory pathways can impair insulin signaling and cause tissue insulin resistance. Therefore, alterations in fatty acid metabolism can lead to an accumulation of intrahepatic (and intramuscular) TG, stimulate VLDL-TG secretion with subsequent hypertriglyceridemia, and cause insulin resistance in the liver (reduced insulin-mediated suppression of hepatic glucose production) and skeletal muscle (reduced insulin-mediated stimulation of muscle glucose uptake)

inversely related to the ability of insulin to suppress endogenous glucose production [58]. Others found a similar relationship between the DAG content of the liver and the HOmeostasis Model Assessment (HOMA) score [59], which is thought to predominantly reflect hepatic insulin resistance. Another possible link between IHTG accumulation and insulin resistance is the endocannabinoid system. Activation of cannabinoid 1 receptor in the liver activates endoplasmic reticulum stress and transcription factors that can induce de novo lipogenesis and activation of the phosphatidic acid phosphatase Lipin-1 [60]. This can increase the formation of DAG species which in turn can inhibit hepatic insulin receptor signaling and reduce insulin sensitivity [60]. Intrahepatic inflammation may also provide a link between NAFLD and insulin resistance. Diet-induced and genetically induced obesity in rodent models are associated with hepatic steatosis, insulin resistance, and increased hepatic nuclear factor (NF)-κB activity [55, 61]. Activation of NF-κB in the liver causes hepatic inflammation and results in both hepatic and skeletal muscle insulin resistance [61]. These observations suggest that steatosis can lead to

impaired local and systemic insulin action (Fig. 9.1). Many studies in human subjects have found that NAFLD is associated with profound insulin resistance in skeletal muscle, i.e., with reduced ability of circulating insulin to stimulate muscle glucose uptake [49–52].

Nevertheless, steatosis does not always coincide with insulin resistance. Studies in rodent models found that overexpression of hepatic DGAT [62], blockade of hepatic VLDL secretion [63], and pharmacological blockade of β-oxidation [64] cause hepatic steatosis but do not impair hepatic or skeletal muscle insulin action, whereas inhibition of IHTG synthesis decreases hepatic steatosis but does not improve insulin sensitivity [65]. Likewise, in patients with familial hypobetalipoproteinemia, hepatic steatosis caused by genetic deficiency of apolipoprotein B-100 synthesis and decreased VLDL secretion is not accompanied by hepatic or peripheral insulin resistance [66]. It seems clear then that IHTG accumulation per se does not necessarily cause insulin resistance. It is thus possible that esterification of surplus fatty acids to biologically inert triglyceride protects the hepatocyte from the potentially cytotoxic effects of excessive fatty acid availability [67–69]. IHTG accumulation may be secondary to a primary defect in skeletal muscle insulin action that diverts carbohydrate from muscle (for storage as muscle glycogen) to the liver (for de novo fatty acid synthesis) [70]. These diverse findings underscore the complexity of the links between NAFLD and insulin action and suggest that the relationship between IHTG and multi-organ insulin resistance is likely multifactorial and certainly not unidirectional.

Lipid Metabolism

Steatosis develops when the rate of fatty acid input (uptake from plasma and de novo synthesis) is greater than the rate of fatty acid output (oxidation and secretion). Therefore, the amount of triglyceride present in hepatocytes represents the net result of complex metabolic interactions among: (1) hepatic uptake of plasma free fatty acids (FFA), released mainly from hydrolysis of adipose tissue triglyceride but also from hydrolysis of circulating triglyceride, (2) de novo lipogenesis (i.e., synthesis of fatty acids from simple precursors), (3) fatty acid oxidation, and (4) fatty acid secretion (export) in VLDL (Fig. 9.1).

Fatty Acid Uptake

Hepatocytes take up fatty acids from the circulation both via simple diffusion (non-saturable) and facilitated transport (saturable). Facilitated transport accounts for more than two-thirds of total fatty acid uptake under most circumstances and is mediated by various fatty acid carrier proteins, e.g., fatty acid binding protein (FABP), fatty acid translocase (FAT/CD36), and fatty acid transport polypeptide (FATP) [71, 72]. The total uptake of FFA by hepatocytes directly depends on the concentration of FFA in plasma (within the physiological range, i.e., <1 mmol/l) as well as on the capacity of hepatocytes for FFA uptake which is predominantly determined by the number and/or activity of transporter molecules [71]. During post-absorptive conditions, the major source of hepatic fatty acids is the systemic plasma FFA pool. These are FFA released predominantly from subcutaneous adipose tissue, but also fatty acids generated during the hydrolysis of circulating lipoproteins in the capillary endothelia of peripheral tissues, which escape tissue uptake, spill over into the systemic circulation, and reach the liver via the hepatic artery and the portal vein after passage through splanchnic tissues. Although lipolysis of visceral adipose tissue triglyceride releases additional FFA directly into the portal vein, the relative contribution of visceral adipose tissue is small: only about 5 % and 20 % of portal vein FFA originate from visceral fat in lean and obese subjects, respectively [73].

The basal rate of adipose tissue fatty acid release into the systemic circulation increases directly with increasing fat mass in both men and women [74]. Independent of the degree of obesity (BMI and total body fat), however, NAFLD is associated with 35–45 % greater basal lipolytic rates [52, 75, 76], and also with impaired insulin-mediated suppression of adipose tissue lipolysis (indicative of adipose tissue insulin resistance) [8, 52, 75]. Hence the release of FFA into the

circulation proceeds at greater rates in patients with NAFLD than those without NAFLD during most physiological states (i.e., fasting and feeding). Furthermore, the gene expression of hepatic lipase and hepatic lipoprotein lipase are greater in obese subjects with NAFLD than those without NAFLD [77, 78]. These data suggest that NAFLD is associated with a substantially greater delivery of systemic plasma FFA to the liver, derived from lipolysis of subcutaneous adipose tissue triglyceride and lipoprotein-triglyceride. The capacity of the liver in NAFLD to take up fatty acids is also likely augmented, because of increased hepatic gene expression of several proteins involved in lipid uptake and intracellular transport [79]. For instance, hepatic mRNA and protein levels of CD36 are 65–85 % greater (and proportionally more of the CD36 protein is localized in the plasma membrane of hepatocytes) in subjects with NAFLD than in BMI-matched subjects without NAFLD [80]. These findings indicate that alterations in adipose tissue lipolytic activity, regional hepatic lipolysis of circulating lipoprotein-triglyceride, and capacity of the liver for FFA uptake contribute to increased intrahepatic fatty acid availability, and possibly also triglyceride accumulation, and therefore to the pathogenesis of steatosis.

De novo Lipogenesis

Besides FFA made available to the liver by the hepatic artery and the portal vein, the liver can also synthesize fatty acids intracellularly from acetyl-CoA that serves as the principal building block. In a complex polymerization process taking place in the cytosol (Lynen cycle), acetyl-CoA is first activated to malonyl-CoA by acetyl-CoA carboxylase (ACC), and undergoes several cycles of condensation, decarboxylation, and reduction reactions to form palmitate [81]. The overall synthesis of fatty acids is catalyzed by the fatty acid synthase (FAS) complex, a single polypeptide containing seven distinct enzymatic activities. Regulation of de novo lipogenesis occurs at a variety of steps and is accomplished by the amount and activity of lipogenic enzymes such as FAS, ACC 1 and 2 (and its regulatory enzyme, AMP-activated protein kinase), diacylglycerol acyltransferase (DGAT) 1 and 2, and stearoyl-CoA desaturase 1 (SCD1), by the expression and activation state of nuclear transcription factors such as sterol regulatory element binding proteins (SREBPs), carbohydrate responsive element binding protein (ChREBP), liver X receptor α (LXRα), farnesoid X receptor (FXR), and peroxisome proliferator-activated receptors (PPARs), as well as by the rate of delivery of acetyl-CoA to the cytosol [72, 81]. In normal subjects, de novo lipogenesis accounts for less than 5 % (in the post-absorptive state) or 10 % (in the postprandial state) of fatty acids incorporated in IHTG and VLDL-triglyceride (~1–2 g/day) [82, 83]. However, the contribution of de novo lipogenesis in subjects with NAFLD is much greater and accounts for 15–23 % of the fatty acids in IHTG and VLDL-triglyceride in the fasting state [82, 84]. De novo lipogenesis increases temporally in the postprandial state [85] and results from a study that used sophisticated MRS techniques suggest that an abnormal increase in hepatic de novo lipogenesis following meal ingestion may precede liver fat accumulation and possibly the development of NAFLD [70]. These observations collectively indicate a key role of hepatic de novo fatty acid synthesis in IHTG accumulation.

Fatty Acid Oxidation

The oxidation of fatty acids is a major source of energy for the liver, and occurs primarily in the mitochondria (β-oxidation) and to a much lesser extent in peroxisomes and microsomes. Transport of fatty acids from the cytosol (where they are found following their uptake from plasma or de novo synthesis) to the mitochondrial matrix requires their "activation" by coenzyme A, and is accomplished by a carnitine-dependent enzyme shuttle, sequentially involving carnitine palmitoyl transferase (CPT) 1, carnitine translocase, and CPT2 [86]. Mitochondrial β-oxidation progressively shortens the fatty acyl-CoA chain by two carbon units at each cycle (released as acetyl-CoA) through a series of dehydrogenation, hydration, and cleavage reactions [87]. Several membrane-bound and soluble enzymes are involved in this process, varying in acyl chain

length specificity [87]. Acetyl-CoA generated during β-oxidation is disposed either to the tricarboxylic acid cycle (Krebs cycle), where complete oxidation to carbon dioxide generates energy for the liver, or to ketogenesis where acetyl-CoA molecules condense to form ketone bodies (acetoacetate and 3-hydroxybutyrate) [88], which are then released into the bloodstream and provide a source of energy for extrahepatic tissues, including the brain [86]. Control of flux through β-oxidation occurs at many levels; in vivo, it largely depends on the rate of entry of fatty acyl groups into the mitochondria, which is modulated by substrate supply and CPT1 activity [89]. A long-known inhibitor of CPT1 is malonyl-CoA, which is the first metabolic intermediate in the de novo synthesis of fatty acids [90]. The rate of ketogenesis depends on all factors controlling β-oxidation flux, as well as the relative availability of acetyl-CoA to free CoA inside the mitochondrial matrix [88].

Data from studies conducted in rodent models demonstrate that inhibition or activation of intrahepatic fatty acid oxidation by a variety of means can influence IHTG content. Genetic or experimentally induced deficiencies in mitochondrial enzymes involved in the oxidation of fatty acids lead to accumulation of IHTG and hepatic steatosis [91, 92], whereas greater expression or activity of these enzymes reduces IHTG content and ameliorates steatosis [93–96]. Given that hepatic de novo lipogenesis is upregulated in NAFLD [82, 84], it is tempting to speculate that NAFLD is also associated with a coordinate downregulation of hepatic fatty acid oxidation [97] perhaps through the overproduction of malonyl-CoA which would then inhibit CPT1 and the transport of fatty acids into the mitochondria. However, it remains unclear if fatty acid oxidation is reduced in human subjects with NAFLD because there are currently no reliable methods for measuring hepatic fatty acid oxidation in vivo. Indirect measures, such as plasma ketone body concentrations, suggest that hepatic fatty acid oxidation is either normal or, if anything, increased in people with NAFLD [51, 52, 98, 99]. In addition, although CPT1 expression is decreased, gene expression of other hepatic fatty acid oxidative enzymes has generally been found to be greater in subjects with NAFLD than in those with normal IHTG content [79, 100]. In contrast, subjects with NAFLD have evidence of hepatic mitochondrial structural and functional abnormalities, including loss of mitochondrial cristae and paracrystalline inclusions [51, 101], a decrease in mitochondrial respiratory chain activity [102], impaired ability to resynthesize ATP after a fructose challenge [103], and increased hepatic uncoupling protein 2 [100], which could all affect energy production but not fatty acid oxidation. These abnormalities could represent an adaptive uncoupling of fatty acid oxidation and ATP production, which allows the liver to oxidize excessive fatty acid substrates without generating unneeded ATP. At present, therefore, there is little direct evidence to support the notion that decreased hepatic fatty acid oxidation contributes to IHTG accumulation and the pathogenesis of steatosis.

Triglyceride Metabolism and VLDL Secretion

The majority of plasma triglyceride in the postabsorptive state is carried in the hydrophobic core of VLDL. Hepatic triglyceride synthesis and secretion provides a means to buffer excess amounts of FFA (which could otherwise be cytotoxic) and a mechanism whereby energy-dense substrates are delivered to peripheral tissues [104]. Hepatic VLDL assembly takes place in two steps, involving (1) the partial lipidation of a newly synthesized apolipoprotein B-100 molecule, and (2) the fusion of this small and dense precursor with a large triglyceride droplet to form mature VLDL, through the action of microsomal triglyceride transfer protein (MTP) [105]. Each VLDL particle contains a single molecule of apolipoprotein B-100 [106], which remains bound to the lipoprotein particle throughout the intravascular remodeling of VLDL, whereas the amount of core triglyceride varies considerably and determines, in part, the metabolic fate of the whole particle [107].

Fatty acids are made available to the liver from the systemic plasma FFA pool and from several non-systemic fatty acid sources, such as hepatic

de novo lipogenesis, lipolysis of intrahepatic fat, lipolysis of lipoprotein-triglyceride taken up by the liver, and lipolysis of visceral fat [108]. In healthy post-absorptive subjects, the majority (65–75 %) of fatty acids utilized for VLDL-triglyceride secretion are derived from the systemic circulation, whereas only a small portion (<5 %) originates from hepatic de novo lipogenesis [109, 110]. Intrahepatocellular fatty acids that are not oxidized are esterified to triglyceride, which can then be incorporated into VLDL and secreted into the circulation, or stored within the liver. Therefore, VLDL secretion provides a mechanism for hepatic triglyceride export and thereby also for reducing IHTG content. In fact, results from studies conducted in both human subjects and animal models indicate that an impairment in hepatic VLDL secretion, caused by genetic defects, such as familial hypobetalipoproteinemia [111], pharmacological agents that inhibit MTP [112], or deletion of CD36 [113], is associated with an increase in IHTG content. However, data from most [76, 114] but not all [82] studies in human subjects have found that NAFLD is associated with a marked increase in VLDL-triglyceride secretion rate, independent of BMI and percent body fat. This increase is almost entirely accounted for by a marked increase in the contribution of non-systemic fatty acids (presumably derived from lipolysis of intrahepatic and visceral fat and de novo lipogenesis) to VLDL-triglyceride secretion [76]. The above findings notwithstanding, VLDL-triglyceride secretion rate increases in a linear fashion with increasing IHTG content within the normal range (up to 5–10 % of liver volume), but plateaus thereafter, with IHTG content within the NAFLD range (>10 % of liver volume). This suggests that IHTG content may drive VLDL-triglyceride secretion but eventually VLDL-triglyceride export reaches a biological limit beyond which it cannot adequately compensate for the increase in IHTG, so steatosis cannot be avoided or resolved.

The mechanism responsible for the inadequate increase in hepatic triglyceride export in NAFLD is not known, but might be related to physical limitations in the liver's ability to secrete VLDL. The secretion rate of VLDL-apolipoprotein B-100 (which is an index of the secretion rate of VLDL particles themselves, and not their core triglyceride) is not different between patients with NAFLD and BMI- and body fat-matched subjects without NAFLD [76], or is only slightly greater in those with high than those with low IHTG content [115]. Therefore, the molar ratio of VLDL-triglyceride to VLDL-apolipoprotein B-100 secretion rates, an index of the average triglyceride content of nascent VLDL particles, and therefore a marker of their size, is substantially greater (e.g., twofold or more) in those with NAFLD [76]. In a study conducted in transgenic mice that overexpress SREBP-1a and develop massive steatosis, it was observed that very large VLDL particles cannot be secreted from the liver because they exceed the diameter of the sinusoidal endothelial pores, resulting in intrahepatocellular accumulation of triglyceride [116]. Therefore, it may be that the failure to upregulate VLDL-apolipoprotein B-100 secretion in obese subjects with NAFLD to an extent adequate to match the surplus of IHTG available for export results in the packaging of many more triglyceride molecules per nascent VLDL particle, and the formation of triglyceride-rich and very large VLDL particles, some of which cannot penetrate sinusoidal endothelial pores for export out of the liver. Consequently, triglyceride gradually accumulates within hepatocytes and this could eventually lead to the development of NAFLD.

Lifestyle Interventions (Diet and Exercise) and NAFLD

The link between obesity and NAFLD is well established, and is supported by prospective studies of overfeeding and weight gain in human subjects [117]. It is thus not surprising that weight loss provides an effective therapy for obese patients with NAFLD. Many studies have found that weight loss induced by a hypocaloric diet and exercise significantly reduces IHTG content [118–130]. Diet and exercise appear to be interchangeable, since moderate weight loss (~10 %) induced by diet only or diet and exercise (matched for total negative energy balance) reduces IHTG

to the same extent (30–45 %) [120, 125]. Even mild weight loss (~5 % of initial body weight) causes a decrease in IHTG by as much as 20–60 % [118, 119, 124, 126–129], suggesting that weight reduction per se may not be critical for mobilization of liver fat; rather, institution of negative energy balance may be more important. Corroborating this notion, significant reductions in IHTG content (by 10–30 %) have been documented after only 48 h of calorie restriction (~1,000 kcal/day leading to ~2 % weight loss) in obese patients with NAFLD [131]. Interestingly, although not always [132–134], exercise training in the absence of weight loss can also reduce IHTG content [135–139]; aerobic and resistance exercise are equally effective in this respect [140]. These data suggest that increased energy turnover but not necessarily negative energy balance can ameliorate steatosis. Although there is still much to be learned, studies using various lifestyle intervention approaches provide encouraging results in regards to the treatment of NAFLD.

Summary and Conclusions

More often than not, NAFLD is a common feature of obesity, and is characterized by excessive accumulation of triglyceride in the hepatic parenchyma (i.e., liver steatosis) which may progress to steatohepatis and fibrosis. NAFLD develops as a consequence of an imbalance between fatty acids available to the liver and the liver's ability to dispose of these fatty acids. Adipose tissue and skeletal muscle insulin resistance, two common obesity-associated metabolic derangements, can contribute to the pathogenesis of liver steatosis, by increasing hepatic substrate (fatty acids and glucose) availability for triglyceride synthesis. Once steatosis develops, lipid metabolites can contribute to the development and worsening of hepatic insulin resistance, and the further deterioration of metabolic function of peripheral tissues. Therefore, it is still not clear whether NAFLD is a cause or a consequence of metabolic dysfunction. A better understanding of the mechanisms responsible for the pathogenesis of NAFLD will potentially identify both novel biomarkers for metabolic risk and unique targets for therapeutic intervention.

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Mechanisms of Bariatric Surgery

10

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Introduction

Bariatric surgery has been shown to be the most effective treatment for obesity and T2DM, both in large well-matched clinical studies and randomised controlled trials (RCTs) [1–6]. In this chapter, we have discussed the clinical efficacy of bariatric surgery and the physiological mechanisms through which it causes weight loss and improved metabolic control. We have limited our focus to the Roux-en-Y gastric bypass (RYGB), the adjustable gastric band (AGB) and the vertical sleeve gastrectomy (VSG), the procedures that have stood the test of time and are most commonly performed around the world.

Surgical Techniques and Clinical Efficacy

The RYGB procedure typically involves fashioning a 15–20-mL gastric pouch and creating a large new outlet that rapidly empties into the mid small intestine (Fig. 10.1). The continuity of the bowel is restored via a jejuno-jejunal anastomosis, between the excluded biliopancreatic limb and the alimentary limb, performed 75–150 cm distally to the gastrojejunostomy [7]. The gastric remnant is no longer exposed to food, but gastric, pancreatic and biliary secretions still flow undiluted in the biliopancreatic limb and come in contact with food in the jejuno-jejunal anastomosis. It is normally performed laparoscopically and causes 25–30 % weight loss, which is maintained for at least 20 years [2, 8].

The AGB technique involves the insertion of an adjustable silicone ring around the proximal aspect of the stomach, immediately below the gastro-oesophageal junction creating a small proximal pouch (Fig. 10.1). The volume of fluid in the band is adjusted through injections in a subcutaneous port and the procedure results in 20–25 % long-term weight loss [8, 9]. The VSG is fashioned through the reduction of gastric volume by the laparoscopic removal of 70–80 % of the stomach (Fig. 10.1). Previously, VSG was performed as part of the duodenal switch procedure, but is increasingly used as a stand-alone procedure that can cause a weight loss of 20–30 % in the long term [10]. Because of increased rates of postoperative and nutritional complications, the biliopancreatic diversion (BPD) and duodenal switch procedures are performed less frequently compared to the other procedures [8, 9].

The benefits of bariatric surgery extend beyond improvements in weight and glycaemic control (the latter are discussed later in this chapter); patients also exhibit reductions in overall and

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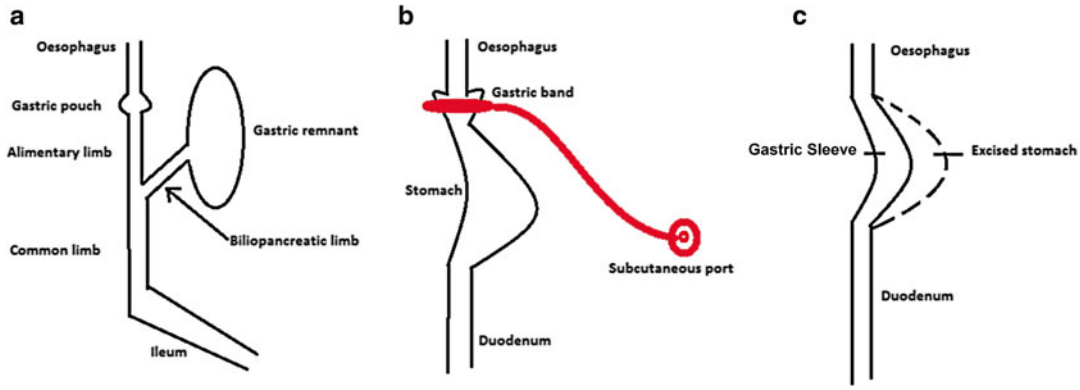

Fig. 10.1 Schematic representation of the surgical manipulations in (**a**) Roux-en-Y gastric bypass, (**b**) adjustable gastric banding and (**c**) vertical sleeve gastrectomy

cardiovascular morbidity and mortality rates, as well as a reduction in cancer incidence in women [1, 2, 11]. Nevertheless, there are no data from RCTs to support the use of surgery for comorbidities that are frequently associated with obesity such as non-alcoholic fatty liver disease, subfertility, renal disease and functional impairment. In terms of obstructive sleep apnoea, AGB resulted in greater weight loss, but did not improve the apnoea–hypopnoea index significantly more than non-surgical weight loss therapies [12]. In the absence of sufficient evidence, the choice of technique depends on patient and multidisciplinary team preference, local expertise and funding.

Complications of Bariatric Surgery

As with any intervention, bariatric surgery is not without complications. The most serious complications associated with bariatric surgery include postoperative sepsis, anastomotic leaks, bleeding and venous thromboembolism, including fatal pulmonary embolism [13]. The risk of early mortality after bariatric surgery ranges from 0.1 to 2.0 % depending on the procedure [8]. The longitudinal assessment of bariatric surgery consortium reported a 30-day postoperative mortality rate of 0.3 % with RYGB [14]. Factors associated with increased mortality include male gender, age older than 65 years, reduced cardiorespiratory fitness levels, and limited surgeon experience [13].

Long-term nutritional deficiencies may occur in some bariatric surgery patients due to changes in the anatomy of the gastrointestinal tract with surgery [15]. Deficiencies in vitamin B_{12}, folate and iron are not uncommon early after surgery and evidence of calcium, vitamin D and trace element deficiencies can also occur months to years after the procedure [15].

Overall, modern bariatric surgery has an acceptable risk/benefit profile, with careful patient selection and the availability of an appropriately experienced multidisciplinary team that is responsible for patient care in both the preoperative and postoperative periods.

Mechanisms Underlying Weight Loss

The first bariatric surgery techniques were developed during the 1950s. At the time surgeons attempted to design procedures that mechanically restricted the consumption of food and/or caused significant malabsorption of the consumed calories. Since then only RYGB, AGB and VSG have stood the test of time and are widely performed around the world. Intriguingly, these procedures appear to promote weight loss through mechanisms that are very different to those in the minds of the clinicians that originally designed them. These mechanisms will be described in this section and summarised in Table 10.1.

Table 10.1 Mechanisms of weight loss and glycaemic improvements after bariatric surgery

	RYGB	VSG	AGB
Appetite	↓	↓	↓
Plasma ghrelin	↑/↓/↔	↓	↑
Plasma GLP-1	↑	↑	↔
Plasma PYY	↑	↑	↔
Plasma oxyntomodulin	↑	?	?
Plasma CCK	↔	↔/↑	?
Plasma leptin	↓	↓	↓
Gastric emptying	↑/↓	↑	↔
Caloric malabsorption	Minimal for fat only	?	?
Energy expenditure	↑/↓/↔	↔	?
Food preferences	↓ Consumption of fat and sugar	↓ Consumption of fat and sugar	↔ or ↑consumption of fat and sugar
Glycaemic improvements	Early and sustained, weight dependent and independent	Early and sustained, weight dependent and independent	Gradual and sustained, weight dependent
Early postprandial insulin release	↑, Early and sustained	↑, Early and sustained	↔
Insulin resistance	↓	↓	↓
Plasma bile acids	↑	↑	↔
Gut microbiota	Significant changes	?	?

RYGB Roux-en-Y gastric bypass, *VSG* sleeve gastrectomy, *AGB* adjustable gastric banding, *GLP-1* glucagon-like peptide-1, *PYY* peptide YY, *CCK* cholecystokinin; ↑: increase in parameter; ↓: decrease; ↔: no change, ?: not known

Appetite

Changes in appetite are reported within days following bariatric surgery. Increased satiety and decreased hunger postoperatively have been reported after the RYGB, VSG and LAGB [16–18]. This is very much in contrast with the reports of patients who consume similar amounts of calories through dieting and describe increases in hunger, decreases in satiation and preoccupation with food (e.g. [19, 20]). This observation suggests that bariatric surgery procedures have an advantageous effect on the control of food intake, in that through changes in physiology they assist the individual reduce their caloric intake and weight loss and maintain them in the long term.

Hypothalamic Signalling After Bariatric Surgery

Only one study so far has assessed the expression of key signalling elements within the hypothalamic nuclei of rodent models of bariatric surgery (e.g. pro-opiomelanocortin, neuropeptide Y, agouti-related peptide). The expression of orexigenic agouti-related peptide remained unchanged in rats undergoing VSG compared with sham surgery, whereas it increased in rats pair-fed to the VSG group [21]; this finding might suggest that the calorically restricted rats were hungry and the VSG were not. Gene expression studies have not been performed after RYGB or AGB. However, RYGB is effective even in patients with heterozygous mutations of the melanocortin 4 receptor gene (e.g. [22]). Therefore based on the currently available data, there is insufficient evidence in support of the hypothesis that bariatric surgery alters signalling within the hypothalamic nuclei controlling food intake.

Hormonal Signalling After Bariatric Surgery

There is substantial evidence that bariatric surgery reduces appetite through alterations in the gut–brain axis signalling. Following RYGB, the postprandial levels of the anorexigenic gut hormones glucagon like peptide 1 (GLP-1), peptide tyrosine tyrosine (PYY) and oxyntomodulin are significantly elevated compared to preoperatively or to levels after AGB (e.g. [17, 23, 24]). Increased postprandial PYY and GLP-1 responses are

observed from the early postoperative days after RYGB, prior to any significant weight loss [25]. Moreover, in a randomised double-blind controlled study of patients after RYGB and LAGB, inhibition of the gut hormone responses with octreotide, a somatostatin analogue that blocks the release of gut hormones, increased food intake in the RYGB group, but not in the LAGB group, suggesting that gut hormones play a role in the reduced food intake after RYGB but not after AGB [17]. Furthermore, PYY and GLP-1 responses correlate with different levels of weight loss post-RYGB; patients with 20 % weight loss had lower PYY and GLP-1 levels compared to patients that lost 40 % of their weight after surgery [17]. The exaggerated release of these anorexigenic hormones may be due to heightened stimulation of the small bowel L cells by undigested nutrients or nutrient sensing in the proximal small bowel that signals to the distal small bowel to release gut hormones [26].

What is intriguing is that postprandial GLP-1 and PYY responses after VSG (e.g. [27, 28]), which was originally thought to be a restrictive procedure, are comparable to RYGB and probably mediating the reduction in appetite observed postoperatively. The mechanism underlying this unexpected observation is not understood, but may be due to the rapid gastric emptying propelling nutrients to the distal small bowel and stimulating L cells [29]. The AGB is not associated with significant changes in the release of these anorexigenic gut hormones (e.g. [17, 23]).

Ghrelin is produced by the stomach and is the only known orexigenic hormone. Even though earlier studies showed that plasma levels are substantially decreased after RYGB, others have shown that it either remains stable or decreases (e.g. [30, 31]). These discrepancies may be due to the different laboratory handling of ghrelin samples, nutritional state of participants and whether total or active ghrelin is assayed [32]. The results appear to be more consistent for VSG and AGB, with decreases and increases in plasma ghrelin reported respectively [18, 33].

Plasma levels of leptin are lowered after any weight loss intervention in proportion to fat mass loss, and result in increases in the feeling of hunger (e.g. [19, 34]). However, even after substantial reductions of plasma leptin after all bariatric surgery procedures, rebound hyperphagia is not observed, suggesting that their other anorexigenic mechanisms might be enough to compensate for lower leptin levels.

More recently, a series of publications by one group has casted some doubt as to the physiological importance of alterations of gut hormone levels after VSG [35, 36]. In these studies, GLP-1 and ghrelin knockout rodent models of VSG reduced their weight and food intake similarly to the wild type animals. Whilst there is a need for these results to be replicated by other researchers, it may be the case that these knockout models develop compensatory mechanisms to compensate for their genetic defect, allowing them to behave like the wild type animals.

Neural Signalling After Bariatric Surgery

The vagal nerve plays an important role in the regulation of food intake and body weight [37]. Vagal afferents are activated by the presence of nutrients in the stomach and the intestine. The release of gut hormones, as well as mediation of their effects, is influenced by the functionality of the vagus. Indeed, the preservation of vagal fibres during surgery leads to greater and more sustained body weight loss in animal models of the RYGB [38]. Pressure generated in the proximal alimentary limb of the RYGB by a 20 mL balloon appears to predict the meal size of a patient [39]. Thus the rapid entry of food from the oesophagus, through the small gastric pouch and the gastro-jejunal stoma may trigger neural signals in the alimentary limb which may contribute to long-term weight loss maintenance [39].

Whilst it is still unknown as to whether the vagus contributes to weight loss after VSG, a few elegant experiments have shown that it may be the predominant mechanism after AGB. In a randomised controlled double-blind study in humans, optimal adjustment of the band through insertion of fluid was associated with reductions in hunger ratings before a meal and increases in satiation ratings after a meal, as compared to when the fluid was completely or partially

removed from the band [18]. Additionally, acute and chronic inflation of the banding mechanism in rodents was accompanied by stimulation of vagal afferents and increased neuronal activity in the nucleus of the solitary track, a brainstem region involved in the control of food intake [40]. These findings suggest that the higher intraluminal pressure in the gastric fundus generated as a result of placement of the band itself, and further amplified by food intake, may trigger a cascade of signalling in the vagus–brainstem–hypothalamic axis resulting in decreased caloric intake and weight loss. The optimal pressure of 25–30 mmHg within the banding system is achieved through insertion of different amounts of fluid between patients, with exponential increase in pressure when too much fluid is inserted [41]. It is therefore crucial that adjustments are carefully made if the unwanted complication of mechanical restriction and vomiting are to be avoided.

Energy Expenditure

Chronic caloric deprivation is normally accompanied by a decrease in resting energy expenditure as the body strives to conserve energy [42]. These are some inconsistencies as to what happens to resting energy expenditure after bariatric surgery, but the majority of human and/or animal studies have shown that it remains stable on decreases after RYGB, VSG and AGB [21, 43–52]. However, a more consistent finding from both humans and rodents is that postprandial energy expenditure is higher after RYGB compared to controls [53–55]. Similar experiments have not been performed after VSG or AGB.

The postprandial energy expenditure increases after RYGB are mechanistically intriguing. Gut hormones may contribute to enhanced postprandial thermogenesis through centrally mediated sympathetic nervous system activation. Against this hypothesis, acute peripheral administration of exendin (9–39), a GLP-1 receptor antagonist did not alter energy expenditure in rodent models of RYGB [56]. An alternative hypothesis is that the elevation in the plasma levels of bile acids after RYGB may lead to heightened activation brown adipose tissue and consequently higher postprandial thermogenesis. Unfortunately, the only available rodent study failed to demonstrate this [57]. Therefore the mediators underlying this paradoxical increase in energy expenditure in the context of weight loss remain elusive, but have attracted considerable interest as they may be the targets of novel anti-obesity pharmacotherapy.

Gut Microbiota

The role of gut microbiota in the context of obesity and weight loss has attracted significant interest. Obesity is associated in some, but not all studies, with an unfavourable colonisation of the bowel with bacteria that are more efficient in extracting energy from nutrients and storing it as fat [58]. A profound disturbance of this colonisation has been observed after RYGB in particular and includes the reduction in Prevotellaceae, Archea, Firmicutes, Bacteroidetes and an increase in the Bacteroidetes/Prevotella ratio and Gammaproteobacteria [59–61]. These alterations may be due to weight loss itself, changes in macronutrient proportions in the diet, anatomical manipulations, pH and bile flow amongst others. The confounding effects of variations in these factors together with the antibiotic use and metabolic control may be the cause of the variability of the results in the handful of published studies. More recently, other novel mediators that may contribute to weight loss have surfaced. In a series of very elegant experiments, the transfer of gut microbiota from mice that have undergone RYGB to germ-free mice lead to 5 % weight loss in the latter group, potentially through altered short-chain fatty acid production and signalling [62].

Food Preferences

A number of human studies have reported that it is not only total caloric intake that is lower after RYGB, but also the percentage of calories from fat and sugar as compared to preoperatively or

after other bariatric surgical techniques such as the vertical/horizontal banded gastroplasties [43, 63–69]. Similar to the energy expenditure observation, this finding is somewhat paradoxical considering that diet-induced weight loss is normally associated with more "cravings" for high-calorie, energy dense, fatty and sweet foods in the majority of cases (e.g. [20]). The human literature does suffer from some inconsistencies as to the magnitude and durability of this observation. Indeed, the study of human eating behaviour is notoriously difficult due to the variability of human nature itself and the imprecise methods of assessing it, which is further amplified by the stigma and underreporting of caloric intake associated with obesity. Nevertheless, the caveats of human eating behaviour research can be largely avoided through the use of animal models of RYGB. The relative consumption of fat and sugar is lower in rodents after RYGB compared to sham-operated rats, a finding consistent amongst different laboratories and with the majority of the human literature (e.g. [70, 71]).

The mechanisms responsible for this "healthy" shift in food preferences have attracted considerable interest in the last few years. The available literature suggests that the mechanism is multifactorial; patients after RYGB exhibit increased taste acuity for sweets [72], the appetitive reward value of fat/sweet taste is decreased [73] and in brain reward system activation in response to food and/or high-calorie food pictures, as assessed by functional neuroimaging, is lower after RYGB compared to preoperatively or after AGB (e.g. [74, 75]). These responses may be further amplified by unpleasant post-ingestive effects of energy dense food, in the form of the dumping syndrome and condition taste aversion (e.g. [70]). VSG is also associated with similar responses to food in rodent models of the procedure [76]. The mediators underlying the lower consumption of fat and sugar after RYGB and VSG have not been elucidated yet, but may include the action of gut hormones on taste afferents and the mesolimbic brain reward system, and altered nutrient sensing and vagal signalling in the gut.

Bariatric Surgery and Type 2 Diabetes Mellitus

Clinical Efficacy of Metabolic Surgery

Out of all the comorbidities associated with obesity, bariatric surgery is particularly effective in improving glycaemic control in patients with T2DM. A substantial proportion of these patients achieve euglycaemia, or even normoglycaemia, in the absence of active glucose-lowering pharmacotherapy [3–6]. The high rates of glycaemic "remission" after bariatric surgery have led to the adoption of the term "metabolic surgery" to describe its potent metabolic efficacy. In the absence of a consistent definition, a high-profile meta-analysis reported remission rates of 78 % of patients after surgery [77]. Subsequent analyses of different cohorts have shown that the remission rates are 34–41 % when the more stringent glycaemic criteria of the American Diabetes Association are applied [4, 78]. Recognising the need for more holistic outcomes, the International Diabetes Federation (IDF) introduced their own criteria of optimisation of the metabolic state which incorporate markers of glycaemia, but also weight loss, plasma lipids, rates of hypoglycaemia, blood pressure control and use of medications [79]. Using these criteria in a small cohort, remission rates of only 8–14 % were achieved 1–2 years after metabolic surgery, suggesting that surgery may be better used together with, and not instead of, lifestyle modification and pharmacological treatments for T2DM for optimal metabolic outcomes [80]. Independently of what criteria are used to define metabolic remission, the clinical efficacy of metabolic remains substantial and superior to currently available best medical care. This has now been consistently proven by four RCTs [3–6] and a number of others are ongoing.

Glycaemic improvements after surgery do not follow the same pattern after all metabolic procedures. The BPD, RYGB and VSG cause rapid reductions in blood glucose within days after surgery and before significant weight loss has been achieved, in contrast to the AGB after which the

reductions are slower and gradual [81–83]. As the criteria used to define T2DM remission, change from study to study, it is very difficult to make definitive conclusions on the relative efficacy of each procedure. However, the available evidence suggest that BPD is superior to RYGB and VSG, with the latter two having very similar success rates in the medium term, followed by the AGB [3–5]. These results remain the same even when patients in each surgical group are matched for weight loss, suggesting that some of these procedures have weight-loss-independent effects [3, 25]. In this section, we discuss the mechanisms underlying the observations of these RCTs. These are also summarised in Table 10.1.

Mechanisms Underlying Metabolic Improvements

Beta-Cell Function

After RYGB, first phase and early insulin release is increased both early postoperatively and late after significant weight loss. This is supported by the vast majority (e.g. [34, 84–98]), but not all [99], of the studies that used oral glucose/mixed meal tolerance or intravenous tests. These have shown that both the glucose and insulin responses after an oral challenge are shifted to the left, as the result of faster glucose absorption and exaggerated and rapid insulin secretion. Indeed, after RYGB, the disposition index, acute insulin response to glucose and the insulinogenic index increase in patients with T2DM, but remain stable or may even be reduced in subjects with normal glucose tolerance [94, 95, 97, 98]. Additionally, both the beta-cell sensitivity is increased and the proinsulin/insulin ratio decreases after RYGB [84, 96, 100]. As would be expected in response to weight loss and improvements in peripheral insulin resistance, the decline in insulin release after a meal is rapid, and the total postprandial area under the curve (AUC) for insulin is lower compared to preoperatively [86, 88, 89, 91, 101]. When patients after RYGB and AGB are studied following 20 % weight loss, total postprandial AUC is reduced similarly by these procedures [102]. However, the insulin curves look very different, with a characteristic earlier and greater insulin peak after RYGB, but not AGB [102]. The responses after VSG are similar to those observed after RYGB (e.g. [28, 103, 104]). The BPD is unique in that it profoundly reduces both hepatic and peripheral insulin resistance very early after surgery and before significant weight loss has taken place, but also increases early insulin secretion in patients with T2DM, but not normoglycaemic patients (e.g. [105, 106]). Again following weight loss after BPD, total postprandial AUC is substantially decreased compared to preoperatively [107].

The mechanism underlying the increased early postprandial release of insulin after RYGB is in part due to the rapid and exaggerated rise in the incretin hormone GLP-1, as administration of the GLP-1 receptor antagonist exendin (9–39) attenuates this response [108]. Whilst such mechanistic studies have not been performed after BPD, similar results to RYGB are observed after VSG in animal models [109].

There is however another side to the reversal of beta-cell dysfunction after RYGB and this is postprandial hyperinsulinaemic hypoglycaemia. In the largest patient cohort even examined through a national registry in Sweden, the relative risk of hypoglycaemia was two- to sevenfold higher after RYGB, but not VBG or AGB, compared to the general population [110]. However, the absolute rates of symptomatic hypoglycaemia remain low at 0.2–1 %.

There is controversy as to the mechanism underlying this phenomenon with some studies suggesting it is the result of beta-cell hyperplasia (e.g. [111]), whereas others supporting that it is due to "extreme" restoration of beta-cell function and GLP-1 release (e.g. [112]). Hyperinsulinaemic hypoglycaemia can be treated through dietary modification and avoidance of foods with a high glycaemic index. Pharmacological therapies include acarbose, somatostatin analogues and diazoxide. The last resort, in the rare unresponsive cases, involves reduction in beta-cell mass through a partial pancreatectomy.

Insulin Resistance

The RYGB, AGB and VSG procedures cause reductions in peripheral insulin resistance directly as a result of gradual weight loss [81]. However, in some human studies, hepatic insulin resistance is reduced within days after RYGB before any clinically significant weight loss has taken place (e.g. [25, 113]). Whilst this may be a direct result of a reduction in caloric intake [114], the reduction in hepatic insulin resistance in some studies is greater in patients after RYGB compared to patients undergoing similar caloric restriction after AGB or a hypocaloric diet [25, 84, 113]. Even though these findings are not universal, they suggest that the bypass of the proximal bowel may have caloric intake and weight-loss-independent effects on hepatic insulin resistance and hepatic glucose output. This potential mechanism may also underlie the mode of action of the endoluminal duodenal-jejunal bypass liner, an endoscopically placed fluoropolymer 60 cm sheath, which improved glycaemic control within 1 week after implantation and causes 10–20 % weight loss within 6–12 months [115].

Bile Acids

Changes in the levels or types of bile acids in the gut or the circulation after bariatric surgery have been implicated in the glycaemic improvements and the reduction in caloric intake observed after RYGB. Total plasma bile acids and their subfractions are higher after RYGB [50, 116–118], but not AGB, and their levels correlate negatively with glycaemic excursions [116]. Plasma bile acids are also elevated in animal models of VSG [119], but have not been measured in humans after the procedure as yet. Bile acids can directly or indirectly improve glycaemic control, reduce food intake and increase energy expenditure through their actions on membrane TGR5 receptors or nuclear FXR receptors and the release of fibroblast growth factors. These have pleiotropic effects in a wide range of tissues including the hypothalamus [120–122]. Bile acids cross the blood–brain barrier [123] and the TGR5 receptor has also been identified in brain tissue in animals [124]. Even though their study is a research priority, so far their mechanistic role in the context of bariatric surgery has not been conclusively demonstrated.

Intestinal Glucose Disposal

A consistent observation in animal models of RYGB is that the alimentary limb undergoes significant hypertrophy, probably in the attempt to increase the absorptive surface area of the gut (e.g. [55]). More recently Saeidi et al. performed a very elegant series of experiments in rat models of RYGB and demonstrated that glucose uptake by the alimentary limb is significantly higher compared to sham-operated animals and glucose is "shunted" into anabolic pathways that support tissue growth [125]. The magnitude of the contribution of this mechanism in the improved glycaemic control of the RYGB was not conclusively shown, but the finding remains very exciting and may form the basis of translational research in humans.

Conclusion

In this chapter, we have summarised and discussed the plethora of known or potential mechanisms through which bariatric surgery exerts its effects on body weight and glycaemia. What is apparent is that these mechanisms are much more complex and intriguing than originally thought when these procedures were being designed. They have revealed that anatomical rearrangement of the gut has profound physiological effects. The molecular, hormonal and neural mediators are currently being investigated and this should hopefully lead to their targeting through pharmacological agents that promote weight loss and metabolic improvements control more safely than surgery. Bariatric surgery is therefore not just clinically useful, but can also serve as a model that can help us improve our limited medical treatments and even understand the pathophysiology of obesity and T2DM itself.

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Part II

Clinical Management

Recent Developments in the Epidemiology of Obesity

11

E. Whitney Evans and Aviva Must

Abbreviations

AMA	American Medical Association
AVG	Active video games
BMI	Body mass index
EPIC-PANACEA	European Prospective Investigation into Cancer and Nutrition-Physical Activity Nutrition, Alcohol Consumption, Cessation from Smoking, Eating out of the Home, and Obesity
GWAS	Genome-wide association studies
IASO	International Association for the Study of Obesity
IOTF	International Obesity Taskforce
MAPS	Microscale Audit of Pedestrian Streetscapes
MVPA	Moderate-to-vigorous physical activity
NHANES	National Health and Nutrition Examination Survey
OECD	Organization for Economic and Cooperative Development
SES	Socioeconomic status
SSB	Sugar-sweetened beverages
WHO	World Health Organization

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Introduction

Obesity, a multifactorial condition characterized by excessive fat accumulation, is a global problem that affects individuals of all ages, socioeconomic groups, and nationalities. Global estimates from 2010 suggest that one billion people are overweight and another nearly 500 million people are obese [1]. At the most basic level, obesity results from an imbalance between energy consumed and energy expended. Obesity increases a person's risk for the most common chronic diseases, including cardiovascular disease, type II diabetes mellitus, musculoskeletal disease, and some cancers; it ranks fifth among the leading causes of death worldwide, according to the World Health Organization (WHO) [2]. Despite its high prevalence and associated morbidity, whether obesity should be considered a disease has long been the source of contentious debate. Despite some detractors within the organization, the American Medical Association (AMA) declared obesity a disease in 2013 [3]. Much of the controversy rests on semantics and the definition of a disease; nonetheless, diagnostic challenges and inconsistencies in the

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manifestation of obesity-related comorbidities fuel this debate. Many of the challenges that complicate the treatment of the obese patient add similar complexity to the epidemiology of obesity.

The word epidemiology comes from three Greek words: *epi*, meaning upon, *demos*, meaning people or population, and *logos*, meaning study. Thus, epidemiology literally means "the study of what is upon the people." As the basic science of public health, epidemiology is the study of the distribution and determinants of disease at the population level and the application of this study to prevent and control disease [4]. The examination of recent developments in the epidemiology of obesity, therefore, includes characterizing changes in the prevalence and incidence of obesity, examining the demographic trends of those most affected, and evaluating newly identified risk factors for excess weight gain. Regardless of whether obesity should be considered a disease, its individual, social, and economic impact globally is monumental in magnitude and far-reaching in scope. It therefore requires immediate attention at both the population and individual level.

Definition of Obesity

The WHO defines overweight and obesity as an "abnormal or excessive fat accumulation that may impair health" [2]. The WHO [5], the US Center for Disease Control and Prevention (CDC) [6], and other health agencies worldwide [7] currently use body mass index (BMI) to identify both adult and childhood overweight and obesity. BMI is a measure of an individual's weight in kilograms divided by the square of height in meters (kg/m^2), and generally expressed without units. In adults, a BMI greater than or equal to 25 kg/m^2 defines overweight, and a BMI greater than or equal to 30 kg/m^2 defines obesity. Given the natural variation in BMI in childhood due to growth, the WHO and several individual countries, including the United States, Italy, Korea, and the United Kingdom, have developed population-specific reference standards based on age and sex [5, 7–10]. The Council on Science and Public Health of the AMA cited the poor sensitivity of BMI cut-offs as an argument against defining obesity as a disease. Specifically, they argued that an individual may have a BMI > 30 kg/m^2 and be metabolically healthy, while another individual with a BMI of 24 kg/m^2 may have several weight-related comorbidities [11]. Although this contention may have merit in a clinical setting, as discussed in Chap. 12, epidemiologic studies rely on BMI to identify overweight and obesity given its value as a noninvasive, a low-cost measure which consistently predicts morbidity in adults and children [12–14].

Distribution of Obesity

In 1995, the International Obesity Taskforce (IOTF) was convened by the International Association for the Study of Obesity (IASO) to create the first scientific report on global obesity. The IOTF report brought attention to the global burden of obesity and led to its recognition in 1998 by WHO as an epidemic [15]. The word epidemic is defined as an occurrence in which the incidence of a disease, in a given population and during a specific timeframe, substantially exceeds what is expected based on past experience. An estimated 200 million adults were obese worldwide when the IOTF report was published [16]. By 2000, that number had increased to more than 300 million, and 2010 estimates suggest that approximately 475 million adults are currently obese [17]. Further, the IOTF report estimates that 40–50 million school-age children are obese globally [18]. Given the rapid increase in the incidence of obesity from the 1970s to the present, along with the fact that obesity affects adults and children alike, the "obesity epidemic" has become a nearly ubiquitous term in the scientific and lay literature.

To track the obesity epidemic, the WHO and the IASO/IOTF monitor global obesity rates using country-specific surveillance data. Whereas statistics from individual surveillance programs are often not directly comparable given differing data collection and analytic approaches, they can indicate where the global burden of obesity is the greatest. Figure 11.1 shows the prevalence of

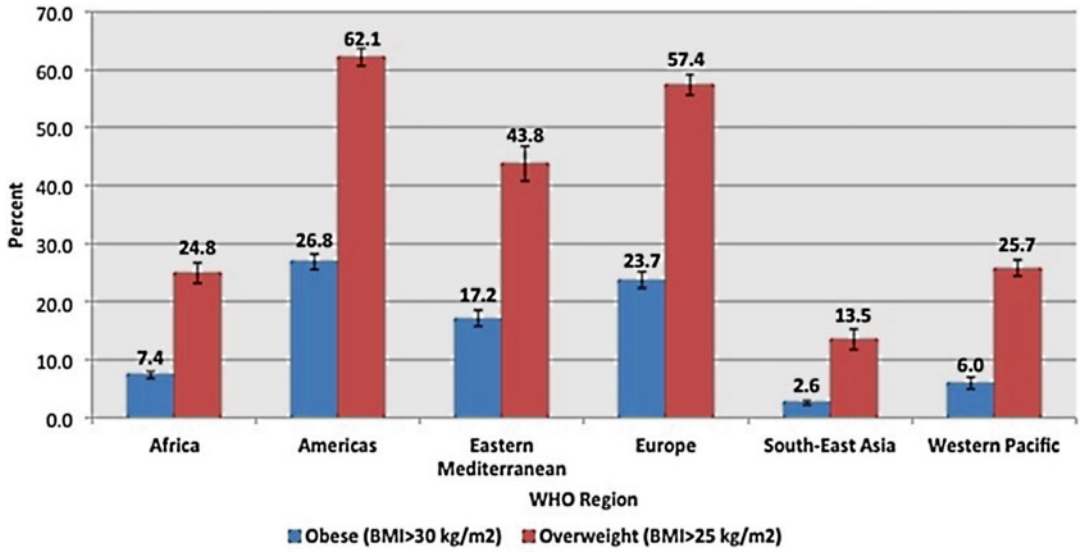

Fig. 11.1 Global overweight and obesity prevalence by WHO region

adult overweight and obesity in each WHO global region. These data suggest that adult overweight and obesity prevalence is highest in the WHO regions for the Americas and Western Europe and lowest in the WHO region for Africa. Similar patterns are evident from childhood data: 27.3 % of boys and 26.2 % of girls from the Americas Region are overweight or obese, whereas only 1.9 % of boys and 2.6 % of girls are overweight or obese in the Africa's Region [19]. Inter-country variability exists within each region. For example, data from the 2009–2010 National Health and Nutrition Examination Survey (NHANES), a nationally representative survey in the United States, suggest that nearly 35 % of adults [20] and 17 % of children ages 2–19 years are obese [21]. Estimates from the United Kingdom's National Health Service indicate that 24 % of adult men and 26 % of adult women are obese, and 31 % of boys and 29 % of girls are either overweight or obese [22]. In contrast, as few as 5 % of rural adult Ugandans are obese [23]. Similarly, the obesity prevalence in Chinese children is less than 4 % [24]. Taken together, these data document the highest levels of obesity in western developed countries.

After decades of increase, reports from several western countries suggest that the prevalence of obesity in adult and pediatric populations may be leveling off or beginning to decline. In contrast, in developing countries, particularly those undergoing modernization and urbanization, trend data suggest that obesity prevalence is on the rise. A 2012 publication from the global Organization for Economic and Cooperative Development (OECD) reports that obesity rates have stabilized in Korea at 3–4 %, in Switzerland at 7–8 %, in Italy at 8–9 %, in Hungary at 17–18 %, and in England at 22–23 % [25]. Analyses that compared US NHANES data from 1999–2000 to data from 2009–2010 yielded similar findings: obesity prevalence in American men and women did not change significantly between 2003 and 2010 [20], whereas data from the China Health and Nutrition Survey indicate that among Chinese adults, the prevalence of obesity is still increasing, with the prevalence of general obesity (BMI > 27.5) increasing from 2.9 to 11.4 % among men and from 5.0 to 10.1 % among women [26]. A similar pattern of obesity trends in developed and developing countries is also observed in children. US Pediatric Nutrition Surveillance System data, derived from surveys that track health and health-related outcomes in 2- to 5-year-old low-income children, show that the prevalence of obesity in children decreased in 18 states and in the US

Virgin Islands from 2008 to 2011 [27]. In China, by contrast, the standardized prevalence of obesity increased in children of all ages between 2005 and 2008 [28]. Similarly, a study conducted in 24,000 school-age children in India, showed that the prevalence of overweight children increased from under 4.9 % in 2003 to 6.6 % in 2005 [29]. Whereas data from the West may be encouraging, obesity remains a significant problem worldwide. In Western countries, the current obesity prevalence is high, and obesity is increasing rapidly in both adults and children in developing nations.

The Demographics of Obesity

Like the differences in obesity trends between the developed and developing world, the demographics of overweight and obesity also vary globally. Differences in obesity prevalence by sex, socioeconomic status (SES), and rural versus urban living reflect the complexities of the descriptive epidemiology of obesity. Male–female differences in obesity prevalence are not a recent development: in all WHO regions women are more likely to be obese than men. Estimates by WHO region show that in 23 % of European women, 24 % of Eastern Mediterranean women and 29 % of women in the Americas regions are obese [2]. In Africa, prevalence studies conducted across the continent during the 2000s also show that obesity rates were higher in women than in men [30]. Recent evidence, however, suggests that in many African and Middle Eastern nations these gender differences in obesity prevalence may reflect a societal preference for female overweight rather than normal weight [31].

Additional new evidence supports the interdependence of sociodemographic factors on obesity risk. SES is typically operationalized by educational attainment or income in population studies. The effect of SES on obesity appears to differ by gender, and the effect of living in a rural versus urban environment on obesity differs by SES. A 2013 review of the role of education on obesity prevalence concluded that an inverse association between education and obesity is more common in higher-income, developed countries, whereas a positive association is more common in lower-income and developing countries, with observed differences in these relationships by gender [32]. Further support for these complex inter-relationships comes from a comparison of data from the UK and China. The Health Survey for England 2006–2010 found obesity rates over 30 % in both men and women with no qualification (secondary education) and lowest in men and women with graduate degrees [33]. In China, the relationship between educational attainment and obesity differs between women and men. Specifically, in Chinese women, lower SES is associated with a greater likelihood of obesity [34], while in Chinese men, income and obesity are positively linked [35]. Effects of rural versus urban settings on obesity risk are further influenced by socioeconomic indicators. Obesity rates are highest in rural and lower-income regions in Western countries. In the United States, for example, 2012 estimates from the CDC documented five states with obesity rates greater than 30 %: Louisiana, Mississippi, West Virginia, Alabama, and Michigan [36]; these states are rural and/or relatively poor. Furthermore, 26 of the 30 states in the United States with the highest obesity prevalence are in the South and the Midwest, which are traditionally more rural and have lower average incomes than Northeastern and Western states [37]. In developing countries, opposite patterns are evident. The higher obesity rates in urban areas compared to rural ones are generally attributed to dietary and lifestyle changes that accompany urbanization [38]. A recent review of studies conducted in Africa found that obesity prevalence was higher in urban versus rural populations [30]. The observed pattern appears to be attributable to the effects of modernization, including sedentary behavior and shift to a Western diet, behaviors manifested by more affluent Africans [30]. Populations worldwide are vulnerable to obesity regardless of age, gender, educational attainment, income level, or urbanicity. Clearly, globalization will continue to influence existing patterns, with region- and country-specific responses.

Determinants of Obesity

Obesity is a unique condition in that it can be viewed as an exposure or as a risk factor for comorbidities, as well as a health outcome itself. When considered as an outcome, understanding the exposures or behaviors that contribute to its development is imperative, particularly in the context of treating the obese patient. In previous and subsequent chapters of this book, many of these exposures, which were identified through epidemiologic investigation, are reviewed in detail. Specifically, Chap. 4 reviews the relationship between the perinatal period and obesity, Chap. 5 explores the emerging body of work on the role of the gut microbiome, and finally in Chap. 8, the authors examine the relationship between sleep and obesity. To avoid duplication, this chapter reviews recent developments in the genetics of obesity and more proximal factors and behaviors including, diet, physical activity, sedentary time, and stress.

Genetics

Understanding the genetics of metabolism and excess weight gain is important, particularly for the continued development of pharmacological and behavioral interventions and the movement toward personalized medicine. Over the last decade, large scale genome-wide association studies (GWAS) have identified a number of genes related to excess weight gain [37] and that number continues to grow. In 2013, a mutation in the MRAP2 gene, a gene involved in the signaling of melanocortin-4 receptors, was identified as being associated with severe, early onset of obesity in mice and humans [38]. The melanocortin-4 receptor plays a key role in hypothalamic control of appetite—individuals with this mutation are not able to identify satiety effectively. A second recently identified obesity-related gene is FTO, which affects ghrelin levels, a hunger hormone. In a study of 359 healthy, normal weight men, those with a mutation in their FTO gene (TT) had higher postprandial levels of ghrelin than those with the low-risk FTO genotype (AA) [39]. Accordingly, those with the homozygous recessive mutation continued to feel hungry after eating a meal. GWAS studies contribute importantly to obesity research in their identification of genetic variants that may explain the some of the heritability of obesity.

Given that the human genome has not changed substantially over the last three decades, the causes of the obesity epidemic cannot be purely genetic. Instead, it is more likely that the obesity epidemic reflects the intrinsic interplay of an individual's genetics with environmental exposures. The field of epigenetics examines how developmental and environmental cues affect the expression of genes into various phenotypes [39]. The specifics of the mechanisms behind the alteration of gene expression are beyond the scope of this chapter; however, briefly, gene expression is affected via DNA methylation, histone-tail acetylation, poly-ADP-ribosylation, and ATP dependent chromatin remodeling processes, all of which can be attributed to specific environmental exposures. Because maternal or perinatal lifestyle choices may alter developmental programming of the fetus [40], epigenetic investigation in obesity focuses on in utero and early life exposures. The marked environmental shifts that accompany global modernization influence behavior at the individual, and in some instances, the epigenetic level. For example, the adoption of a Western diet and more a sedentary lifestyle appears to elicit changes in gene expression. The new wave of epigenetic studies informs our initial understanding of the interactions among genetics, biology, and environment in excess weight gain and obesity development.

Stress

Recent epidemiologic investigations indicate that stress may affect long-term obesity risk. Evidence supports that both physiological and psychological "chronic stress" contribute to the development of adiposity. Specifically, long-term exposure to physiologic stress mediators, such as cortisol, can induce chronic low-grade inflammation,

which is associated with obesity and has been implicated in the pathogenesis of many health conditions (including type 2 diabetes, fatty liver disease, heart disease, metabolic syndrome). Psychological stress can lead to under- or overeating, and several studies have shown that cortisol can stimulate appetite and disregulate the balance between hunger and satiety [41, 42]. In a recent population-based study of Canadians, self-perceived lifetime stress was related to obesity. As compared to individuals reporting they were not at all stressed, those who reported being extremely stressed had an increased risk of obesity (adjusted OR = 1.23, 95 % CI 1.13, 1.35). When stratified by gender, this effect was significant only among women [43]. In a study of 822 adults 18–83 years of age, those with the highest level of emotion- and stress-related eating were 13 times more likely to be overweight or obese, compared with those in the highest quartiles [44]. Perceived stress has been shown to modify the association between sleep quality and obesity in women [45].

Work-related stress, parenting stress, and posttraumatic stress disorder have also been associated with weight status in population-based studies. In a longitudinal study of perceived stress and weight gain in adolescence, Van Jaarsveld et al. found that although persistent stress was associated with higher waist circumference and BMI in adolescence, higher stress over the 5-year period was not prospectively associated with greater weight gain [46]. A meta-analysis of the relationship between stress and adiposity in longitudinal studies found that stress was associated with increasing adiposity overall. Moreover, stronger associations were observed between stress and adiposity in men compared with women, and in better quality studies with longer rather than shorter follow-up. The authors concluded that psychosocial stress is a risk factor for weight gain, but that the magnitude of the observed effects is very small [47].

Diet

At the most basic level, excess weight gain results from an imbalance between energy consumed and energy expended; therefore, dietary intake continues to be a focus of epidemiologic studies of obesity. Despite the simplicity of the energy balance equation, the role of diet in obesity is complex due to the unique characteristics of obesity as an outcome and diet as an exposure. First, obesity often develops through small weight gains over several years or decades. The fact that obesity has a variable latency period and affects people of all ages makes the entire life-course relevant to study. Further, diet is not a single exposure, but a complex set of correlated nutrients and foods which together comprise food groups and, with intake behaviors, manifest as overall dietary patterns [48]. Finally, diet is notoriously difficult to measure in population studies because dietary factors occur together, exposures are continuous, dietary behaviors shift over time, and dietary assessment methods are imperfect [49]. In light of these challenges, this review prioritizes recent evidence from prospective studies and those that consider dietary exposures using complementary approaches.

Recent research supports the notion that, independent of overall dietary patterns and behaviors, the consumption of single foods contributes to excess weight gain in adults. Specifically, longitudinal analyses combining data from three large prospective cohort studies of US health professionals found that 4-year weight gain was positively associated with consumption of potato chips (1.69 lb), potatoes (1.28 lb), sugar-sweetened beverages (SSB) (1.0 lb), unprocessed red meat (0.95 lb), and processed meats (0.93 lb). Conversely, intake of nutrient-rich, less energy-dense foods, including vegetables (−0.22 lb), whole grains (−0.37 lb), fruit (−0.49 lb), nuts (−0.57 lb), and yogurt (−0.82 lb) are associated with lower 4-year weight gain [50]. Of these single foods, the positive association between sugar-sweetened beverages and excess weight gain in adults has been replicated in prospective studies in Europe and the United States. Specifically, studies suggest that consuming as few as one SSB per day is associated with increased risk for obesity [51–53]. Researchers attribute this association to the inability of liquid foods to affect hunger and satiety cues in the same way that solid foods do, despite their high calorie and sugar content. The focus on the role of SSB in

excess weight gain has fueled subsequent investigations into the role of sugar in obesity and other chronic diseases. Whereas some researchers attribute the entire obesity epidemic to sugar intake [54], a recent meta-analysis using data from trials of individuals eating ad libitum diets suggests that sugar intake is responsible for a gain of only 0.75 kg (95 % CI 0.30, 1.19) over the intervention period [55]. The evidence for the role of individual foods in excess weight gain and obesity development is compelling, particularly for SSB and added sugar.

Given the complexity of diet, epidemiological investigations into the role of diet in obesity development often utilize integrated measures of dietary exposures, such as dietary patterns and dietary quality indices. Dietary patterns analysis examines nutrient, food, and food group intake comprehensively to better understand how overall intake patterns affect disease risk. The Mediterranean diet pattern, which is characterized by high consumption of olive oil, whole grain cereals, legumes, fruits, vegetables and fish, moderate consumption of dairy and wine, and low consumption of meat and meat products, has been associated with lower odds of obesity development in prospective studies. In the European Prospective Investigation into Cancer and Nutrition-Physical Activity, Nutrition, Alcohol Consumption, Cessation from Smoking, Eating out of the Home, and Obesity (EPIC-PANACEA) project, men and women who closely followed the Mediterranean diet pattern were 10 % (95 % CI 4 %,18 %) less likely to become overweight or obese over 5 years of follow-up compared to those with low adherence to the dietary pattern [56]. In a 16-year follow-up of normal weight women participating in the Framingham Offspring and Spouse Study, Wolongevicz et al. found that women in the lowest tertile of diet quality, those with the lowest intakes of fiber and micronutrients and the highest intakes of alcohol and total, saturated and monounsaturated fats, were nearly two times more likely to become overweight or obese during follow up as compared to those in the highest tertile of diet quality (OR = 1.75,95 % CI 1.16, 2.39) [57]. Together with the findings on consumption of single food items and obesity risk, these results confirm that excess weight gain and obesity risk are associated with consistent consumption of nutrient-poor, energy-dense foods.

With growing appreciation of the central role that changing dietary behaviors play in obesity development, new dietary exposures, such as eating outside of the home, portion sizes, meal and snack patterns, and the timing of energy intake have received increasing attention [58]. Trend data from nationally representative surveys in the United States suggest that since the late 1970s, the average portion size per meal or snack has increased by more than 65 g. Whereas energy density has remained fairly constant, eating frequency, or the number of eating occasions consumed per day, has increased from 3.8 eating occasions per day in 1977–1978 to 4.9 eating occasions per day in 2005–2006 [59]. Although ecologic, the concurrent trends between these dietary patterns and the obesity epidemic are suggestive. In a prospective study designed to evaluate the association between eating away from home and the risk of weight gain in a cohort of young Mediterranean adults, those individuals who ate outside the home two or more times per week had higher adjusted weight gain as compared to those who ate out less frequently [51]. Given that restaurant portion sizes are typically larger than those served at home, it is not surprising that portion size is also positively associated with energy intake and weight gain. For example, in a randomized controlled trial, researchers found that mean energy intake over 4 days was significantly higher when participants were given "larger" compared to "standard" portion sizes (59.1 (SD 6.6) versus 52.2 (SD 14.3) MJ) [60]. Finally, meal and snack patterns along with the timing of energy intake during the day have both been related to weight gain. Although considerably more research has been conducted in children than adults, breakfast consumption is independently associated with lower body weight in adults [61]. Prospective dietary analyses from a 10-year follow up of the Health Professionals Follow-Up Study suggest that breakfast consumption is associated with reduced risk of 5-kg weight gain, independent of lifestyle factors and baseline BMI (hazards ratio = 0.87, 95 % CI 0.82, 0.93) [62]. In a second study conducted in the

UK, consuming breakfast was associated with lower 3-year weight gain (adjusted β-coefficient = −0.021 kg, 95 % CI −0.035, −0.007) [63]. The timing of energy intake appears to drive these associations; in a study of American men and women, Wang et al. found those who consumed more than one-third of their daily energy intake in the morning were less likely to be overweight or obese compared to those who did not (OR = 0.34, 95 % CI 0.12, 0.95) [64].

The dietary risk factors for childhood obesity are very similar to those for adult obesity. A recent evaluation of 2007–2008 NHANES dietary data found that the top energy sources for American children ages 2–18 years include desserts, pizza, and soda, with almost 40 % of total energy consumed by 2- to 18-year olds as empty calories [65]. Further, increased consumption of sugar-sweetened beverages (SSB) [66–70], and eating more meals away from home [67, 71], and increased portion sizes [72, 73] are all established risk factors for childhood obesity.

Physical Activity

Physical activity represents the modifiable aspect of the energy expenditure side of the energy balance equation, and can be conceptually divided into occupational and leisure-time physical activity. For most adults, time spent in leisure-time activity accounts for a fairly small portion of any given day (especially work-days). Therefore, occupational activity may be a key factor in total caloric expenditure among adults. Church et al. examined energy expenditure for various occupations in the United States (private industry) using data from the US Bureau of Labor Statistics, in relation to body weight taken from NHANES [74]. They found that in the early 1960s, moderate intensity physical activity was required for nearly half of the jobs in private industry; in the 2010s, that number is approximately 20 %. Decreases in manufacturing, agriculture, mining, and logging occupations, and increases in professional services and leisure/hospitality jobs (which require more sitting) account for a large part of this decrease. Church et al. concluded that the reduction in occupational energy expenditure, which they estimate is in excess 100 cal, accounts for a significant portion of the increase in mean US body weight for women and men over the last 5 decades [74]. Similar decreases in occupational sitting have been observed in other developed countries [75].

In experimental studies in adults, prolonged sitting reduces insulin sensitivity and increases plasma glucose levels [76, 77]. Similar results showing the negative impact of prolonged sitting on cardio metabolic risk factors have been observed in cross-sectional studies [78]. In prospective cohort studies, all-cause mortality is higher among adults who do more sitting, after adjustment for physical activity. Statistical modeling of NHANES data projects that American adults could add an extra two years to their lifespan by reducing their daily sitting time to less than 3 h [79]. A recent review by Bauman et al. noted that more longitudinal data in diverse populations are needed to support a causal assertion that "not sitting" prevents weight gain [80]. Longitudinal data from the Helsinki Health Study showed that working conditions were largely unrelated to weight gain over a 5-to 7-year follow-up period [81].

Breaks in prolonged sitting have been shown to attenuate its negative metabolic, and work place interventions are effective at reducing sitting time when special devices are installed at employee work stations [82, 83]. The "Take-A-Stand" project reduced sitting time by 66 min per day [83]. Whether such reductions in sitting time translate into decreases in energy expenditure is unknown [84].

The Built Environment

Built environment is a newer construct that refers to the physical characteristics of places designed and built by humans, including the availability and safety of sidewalks, parks, trails, and public transportation in cities and neighborhoods. In addition to the individual-level factors that influence weight status, there is growing appreciation

that the characteristics of this built environment may impact levels of obesity in a community by promoting or inhibiting physical activity, and by increasing energy intake via proximity to different types of food purveyors and eating establishments.

Several recent reviews have synthesized the extant research on the relationship between the built environment and physical activity and obesity [85–88]. The emergent built environment characteristics include street connectivity and density, land-use mix, and walkability. Availability and proximity to recreation facilities have been correlated with greater physical activity levels in several studies of children and adults [89]. For example, a recent study of over 300 children residing in East Harlem, New York found that the presence of at least one playground on a child's block increased the odds of unscheduled outdoor physical activity about twofold (OR = 1.95, 95 % CI 1.1–3.4) and that the presence of an after-school program on a child's block was strongly associated with increased hours of scheduled physical activity (OR = 3.25, 95 % CI 1.3–8.1) [90]. Safety from crime represents another key factor that has been positively associated with physical activity, especially in minority populations [89].

Less conclusive information is available about the link between built environment characteristics and weight status, particularly from longitudinal studies. Epstein et al. assessed whether neighborhood characteristics moderated the relationship between participation in one of four RCT's for obesity treatment and weight loss in children 8–12 years old [91]. Greater reductions in BMI *z*-score were associated with more parkland and fewer convenience stores and supermarkets in all of the treatment programs. In one recent longitudinal cohort study of children, Wolch et al. found that the proximity of park acres and recreation programs was significantly and inversely related to attained BMI at age 18 [92]. Some longitudinal studies of adults have found associations between built environment characteristics [93, 94] and weight status, while others have observed no significant association [95]. In the review by Ferdinand et al., studies in which PA was measured objectively were less likely to find a beneficial relationship and the use of a direct measure of body weight was associated with a reduced likelihood of finding a beneficial relationship [87].

The spatial layout, density, and types of food establishments present in a community represent additional components of the built environment that may affect weight status on the energy intake side of the equation. Disparities in the prevalence of obesity among persons of lower SES and black race or Hispanic ethnicity might reflect exposure to different, and potentially obesogenic, environments. National zip-code level data have shown that poorer neighborhoods have less access to large chain supermarkets, but more access to small grocery and convenience stores [96], where the quality of produce is typically be more expensive and of lower quality. Living near a convenience store has been associated with a slightly higher prevalence of overweight and obesity (obesity prevalence ratios [PR] = 1.16, 95 % CI 1.05–1.27; overweight PR = 1.06, 95 % CI 1.02–1.10), whereas proximity to a supermarket has been associated with less overweight and obesity (obesity prevalence ratio [PR] = 0.83, 95 % CI 0.75–0.92; overweight PR = 0.94, 95 % CI 0.90–0.98) [97].

Although fast-food availability has been linked to fast-food consumption, and consumption in turn has been linked to weight status, the question of whether availability is related to weight status is methodologically difficult to assess. In predominantly white, rural samples no association between fast-food availability and weight status has been observed [98]. However, in a sample of non-white rural residents greater availability of fast-food was associated with the number of meals consumed and overall weight status [99].

Many new techniques for assessing characteristics of the built environment, such as omnidirectional imagery and the Microscale Audit of Pedestrian Streetscapes (MAPS) tool, have become available in the past 5 years [100] and show promise for improving the accuracy, reliability, and consistency of built environment measures. A growing interest in this area and

appreciation of related methodological issues in spatial epidemiology, such as inconsistencies in the definition of place and how it is measured, and objective versus perceived measures of the built environment, are likely to spawn improvements in our approaches to linking built environment to chronic disease health outcomes like obesity.

Screen Time

An increase in time spent using electronic screen media is regarded as a key factor in the decline of physical activity levels, especially the amount of free and outdoor play among children. Video games are played in a large percentage of American households and are a popular leisure-time activity choice across all age groups [101]. Screen-time activities are increasingly done simultaneously with other sedentary and non-sedentary activities, with implications for public health messaging as well as measurement challenges.

Relatively new to the range of options are traditional video game systems that incorporate partial or whole-body physical activity ("active video gaming" or "exergaming"). According to a recent report on the use of media among children ages 8–18 years, over an hour per day is spent playing video games; 64 % of the respondents reported having ever played active video games such as WiiPlay/WiiSports [102]. Working within this new reality of an increasingly electronic world, the potential for these active video game systems to reduce the amount of time spent in sedentary behavior and increase energy expenditure is of particular interest.

In a recent systematic review which included 52 articles on active video gaming, LeBlanc et al. summarized the current state of knowledge about the potential for active video games (AVG's) to impact the physical activity levels and overall health of children and youth [103]. Recent studies of AVG use have focused on several major outcomes: appeal, adherence, energy expenditure, body composition, energy intake, and use in special populations. There is evidence from cross-sectional and intervention studies that children using AVG's increase energy expenditure both above rest and above levels that would be observed during passive video game use; however, they do not consistently result in physical activity levels that meet the current recommendation of 60 min of moderate-to-vigorous physical activity (MVPA), and they may not increase energy expenditure to the levels observed for traditional physical activities [103–105]. Of the 28 laboratory studies included in a systematic review, 12 found that the AVG's assessed were equivalent to light-to-moderate physical activity, for both children and adults [104]. A study that compared traditional and two different AVG's found that energy expenditure could be increased up to 2.9 kcal/min, or 172 kcal/h [106], roughly equivalent to an hour of heavy housework, doubles tennis, or brisk walking [107].

In overweight children, the use of AVG's may attenuate weight gain. In a recent randomized controlled trial conducted in overweight/obese children, Maddison et al. found that compared to the control group, the AVG condition resulted in a small but statistically significant difference in BMI at the end of the 6-month trial [108]; however, no differences in levels of physical activity measured by accelerometry or by VO_2max were observed. When asked to rate their perceived exertion while playing AVG's, both children and adults rate it as similar to activities with lower intensities, suggesting that their engagement with the game may distract them from the physical exertion involved, especially at moderate intensities [104, 105]. Warburton argues that even this light-to-moderate intensity activity attained during AVG use has health benefits, and that comparison to the 60-min MVPA guideline is too narrow. In their review, LeBlanc et al. note that many studies of AVG use have small samples and are underpowered, and that future research should be designed with longer follow-up periods and should include both direct (accelerometry, heart rate) and indirect (self- and parent-report) outcomes [103]. Additionally, the heterogeneity in the type of AVG platforms, which focus on different types of body movements, limits comparison across studies, and the long-term effectiveness of AVG's in

non-structured and self-regulated settings remains largely unknown [104].

Social Networks and Obesity

Growing evidence suggests that social networks contribute to overweight and obesity in that having obese social contacts may influence behaviors. This idea was first explored in 2007 by Christakis and Fowler, who used data from a social network constructed from 12,067 members of the Framingham Heart Study cohort with longitudinal BMI data collected from 1971 to 2003 [109]. They examined the effect of weight gain among social contacts and found that an individual's risk of becoming obese increased by 57 % if a friend became obese, 40 % if a sibling became obese, and 37 % if a spouse became obese, after accounting for previous weight. Similar associations between neighbors were not observed, suggesting that more than shared environment ultimately influences obesity risk. This study sparked several subsequent studies designed to elucidate which obesogenic behaviors are most effectively shared across social networks.

Studies in both adults and adolescents have focused on the transmission of eating, physical activity, and sedentary behaviors among individuals in shared social networks. Pachucki et al. studied a subsample of the Framingham Heart Study cohort to examine how food intake patterns are distributed throughout social networks in adults [110]. They identified seven food patterns including: "meat and soda," "sweets," "alcohol and snacks," "light eaters," "caffeine-avoidant," "offsetting," and "healthier." They found strong associations between spouses across all food patterns, whereas only modest associations were identified among siblings. Across peer groups, they found that the "alcohol and snacks" eating pattern was most likely to be shared. To explore the effect of physical activity-related behaviors, Yu et al. utilized survey and interview data from residents in low-income neighborhoods in London and did not identify a role for social networks in leisure-time physical activity [111]. In contrast, in a school-based study in Australian adolescents, ages 13–14 years, researchers found that same-sex friends were likely to share similar physical activity behaviors, female friends were more likely to engage in similar screen-time behaviors, and male friends were similar in their consumption of energy-dense foods [112]. The effect of social networks on obesity is difficult to separate from the effects of genetics and shared environments, but underscores the potential for targeting social networks in obesity interventions.

Conclusions

The new millennium has been an active period for research activity in the epidemiology of obesity, with numerous important developments. One recent insight is the apparent leveling off of prevalence in adults and children in the United States. Inasmuch as the United States was among the countries on the leading edge of the epidemic, any halt to the seeming endless increases is cause for cautious optimism. It is noteworthy that parallel improvements in some of the classic obesity risk-related behaviors in children have been reported in nationally representative data from the Health Behavior in School-aged Children quadrennial surveys comparing data from 2001–2002 to 2009–2010 [64]. For example, adolescents ages 11–16, have significantly increased the number of days per week in which they are physically active for 60 or more minutes from 4.3 to 4.5 days per week, reduced sedentary screen time from 3.1 to 2.4 h per day, reduced consumption of sugar-sweetened beverages, and increased fruit and vegetable consumption. These are modest improvements relative to national recommendations, but may account for the observed stabilization of obesity rates in the United States. Whether these recent changes are sustained and whether they extend to high risk subpopulations in the United States will not be evident for several years. Since global trends trail US patterns, and individual countries and regions have unique forces at play, future patterns of prevalence worldwide are uncertain.

A second striking change in population-based studies of obesity has been a growing awareness of the limits of reductionist approaches that attempt to isolate risk factors from the context in which they operate. Obesity has been aptly called a "wicked" problem—due to its multifactorial nature, complexity, need for innovative approaches, and interconnections to socioeconomic and political realities [113, 114]. The 2007 Foresight Obesity Map makes evident that multidisciplinary thinking and multilevel perspectives are essential [115, 116]. At the same time, community engaged research and community based participatory research show great promise in addressing obesity prevention at the local level [117, 118]. The next decade is likely to bring about new methods to support systems and other multilevel analyses and with them the promise of new policy and intervention approaches to tackle obesity locally and globally.

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Assessment of the Obese Patient

12

Daniel H. Bessesen

Introduction

Data from the National Health and Nutrition Examination Survey, demonstrated that more than one-third (34.9 %) of adults were obese in 2011–2012 [1]. It has been estimated that the annual medical cost of obesity in the United States in 2008 was $147 billion and the medical costs for people who are obese were $1,429 higher than those for people of normal weight [2]. Obesity is clearly associated with a number of diseases including type 2 diabetes, hypertension, hyperlipidemia, coronary artery disease, degenerative joint disease, depression, polycystic ovarian syndrome, some forms of cancer, sleep apnea, urinary stress incontinence, and erectile dysfunction among others [3]. Obesity is one of the leading causes of preventable morbidity and mortality in the United States and increasingly is a cause of health problems around the world.

As a result of the increasingly compelling data on the adverse effects of obesity on health and the growing costs associated with this condition, a broad consensus has emerged that evaluating patients for obesity should be an integral part of usual clinical care. One of the first groups to provide guidance on this topic was the National Heart Lung and Blood Institute (NHLBI) who published Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults in 1998 [4]. Since this seminal guideline was released a wide range of organizations including the U.S. Preventive Services Task Force (USPSTF), the American College of Physicians (ACP) [5], the American Academy of Pediatrics [6], the American Gastroenterological Association [7], the American College of Preventive Medicine [8], the American Diabetes Association [9] and the Surgeon General [10] to name just a few have all taken the position that physicians should address the problem of obesity in their patients. Most recently the American College of Cardiology, the American Heart Association and the Obesity Society published an updated Guideline for the Management of Overweight and Obesity in Adults [11]. This document published in 2013 addresses a number of core questions in the assessment of obesity that have not been systematically reviewed since the original NHLBI guideline was written. The conclusions reached by this group are very much in line with the earlier guideline continuing to encourage clinicians to measure height and weight and calculate BMI at annual visits or more frequently, to advise overweight and obese adults that the greater the BMI, the greater the risk of CVD, type 2 diabetes, and all-cause mortality and to

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use waist circumference to help identify those at greatest risk of adverse metabolic consequences of excess weight.

Despite the weight of the evidence and the broad consensus, there remains a great deal of clinical inertia against making a diagnosis of obesity and advising patients to lose weight. In one study of more than 12,000 obese adults, only 42 % were advised to lose weight [12], and yet this study and others have shown that those that were so advised were more likely to try [13]. One might think that things have improved over the last 20 years, but a recent study examining 32,519 adult primary care visits with PCPs conducted between 1995 and 2008, as part of the National Ambulatory Medical Care Survey found that rates of weight counseling declined from 7.8 % of visits in 1995–1996 to 6.2 % of visits in 2007–2008 [14]. The greatest declines in the odds of PCPs providing weight counseling were seen in patients with hypertension, diabetes, and obesity, the very patients who stand to gain the most from losing weight. This is despite the fact that helping patients change their lifestyle behaviors, use weight loss medications, or have bariatric surgery results in measurable health benefits [15–17]. Surveys have found that patients want their physicians to address weight during office visits, to give specific weight loss advice and provide encouragement to foster self-motivation for weight loss [18]. Physicians feel that there are many barriers to counseling their patients about weight loss. These include insufficient confidence, knowledge and skills as well as a perception that there are no effective therapies [19]. The health benefits of treating obese patients are discussed in more detail in other parts of this volume. Perhaps as physicians gain broader experience in the treatment of obese patients and healthcare delivery systems invest in the management of this chronic disorder this unfortunate circumstance will change. Obesity is a diagnosis that is easy to make and one for which proven treatment modalities exist [20]. Even the simple act of putting obesity on the problem list can increase the likelihood that the problem will be addressed at future visits [21].

Screening for Obesity with the BMI and Waist Circumference

The standard approach to the assessment of health risks associated with body weight is the calculation of body mass index (BMI) from height and weight. BMI values can be calculated using on line calculators (http://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm and others) and a number of smart phone applications (http://apps.usa.gov/bmi-app.shtml and others). The definitions of overweight and obesity reflect levels of excess weight that are associated with adverse health consequences, including increased levels of diabetes, cardiovascular disease, and overall mortality as reflected in a large number of epidemiological studies. The specific cut points that are used in common clinical practice initially came from the World Health Organization [22] and the NIH-sponsored Practical Guide to the Identification, Evaluation and Treatment of Overweight and Obesity [4]. The recent update of these guidelines retains the same cut points. It is clear that health risks are associated with increased levels of adiposity, in particular visceral or intra-abdominal adiposity [23, 24]. Estimating central fat accumulation by measuring waist circumference adds information to the BMI in assessing health risks in overweight and obese individuals by differentiating those with visceral obesity from those who may have an increased BMI due to increased levels of lean body mass. Waist circumference is most useful in individuals with a BMI between 25 and 35 kg/m^2. Individuals with a BMI below 25 kg/m^2 have low/normal health risks and those with a BMI greater than 35 kg/m^2 are at high risk independent of waist circumference. Those with a BMI between 25 and 30 kg/m^2 who have an increased waist circumference have the health risks similar to those seen in an obese individual. Those with a BMI between 30 and 35 kg/m^2 but with a low waist circumference have the health risks of an overweight individual. The guidelines established cut points of 40″ in men and 35″ in women for waist circumference. This widely accepted

Table 12.1 Classification of patients for assessment of disease risk by BMI and waist circumference

			Disease risk[a] (Relative to normal weight and waist circumference)	
	BMI (kg/m^2)	Obesity Class	Men ≤40 in. (≤102 cm) Women ≤35 in. (≤88 cm)	>40 in. (>102 cm) >35 in. (>88 cm)
Underweight	<18.5		_	_
Normal[b]	18.5–24.9		_	_
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	I	High	Very high
	35.0–39.9	II	Very High	Very high
Extreme obesity	≤ 40	III	Extremely High	Extremely high

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

classification scheme is depicted in Table 12.1. Epidemiological data suggest that these cut points may not be appropriate for Asian individuals and other racial and ethnic groups. These individuals appear to experience increased rates of metabolic diseases at levels of visceral adiposity that are lower than what is seen in Caucasians. The specific cut points suggested for use in these populations are shown in Table 12.2.

Limitations of the BMI and Proposed Staging Strategies

The primary advantages of the BMI are that it is easy to measure and calculate and correlates reasonably well with both body fatness and health risks. However, the BMI is far from a perfect tool for assessing body fat and health risks. In children, the elderly and athletic individuals it does not accurately reflect body fat [25]. Alternative methods for assessing body fat and data suggesting the relationships between BMI and morbidity and mortality are complex will now be discussed.

Assessing Body Composition

There are a range of methods that are more accurate than BMI for estimating body fat [26]. The most precise methods are imaging approaches

Table 12.2 Waist circumference cut points for various ethnic groups

Ethnic group	Waist circumference (cm) (as measure of central obesity)
Europids[a]	
Men	≥94
Women	≥80
South Asians	
Men	≥90
Women	≥80
Chinese	
Men	≥90
Women	≥80
Japanese	
Men	≥85
Women	≥90
Ethnic south and central Americans	Use south Asian recommendations until more specific data are available
Sub-Saharan Africans	Use European data until more specific data are available
Eastern Mediterranean and middle east (Arab) populations	Use European data until more specific data are available

Data are pragmatic cutoffs and better data are required to link them to risk. Ethnicity should be basis for classifications, not country of residence
[a]In the United States, Adult Treatment Panel values (102 cm male, 88 cm female) are likely to continue to be used for clinical purposes. In future epidemiological studies of populations of Europid origin (white people of European origin, regardless of where they live in the world), prevalence should be given, with both European and North American cutoffs to allow better comparisons

including CT and MRI. These methods are used in research studies to not only measure body fat but to measure visceral fat content which is more closely related to metabolic disorders than total body fat. Dual energy X-ray absorptiometry (DXA) provides accurate estimates of body fat and can provide some information on the relative amount of abdominal fat as compared to lower body subcutaneous fat. However, DXA has limited clinical utility because of cost and patient exposure to radiation. Underwater weighing used to be used to estimate percent body fat based on the principle that lean tissue is more dense than fat. This method used body weight and volume to calculate density and from that, estimate body fat content. A more recent technique that uses this same principle is air displacement plethysmography (Bod Pod; Cosmed and others). The advantages of this method are that it is almost as accurate as DXA, is quick and relatively easy to perform, is less expensive than DXA and does not expose the patient to radiation. It however does not provide information on regional fat distribution. Bioelectrical impedance analysis (BIA) provides an estimate of body fat based on the differential conductivity of lean tissue as compared to fat tissue. A range of devices are available that measure conductivity between 2 fingers, 2 hands, a hand, and a foot or 2 feet (Tanita, Omron, and others) and use this measurement to estimate body fat. While this method is portable, easy to perform, inexpensive and has minimal risk (not recommended for individuals with pacemakers), it is not as accurate or reproducible as the other methods listed above. It is affected by a patient's state of hydration and is less accurate in very obese individuals [27].

While obtaining estimates of body fat from one of these methods is more accurate than estimates of fatness determined by BMI, there are currently no broadly accepted guidelines for what a healthy level of body fat is for adult men and women across the lifespan. Estimates of body fat may be helpful in motivating patients to start a weight loss program and in providing ongoing positive feedback and motivation during weight loss.

BMI and Mortality

Recently the relationship between modest increases in BMI and mortality has been reexamined. A meta-analysis of 97 studies of more than 2.88 million individuals and more than 270,000 deaths found that the lowest relative risk of mortality was seen in individuals with a BMI between 25 and 30 kg/m^2, not those with a BMI < 25 kg/m^2. This study found that while the risk of mortality rose in obese individuals considered together, there was no evidence of increased mortality in those with a BMI between 30 and 35 kg/m^2 [28]. While this conclusion has been challenged [29] it may be that adverse effects of obesity are mostly seen in younger and middle aged individuals where excess adiposity predisposes to the development of diabetes and cardiovascular diseases but that once these disorders develop excess weight may be less harmful or may even be advantageous. The surprising finding that obese individuals with a range of health problems may actually do better than their lean counterparts has been termed the "obesity paradox" [30].

Metabolically Healthy Obesity

In addition, studies have shown that 25–30 % of obese individuals do not have evidence of metabolic disease [31, 32]. It is not clear that these so-called "healthy obese" individuals are at increased risk for morbidity or mortality when compared to normal weight individuals who have markers of insulin resistance. One recent meta-analysis that included eight studies of more than 61,000 individuals found that metabolically healthy obese individuals had increased risk of all-cause mortality and/or cardiovascular events as compared to metabolically healthy normal weight individuals. However, all metabolically unhealthy groups, normal weight, overweight and obese had increased risk compared to the metabolically healthy obese subjects [33]. This study found no difference in risk between normal weight, overweight and obese subjects who were metabolically unhealthy. While this issue is

controversial and far from settled, it does seem clear that BMI alone is not sufficient for risk assessment in overweight and obese individuals and that other factors such as blood pressure, insulin resistance, hyperlipidemia, and systemic inflammation likely play important roles in the development of metabolic disease and should be considered when assessing the overweight or obese patient.

Alternative Strategies for Risk Stratification

In response to the perceived limitations of a "BMI centric" approach to obesity risk assessment, a number of alternative strategies to risk assessment have been proposed. The oldest is the concept of the "metabolic syndrome." The cluster including insulin resistance, glucose intolerance, hypertension, hyperlipidemia, activation of inflammatory pathways, endothelial dysfunction, and non-alcoholic steatohepatitis has been called syndrome X, the insulin resistance syndrome and other names, but most now refer to this condition as the metabolic syndrome. The metabolic syndrome came into broader awareness when formal diagnostic criteria were proposed first by the World Health Organization and then the National Cholesterol Education Program in their Adult Treatment Panel III guidelines (NCEP-ATPIII) [34]. Table 12.3 lists the diagnostic criteria for the metabolic syndrome advocated in these older guidelines. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) took the provocative position that there is currently inadequate information available to accurately define the metabolic syndrome and that this designation should not be used in routine clinical practice [35]. This view grew out of a belief that the root cause of this clustering is not known and could include obesity, insulin resistance, or inflammation. The authors of this paper also felt that while the clustering of these conditions increases the risk of cardiovascular disease, it was not clear that the syndrome had any greater risk than the sum of the component parts. However, most experts agree that considering a range of variables in the risk stratification of overweight and obese patients is important. Disagreement comes in what variables to include and how to weigh these variables [36, 37].

A second approach to risk stratification was proposed in 2009 by Sharma and Kushner [38].

Table 12.3 Diagnostic criteria for the metabolic syndrome

Measure (any three of five constitute diagnosis of metabolic syndrome)	Categorical cut points
Elevated waist circumference[a,b]	≥ 102 cm (≥40 in.) in men
	≥88 cm (≥35 in.) in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L)
	Or On drug treatment for elevated triglycerides[c]
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men
	<50 mg/dL (1.3 mmol/L) in women
	Or On drug treatment for reduced HDL-C[c]
Elevated blood pressure	≥130 mmHg systolic blood pressure
	Or ≥85 mmHg diastolic blood pressure
	Or On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥ 100 mg/dL
	Or On drug treatment for elevated glucose

[a]To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to the floor. Measurement is made at the end of a normal expiration

[b]Some US adults of non-Asian origin (e.g., white, black, Hispanic) with marginally increased waist circumference (e.g., 94–101 cm [37–39 in.] in men and 80–87 cm [31–34 in.] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. A lower waist circumference cut-point (e.g., ≥90 cm [35 in.] in men and ≥80 cm [31 in.] in women) appears to be appropriate for Asian Americans

[c]Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking one of these drugs are presumed to have high TG and low HDL

Table 12.4 Edmonton obesity staging system

Stage	Description	Management
0	No apparent obesity-related risk factors (e.g., blood pressure, serum lipids, fasting glucose, etc. within normal range), no physical symptoms, no psychopathology, no functional limitations and/or impairment of well-being	Identification of factors contributing to increased body weight Counseling to prevent further weight gain through lifestyle measures including health eating and increased physical activity
1	Presence of obesity-related subclinical risk factors (e.g., borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.), mild physical symptoms (e.g., dyspnea on moderation exertion, occasional aches and pains, fatigue, etc.), mild psychopathology, mild functional limitations and/or mild impairment of well-being	Investigation for other (non-weight related) contributors to risk factors More intense lifestyle interventions, including diet and exercise to prevent further weight gain. Monitoring of risk factors and health status
2	Presence of established obesity-related chronic disease (e.g., hypertension, type 2 diabetes, sleep apnea, osteoarthritis, reflux disease, polycystic ovary syndrome, anxiety disorder, etc.), moderate limitations in activities of daily living and/or well-being	Initiation of obesity treatments including considerations of all behavioral, pharmacological and surgical treatment options. Close monitoring and management of comorbidities as indicated
3	Established end-organ damage such as myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis, significant psychopathology, significant functional limitations, and/or impairment of well-being	More intensive obesity treatment including consideration of all behavioral, pharmacological, and surgical treatment options. Aggressive management of comorbidities as indicated
4	Severe (potentially end-state) disabilities from obesity-related chronic diseases, severe disabling psychopathology, severe functional limitations and/or severe impairment of well-being	Aggressive obesity management as deemed feasible. Palliative measures including pain management, occupational therapy and psychosocial support

From Sharma AM, Kushner RF. A proposed clinical staging system for obesity. Int J Obesity 2009; 33:289–295. Reprinted with permission from Nature Publishing Group

This system known as the Edmonton Obesity Staging system is depicted in Table 12.4. It focuses on the patient's risk for and the presence of both cardiovascular and mechanical complications of obesity to "stage" obese patients with the goal of targeting treatment efforts to those who are the most likely to benefit. A strength of this system is that it takes into account more than just cardiometabolic risk in assessing the burden of disease associated with obesity. One limitation of this system is that it relies on clinical judgment to determine the specific level of disability. A second concern is that it does not establish quantitative cut points for many of the characteristics that are in the evaluation scheme.

A third approach has recently been proposed by Garvey and coworkers [39]. This approach that they call the "Cardiometabolic Disease Staging System" depicted in Table 12.5, divides patients into five risk categories using specific measurable parameters readily available to care providers including waist circumference, blood pressure, fasting blood levels of glucose, 2 h glucose levels during an oral glucose tolerance test (OGTT), fasting triglycerides, and HDL-C. The advantages of this system are that the parameters are quantitative and the cut points are based on several large epidemiological studies of the Coronary Artery Risk Development in Young Adults (CARDIA) cohort and the National Health and Nutrition Examination Survey (NHANES) cohort.

One should not conclude that there is doubt about the adverse health effects of obesity, only that emerging data suggests that the relationship between weight and health is complex. These different staging approaches have not been embraced by the most recent guideline documents but both the 2013 AHA/ACC/TOS Obesity Guideline as well as the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk [37] advocate consideration of other factors besides BMI in the risk stratification of obese patients.

Table 12.5 Cardiometabolic disease staging system

Stage	Description	Criteria
0	Metabolically healthy	No risk factors
1	One or two risk factors	Have one or two of the following risk factors: (a) High waist circumference (≥88 cm in women; ≥102 cm in men; and ≥80 cm in southeast Asian women and ≥90 in southeast Asian men) (b) Elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) or on antihypertensive medication (c) Reduced serum HDL cholesterol (<1.0 mmol/l or 40 mg/dL in men; <1.3 mmol/l or 50 mg/dL in women) (d) Elevated fasting serum triglycerides (≥1.7 mmol/l or 150 mg/dL)
2	Metabolic syndrome or prediabetes	Have only one of the following three conditions in isolation: (a) Metabolic syndrome based on three or more of four risk factors: high waist circumference, elevated blood pressure, reduced HDL-C, and elevated triglycerides (b) Impaired fasting glucose (fasting glucose ≥5.6 mmol/l or 100 mg/dL) (c Impaired glucose tolerance (2-h glucose ≥7.8 mmol/l or 140 mg/dL)
3	Metabolic syndrome and prediabetes	Have any two of the following conditions: (a) Metabolic syndrome (b) IFG (c) IGT
4	T2DM and/or CVD	Have T2DM and/or CVD: (a) T2Dm (fasting glucose ≥126 mg/dL or 2-h glucose ≥200 mg/dL or on anti-diabetic therapy) (b) Active CVD (angina pectoris, or status after a CVD event such as acute coronary artery syndrome, stent placement, coronary artery bypass, thrombotic stroke, nontraumatic amputation due to peripheral vascular disease

From Daniel S, Soleymani T, Garvey WT. A complications-based clinical staging of obesity to guide treatment modality and intensity. Curr Opin Endocrinol Diabetes Obes. 2013 Oct;20(5):377-88. Reprinted with permission from Wolters Kluwer Health

Evaluating Patients to Determine the Causes of Obesity

Before discussing treatment options, it is important to evaluate the overweight patient with a focused history and physical examination designed to identify factors associated with weight gain, identify possible weight related comorbidities and understand previous weight loss attempts. Assessing food intake, energy expenditure, physical activity and medications that potentially promote weight gain are all important. Some patients feel that they have an endocrine problem causing their weight gain. Performing a careful history and physical examination and obtaining targeted laboratory studies to exclude Cushing's syndrome and hypothyroidism can address these concerns. While rare a number of genetic causes of obesity have been described.

Obtaining a Weight History and Exploring Previous Weight Loss Attempts

The pattern of weight change over time in an individual patient often gives important clues as to likely causes of weight gain, past successes and challenges in weight loss and the reasons why the person is seeking assistance with their weight at this time. Asking questions about the history of weight gain including maximum lifetime weight, factors that were associated with periods of weight gain, successes and limitations of previous weight loss attempts. Kushner has suggested that one way to get at this information efficiently is to have the patient draw a graph of their weight over time [40]. In this manner, triggers for weight gain such as pregnancy, smoking cessation, the introduction of a new medication,

depression or a musculoskeletal injury can be identified and the clinician can help the patient see the connection between these events and weight gain [40]. A history of obesity during adolescence with progressive weight gain during adulthood strongly argues against a medical condition such as Cushing's syndrome or hypothyroidism as the cause of obesity.

Assessing previous weight loss efforts is also important. Many patients comment with frustration that "diets never work for me." Often though, when discussed in greater detail, previous efforts are revealed to have produced the expected degree of weight loss (3–8 %) that was not maintained because of difficulties in sustaining the chosen weight loss strategy. Acknowledging and exploring these previous weight loss attempts can provide a useful platform for discussing the amount of weight that is commonly lost with a diet and exercise program and to explore strategies that were or were not successful previously as a prelude to a discussion of potential future approaches to treatment. Asking specifically about what prompted previous weight loss attempts, how much weight was lost, what was successful about those previous attempts and what were the circumstances of the termination of those efforts can help you understand how to help the person plan future weight loss attempts. This kind of discussion allows the clinician to provide empathy and support around what are extremely common, almost expected periods of relapse. In addition, the patient's own experiences can be leveraged to emphasize the critical need for long-term behavior change strategies if maintenance of weight loss is the goal. It is important to emphasize to the patient that they can learn from previous weight loss attempts and that if they do, future attempts need not be a replay of prior attempts. Elements of treatment such as cost, time commitment, social support, types of foods consumed, self-monitoring, exercise, and the impact of special occasions, chronic illnesses, vacations and work can be explored. Things that did work as well as barriers to success can be identified and incorporated into a new plan.

Assessing Food Intake

Weight change is produced by a long-term imbalance between energy intake (EI) and energy expenditure (EE). Weight gain only occurs when EI > EE, and weight loss will only occur when EE > EI. The problem is that it is extremely difficult to accurately measure either EI or EE in a clinical environment. An extensive body of research demonstrates that virtually everyone underestimates EI when asked to self-report food intake. The best measure of EE is a method known as doubly labeled water. This method can accurately determine EE over a period of weeks in free living individuals. If weight is stable then EE = EI. In a number of studies self-reported food intake underestimated measured EE by an average of almost 30 % [41, 42]. A number of factors including BMI, previous weight loss history, and fear of negative evaluation have been shown to be associated with underreporting of EI [43].

The reality that people tend to underreport food intake however does not undermine the importance of gaining as much information as is reasonably possible on this important parameter. Information on food intake can be easily obtained in an office visit using a 24 h., 3 day or 7 day dietary recall or a food frequency questionnaire. Information about meal patterns, fast food consumption, calories consumed in beverages and "trigger foods" that tend to be overeaten can be identified. Diet record forms can be printed and available in the office so that patients can collect more extensive information between visits. Tools that help patients estimate portion sizes can help improve the quality of information obtained from diet records as well as building a foundation on which dietary interventions can be built. In fact self-monitoring of the diet appears to be one of the most important features of both successful short and long-term weight loss [44]. Keeping detailed food records can provide useful information not only about the foods that were consumed but about situations and precipitating factors associated with overeating. The patient can be encouraged to look for and record details of the "chain of events" that led to a loss of control over

food choices. Were meals skipped? Was stress involved? What were the circumstances around which the particular foods overeaten were available? Was food eaten while the person was engaged in other activities such as television watching? In this manner the patient can begin to identify points along this sequence of events that could be modified through alternative approaches to similar situations that will likely recur in the future. While the information may not be completely accurate, asking for a self-report of food intake such as a 24-h dietary recall on each office visit emphasizes to the patient that the clinician feels that this information is critical in assessing weight health.

For those patients who use the internet and computer programs regularly, a number of diet monitoring tools are available for either PDA or PC based use. The US Department of Agriculture has a website that allows individuals to track their diet (https://www.supertracker.usda.gov/default.aspx) and another site where information on recommended intakes of a wide variety of nutrients can be found (http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes). While these sites are free and contain a good deal of useful information, many patients find them difficult to navigate and find the lists of foods incomplete for diet logging. Some other sites that are well reviewed by consumers for dietary self-monitoring include MyFitnessPal (www.myfitnesspal.com), Sparkpeople (www.sparkpeople.com, also provides social support and weight loss advice) and CalorieKing (www.calorieking.com, has an extensive database of foods that can be used to estimate energy intake). These are just a few of the many excellent sites available at this time for dietary self-monitoring.

Assessing Energy Expenditure

Energy expenditure is made up of three components: basal metabolic rate (BMR), which can be estimated as resting energy expenditure (REE) which has also been called resting metabolic rate (RMR), thermic effect of food, which makes up only a small fraction of total daily energy expenditure, and energy expended in physical activity (EEPA), which is by far the most variable between individuals. Although patients often complain that they have a "low metabolic rate," careful studies have conclusively shown that REE is linearly related to lean body mass [45]. This means that heavier people have higher REE than thin individuals, and as a result need to eat more on average each day to maintain their higher weight. It is likely that the rise in prevalence of obesity is the result not only of increased EI associated with the modern food environment, but also due to a reduction in the habitual levels of EEPA associated with a modern environment filled with technologies designed to reduce the need for physical labor [46, 47]. There is increasing evidence that the low levels of physical activity that characterize a sedentary lifestyle are associated with not only obesity, type 2 diabetes, cardiovascular disease, but also some types of cancer and increased overall mortality [48–52]. Conversely, increased levels of physical activity and high levels of cardiorespiratory fitness are associated with reduced levels of morbidity and cardiovascular mortality [53–55]. A physically active lifestyle is one of the top ten health indicators for Americans in the Healthy People 2020 objectives [56].

Physical Activity

Clinicians can and should solicit information about usual levels of physical activity as part the initial evaluation and at follow up visits. Questions such as "how often do you engage in planned physical activity?" or "do you ever walk for exercise?" can be helpful. Asking about participation in sports or active pursuits in the past can also provide a useful background on which plans for increases in physical activity to manage weight can be based. Questions about the amount of time spent in sedentary activities such as television watching, using the computer, or reading also provide useful information about habitual activity levels. In addition, time spent in these sedentary activities may be available for active

pursuits should the person choose to increase their physical activity level. A number of physical activity questionnaires are available to obtain more in depth information on energy expended in activities of daily living as well as planned bouts of exercise (http://www.health.gov/PAGuidelines/). As is the case with assessing EI, there are substantial limitations to the assessment of EE by self-report. People tend to underreport food intake and over report levels of physical activity. Adults overestimate EEPA by as much as 50 % [57, 58]. A recent scientific statement from the American Heart Association provides a comprehensive guide to the tools available to assess physical activity [59].

More objective information about habitual levels of physical activity can be obtained through the use of physical activity monitoring systems. The simplest of these is the pedometer or step counter. These devices are worn at the waist and count the number of steps accumulated over a day or week [60, 61]. A pedometer can be purchased for $10–$30 and can be used to characterize an individual as sedentary (2–5,000 steps/day), normal activity (5–8,000 steps/day), meeting guidelines for PA at a level to prevent weight gain (8–11,000 steps/day), highly active or active at a level commensurate with that needed to produce and maintain weight loss (11–15,000 steps/day). Pedometers have limitations. Some cheaper models may be inaccurate, and accuracy may be reduced in obese individuals due to difficulties in keeping the device in a proper vertical alignment when worn on the belt and reduced sensitivity with slow walking speeds. Like dietary self-monitoring, physical activity self-monitoring using either a pedometer or minutes of moderate physical activity per week is valuable not only in assessing the causes of weight gain, but for laying a foundation for subsequent interventions [62, 63]. Over the last few years a large number of new physical activity monitoring systems have emerged for the consumer market. These devices cost about $100–$200 and provide data that some patients find more helpful than that provided by a typical pedometer. While the field is moving rapidly some of the leaders in this market include several Fitbit devices, the Nike Fuel, the Jawbone, and several devices from BodyMedia. These devices and others under development combine measures of movement in space with other physiological measures such as heart rate, skin temperature and galvanic skin response to estimate EEPA in free living individuals. Many of these devices interface with computer software packages that allow the tracking of specific activities at specific times of day, logging of activities over time and even the potential to provide data to personal trainers or healthcare providers. A number of other devices including the Actical (Philips), ActiGraph (Actigraph Corp.), ActivPAL (PAL Technologies Ltd) and the RT6 (Stayhealthy) have been used in research settings and have been well validated [64]. However, these systems tend to be more costly and complex requiring specialized software for analysis making them much less user friendly than the devices designed for the consumer market.

Indirect Calorimetry to Measure Energy Expenditure

Another tool that can be used clinically to measuring energy expenditure is indirect calorimetry. The indirect calorimeter measures air flow and the difference in the concentration of oxygen between inspired and expired air to determine oxygen consumption, which is then used to calculate energy expenditure in kcal/h. When measured in the resting state, indirect calorimetry gives an estimate of REE/RMR that can be used to estimate daily energy requirements. For most people, total daily energy expenditure (which equals daily energy intake for weight maintenance) is roughly 1.3–1.5 times RMR. A number of indirect calorimetry systems are commercially available to consumers and healthcare providers for the measurement of RMR. These MedGem/BodyGem products [65] (Microlife Medical Home Solutions), the Reevue indirect calorimeter (Korr Medical Technologies Inc.) and several instruments manufactured by the Cosmed Pulmonary Function Equipment company to name just a few [66]. It is not clear how accurate these devices are in real clinical environments.

The primary role for these devices at this time is to provide patients with some objective information about their energy intake needs. Many patients believe that they have a "low metabolic rate" and devices like these can provide direct evidence of what their metabolic rate is.

Medications that Promote Weight Gain

Weight gain associated with the introduction of medications to treat comorbid illnesses is a common problem. The most commonly implicated medications include anti-diabetic medications [67] (sulfonylureas, thiazolidinediones, insulin) as well as a wide range of psychotropic medications. The antipsychotic drugs clozapine, olanzepine, risperidone, and quetiapine have all been associated with weight gain as well as abnormalities in glucose homeostasis [68]. A number of antidepressant medications including amitriptyline, mirtazapine, and some serotonin reuptake inhibitors may promote weight gain in some patients. Other drugs that are used as mood stabilizers including lithium, valproic acid, and carbamazepine and the anti-epileptic drugs valproate, carbamazepine, and gabapentin can also promote weight gain. Historically psychiatrists and neurologists have paid little attention to the weight related side effects of some of the medications that they commonly prescribe. This situation is fortunately changing, but it is still common for a patient to be placed on a psychotropic medication or an anti-epileptic medication, experience substantial weight gain without the knowledge of the provider that initially prescribed the medication.

Fortunately, there are alternatives for each of these medications that could be considered if drug associated weight gain is a serious problem. Metformin, GLP-1 analogues, DPP-IV inhibitors, and SGLT2 inhibitors offer people with diabetes the benefits of glucose lowering without weight gain even weight loss with some of these medications. Bupropion is an antidepressant medication that has some weight loss properties, although it does not have an FDA indication for weight loss [69]. Topiramate is a medication that is FDA approved as an anti-epileptic medication and also for use in the treatment of migraines. It has some utility as a mood stabilizer and in the treatment of neuropathic pain. It has moderate weight loss promoting properties [70, 71]. The issue of medication induced weight gain and its treatment are discussed in more detail in the chapter by Smith in this volume.

Hypothyroidism

Many overweight and obese patients suspect that they have an underlying hormonal problem that has produced their excessive weight gain. These beliefs have been fueled in part by a large body of misinformation about thyroid disorders on the internet. Unfortunately, true thyroid pathology is not often the cause of obesity. It is also common to encounter patients seeking care for obesity who have hypothyroidism who want to optimize their thyroid hormone replacement medication. Both the American Thyroid Association [72] and the American Association of Clinical Endocrinologists [73] have published guidelines on the assessment and management of hypothyroidism that are evidence based and should be used in the management of these patients. These guidelines emphasize the importance of the TSH in determining the presence of hypothyroidism and guiding treatment. TSH is not a "normally distributed" parameter being skewed to the lower end of the normal range. The median value is 1 mIU/L which is lower than the arithmetic mean of the upper and lower end of the normal range. Some have advocated making the upper limit of the normal range 4 or even 2.5 mIU/L. It is reasonable to initiate thyroid hormone treatment in those patients who have a TSH value above five or especially if they have evidence of underlying autoimmune thyroid disease such as a positive thyroid peroxidase (TPO) antibody level. In addition, it is reasonable to make a modest increase in thyroid hormone replacement in a person on thyroid hormone who has a TSH value in the upper part of the normal range with the goal of reducing the TSH to an "ideal level" of 1 mIU/L. A number of studies have examined the utility of adding T3

to LT4 in the treatment of hypothyroidism. Despite initial enthusiasm, well done randomized controlled trials have not demonstrated the superiority of combination therapy to LT4 alone which remains the standard approach to treatment [74]. Despite the fact that desiccated thyroid hormone products and compounded thyroid hormone may have better pill to pill consistency than products did in the 1960s they have not been shown to be superior to pharmacological preparations of T3 and T4 and so are not advocated by clinical guidelines as standard forms of therapy for hypothyroidism. Thyroid hormone dosing is weight based so as patients lose weight their TSH should be monitored and the dose reduced if indicated.

Hypercortisolism

Hypercortisolism, while a rare cause of weight gain, is another endocrine condition that should at least be considered in the initial evaluation of overweight and obese patients. Although central obesity, a buffalo hump and full supraclavicular fat pads are common in people with Cushing's syndrome, they are also common in obesity not caused by hypercortisolism. Because biochemical testing for hypercortisolism is subject to false positives in obese individuals, it is important to have a relatively high clinical suspicion of the disorder before embarking on diagnostic testing. For this reason the less common but more specific features of Cushing's syndrome should be looked for on history and physical examination. These include proximal muscle weakness, thin skin, easy bruising, and wide (>1 cm) purple striae. Unexplained osteoporosis in an obese man is another condition that should raise the possibility of hypercortisolism. A recent change in appearance as documented by a survey of old photographs is also suggestive of the development of hypercortisolism.

The Endocrine Society has published a Clinical Practice Guideline on the diagnosis of Cushing's syndrome [75]. This document gives comprehensive and up to date guidance on the clinical features and diagnostic evaluation of the patient with suspected hypercortisolism. The first step in this evaluation is to establish the presence of hypercortisolism. To accomplish this goal there are three useful tests, the 24 h urine cortisol, the overnight 1 mg dexamethasone suppression test, and the late night salivary cortisol test. The guideline document discusses the advantages and limitations of each of these and concludes that each is reasonable screening test. The next step in the evaluation of hypercortisolism after over-secretion is established is determining the specific cause. Hypercortisolism can be caused by a pituitary ACTH secreting tumor, ectopic ACTH secretion or an adrenal adenoma. Measuring serum ACTH levels and the response of cortisol to the 8 mg dexamethasone suppression test are not used for establishing the presence of hypercortisolism but rather are used for determining the specific cause of hypercortisolism that has already been established by one of the screening tests.

Genetic Causes of Obesity

The genetic contribution to body weight has been estimated at between 30 and 50 %. Genome-wide association studies suggest that, for most obese individuals, a moderate number of different gene polymorphisms, each with relatively small effect sizes, combine with environmental influences to determine body weight [76]. The genetic polymorphism that appears to be the most common in human obesity is of the FTO gene [77]. The polymorphism of this gene that is associated with obesity is found in 16 % of adults. Those with the risk allele weigh an average of 3 kg more than those without the allele. Early-onset (<2years of age) severe obesity, on the other hand, may be associated with rare monogenic forms of obesity [78]. Early-onset severe obesity occurs in <0.01 % of the general population. Mutations of the leptin gene have been found in only 12 individuals in the world to date. Mutations of the leptin receptor have been found in more individuals but are also extremely rare [79]. The most common monogenic form of early-onset obesity involves mutations of the melanocortin 4 receptor (MCR4) [80]. MC4R is involved in

hypothalamic signaling along the neural pathway that responds to leptin. Individuals who have mutations in the leptin gene or the leptin receptor have hypothalamic hypogonadism and subtle impairments in growth hormone and immune function. In contrast, individuals with MCR4 mutations present with severe obesity but with normal reproductive function.

A relatively common genetic form of early-onset severe obesity is the Prader-Willi syndrome (PWS) [81]. PWS is a multisystem disorder that is caused by the lack of expression of paternally inherited imprinted genes on chromosome 15q11–q13. The features that are typical include hypotonia and poor feeding shortly after birth; learning disabilities, growth retardation, behavioral problems, hypothalamic hypogonadism, and cryptorchidism in childhood. The initial screening genetic test, a DNA methylation analysis, is useful in making a definitive diagnosis. Hypothyroidism, adrenal insufficiency, and hypogonadism have all been associated with PWS. Growth hormone deficiency is also part of PWS and a number of controlled trials have demonstrated that GH treatment before puberty markedly improves body composition and adult height [82]. If untreated, progressive obesity leads to the development of type 2 diabetes in 25 % of affected individuals by age 20. GH treatment should be started as early as 2 years of age. Hypogonadism is virtually always present, but treatment with testosterone needs to be carefully considered and only after the initiation of growth hormone (GH) treatment because of the effects that it will have on behavior and bone maturation.

Screening for Associated Health Problems

It is clear that obesity is associated with a wide range of adverse health consequences [83]. These include type 2 diabetes, hypertension, hyperlipidemia, coronary artery disease, sleep apnea, polycystic ovarian syndrome, degenerative joint disease, depression, some forms of cancer, urinary stress incontinence, and erectile dysfunction among others. Therefore, when evaluating an obese patient, it is important to tailor the office visit in part to looking for evidence of these associated comorbid conditions. The initial evaluation should involve performing a directed history and physical examination with particular emphasis on screening for the causes of weight gain outlined above as well as the commonly associated comorbid conditions (Table 12.6). Laboratory studies should be obtained to rule out common disorders with specific laboratory studies ordered as indicated by findings on history and physical examination. Evidence of the presence of any of these comorbid conditions not only warrants further evaluation, but also has implications for the interventions that will be suggested to manage weight.

Hyperlipidemia, Hypertension, and Cardiovascular Disease

Obesity is clearly associated with an increased risk of cardiovascular morbidity and mortality. Asking questions about cardiovascular risk factors and obtaining a fasting lipid panel are the first step in risk assessment. For many years the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) guidelines provided guidance on the evaluation and management of cardiovascular disease risk [84]. However, in late 2013 the American College of Cardiology and the American Heart Association released new guidelines on both the assessment of atherosclerotic cardiovascular disease (ASCVD) risk [37] and the treatment of blood cholesterol [85]. These new guidelines are a substantial departure from the ATPIII guidelines. The new guidelines move focus away from risk groups based on the older risk factors and target LDL goals towards the categorization of patients into 4 "statin benefit groups." Specifically, the new cholesterol guideline replaces the older risk stratification scheme with a new approach that incorporates a new risk calculator (http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp). The new guidelines identify four groups of patients as being likely to benefit

Table 12.6 Assessment of the obese patient

Condition	History	Physical examination	Laboratory
Diabetes	Polyuria, polydipsia	Acanthosis nigricans	Fasting glucose
	Blurry vision	Skin tags	Or HbA1C
	Weight loss		Or OGTT
	Family history of DM		
Cardiovascular disease	Chest pain	Blood pressure	Fasting lipids
		Xanthomas	EKG if indicated
		Cardiac exam	
Pulmonary	Snoring	Hypertension	Sleep study if indicated
Sleep Apnea	Daytime hypersomnolence	Increased neck circumference	
	AM headaches	Small hypopharynx	
Gastrointestinal	GERD	Rectal exam	Fecal occult blood
GERD	Dark stools	Enlarged liver	Liver function tests
Gallstones	Abdominal pain		
NASH	Heartburn		
Colon cancer			
Genitourinary			
Stress incontinence	Urinary incontinence	Rectal exam	
Prostate cancer			
Endocrine			
Cushing's Syndrome	Easy bruising	Bruising	Midnight salivary cortisol if indicated
	Proximal muscle weakness	Proximal muscle weakness	Or overnight Dex. Supp. test
	Change in appearance	Central obesity	Or 24 h urinary free cortisol
		Wide purple striae	
Hypothyroidism	Cold intolerance	hypertension	TSH
	Constipation	bradycardia	Thyroid peroxidase antibodies if indicated
	Menorrhagia	Abnormal thyroid exam	
	fatigue	Delayed reflexes	
Reproductive	Men: Sexual function	Women: hirsutism	Men: testosterone if indicated
	Women: hirsutism,	Pelvic exam	Women: ovarian ultrasound if indicated
	Menstrual function		17-OH progesterone if indicated
	Fertility		
Breast cancer	Family history	Breast exam	Mammography
	Lumps, self-exam		

from statin therapy. These include individuals (1) with clinical ASCVD, (2) primary elevations of LDL–C >190 mg/dL, (3) diabetes aged 40–75 years with LDL–Cholesterol levels of 70–189 mg/dL without clinical ASCVD, or (4) without clinical ASCVD or diabetes with LDL–cholesterol levels of 70–189 mg/dL and an estimated 10-year ASCVD risk >7.5 %. The new guidelines remove the use of LDL cholesterol targets and emphasize instead the intensity of statin therapy. These new guidelines have met with some early criticism, in particular over the accuracy of the risk calculator [86, 87]. Because they are a substantial change from previous recommendations it will likely take several years for healthcare systems and patients to adapt to the new approach. During this time it seems that clinicians caring for overweight and obese patients should be flexible and keep an open mind about both the logic of the previous guidelines and the potential advantages of the new approach.

The physical examination should include measurement of blood pressure in the seated position with an appropriately sized cuff. The Joint

National Commission has recently updated their guidelines on the management of hypertension in adults [88]. While the changes in JNC8 as compared to JNC7 are not as dramatic as the changes seen in the AHA cholesterol guidelines were to the ATPIII guidelines they too move care in a new direction suggesting a generally less aggressive approach to blood pressure control. These new guidelines suggest treating hypertensive patients aged 60 years or older to a blood pressure goal of less than 150/90 mmHg and a goal blood pressure of 140/90 mmHg for adults 30–59 years of age. They also recommend a goal blood pressure of 140/90 mmHg for adults > 18years of age with non-diabetic chronic kidney disease or diabetes. Weight loss can modestly improve blood pressure in obese patients with hypertension but the benefits are not as dramatic as what is seen with glucose metabolism in those with diabetes.

Diabetes

Weight gain and obesity along with age, ethnicity, and family history are the most powerful predictors of the development of type 2 diabetes in adults. Acanthosis nigicans and skin tags are cutaneous manifestations of insulin resistance and hyperinsulinemia that may be seen. All obese adult patients should have a test of carbohydrate metabolism to screen for diabetes. The diagnosis of diabetes comes from a level of glucose that is associated with microvascular complications. Levels of glycemia that establish a diagnosis of diabetes can be assessed with fasting glucose determinations, 2 h glucose levels after ingestion of oral glucose in an oral glucose tolerance test (OGTT), or a glycosylated hemoglobin level (HbA1C). The specific diagnostic cut points come from the American Diabetes Association guidelines which are updated each year [9]. Diabetes is diagnosed if fasting glucose is >126 mg/dL, HbA1C is >6.5 % or a 2 h glucose in an OGTT is >200 mg/dL. Because a diagnosis of diabetes has significant implications for the person being diagnosed, the diagnostic test should be repeated to confirm the diagnosis. This is to say a diagnosis of diabetes should not be made on the basis of a single test. With the availability of three different tests to diagnose diabetes, there will be situations where one test is diagnostic of diabetes and another is not. The guidelines advise that in this situation, the diagnostic test that establishes a diagnosis of diabetes takes precedence. Normal glucose tolerance is defined as a fasting glucose < 100 mg/dL, an HbA1C <5.7 % and a 2 h glucose in an OGTT < 140 mg/dL. Impaired fasting glucose is a fasting glucose between 100 and 125 mg/dL. Impaired glucose tolerance is a 2 h. glucose between 140 and 199 mg/dL. Prediabetes could be diagnosed with either of these tests or an HbA1C between 5.7 and 6.5 %.

Sleep Apnea

The prevalence of disordered breathing during sleep increases markedly with increasing weight. In addition, weight loss improves sleep apnea [89, 90]. For this reason it is important for clinicians to assess all obese patients for the presence of this common and underdiagnosed problem. A recent guideline on this topic from the American Academy of Sleep Medicine outlines an approach to the assessment of patients at risk for obstructive sleep apnea (OSA) and obesity hypoventilation [91]. The signs and symptoms of OSA include daytime hypersomnolence, hypertension, snoring, morning headaches, nocturia, difficulty concentrating, decreased libido, irritability, and disturbed sleep. The Epworth sleepiness scale can be used to screen for OSA [92]. In patients suspected of having OSA a diagnostic test should be performed. Neck circumference can be measured and increased values (> 17 in. in men, > 16 in. in women) are associated with an increased risk for OSA. While polysomnography is the "gold standard" diagnostic test, portable monitoring is a reasonable alternative when supervised by a practitioner with board certification in sleep medicine or an individual who fulfills the eligibility criteria for the sleep medicine certification examination.

Reproductive Disorders and Polycystic Ovarian Syndrome

Obese women are more likely than lean women to experience a range of reproductive problems including anovulatory cycles, hirsutism, infertility, and fetal loss. These problems can bring these women to medical attention or may be present in women seeking help with weight loss. Obese men are more likely than their lean counterparts to experience decreased libido and have low testosterone levels [93]. Weight loss can ameliorate these problems in both men and women [94]. However, it is important to identify these problems in obese patients as they may benefit from treatment directed primarily at these disorders.

Polycystic ovarian syndrome (PCOS) is characterized by reproductive and metabolic dysfunction that begins in adolescence. The diagnosis of the disorder remains controversial. In the most recent guidelines from the Endocrine Society [95], PCOS is defined using the so-called Rotterdam criteria by the presence of two of the following: clinical evidence of androgen excess, ovulatory dysfunction or polycystic ovaries seen by ultrasound. The guidelines advise that in addition to screening for diabetes, hyperlipidemia and sleep apnea, women with a clinical diagnosis of PCOS should be evaluated for other androgen excess disorders including thyroid disease, hyperprolactinemia and non-classic congenital adrenal hyperplasia. These disorders can be ruled out with blood determinations of TSH, prolactin and 17-OH progesterone. Treatment of PCOS typically is directed at the symptom that is most troubling for the patient, either irregular menses, hirsutism or infertility.

Other Disorders

Musculoskeletal problems including degenerative arthritis are very common in obese patients and are the source not only of pain and decreased quality of life but decreased functional capacity and disability [96, 97]. Gathering information about joint pain and functional capacity are important to obtain before making recommendations about an exercise program. Gall stones are more common in obese patients and an inquiry should be made for symptoms consistent with episodic biliary obstruction. Non-Alcoholic Steatohepatitis (NASH) is a common complication of obesity that is discussed in another chapter of this volume. Symptoms of reflux esophagitis, urinary stress incontinence may be present as a result of increased intra-abdominal pressure which is a feature of serious obesity. Because of the increased risk of cancer in obese patients it is important to do a breast or prostate exam where appropriate and make sure that appropriate screening for colorectal cancer including stool hemoccult testing or screening colonoscopy are done [3]. Endometrial cancer is also more common in obese women so questions about abnormal menstrual bleeding should be asked and a pelvic exam should be performed if indicated.

Assessing Readiness to Make Lifestyle Changes

In many health problems the physician plays the role of "manager." The physician is in control, makes the relevant decisions, has responsibility for the outcome and is accountable for the patient's course. However, when helping overweight or obese patients make lifestyle changes, it is clear that the physician is not in control, is not the decision maker and does not have the authority to make the relevant choices. Quite the contrary, the patient really is in charge of all of the relevant decisions. If you as the physician are not in charge, what then is your role? It may be more useful for you to adopt the role/posture of a consultant, coach or advisor. If you accept this role, the approach that you will use to assess the patient's readiness to make changes may become clearer. The key elements of effective counseling for behavior change and assessing readiness for making lifestyle change include:

- Acknowledging that ultimately the behavior change needs to come from the patient and cannot be imposed from the outside.
- For a person to change their behaviors they must first see a compelling need for change.

- Even if they see a compelling need for change, meaningful behavior change will not occur until the patient feels confident that they can/will be able to do the new behavior.
- To establish a highly effective counseling relationship you need to be empathic and demonstrate it.

During an office visit it may be useful to identify motivations for weight loss, goals and expectations, potential barriers and whether the patient has considered potential solutions to likely challenges. Discussing social support systems, current stressors and screening for serious emotional disorders before giving specific lifestyle advice will increase the likelihood of success.

Summary

Obesity is one of the most common problems seen in clinical practice. It is associated with an increased risk for a wide range of comorbid conditions, increased healthcare costs, and disability. Clinicians are in a unique position to have a positive impact on the health of their obese patients. There is a broad consensus now that the BMI should be calculated for all adult patients and that this number should be used in risk stratification. For those with a BMI between 25 and 35 kg/m^2, the waist circumference adds clinically useful information and should also be obtained.

Overweight and obese patients should have a complete history and physical examination and targeted laboratory studies to screen for potential causes of obesity and associated comorbid conditions. Assessing food intake and physical activity behaviors is the foundation on which treatment recommendations can be built. A number of tools are now available to assist the clinician in assessing these parameters which are subject to inaccurate self-reports. To successfully manage obesity the clinician should take care to assess the patient's readiness to change as well ask questions that will help reveal the presence of any comorbid psychological conditions. Finally, the clinician should develop relationships with other professionals such as dieticians, psychologists, exercise physiologists and pharmacists to help them in the evaluation and management of their obese patients. Other chapters in this book will provide specific advice on treatment approaches that can be used to help overweight and obese patients lose weight and maintain a reduced state.

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Behavioral Strategies in Weight Management

13

Jason Lillis and Rena R. Wing

Introduction

Behavioral approaches to weight control are recommended as the treatment of choice for overweight and moderately obese adults. The goal of these approaches is to help participants make healthy, permanent changes in their eating and exercise behaviors, and thereby achieve long-term weight loss and maintenance.

In this chapter, we will describe the history of behavioral approaches to obesity and the key components of these approaches. We will then review the results that can be achieved in these programs and the health benefits that occur. Finally, the chapter will discuss current and future efforts to both improve the outcomes of these approaches and extend their reach to large numbers of overweight/obese adults.

History

First Generation: Behavior Therapy

Behavior therapy began in the 1960s as a response to the current state of psychosocial clinical interventions, which was dominated by psychoanalytic approaches. Research and adherence to empirical findings was lacking. The first generation of behavior therapy aimed to establish basic behavioral principles and applied technologies that were well specified and subject to rigorous scientific testing [1]. Traditional behavior therapy was based largely on social learning theory, focused on direct, overt behavior change, and many of its techniques comprise modern day standard behavioral treatments, including self-monitoring, stimulus control, and goal setting.

Second Generation: Cognitive Behavior Therapy

Clinicians became aware over time of the limitations of first generation behavior therapy. Primary among these concerns was an inadequate account of, and technology to address, cognition. Behavior therapy's focus on manipulating observable contextual variables naturally led to a de-emphasizing of private experiences (such as thoughts and feelings). In response, clinicians began documenting patterns of clinical phenomena, such as the occurrence of poor mood, self-focused judgmental thoughts, and a lack of goal-directed behavior. Soon after, techniques targeting cognitive and emotional change were added to clinical interventions, giving rise to Cognitive Behavior Therapy (CBT). A number of cognitive and emotional change techniques remain widely used in evidenced-based treatments today [2], many of which are present in

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standard weight loss interventions, including: (a) identifying negative, automatic thoughts and replacing them with more useful, reality-based thinking, (b) challenging cognitive distortions, (c) restating problems in behavioral terms, (d) distraction, and (e) self-soothing techniques.

Cognitive change techniques were a departure from the roots of behavior therapy as these techniques were being developed on clinical theories as opposed to well-established basic behavioral processes. Thoughts and feelings were being treated as independent variables—the causes of behavior. This had the unintended effect of making many of these working cognitive theories unfalsifiable. Cognitive change techniques have been shown to be useful as a part of larger CBT packages, however they have shown little to no incremental utility when examined in large dismantling studies [3]. More recent evidence suggests the possibility that attempts to control cognition can be detrimental [4].

Third Generation: Acceptance and Mindfulness

The third generation of behavior therapy returned to traditional roots by re-emphasizing basic behavioral principles. Language and cognition is now seen as a learned operant and its manifestation determined by a learning history and current contextual factors (emphasis placed back on the environment). From this perspective, thoughts and emotions are no longer seen as independent variables, but instead dependent variables. This led to a proliferation of new techniques that focus on changing the function of thoughts and emotions, as opposed to changing them in form or frequency [5]. These techniques are frequently called mindfulness and acceptance-based, and are found in treatments such as Acceptance and Commitment Therapy [6], Dialectical Behavior Therapy [7], and Mindfulness-Based Cognitive Therapy [8] among others. Acceptance and mindfulness-based strategies have been added to many weight control packages and are just recently being evaluated empirically [9, 10].

Overview of Behavioral Weight Loss Treatment

Format

Behavioral treatment is typically delivered once weekly to groups of 10–15 individuals. Group treatment has been shown to be superior to individual care [11]. After an initial weight loss period of 4–6 months, there may be an extended treatment, or maintenance, phase that lasts 6–12 additional months, usually at a reduced contact rate of 1–2 times per month. Treatment sessions are 60–90 min in duration and the format is typically closed (meaning individuals start at the same time and remain in the same group throughout treatment). Each session includes a private weigh in, review of material and homework from the prior session, and then presentation of new lesson material (following a structured written protocol).

Interventionists

Groups are typically run by co-leaders or multidisciplinary teams. Interventionists are most frequently nutritionists, exercise physiologists, and behavior therapists. Interventionist education level varies by setting from master's to doctoral level.

Focus

The primary focus of behavioral weight loss treatment is to improve dietary and physical activity behavior patterns. Specific recommendations and empirical support for nutrition and exercise educations strategies are reviewed elsewhere in this book. The behavioral approach, however, assumes that providing information about diet and activity may be important and helpful to individuals, but it is not sufficient for establishing behavior change. Behavioral treatment programs focus on teaching individuals strategies for changing unhealthy behavior patterns by addressing the variables that are leading to inappropriate eating and sedentary activity.

Behavioral Weight Loss Strategies

Self-Monitoring

The systematic recording of body weight, caloric intake, and physical activity is the foundation of behavioral weight loss treatment. Self-monitoring allows individuals to assess their progress toward treatment goals and to receive feedback on the adequacy of their goal-directed behaviors. Throughout treatment, individuals keep a daily record of food intake and physical activity, allowing both the individual and the group leader to see if target behaviors are improving, deteriorating, or remaining the same. Individuals typically record all food and beverages consumed along with the calories for each item, and sometimes additional information, like the number of fat grams. Individuals also record their daily weight and number of minutes engaged in moderate intensity physical activity. Daily records are used as a clinical tool during sessions and group leaders often provide written feedback after a more thorough review in between sessions. Adherence to self-monitoring has been demonstrated to be significantly associated with success at both weight loss and maintenance [12, 13]. Recent research suggests that using a smart-phone (or similar device) increases self-monitoring and can improve weight control [14, 15].

Goal Setting

Setting clear goals for caloric intake and physical activity provide structure and direction for individuals. Behavioral weight loss interventions are designed to produce a weight loss of 1–2 lb per week, with an overall target of a 7–10 % reduction from baseline weight. To accomplish this, participants are prescribed a daily calorie goal between 1,200 and 1,800 cal (depending on the starting weight of the individual), and a weekly exercise recommendation that starts low (e.g., 20–50 min) and works up to a goal of 250 min per week of moderately intense physical activity by about 6 months. Individuals are also encouraged to set additional behavioral goals. Behavioral weight loss treatment promotes the use of SMART goals (see Table 13.1). When setting a new goal, individuals are encouraged to carefully consider factors such as how, when, and where the behavior will be completed. Goal setting is used in conjunction with self-monitoring to keep track of both short- and long-term goal achievement progress. Although goal setting has not been systematically studied within the paradigm of weight loss treatment research, research suggests that it can contribute to behavior change in general [16].

Table 13.1 SMART goals

*S*pecific	"I will eat 1,200 cal per day" as opposed to "I will eat fewer calories"
*M*easurable	"I will walk for 15 min on 5 days this week" as opposed to "I will walk more this week"
*A*ttainable	A weight loss goal of 5 lbs in 5 weeks, as opposed to 5 lbs in 5 days
*R*ealistic	"I will eat ice cream no more than twice per month" as opposed to "I will never eat ice cream again"
*T*ime sensitive	"I will walk the dog when I wake up on Monday, Wednesday, and Friday," as opposed to "I will take the dog for a walk this week"

Problem Solving

Problem solving is a process through which individuals can address barriers to change. Individuals are taught to use a systematic process for solving problems that includes describing the problem in detail, brainstorming potential solutions, making an action plan, and evaluating the effectiveness of the chosen strategy. This process can be repeated as many times as is necessary to successfully address a specific barrier. A key point of emphasis is teaching individuals how to analyze chains of behavior and identify multiple potential points of intervention within these chains. For example, an individual might skip lunch, receive some criticism from their boss, feel stressed and upset, come home tired and hungry, go right to the kitchen, see cookies on the counter, and finally eat a lot of cookies. Table 13.2 shows several links in this behavioral chain and possible problem-solving solutions at each point in the chain.

Table 13.2 Problem solving ways to interrupt a behavioral chain

Behavioral links	Problem-solving options
Sarah didn't eat lunch	Pack a quick bag lunch before leaving for work
Her boss was critical	Talk to her boss, take a break
She felt stressed	Get support from a coworker
She came home tired and upset	Go for a walk to improve energy and mood
She went right to the kitchen	Plan something to do for night when you get home
She saw cookies on the counter	Don't buy cookies/keep them out of sight
She ate the cookies	Have prepared healthy snacks available

Stimulus Control

Environmental factors, such as plate size and shape, food packaging, socializing, and distraction play a role in overeating [17]. Thus, a key strategy to promote weight loss is creating an environment more conducive to healthy eating and physical activity. Stimulus control principles are used to reduce cues for unhealthy eating and sedentary behavior and increase cues for healthy eating and activity. For example, placing equipment for physical activity (e.g., walking shoes or exercise equipment) in a prominent place in the house can help remind individuals to become more active during the day. Reducing exposure to tempting foods, by removing them from the house or putting them on a difficult to reach shelf, should reduce the consumption of those foods. Washing and preparing fresh fruits and vegetables can lead to healthier snacking choices. Although individuals do not have complete control over their environments, they can often enact meaningful environmental change at home and work.

Strategies for Addressing Cognitive and Emotional Barriers

Cognitive and Emotional Change Strategies

According to the cognitive behavior model, thoughts and feelings can be triggers for maladaptive behavior (e.g., excessive eating, sedentary behavior). For example, an individual may have the thought "I'll never lose the weight" and then stop exercising and monitoring their food intake. The process of cognitive restructuring involves identifying maladaptive thoughts, labeling these thoughts, and replacing them with a more rational thought. For example the thought "I'll never get the weight off" can be replaced with the thought that "I may have had a difficult week, but I can recover from this slip." Another strategy would be to challenge the thought, for example by stating "There are times when I've lost weight and I've already lost 15 lb in this program." Other techniques include thought-stopping (breaking a negative thinking chain) and distraction (focusing on something else, for example a to-do list).

Emotional change techniques focus on reducing a problematic emotion, such as stress. Individuals can be taught systematic relaxation skills in which they learn how to progressively relax their muscles, one muscle group at a time. Self-soothing is taught as a way to change mood by engaging in non-eating pleasurable events (e.g., taking a bath or a walk). Another strategy is seeking social support from friends or family members. These techniques have been a part of evidenced-based behavioral weight loss treatment packages for years; however they have never been systematically evaluated as components.

Mindfulness and Acceptance Strategies

Excessive attempts to change thoughts and feelings can lead to maladaptive behavior [4]. Mindfulness and acceptance strategies are an alternative to cognitive and emotional change. Mindfulness techniques teach individuals to notice their thoughts as simply thoughts by training the ability to watch the process of thinking. For example, one might imagine their thoughts as leaves on a stream and envision them floating by. Mindfulness allows individuals to experience a distance between themselves and their thoughts, allowing for more behavioral flexibility (i.e., thoughts no longer need to be responded to/fought with because they are seen as just thoughts).

Acceptance strategies teach individuals how to behave consistently with their values and goals even when unwanted emotions are present. Behavioral repertoires tend to narrow in the presence of difficult emotions. For example, when individuals experience stress, they may stop doing things that matter but take effort, like monitoring calories, exercising, engaging social relationships, and instead engage in a narrow set of behaviors, such as eating and isolation, in an attempt to feel better. The goal of acceptance work is repertoire expansion. The main technique is exposure, though not for the purpose of emotion reduction, but rather to practice sitting with discomfort and also practice making positive behavioral choices in the presence of discomfort. For example, individuals may be taught in session how to notice and experience deprivation by mindfully focusing on different aspects of the emotional experience without pushing it away. Later they are asked to practice this in their natural environment in the presence of tempting foods. An additional acceptance strategy is orienting to the cost of avoidance. For example, if an individual uses food as a way to reduce stress in the short-term, they are encouraged to note the long-term costs of being unwilling to experience stress over the long-term (e.g., weight gain, disease, low energy). Recent studies have shown the potential for adding these techniques to behavioral weight loss interventions [9, 18].

Motivational Interviewing

Motivational Interviewing (MI) is a therapeutic approach that focuses on helping individuals work through ambivalence about behavior change. In a MI approach there is generally no direct attempt to confront irrational or maladaptive beliefs, address denial, or to convince or persuade [19]. Instead, the goal is to help clients think about and express their own reasons for and against change and how their current behavior or health status affects their ability to achieve their own values and goals. MI interventionists use reflective listening skills and positive affirmations to help motivate individuals to change their behavior without telling them what to do. Other core MI techniques include allowing the client to interpret information, rolling with resistance, building discrepancy (between statements made by the individual, their behavior, and their core values), and eliciting self-motivational statements [19].

In a standard behavioral approach, interventionists provide education and goals. Individuals may be told about the risks of being overweight and the benefits of weight loss, given specific calorie intake and exercise targets, and instructed to self-monitor their behavior. In contrast, a MI approach would first elicit the person's understanding and information needs, then provide this in a more neutral manner, followed by allowing space for the individual to express what this means for them, with a question like, "How do you make sense of all this?" MI assumes that individuals are more likely to make behavior changes that they identify and commit to, as opposed to being told what to do. A number of studies have shown that MI can produce improvements in diet and physical activity (e.g., [20, 21]).

Outcomes Achieved in Current Behavioral Programs

The strategies described above are utilized in combination in standard behavioral weight loss programs to help participants change their eating and exercise behaviors. The efficacy of these standard programs has been evaluated in a wide variety of trials. Most of these behavioral weight loss studies are conducted in a single clinical site, with approximately 100–200 participants who are followed for up to 2 years. Reviewing these studies, Wing [22] showed (Fig. 13.1) that these studies typically produce initial weight losses of approximately 10 kg, with maintenance of an 8 kg weight loss at 1–2 year follow-up. These studies have carefully evaluated many of the specific strategies used in behavioral treatment, and have included randomized trials comparing different approaches to changing dietary intake [23], physical activity [24, 25], and motivation [26, 27].

Using the findings from these trials, there have been several multi-center studies in which a

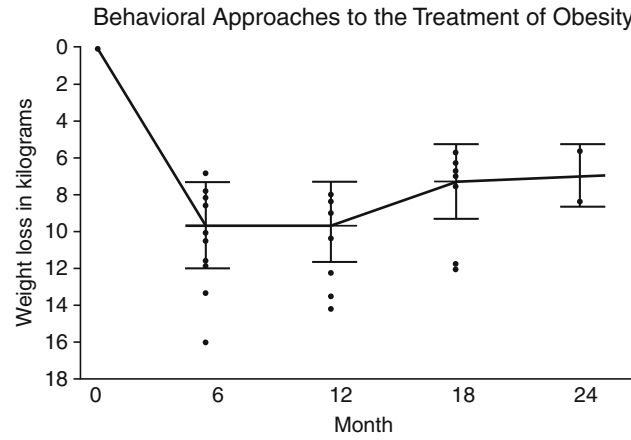

Fig. 13.1 Weight loss outcome in behavioral treatments from 1990 to 2000. Reprinted from Wing, R.R., Behavioral approaches to the treatment of obesity, in Handbook of Obesity: Clinical Applications, G. Bray and C. Bouchard, Editors. 2008, Informa Health Care USA, Inc.: New York

standard behavioral weight loss intervention was used in all clinical sites and the health impact of the intervention was evaluated. These studies are described in detail below as they provide an excellent way to showcase the format, content, and results of current behavioral approaches.

The Diabetes Prevention Program (DPP)

The goal of DPP was to determine if an intensive lifestyle intervention could reduce the risk of developing diabetes in individuals with impaired glucose tolerance (IGT). A total of 3,000 overweight/obese individuals with IGT were recruited at 27 clinical sites and randomly assigned to receive the lifestyle intervention, metformin (a medication used to treat diabetes) or placebo. The lifestyle intervention was developed centrally and all counselors, who were typically master's level nutritionists, received training in the administration of the intervention. The intervention was conducted individually and involved a 16-session core curriculum delivered over 16–24 weeks, followed by ongoing group and individual contact. The goal was to help participants achieve and maintain at least a 7 % weight loss. To achieve this, changes in both diet and activity were stressed. The dietary intervention focused primarily on decreasing fat intake and participants were assigned both a fat gram goal and a calorie intake goal. Physical activity was gradually increased to a goal of 150 min/week of moderate intensity activity such as brisk walking. Participants recorded their intake and exercise daily throughout the core curriculum, and were encouraged to record as needed during maintenance. The lessons used in DPP are available on the DPP website (http://www.bsc.gwu.edu/dpp/lifestyle/dpp_part.html) and focus on the key behavior change strategies, such as stimulus control, changing cognitions, and problem solving.

Participants who received the behavioral intervention achieved an average of 6.9 ± 4.5 % (6.5 ± 4.7 kg) weight loss at the end of the 16 session core curriculum and maintained a weight loss of 4.9 ± 7.4 % (4.5 ± 7.6 kg) at 3.2 year follow-up. Fifty percent of participants achieved the 7 % weight loss goal initially and 38 % at final follow-up [28]. The study was stopped at that time because these weight losses, although modest, were effective in reducing the risk of developing diabetes by 58 % relative to placebo [29]. The lifestyle intervention was also twice as effective as metformin. A follow-up of the DPP, conducted after year 10, showed that although the weight losses in the intensive lifestyle intervention no longer differed significantly from placebo or metformin, the impact on development of diabetes remained highly significant [30].

Based on the success of DPP, another larger trial was launched to examine the long-term

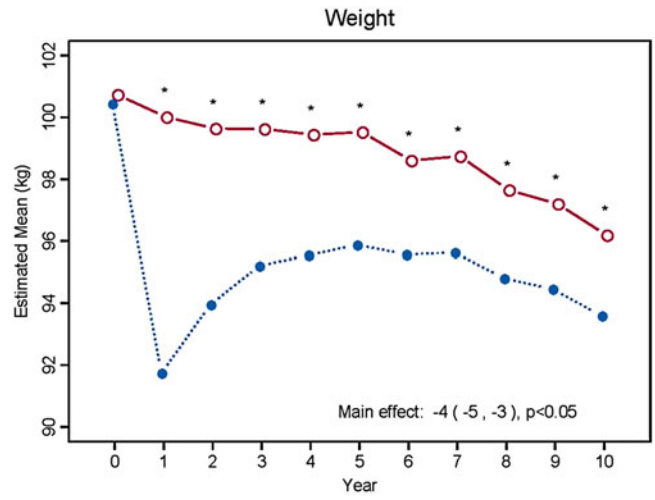

Fig. 13.2 Changes in weight during 10-year follow-up in the Look AHEAD Trial. From Wing, R.R., et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med, 369(2): pp. 145–54. Copyright © (2013) Massachusetts Medical Society. Reprinted with permission

health effects of intensive lifestyle intervention in individuals who were overweight or obese and had already developed type 2 diabetes. In this study, called Look AHEAD, 5,145 individuals were recruited at 16 centers and randomly assigned to intensive lifestyle intervention (ILI) or a control group, referred to as Diabetes Support and Education (DSE). The design [31], rationale for the specific components of the lifestyle intervention [32] and the initial and longer term results have been published previously [33–35]. In brief, the lifestyle intervention in Look AHEAD was implemented primarily in groups, with 3 group meetings and 1 individual session during each of the first 6 months, and 2 group meetings and 1 individual session for months 7–12. Subsequently the frequency of contact was decreased, but an effort was made to have contact with each participant at least monthly for years 1–4 and every 3 months in later years.

The intervention was very similar to DPP, with the following modifications [32]. Participants were encouraged to lose 10 % of their body weight and then maintain this. The dietary intervention focused more on reducing caloric intake, since lowering total calories is recognized as more important for weight loss than is the macronutrient composition of the diet. To help participants achieve this caloric reduction, meal plans and meal replacement products were provided to participants for use initially for two meals per day and later for one meal per day. The physical activity goal was increased to 175 min per week based on recent evidence that higher levels of physical activity were important for weight loss maintenance [36]. The lessons used in Look AHEAD are available on the Look AHEAD website (http://www.lookaheadtrial.org/).

On average, participants in the ILI group lost 8.7 % at 1 year, compared to 0.7 % in DSE. Although the ILI group had a gradual weight regain between years 2 and 4, their weight then plateaued and they maintained weight losses of 6.0 % (vs 3.5 %in DSE) at a median of 9.6 year follow-up (Fig. 13.2). These outcomes were better than seen in DSE at each time point.

The weight losses achieved in Look AHEAD had important health benefits. The ILI group had greater improvements in glycemic control, while requiring less use of insulin, and better improvements in systolic blood pressure with less hypertensive medications. HDL cholesterol improved more in ILI than DSE, but the DSE group had lower levels of LDL-C during the study, due to their greater use of statins. Despite these positive effects on cardiovascular risk factors, the ILI did not reduce the risk of cardiovascular morbidity and mortality. However, it did lead to a large number of other health benefits. Patients in ILI had greater improvements in sleep apnea [37],

urinary incontinence [38], and sexual dysfunction [39], reported less depressive symptoms [40] and better physical quality of life [41], and maintained better physical function over time [42].

Variability in Outcome and Demographic and Behavioral Predictors of Success

Although the average weight losses in behavioral weight loss programs are quite good, the outcome for any individual patient is extremely variable; some participants lose little or no weight whereas others are very successful. This has led to efforts to identify predictors of treatment outcomes. Ideally, those would be characteristics that could be assessed easily at baseline and indicate who should be enrolled. Unfortunately there are no baseline variables that have such predictive value [43].

Several variables have been identified that relate to group differences in outcomes, but none are strong enough to determine which individuals will be most successful. For example, older individuals typically do better in behavioral weight loss programs than younger ones [28, 44]. This was noted in both DPP and Look AHEAD. Moreover, older individuals have been shown to attend more treatment sessions and adhere better to both the diet and physical activity recommendations [44]. In contrast, young adults have been shown to drop out of treatment more frequently and to achieve poorer outcomes [45]. However, not all older individuals will be successful and vice versa.

Behavioral weight loss programs have also reported ethnic differences in outcomes; initially, African Americans lose less weight than whites in these trials [46], but when followed long-term, there are no differences in outcomes by ethnicity [44].

Although behavioral programs are often recommended for those who are moderately obese, more intensive approaches, involving pharmacotherapy or surgery, are suggested for heavier patients. However, severely obese patients actually do quite well in behavioral programs. Using data from Look AHEAD [47], Unick and colleagues reported that severely obese participants in the lifestyle intervention group lost as much or more weight than others who were less overweight and had similar changes in CVD risk factors through 4 years.

Psychological factors at baseline, for example depression, binge eating, and emotional eating have been inconsistent predictors of outcome. In the largest study to address this, Look AHEAD found no effect of Beck Depression Scores on weight loss or maintenance, but the mean levels of BDI scores in this trial was quite low [40]. In clinical settings, both depression and binge eating have been related to poorer weight loss outcomes [48]. Participants who report eating in response to negative emotions have been shown to perform less well in some studies when treated with standard behavioral weight loss [9] and may be particularly appropriate for intervention strategies including Acceptance and Commitment Therapy [49].

The strongest predictor of outcome in a behavioral weight loss program is the success during the initial weeks of the intervention [43]. Several studies have shown that those who lose the most weight during the intensive phase of the intervention are far more likely to be successful long-term compared to those who perform less well initially. For example, in DPP, comparisons of those who did or did not achieve the 7 % weight loss goal at the end of the initial 6 months showed that those who were initially successful were three times more likely to also achieve this goal at the end of the study (3.2 years) [28]. The same can be shown with even earlier weight loss; weight loss in the first month of the program predicts outcomes over the entire program [50]. This information should be used clinically to determine whether to provide rescue efforts to those who are doing poorly after 4 weeks or to consider referring these individuals to alternative treatment approaches.

The variable that is most consistently related to long-term outcome in behavioral weight loss programs is physical activity. Jakicic [51, 52] has conducted several retrospective analyses showing that women in behavioral weight loss

programs who report greater than 200 min of physical activity at 6, 12, and 18 months have better long-term outcome than those reporting lower levels of activity. Physical activity is important for increasing caloric expenditure, but may also facilitate weight loss through psychological mechanisms and direct effects on hunger and intake.

Maintenance of Weight Loss

The biggest problem in the treatment of obesity at this time is the problem of long-term maintenance of weight loss. As seen in the weight loss graph from Look AHEAD (Fig. 13.2), participants in intensive lifestyle programs tend to gradually regain their weight over time. To address this concern, researchers have conducted both observational studies of successful weight losers and randomized trials evaluating specific maintenance strategies.

The largest study of successful weight loss maintainers is the National Weight Control Registry (NWCR) [53]. Currently the registry has over 10,000 members, all of whom lost >30 lbs (mean = 30 kg) and have kept it off >1 year (mean = 5 years). In a number of publications, the NWCR members were noted to continue to consume a low calorie, low fat diet, maintain high levels of physical activity, and remain vigilant about their diet, exercise, and weight [53, 54]. Approximately 36 % of these individuals report weighing themselves every day and an additional 42 % report weighing at least once per week [12]. The majority eat breakfast every day and watch very little television [55, 56].

Recently, data were reported for almost 2,900 Registry members who had reached 10 years of follow-up as members [57]. These members reported losing 31.3 kg initially. On average, they had kept off 23.8 kg at 5 years and 23.1 kg at 10 years. Weight regain was curvilinear, with the greatest weight regain during the initial year of follow-up and decreasing each subsequent year. Eighty-seven percent were still maintaining at least 10 % weight loss at year 10. The magnitude of weight regain was greater in those who at entry into the NWCR had lost the most weight and in those with shorter duration of maintenance. Keeping weight off for at least 2 years was related to better long-term success. In addition, weight regain was strongly associated with decreased adherence to the behaviors associated with successful weight loss maintenance. Those who had decreases in physical activity, restraint, and self-weighing frequency or increases in dietary intake of fat or disinhibition regained more weight than those who maintained these behaviors. The best maintenance was seen in those who maintained all of these behaviors, and failure to maintain each of the other behaviors contributed additional to the amount regained.

Findings from the NWCR were used as the basis for a randomized trial testing the efficacy of these strategies to individuals who had recently lost weight as a means of helping them maintain their weight loss. Wing et al. [58] randomly assigned 314 individuals who had lost at least 10 % within the past 2 years to either a newsletter control group, or to a face-to-face or Internet intervention condition. The two interventions were identical in content, and differed only in the delivery system. Both interventions taught participants to self-regulate their behavior by weighing themselves daily and using the weight information to determine if changes in diet and physical activity were needed. This study found that both intervention groups were less likely than the control group to regain >5 lbs over 18 months, but only the face-to-face group differed from the control group in the absolute magnitude of weight regain. In addition, decreases in physical activity and increases in depressive symptoms, disinhibition, and hunger were related to weight regain in all groups [59]. In contrast, increased frequency of self-weighing was protective only in the two intervention groups, which had been taught how to use the information from the scale to self-regulate eating and activity behaviors.

Individual trials and a meta-analysis have provided strong evidence that continuing to see participants over the long-term is critical for

successful weight loss maintenance [60]. Other randomized trials have shown that social support [26] and financial contingencies based on group performance [61] can improve weight loss maintenance. Recently, there has been evidence that adding variety to a maintenance program may improve long-term results [62].

Dissemination

Lifestyle interventions, with regular face-to-face group or individual sessions, are expensive to implement and time-consuming for participants. Therefore, efforts have been made to provide these approaches in more cost-effective formats. Several studies have suggested that providing behavioral weight control via regular phone calls is very effective for treatment and maintenance [63, 64]. Delivering the program via the internet has also been successful [65]. The best weight losses in internet programs are seen when the components of standard behavioral approaches are delivered via the internet. For example, a key component is for participants to have goals for their weight, eating and activity, and to self-monitor these behaviors, and submit these data at least weekly. Feedback on the extent to which the goals were accomplished is a critical component, but this feedback can be provided either by live therapists or even through automated feedback [66]. Given the prevalence of obesity, it is important to continue to develop treatment approaches that can be implemented cost-effectively.

Conclusion

This chapter has highlighted the progress that has been made in the behavioral treatment of obesity. With current programs, participants can be expected to lose approximately 7–10 % of their body weight at 1-year, which has an important health impact. The challenge for the field lies in the development of strategies to improve the maintenance of weight loss and to extend the reach of behavioral treatments.

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Dietary Modification as a Weight Management Strategy

14

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Introduction

Dietary prescriptions for weight management alter the energy intake side of the energy balance equation. During weight loss, the goal of all dietary prescriptions is to reduce energy intake so that a meaningful energy deficit occurs, allowing a rate of weight loss that is clinically significant. In addition to assisting with reducing energy intake, the ideal dietary prescription for obesity treatment should also improve the cardiometabolic profile, enrich diet quality, and enhance appetite regulation. While weight loss itself greatly improves glucose and lipid parameters, a dietary prescription can also enhance these physiological outcomes, and ideally a dietary prescription for obesity treatment can augment cardiometabolic outcomes beyond what is achieved with weight loss alone [1]. For enriching diet quality, the prescription should assist with meeting recommendations that are provided in the *Dietary Guidelines for Americans, 2010* [2]. Finally, as long-term adherence to a dietary prescription continues to be a challenge, especially during weight loss maintenance, a prescription that can enhance satiation and/or satiety and minimize hunger, either through physiological or cognitive factors, could increase the ease of continuing the prescription over an extended period of time [3].

The purpose of this chapter is to provide an overview of dietary prescriptions that have been investigated for obesity treatment in adults. Only studies examining dietary prescriptions within randomized controlled trials (RCTs) for weight loss of at least 3 months in length, with participants randomized to receive the same diet throughout the length of the trial, are included. This chapter reviews research on different dietary prescriptions by organizing the prescriptions into three main categories: energy-focused prescriptions, macronutrient-focused prescriptions, and dietary pattern-focused prescriptions. Additionally, factors that have been investigated in relation to energy-focused prescriptions, such as meal replacements and consumption patterning (i.e., frequency and timing of consumption) are examined. Outcomes for weight loss, as well as cardiometabolic parameters, diet quality, and appetite regulation, if available, are reported.

Energy-Focused Prescriptions

Energy-focused dietary prescriptions for obesity treatment are based upon the concept of thermodynamics, such that when a negative energy

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deficit of 3,500 kilocalories (kcal) occurs, approximately 1 pound (lb.) of weight is lost [4]. Energy-focused prescriptions generally function under the assumption that the magnitude of the effect of the diet on achieving a negative energy balance is independent of the composition of the diet; however, recent research does suggest that composition of the diet may influence the degree of negative energy balance achieved via differences in energy expenditure [5, 6]. Due to its focus on energy, dietary goals in these types of prescriptions always include a daily energy limit, but may also include other dietary goals that are believed to be helpful in reducing energy intake.

Low-Calorie Diet

A low-calorie diet (LCD) is usually greater than 800 kcal per day, and typically ranges from 1,200 to 1,600 kcal per day [7]. The LCD is designed to induce an energy deficit of 500 to 1,000 kcal per day, producing a weight loss of 1–2 lb. per week [7]. An LCD is most commonly prescribed using a traditional food regime [7, 8]. Fat restriction may be combined with an LCD to assist with reducing energy intake [8]. In 1998, the National Heart, Lung, and Blood Institute (NHLBI) published evidence-based clinical guidelines for the treatment of adult obesity [9]. These guidelines recommend an LCD, with energy prescriptions of 1,000–1,200 kcal per day for women and 1,200–1,500 kcal per day for men. The NHLBI guidelines also recommend restricting fat intake to no more than 30 % of daily energy intake, with the restriction designed to assist with reducing energy intake, thereby aiding with meeting the reduced-energy goal.

The Diabetes Prevention Program (DPP) provides an example of weight, cardiometabolic, and dietary outcomes commonly found when an LCD with fat restriction is prescribed [10]. Within the DPP, overweight and obese individuals with elevated fasting glucose levels who were randomly assigned to the lifestyle intervention condition received an LCD (ranging from 1,200 to 1,800 kcal per day depending on initial body weight), with a fat restriction of 25 % energy from fat. This intervention also included a moderate- to vigorous-intensity physical activity goal of 150 min per week, and provided a behavioral intervention to assist with changing dietary and physical activity behaviors to aid with achieving a weight loss goal of 7 % of initial body weight. The other two conditions that participants were randomized to were a medication (metformin) or placebo intervention. In DPP, participants were followed for an average of 2.8 years, and in the lifestyle intervention, the mean weight loss was −5.6 kilograms (kg), which was significantly greater than the two other conditions, medication, or placebo, that had not been prescribed the LCD. The pattern of weight loss and maintenance of weight loss seen in the lifestyle intervention showed the greatest degree of weight loss occurring at 6 months (approximately −7.0 kg), which was maintained for another 6 months, with weight regain occurring over longer follow-up. However, at 4-year follow-up, the lifestyle intervention still maintained a weight loss of almost −4.0 kg.

For cardiometabolic outcomes, fasting glucose and glycosylated hemoglobin (HbA_1) significantly decreased more so in the lifestyle intervention as compared to the medication and placebo intervention [10]. Over the mean 2.8-year follow-up, the lifestyle intervention showed a significantly reduced prevalence of hypertension and dyslipidemia as compared to the medication and placebo interventions. Additionally, significantly fewer lifestyle participants required medication for treatment of elevated triglycerides or high levels of low-density lipoprotein (LDL)-cholesterol than the other conditions. However, as weight loss alone enhances cardiovascular outcomes and the lifestyle intervention had the greatest weight loss, it is not clear if the enhanced cardiovascular outcomes found in the lifestyle intervention are a consequence of the LCD or other factors, such as greater weight loss, found within the lifestyle intervention.

Analyses of 1-year changes in dietary intake showed that the lifestyle intervention had significantly greater reductions of energy (−452 kcal per day) and percent energy from fat (−6.6 %) intake than the medication and placebo interventions [11].

Additionally, the lifestyle intervention showed significantly greater increases in intake of dietary fiber and weekly intake of servings from fruits and significantly greater reductions in weekly intake of servings from red meat and sweets than the other two conditions [11].

Meal Replacements

Meal replacements are portion-controlled products, usually liquid shakes and bars, containing a known amount of energy and macronutrient content, that are considered to be a useful strategy to reduce problematic food choices and decrease challenges with meal planning when engaging in an LCD [8]. Additionally, as adherence to any dietary prescription requires consuming foods of an appropriate portion size, meal replacements may enhance dietary adherence since they reduce the burden of weighing and measuring all foods consumed due to their portion-controlled quality [7, 12–15]. The most commonly investigated dietary prescription that has been examined with meal replacements is a partial meal replacement (PMR) plan, which prescribes two portioned-controlled, vitamin/mineral fortified meal replacements per day, with a reduced calorie meal and snack comprised of conventional foods [7, 16].

For weight loss outcomes, a meta-analysis of the effect of meal replacements in comparison to an isocaloric LCD composed of conventional foods found that at the 3- and 12-month follow-up, the meal replacement conditions produced more than 2 kg of greater weight loss, which was significant, than the comparison conditions [7]. The Look AHEAD (Action for Health in Diabetes) trial, which was designed to investigate the impact of a lifestyle intervention that produces a minimum weight loss of 7 % on cardiovascular disease morbidity and mortality in individuals with type 2 diabetes, also prescribed a PMR plan in the lifestyle intervention [16]. The lifestyle intervention lost significantly more percent body weight than a support and education control condition at 1-year (−8.6 ± 6.9 % vs. 0.7 ± 4.8 %, $p < 0.001$) [17]. One-year outcomes also found that the number of meal replacements consumed for the year was associated with weight loss at 52 weeks ($r = 0.30$, $p < 0.001$), and participants in the highest quartile for meal replacement use had four times greater odds of reaching the 7 % weight loss goal [18].

For cardiometabolic outcomes, the PMR plan shows improvements in glucose, cholesterol, and triglycerides, but improvements are not greater than those seen with isocaloric diets composed of conventional foods [7]. Little research has been conducted examining the impact a PMR plan has on diet quality. One RCT did compare a PMR plan to an isocaloric plan using conventional foods and found similar dietary outcomes between the two conditions. The only difference between the conditions was in regard to micronutrient intake, with the PMR plan having a significantly greater intake [19].

Pattern of Consumption

Within an LCD, differing patterns of when energy is consumed have been examined in two RCTs. One pattern of consumption that has been examined is eating frequency. The amount of energy consumed can be spread out into a few meals per day, or into multiple smaller meals and snacks per day. Only one, small, 6-month RCT has examined the influence of eating frequency on weight loss within an LCD, in which participants were randomized into a condition in which participants consumed three meals per day or into a grazing condition in which participants consumed three meals and approximately three snacks per day [20]. While significant reductions in body mass index (BMI) occurred, there were no differences between the conditions. However, self-reported hunger significantly decreased in the condition with more frequent eating bouts, but hunger did not change in the condition consuming only three meals.

The effects of meal timing on weight loss have also been examined in one, 12-week RCT [21]. In this investigation, a prescription of 1,400 kcal per day was spread into three meals, with participants randomized into conditions in which either 1,200 or 700 kcal were consumed by the completion of lunch. The remaining 200 or 700 kcal were consumed at dinner. Results found the condition that consumed more energy earlier in the day lost significantly more weight

(−8.7 ± 1.4 kg vs. −3.6 ± 1.5 kg, $p < 0.0001$). Significantly, greater reductions in triglycerides, cholesterol, and glucose, and increases in high-density lipoprotein (HDL)-cholesterol occurred in the condition that consumed more energy earlier in the day. However, it is not clear if the difference between the conditions on cardiometabolic outcomes is due to the timing of energy intake or the difference in achieved weight loss. Self-reported hunger was also significantly lower in the condition that consumed the majority of their energy intake earlier, rather than later, in the day.

Very-Low-Calorie Diet

A very-low-calorie diet (VLCD) provides ≤800 kcal per day [8, 22, 23]. VLCDs were developed to enhance weight loss by creating a greater energy deficit than what occurs with the LCD. The VLCD is designed to preserve lean body mass, thus large amounts of dietary protein, usually 70–100 grams (g) per day or 0.8–1.5 g protein per kg of ideal body weight, are prescribed [8, 22]. One recommended source of protein for VLCDs is from a milk-, soy-, or egg-based powder, which is mixed with water and consumed as a beverage [22]. These powders also include 100 % of the recommended daily allowance for essential vitamins and minerals [8, 22]. Another recommended source of protein is from lean meat, fish, and fowl, and this form of VLCD is called a protein-sparing modified fast, which must be supplemented with a multivitamin and 2–3 g per day of potassium [22]. VLCDs require consumption of 2 liters (L) per day of noncaloric fluids [22]. VLCDs are considered to be appropriate only for those with a BMI ≥ 30 kg/m^2, and are increasingly used with individuals prior to having bariatric surgery to reduce overall surgical risks in those with severe obesity [8, 22].

One meta-analysis compared VLCDs to LCDs and examined short-term (varied from 8 to 50 weeks) and long-term (varied from 18 to 66 months) weight loss outcomes [22]. Results indicated that in the short-term, weight loss favored the VLCD (−16.1 ± 1.6 % vs. −9.7 ± 2.4 % of initial weight; $p < 0.001$), but long-term outcomes were similar between the two diets (−6.3 ± 3.2 % vs. −5.0 ± 4.0 % of initial weight; $p > 0.2$). The lack of difference between the two diets during the longer-term follow-up was due to greater weight regain occurring in the VLCD conditions. Thus, this meta-analysis suggests that in the long term, the VLCD does not enhance weight loss outcomes as compared to diets of higher energy prescriptions (LCD).

Improvements in glycemic control and blood lipids are also found with VLCDs; however, the degree of improvement appears to be a function of the amount of weight loss rather than any particular factor of the diet [22, 23]. Research on the effect of VLCDs on appetite regulation is very limited, with most research focused on the effect of VLCDs on binge eating, particularly in those with Binge Eating Disorder, and reported outcomes are mixed [23].

Summary of Energy-Focused Prescriptions

Energy-focused dietary prescriptions are successful at producing weight loss and improving cardiometabolic outcomes. Within these types of weight management dietary prescriptions, the improvements in cardiometabolic outcomes appear to mostly be a function of the degree of weight loss achieved, rather than any specific component of the dietary prescriptions. Those prescriptions that are better able to lower energy intake, such as the PMR plan and VLCDs, produce greater weight loss; however, the maintenance of the weight loss becomes more challenging if the degree of energy restriction is such that it cannot be maintained or is not designed to be maintained (VLCDs). Intervention research in the area of the pattern of consumption of energy is beginning to suggest that the frequency of eating bouts and when the greatest amount of energy is consumed during the day may be important in improving weight loss outcomes, but more research is needed in the area.

Very little research has examined changes in overall diet quality in energy-focused dietary prescriptions, but research that has been conducted

shows that besides decreases in energy intake, reductions in fat (especially if this was part of the dietary prescription), red meat, and sweets intake; and increases in fruit and micronutrient (particularly with PMR plans) intake are found with these energy-focused dietary prescriptions. Research is lacking regarding the various energy-focused dietary prescriptions differing abilities to enhance appetite regulation.

Macronutrient-Focused Prescriptions

In addition to energy-focused dietary prescriptions, dietary prescriptions that alter macronutrient composition of the diet can promote weight loss. While an LCD often reduces fat to assist with reducing energy intake so that the energy goal can be more easily met, other macronutrient-focused dietary prescriptions that alter carbohydrate and protein intake were developed to induce ketosis and/or improve appetite control to assist with weight loss [24, 25]. These macronutrient-focused dietary prescriptions Emphasize reducing the amount of carbohydrate consumed without a specific energy restriction, or increasing the proportion of protein consumed within an energy-restricted diet. Furthermore, diets that focus on carbohydrate intake may alter the type of carbohydrate eaten by accentuating a reduction in glycemic index or load consumed.

Low-Carbohydrate Diet

A low-carbohydrate diet does not have a standard definition; however, most interventions define a low-carbohydrate diet as consuming no more than 20 g of carbohydrate per day [26–28]. In low-carbohydrate diets, energy is not restricted, yet research has found that energy intake does decrease when a low-carbohydrate diet is prescribed [29]. This reduction in energy intake, rather than ketosis as initially theorized [24], is the hypothesized mechanism by which a low-carbohydrate diet produces weight loss [30, 31]. A low-carbohydrate diet recommends consumption of conventional foods high in protein and fat, with a focus on consuming mono- and polyunsaturated fats [24]. Carbohydrates are to be consumed from non-starchy vegetables [26]. Once a desired weight is achieved, carbohydrate intake may gradually increase (5 g per day of carbohydrate per week), primarily in the form of vegetables, limited fruits, and eventually small amounts of whole grains and dairy products, to 50 g of carbohydrate per day [24].

A systematic review of RCTs examining the effect of low-carbohydrate diets on weight loss found that low-carbohydrate diets reduced body weight over a >3-month time period when compared to corresponding baseline values [32]. For more long-term outcomes, a meta-analysis examining the effect of low-carbohydrate and energy-restricted, low-fat diets on weight loss found the low-carbohydrate diet produced a significantly greater weight loss at 6 months (−4.3 kg; −5.6 to −3.0 kg, 95 % confidence interval), but not at 12 months (−1.0 kg; −3.5 to 1.5 kg, 95 % confidence interval) [33]. Finally, a 2-year trial also found that weight loss was not significantly different between a low-carbohydrate diet and an energy-restricted, low-fat diet (low-carbohydrate = −6.3 kg [−8.1 to −4.6 kg, 95 % confidence interval]; energy-restricted, low-fat = −7.4 kg [−9.1 to −5.6 kg, 95 % confidence interval]) [34]. Thus, weight loss appears to be greater in low-carbohydrate diets in the short term (<6 months), however over the long term (>12 months), weight loss appears to be comparable between a low-carbohydrate and an energy-restricted, low-fat diet.

For cardiometabolic outcomes, the results of one meta-analysis found that low-carbohydrate diets positively impact HDL-cholesterol and triglycerides, but negatively impact total cholesterol and LDL-cholesterol as compared to energy-restricted, low-fat diets at 6 months [33]. Little research has evaluated overall diet quality of a low-carbohydrate diet prescription. However, the carbohydrate goal in these diets does mean that intake of grains, fruit, starchy vegetables, and dairy is low. Research on the impact of a low-carbohydrate diet on appetite regulation is limited. A secondary data analysis of a 2-year RCT assessing appetite found that individuals

who consumed a low-carbohydrate diet reported being less bothered or distracted by hunger than those on an energy-restricted, low-fat diet [27].

Low Glycemic Index/Load Diet

Within carbohydrate-focused dietary prescriptions for weight loss, low glycemic index, or low glycemic load diets have been examined. Glycemic index is a postprandial measure used to gauge the impact of a certain amount of carbohydrate from a specific food source on blood glucose levels as compared to a reference food, such as white bread or glucose, with the same amount of carbohydrate from each food compared [35]. Thus, a carbohydrate-based food with a high glycemic index will raise blood glucose more quickly and to a higher level than a carbohydrate-based food of low glycemic index [36]. While the glycemic index does not take into account the amount of carbohydrate actually consumed, glycemic load does, and is calculated as the product of the glycemic index of the food multiplied by the grams of the available carbohydrate in the food divided by 100 [37]. A standard dietary prescription for a low glycemic index or load diet does not exist. To alter the glycemic index of the diet, foods are defined as being low or high in glycemic index based on specific cut-offs, and for a low glycemic index diet, low glycemic index foods are encouraged to be eaten instead of higher glycemic index foods. It has been theorized that consuming foods low in glycemic index or reducing the glycemic load of the diet may improve appetite regulation via enhancing glycemic control and this may augment weight loss [38–40].

The effectiveness of an ad libitum low glycemic index diet on weight loss is fairly poor [41]. Moreover, within an energy-restricted diet, several studies have failed to find significant differences in weight loss between energy-restricted, low glycemic index diets as compared to energy-restricted, high glycemic index diets [42, 43]. Furthermore, an energy-restricted, low glycemic load diet did not produce significantly different weight loss outcomes when compared to an energy-restricted, low-fat diet [44]. These findings suggest that consuming a diet low in glycemic index does not enhance weight loss as compared to other diets.

Cardiometabolic outcomes appear to be minimally improved by a low glycemic diet. Glycemic control at 40 weeks measured by changes in HbA_{1c}, appeared to be significantly greater in an energy-restricted, low glycemic diet compared to an energy-restricted, low-fat diet (low glycemic: -0.8 ± 1.3 %; low-fat: -0.1 ± 1.2 %; $p = 0.01$) [44]. Significant differences in fasting glucose, insulin, HOMA-IR, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and high-sensitivity C-reactive protein were not found. Further, an energy-restricted, low glycemic index or load diet does not improve cardiometabolic outcomes when compared to a high glycemic index or load diet [42, 43]. While feeding studies have shown mixed results regarding the impact of a low glycemic index or load diets on appetite regulation [45, 46], RCTs have not adequately tested how reducing the glycemic index or load diet effects satiation, especially when energy intake is reduced.

High-Protein Diet

A high-protein diet is defined as consuming 20–30 % energy from protein [47]. For weight loss, high-protein diets also include an energy restriction. Consumption of a high-protein diet is believed to enhance weight loss due to two mechanisms: increasing dietary-induced thermogenesis [48, 49] and enhancing satiation [47, 50, 51]. Greater dietary-induced thermogenesis boosts overall energy expenditure, which could increase the degree of energy deficit incurred, assisting with weight loss. The enhanced satiation experienced with a diet high in protein may assist with appetite regulation, increasing adherence to a diet that is reduced in energy content [25]. A high-protein diet can be achieved through consumption of conventional foods, particularly meats, dairy, eggs, beans, and nuts; however, high-protein, portion-controlled liquid, and solid meal replacement products are available that may enhance dietary adherence to an energy-restricted, high-protein dietary prescription.

For weight loss outcomes, a meta-analysis compared energy-restricted, high-protein diets (mean percent energy from protein: 30.5 ± 2.4 %) to energy-restricted, standard protein diets (mean percent energy from protein: 17.5 ± 1.5 %) [52]. A subgroup analysis that only included studies with a duration ≥12 weeks found weight loss was not significantly greater in energy-restricted, high-protein diets compared to energy-restricted, standard protein diets (weighted mean difference = −0.49; −1.34 to 0.37, 95 % confidence interval).

A completers analysis from a 52-week RCT found that an energy-restricted, high-protein, low-fat diet had similar increases in HDL-cholesterol, and reductions in total cholesterol, LDL-cholesterol, triglycerides, glucose, insulin, blood pressure, and C-reactive protein as compared to an energy-restricted, high-carbohydrate, low-fat diet [53]. As weight loss was not significantly different between conditions and both groups lost significant weight over time, weight loss may be the contributor to improvements in these cardiometabolic measures.

While associations have been found between high-protein diets and satiation, RCTs investigating the impact of energy-restricted, high-protein diets on satiation are limited. One 12-week trial investigated the impact of an energy-restricted, high-protein diet (30 % energy from protein) vs. an energy-restricted, normal protein diet (18 % energy from protein) on weight loss and appetite [54]. Appetite sensations, specifically hunger, fullness, and desire to eat, were not significantly different between groups.

Diets of Varying Macronutrient Composition

To better understand the impact of differing macronutrient alternations on weight loss, Sacks and colleagues [55] conducted a 2-year RCT with 811 overweight adults, who were randomized to one of four energy-restricted diets: low-fat, average-protein (20 % energy from fat, 15 % energy from protein, 65 % energy from carbohydrate); low-fat, high-protein (20 % energy from fat, 25 % energy from protein, 55 % energy from carbohydrate); high-fat, average-protein (40 % energy from fat, 15 % energy from protein, 45 % energy from carbohydrate); or high-fat, high-protein (40 % energy from fat, 25 % energy from protein, 35 % energy from carbohydrate). Weight loss at 2 years was not significantly different between participants assigned to a 25 % energy from protein diet or 15 % energy from protein diet (25 % protein: −3.6 kg vs. 15 % protein: −3.0 kg) or participants assigned to a 40 % energy from fat diet or 20 % energy from fat diet (40 % fat: −3.3 kg vs. 20 % fat: −3.3 kg). Additionally, percent energy from carbohydrate was found to have no effect on weight loss indicating energy restriction may be the single most important contributor to weight loss.

At 2 years, all four diets improved the cardiometabolic profile as compared to baseline. However, the two low-fat diets and the highest-carbohydrate diet decreased LDL-cholesterol levels more so than the high-fat diets or the lowest-carbohydrate diet (low-fat vs. high-fat, −5 % vs. −1 %, $p < 0.01$; highest-carbohydrate vs. lowest-carbohydrate, −6 % vs. −1 %, $p < 0.05$). The lowest-carbohydrate diet increased HDL-cholesterol levels more than the highest-carbohydrate diet (9 % vs. 6 %, $p < 0.05$). While triglyceride levels significantly decreased, there was no difference between the diets in the amount of decrease. Self-reported hunger and fullness were similar between the diets at 2 years.

Summary of Macronutrient-Focused Prescriptions

Research suggests that no specific macronutrient composition appears to augment weight loss, but rather the degree of energy reduction may be the most important dietary factor for weight loss [28, 55–57]. While there does not appear to be a specific macronutrient-focused dietary prescription to enhance weight loss [55], cardiometabolic outcomes do differ with differing macronutrient prescriptions, though improvements may be due to weight loss. Improvements in HDL-cholesterol are most pronounced in low-carbohydrate diets, while total cholesterol and LDL-cholesterol have

greater improvements in high-carbohydrate and low-fat diets.

Information about overall diet quality of macronutrient-focused diets for weight loss is severely limited and needs further investigation. Research on the role of macronutrient-focused dietary prescriptions on appetite regulation does not show that one type of diet more greatly increases satiation or satiety within the context of RCTs.

Dietary Pattern-Focused Prescriptions

Dietary pattern-focused prescriptions emphasize the cumulative effects of the overall diet by providing recommendations about types of foods to consume, rather than providing goals focused on the large nutrients, such as energy or macronutrients, to consume [2, 58]. The *Dietary Guidelines for Americans, 2010* strongly promotes adopting an eating pattern that promotes calorie balance, weight management, and reduction of disease risk [2]. While a daily energy limit is not typically included as part of a dietary pattern-focused prescription, specific dietary goals for types of food to consume are provided to enhance diet quality and assist with reducing energy intake.

Dietary Approaches to Stop Hypertension

Dietary Approaches to Stop Hypertension (DASH) is an eating pattern that was originally developed to help reduce hypertension in individuals with moderate to high blood pressure. Today, the DASH eating pattern has been accepted as a non-pharmacological treatment for hypertension by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [59]. DASH encourages the consumption of fruits, vegetables, whole grains, nuts, legumes, seeds, low-fat dairy products, and lean meats and limits consumption of sodium, in addition to caffeinated and alcoholic beverages [60]. Specifically the DASH diet recommends 9–12 servings per day of fruits and vegetables, 2–3 servings per day of low-fat dairy products, and <25 % energy from fat [61]. Overall the goal of the DASH eating pattern is to consume foods that are lower in total fat, saturated fat, and cholesterol, but provide good sources of potassium, magnesium, and dietary fiber. A daily energy limit is not a component of the original DASH diet.

For weight loss, the DASH eating pattern alone does not appear to induce weight loss [62, 63]. However, two large RCTs demonstrated an energy-restricted DASH eating pattern significantly reduces weight compared to a usual diet control [62] and advice only [63] conditions. Further, weight loss from an energy-restricted DASH eating pattern as compared to a standard energy-restricted, low-fat diet showed a trend toward significance (energy-restricted DASH: -5.8 ± 5.8 kg vs. energy-restricted, low-fat: -4.9 ± 5.5 kg; $p = 0.07$) [63].

While the impact of a DASH eating pattern on systolic blood pressure has been established, its effects on cardiometabolic outcomes have not been as extensively investigated. One investigation examining the effect of an energy-restricted DASH eating pattern on fasting blood glucose found significant decreases as compared to a comparison group with a dietary prescription without an energy restriction. However, it is not clear if the difference in fasting blood glucose between the conditions is a result of the DASH eating pattern or to the greater weight loss incurring due to the energy restriction [64].

An energy-restricted DASH diet may also help with meeting the recommendations that are provided by the Dietary Guidelines [2]. The DASH eating pattern can significantly improve diet quality, specifically increased consumption of fruits and vegetables, and dairy, and reduced consumption of percent energy from total fat and saturated fat [62, 63]. Due to the foods recommended in the DASH diet, this dietary pattern encourages consumption of a low-energy-dense diet. This type of dietary pattern may enhance appetite regulation [65]. However, more research is needed to investigate how an energy-restricted DASH diet impacts appetite during obesity treatment.

Energy Density Pattern-Focused Diet

Dietary Guidelines for Americans, 2010 encourages consumption of an eating pattern low in energy density (ED) to assist with weight management [2]. The focus on ED for weight management is new and has not previously been encouraged in previous versions of the Dietary Guidelines. ED is the ratio of energy of a food to the weight of a food (kcal/g) and is largely determined by water content (higher water content lowers ED), but is also affected by fiber and fat content (more fiber lowers ED and less fat lowers ED) [66]. Thus, foods naturally low in ED are high in water and fiber content and low in fat. Foods with these nutrient qualities include fruits, vegetables, and whole grains. As low-ED foods have fewer kcal per gram weight, low-ED foods allow individuals to eat a greater weight of food relative to energy consumed, which may assist with reducing energy intake [66–68].

Basic eating research has found that serving meals with foods low in ED results in decreased meal energy intake [69]. Importantly, when the effect of meals with low-ED foods on energy intake is examined across several days, compensation to reduced-energy intake does not occur [70]. For example, when served meals with low-ED foods over 2 days, participants consumed approximately the same weight of food as they did when served meals with high-ED foods, but due to the difference in ED, in the condition consisting of meals with low-ED foods, energy intake was approximately 30 % lower over the 2 days, with no increase in consumption in day 2 to compensate for the reduced-energy intake in day 1 [71]. Additionally, in the condition with meals containing low-ED foods that produced reduced-energy intake, participants rated hunger and satiation at equivalent levels as when they were in the condition with meals containing high-ED foods in which greater energy intake occurred [71]. Due to the consistent results found in experimental basic eating studies examining the effect of ED and intake, it has been suggested that ED has a larger effect on energy intake, and potentially appetite, than any one of the macronutrients [66, 72].

However, few RCTs have been conducted to examine the effect of a low-ED diet on weight loss and currently there is no clearly defined way that is known to best reduce ED in the diet [73]. Strategies that have been examined in RCTs to reduce overall dietary ED include, reducing fat intake and increasing consumption of water-rich foods (i.e., fruits and vegetables), increasing consumption of low-ED soups, providing general guidelines about reducing ED in the diet, and increasing intake of low-ED foods and reducing intake of high-ED foods. Within these differing strategies that have been examined to reduce dietary ED, guidelines specific for reducing energy intake may or may not be included. Results from these trials regarding weight loss are mixed, and this may be a consequence of the methods used to reduce dietary ED, the degree of reduction in ED achieved, and the inclusion or not of an energy restriction.

One investigation by Ello-Martin and colleagues tested two methods for reducing ED in the diet, reducing fat intake (RF) or reducing fat intake and increasing water-rich foods (i.e., fruits and vegetables) (RF + FV), and measured weight loss, blood lipids and insulin, dietary intake, and hunger and satiety [74]. Guidelines for reducing energy intake were not included in either intervention. Over the 1-year trial, RF + FV reported a lower dietary ED than RF (1.23 ± 0.02 kcal/g vs. 1.46 ± 0.02 kcal/g, $p < 0.05$). Results indicated that at 1-year, RF + FV lost significantly more weight (−6.4 ± 0.8 kg vs. −4.9 ± 0.8 kg, $p < 0.05$) and had significantly lower non-HDL-cholesterol (143.1 ± 6.9 mg/dL vs. 152.8 ± 6.2 mg/dL, $p < 0.05$) than RF. It is not clear if the difference in non-HDL-cholesterol between the conditions is due to the difference in weight loss or to factors related to dietary intake. While fat intake was not different between the groups, RF + FV consumed significantly more fruits and vegetables and fiber over the 12 months than RF. Self-reported hunger was also significantly different between the conditions, with RF + FV reporting significantly less hunger during the intervention than RF.

Mediterranean-Style Diet

The Mediterranean diet reflects the dietary patterns of Crete, Greece, and southern Italy in the early 1960s [75]. The traditional Mediterranean diet was focused on plant-based foods (e.g., fruits, vegetables, grains, nuts, seeds), minimally processed foods, olive oil as the primary source of fat, dairy products, fish and poultry consumed in low to moderate amounts, zero to four eggs consumed per week, and minimal amount of red meat [76]. Due to the high life expectancy and low rates of chronic disease reported in Crete, Greece, and southern Italy, a Mediterranean-style diet pattern has been proposed as an eating pattern that may be protective against obesity [77].

For studies investigating the impact of a Mediterranean-style dietary pattern on weight loss, there has been inconsistency regarding the inclusion of energy restriction as part of the dietary prescription. However, it does appear that an energy restricted component needs to be combined with the Mediterranean-style diet if weight loss is desired [78–80]. A meta-analysis that examined the effect of the Mediterranean-style diet on weight loss included studies with and without energy restriction and found the effect of Mediterranean-style diet on weight loss was greater in association with energy restriction or increased physical activity [81]. When an energy-restricted, moderate-fat, Mediterranean-style diet was compared to a low-carbohydrate diet and an energy-restricted, low-fat diet, 2-year weight loss outcomes found that the Mediterranean-style diet performed similarly to the low-carbohydrate diet, and both of these prescriptions performed significantly better than the energy-restricted, low-fat diet condition (Mediterranean: -4.4 ± 6.0 kg; low-carbohydrate: -4.7 ± 6.5 kg; low-fat: -2.9 ± 4.2 kg, $p < 0.001$) [80]. These outcomes indicate that an energy-restricted, Mediterranean-style eating pattern may be an effective alternative to a low-carbohydrate or energy-restricted, low-fat diet.

Few studies have examined the impact of an energy-restricted, Mediterranean-style diet on cardiometabolic outcomes during weight loss. While there appears to be beneficial cardiometabolic effects, it is unclear if these effects can be attributed solely to weight loss or if the diet improves outcomes [79, 80]. For example, one RCT found that women randomized to an energy-restricted, Mediterranean-style diet significantly improved glucose, insulin, HOMA, HDL-cholesterol, triglycerides, and C-reactive protein compared to a control group who received information about a healthy diet, but greater weight loss occurred in the group prescribed the energy-restricted, Mediterranean-style diet [79]. An energy-restricted, Mediterranean dietary pattern does promote diet quality (i.e., increased intake of fruits, vegetables).

Summary of Dietary Pattern-Focused Prescriptions

Dietary pattern-focused prescriptions do not appear to enhance weight loss more so than other types of dietary prescriptions for weight loss. Moreover, to produce weight loss, these types of dietary prescriptions may need to include an energy restriction component along with the goals for other types of foods to consume. Cardiometabolic outcomes appear to be related to the degree of weight loss achieved, rather than the changes in food intake, but more research is needed in this area to ascertain if certain dietary pattern-focused prescriptions can improve cardiometabolic parameters beyond that achieved with weight loss. This type of dietary prescription does improve diet quality, and while not tested in comparison to other types of weight loss dietary prescriptions, a dietary pattern-focused prescription may enrich diet quality more so than most other dietary prescriptions for weight loss. Finally, a dietary pattern-focused prescription that lowers energy density may improve appetite regulation.

Conclusion

Research examining different dietary prescriptions for weight loss indicate that the amount of energy reduction that is incurred appears to be the predominant dietary factor that influences weight

loss. Thus, if a dietary prescription does not include a goal regarding energy intake, if the provided dietary goals in a prescription do not automatically reduce energy intake, an additional goal regarding energy restriction may be needed to induce weight loss. While weight loss improves cardiometabolic parameters, differing dietary prescriptions may be able to enhance these improvements. Limited research has examined the independent effect of dietary intake on cardiometabolic outcomes during obesity treatment, in those investigations in which weight loss is similar, improvements in HDL-cholesterol are most pronounced in low-carbohydrate diets, while total cholesterol and LDL-cholesterol have greater improvements in high-carbohydrate and low-fat diets. Dietary pattern-focused prescriptions for weight loss show the most promise for increasing dietary quality. For appetite regulation, a diet that is lower in ED may assist with reducing hunger and improving satiation. To help identify the optimum dietary prescription for obesity treatment, along with measuring weight loss, investigations should consistently evaluate the independent effects of a dietary prescription's ability to enhance cardiometabolic parameters, diet quality, and appetite regulation.

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Physical Activity as a Weight Management Strategy

15

John M. Jakicic and Renee J. Rogers

Introduction

Obesity, physical activity, and poor dietary behaviors have been linked to increased health risks. These health risks include heart disease, diabetes, and various forms of cancer, asthma, arthritis and other musculoskeletal conditions, and overall poorer health status [1, 2]. The healthcare cost of obesity has been estimated to be significant higher when compared to non-overweight and non-obese individuals [3, 4]. This is a significant public health concern because the estimated prevalence of overweight (BMI $\geq$ 25.0 kg/m^2) in the United States is approximately 70 %, with the estimated prevalence of obesity (BMI $\geq$ 30.0 kg/m^2) approximately 35 % [5]. While it has been suggested that the prevalence of obesity in children and adolescents has been stable over the past few years with no substantial increase, it is still estimated that roughly 17 % of children and adolescents are obese [6].

There is a need to develop and implement effective interventions to both prevent and treat overweight and obesity. While medical approaches to the treatment of obesity include bariatric surgical options and potentially pharmacotherapy, the cornerstone of obesity prevention and treatment lies in lifestyle approaches that reduce energy intake (dietary approaches) and increase energy expenditure (physical activity approaches). Of particular importance is the role of physical activity in the treatment of obesity, and the impact that physical activity has on other health-related outcomes. It is important for healthcare providers and health-fitness professionals to understand the influence of physical activity on body weight regulation, along with a clear understanding of the dose of physical activity that can be effective for managing body weight.

Theoretical Pathways for Physical Activity to Influence Body Weight

In the simplest conceptual model, body weight regulation is dependent on the balance between energy intake and energy expenditure. Energy expenditure consists of resting energy expenditure, the thermic effect of feeding, and voluntary physical activity that can be subdivided into occupational, household, lifestyle, or leisure-time physical activity [7]. Of these components of total energy expenditure, voluntary physical activity is the most highly variable. Individuals who are relatively inactive will expend approximately 30 % more calories above what is expended in resting energy expenditure, with this increasing to approximately 50–80 % for individuals participating in moderate or higher levels of voluntary physical activity.

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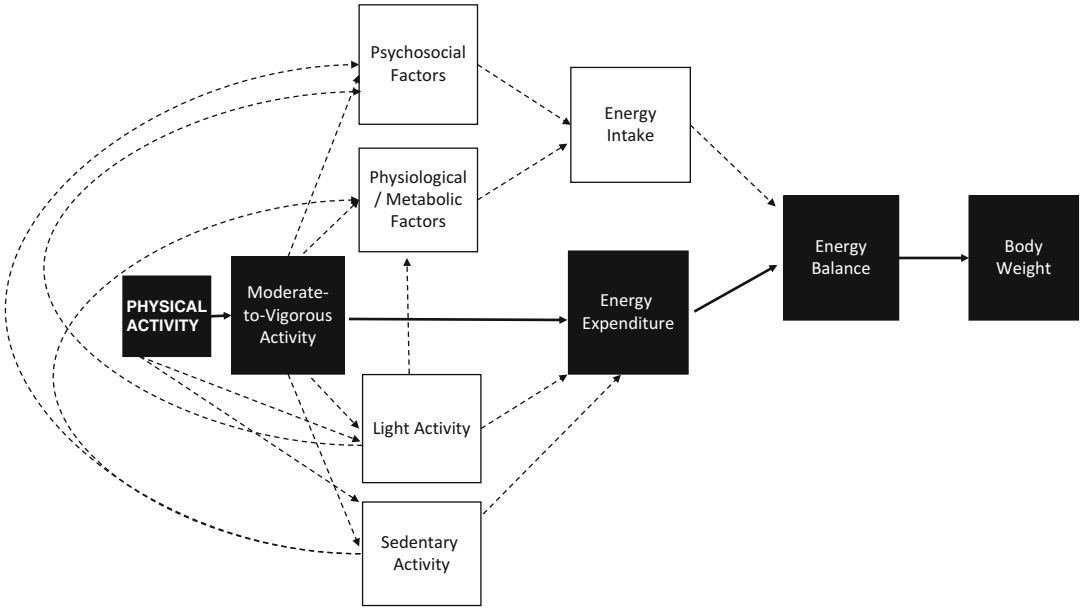

Fig. 15.1 Theoretical pathways for physical activity to influence body weight

Moderate-to-vigorous physical activity (MVPA) has been the most widely examined component of energy expenditure related to body weight regulation and is typically an intervention target. It is widely believe that MVPA primarily influences body weight by increasing total energy expenditure. However, as shown in the conceptual model depicted in Fig. 15.1, there are additional indirect pathways by which MVPA may influence energy expenditure, energy balance, and ultimately body weight.

The Effects of Physical Activity Without Prescribed Reduced Calorie Intake on Weight

Physical activity is a key behavior for treating overweight and obesity [2]. However, weight loss resulting from physical activity when not coupled with a concurrent reduction in energy intake appears to be quite modest. The 2008 Physical Activity Guidelines Advisory Committee Report [8] concluded that 180–270 min/week of physical activity results in a weight loss of approximately 0.5–3.0 kg. This magnitude of weight loss resulting from an increase in physical activity alone is consistent with the conclusions drawn from other systematic literature reviews [9]. In studies of 3–6 months in duration, interventions that have focused exclusively on physical activity have resulted in weight loss of approximately 0.5–2.0 % of initial body weight [10, 11]. Jakicic et al. reported a similar degree of weight loss of approximately 2 % of initial body weight at 6 month and 1 % at 18 months in overweight adults prescribed home-based physical activity [12].

Despite reports of these modest effects of physical activity on weight loss, there may be a dose–response effect, with greater weight loss being achieved with higher doses of physical activity. A recent systematic review of the literature reported that while there does not appear to be a significant change in body weight in response to <150 min/week of physical activity, physical activity of >150 and 225–440 min/week is associated with weight loss of 2.0–3.0 and 5.0–7.5 kg, respectively [13]. A secondary analysis of an 18-month intervention study conducted by Jakicic et al. also found a dose–response relationship [12]. Moreover, it was reported that a higher level of physical activity (approximately

160 min/week above baseline levels) was observed in participants who lost >3 % of their initial weight (mean weight loss of approximately 8 %) compared to those who remained weight stable or gain weight over the 18 months of follow-up [12].

Effects of Physical Activity with Prescribed Reduced Calorie Intake on Weight

Clinical guidelines recommend the inclusion of both dietary modification and physical activity to maximize weight loss [2, 13, 14]. Physical activity adds approximately 0.5–3.0 kg of weight loss to what can be achieved with a dietary intervention alone [2, 9, 13, 15]. For example, over a 6-month intervention, Goodpaster et al. reported a weight loss of 8.2 kg in response to diet alone versus 10.9 kg in response to the combination of diet plus physical activity, a difference of 2.7 kg [15]. A similar pattern has been reported by others [10, 11]. Based on a systematic review, Curioni and Lourenco [16] concluded that there is a 20 % greater weight loss with diet combined with physical activity compared to diet alone.

Physical Activity Predicts Long-Term Weight Loss

Physical activity appears to be an important predictor of improved weight loss in interventions of ≥12 months duration, and close examination of these data suggest that relatively high doses of physical activity improve long-term weight loss outcomes [13]. Wadden et al. [17] report that a mean dose of 287 min/week of physical activity was associated with a mean 1-year weight loss of 11.9 % in the Look AHEAD Study, and physical activity was the strongest correlate of weight loss achieved at 1 year. Unick et al. have also shown MVPA to be the strongest correlate of the ability to achieve a ≥10 % weight loss within the context of an intervention that also include a prescribed reduce calorie diet [18]. Secondary data analysis from another study of obese adults that has shown that followed subjects for an additional 6 months after an initial 6-month weight loss intervention, those individuals who lost weight in response to the intervention increased objectively measured physical activity, represented as MVPA and steps per day, while those who gained weight reduced their levels of physical activity [19]. Furthermore, change in steps per day ($r=-0.29$, $p<0.007$) and minutes of MVPA ($r=-0.27$, $p<0.01$) were inversely correlated with weight change. These findings across studies support the importance of physical activity as an important lifestyle behavior that is associated with improved long-term weight loss and the prevention of weight regain.

There is a growing body of literature suggesting that a relatively high dose of physical activity is associated with improved long-term weight loss and prevention of weight regain following significant weight loss. Jakicic and colleagues have repeatedly shown that ≥250 min/week of MVPA (~2,000–2,500 kcal/week) is associated with the greatest long-term weight loss and prevention of weight regain [20–23]. Results of a randomized trial conducted by Jeffery et al. [24] also demonstrate that prescription of 2,500 kcal/week of physical activity resulted in greater weight loss than prescription of 1,000 kcal/week, when both doses of physical activity were combined with a reduced calorie diet. Tate et al. [25] has also reported that continued engagement in ≥2,500 kcal/week of physical activity is associated with improved long-term weight loss within the context of a comprehensive weight loss intervention program.

Additional evidence supporting the idea that relatively high amounts of physical activity promote long-term weight loss maintenance comes from the National Weight Control Registry, which is an observational study of individuals who have sustained a weight loss of ≥30 lb for at least 1 year. Klem et al. initially characterized this sample ($N=784$) and observed that individuals in this registry were reporting >2,800 kcal/week of physical activity [26]. A follow-up analysis of individuals in this registry ($N=3,683$) conducted by Catenacci et al. confirmed that relatively high levels of physical activity were associated with sustained weight loss [27]. While these findings

were based on self-reported physical activity, a more recent report that objectively measured physical activity supports the hypothesis that participants in the National Weight Control Registry are engaging in more structured period of physical activity (approximately 41 min/day) when compared to normal weight adults (approximately 26 min/day). These results suggest that relatively high amounts of physical activity are needed to sustain weight loss and prevent weight regain. This dose of physical activity is also consistent with the 250–300 min/week of physical activity that is recommended by the American College of Sports Medicine to improve long-term weight loss and to prevent weight regain [13].

Light-Intensity Physical Activity and Weight Change

Unpublished data from a recently conducted study by Dr. Jakicic and colleagues used objective methods to assess physical activity and its association with long-term weight loss [22]. The use of objective measurement of physical activity has allowed for improved understanding of the patterns of physical activity that may be associated with successful weight loss, and allows for the examination of the association between light-intensity physical activity (1.5 to <3.0 metabolic equivalents [METS]) and weight loss. The preliminary findings of this study demonstrate that ~250 min/week of objectively measured MVPA that was accumulated in bouts of ≥10 min was associated with the greatest weight loss averaging ~15 % of initial body weight at 12 and 18 months of the intervention. These findings also show that participants who had the greatest weight loss and the greatest increase in MVPA also had the greatest increase in light-intensity physical activity, suggesting that this may have also contributed to improved weight loss. While not definitive, these preliminary findings suggest that while weight loss interventions should focus primarily on increasing MVPA in overweight and obese adults, recommendations to also increase light-intensity physical activity within the context of one's occupation, household, or other lifestyle activities may also be important to maximize long-term weight loss.

Sedentary Behavior and Weight Change

The inverse of physical activity is sedentary behavior, and there is increasing interest in the role that sedentary behavior plays in both the development and treatment of obesity. A consistent association has been observed between measures of sedentary behavior and increased risk of developing obesity [28]. Ball et al. [29] reported an association between hours of sitting and risk of gaining ≥5 % of initial body weight over a period of 4 years. Using television viewing as a proxy for sedentary behavior, Hu et al. [30] reported that television viewing time was associated with an increased risk of becoming obese over a 6-year period. Moreover, each additional 2 h/day of television viewing was associated with a 23 % increased risk of becoming obese. In contrast, Ekelund et al. reported that sedentary behavior was not predictive of future weight gain and obesity in adults [31]. Thus, additional research is necessary to determine the degree to which sedentary behavior contributes to weight gain and obesity.

Sedentary behavior may be linked to weight gain and the development of obesity due to a number of factors [28]. For example, sedentary behavior may substitute for engagement in other more active behaviors, which results in an overall reduction in energy expenditure. Engagement in sedentary behavior may also be linked to more frequent eating which results in increased energy intake and weight gain. These two factors may also work in combination, resulting in both a decrease in energy expenditure coupled with an increase in energy intake.

Physical Activity May Be Associated with Other Weight Loss Behaviors

In addition to physical activity influencing body weight by increasing energy expenditure, it may also influence body weight indirectly by affecting

energy intake and eating behaviors. Jakicic and colleagues have shown that overweight and obese adults who are compliant with engagement in higher amounts of physical activity also appear to have higher compliance with dietary change [18, 32]. Based on secondary data analysis, change in physical activity was significantly correlated with weight loss ($r=0.33$), reductions in energy intake ($r=0.20$), and improvements in eating behaviors associated with weight loss ($r=0.24$; $p<0.05$). Change in physical activity remained a significant predictor of weight loss after controlling for changes in energy intake and weight loss eating behaviors. These results suggest that physical activity has a direct influence on body weight; however, it may also indirectly affect body weight by influencing energy intake and eating behaviors. Unick et al. has also reported that physical activity was the most significant predictor of the ability of subjects to achieve ≥10 % weight loss, with physical activity outweighing engagement in various dietary behaviors that are associated with weight loss [18]. DeLany et al. [19] found an association between both increased physical activity and lower energy intake with weight change over a 6-month intervention period. These findings suggest that a significant increase in physical activity during a weight loss intervention may be accompanied by a greater reduction in energy intake, which may contribute to the greater magnitude of weight loss. However, it is unclear if physical activity has a direct influence on energy intake or whether physical activity and diet operate as independent lifestyle behaviors for weight loss.

Physical Activity, Psychosocial Factors, and Weight Loss

Unpublished observations from studies conducted in our research laboratory at the University of Pittsburgh have shown that in response to an exercise alone intervention in overweight adults, there is a significant ($p<0.001$) increase in dietary restraint, even when the intervention did not include recommendations for dietary restriction. Moreover, we have been interested in whether the type of dietary restraint, based on subscales of rigid (strict approaches to dietary change) or flexible (moderate approach to dietary change) restraint, is associated with changes in physical activity that may mediate the observed change in body weight over 6–18 months. We examined data from overweight adults (BMI = 27 ± 1.73 kg/m^2; age = 45.5 ± 7.69 years) and found that both total dietary restraint and the flexible dietary restraint subscale partially mediated the relationship between physical activity and change in body weight. We also retrospectively grouped subjects based on having lost >3 % of baseline weight (−7.16 ± 3.43 kg), remaining weight stable defined as within ±3 % of baseline weight (−0.061 ± 1.73 kg), or gaining >3 % of baseline weight (+5.07 ± 2.15 kg) in response to a physical activity only intervention. This analysis showed a significant increase in flexible dietary restraint in those who lost weight in response to a physical activity intervention compared to those who remained weight stable or those who gained weight. However, there were no differences for change in rigid dietary restraint between these three weight change groups in response to physical activity. Thus, it appears that dietary restraint, and in particular flexible dietary restraint, may partially mediate the association between physical activity and weight change in overweight adults. These findings may suggest a pathway by which physical activity affects dietary intake and eating patterns; however, whether this varies by the dose of physical activity is unclear.

It has been shown that positive affect increases in response to acute physical activity, with no change in negative affect [33, 34]. Moreover, when grouped by whether there was an increase or decrease in positive affect in response to physical activity, it was reported that subjects who had an increase in positive affect in response to exercise ate fewer calories when presented with an ad libitum meal compared to subjects who had a decrease in positive affect with physical activity. There was no association between change in negative affect in response to physical activity and calories consumed when presented with an ad libitum meal. Thus, it appears that changes in positive affect in response to physical activity may be associated with energy intake. This may

suggest that physical activity modes and doses that result in an increase in positive affect may be preferred when prescribing physical activity to overweight and obese adults. However, this may need to be based on the individual preferences of the participant.

Physical Activity Considerations in Bariatric Surgery

Bariatric surgery has become a more widely used treatment for overweight and obesity. Bariatric surgery is based on the foundation of reducing energy intake by restricting energy intake and/or reducing nutrient absorption. Bariatric surgery has typically been shown to result in a greater magnitude of weight loss than what is typically observed with traditional nonsurgical procedures that focus on reducing energy intake and increasing energy expenditure through physical activity. However, there appears to be a need for patients who undergo bariatric surgery procedures to also focus on engagement in physical activity to improve long-term weight loss outcomes. Bond et al. [35, 36] showed that physical activity contributed to improved weight loss outcomes at both 1 and 2 years following bariatric surgery. Greater weight loss has also been reported following bariatric surgery in patients who participated in ≥150 min/week compared to those participating lesser amounts of physical activity <150 min/week at both 6 and 12 months post-surgery [37]. These findings suggest that physical activity is an important lifestyle factor that can improve long-term weight loss following bariatric surgery, and therefore should be emphasized by clinicians who treat these patients.

Application to Prescription of Physical Activity for the Obese Adult

The vast majority of the evidence supporting the importance of physical activity in the treatment of obesity is based on modes of activity similar to brisk walking or other aerobic forms of exercise. Thus, in general, prescription of physical activity for overweight and obese adults should follow current physical activity guidelines. These guidelines recommend the progression to at least 150 min/week of moderate-to-vigorous intensity physical activity [8]. However, when necessary to further impact body weight or other comorbidities, overweight and obese adults may need to progress to approximately twice this amount (250–300 min/week) of physical activity [13].

When prescribing physical activity when weight loss is the goal, the focus should be placed on maximizing the energy expenditure, with intensity of the activity playing less of a role. For example, studies have shown that when comparing activities performed at varying intensities with the total energy expenditure the same across activities, the change in body weight has been equal across these conditions [20, 38]. However, there are advantages to prescribing activity at a higher intensity. It has been shown that vigorous intensity exercise results in greater improvement in cardiorespiratory fitness than less intense forms of physical activity [20, 38]. Because of the association between cardiovascular fitness and improved health risks [39–42], prescription of physical activity for obese adults should balance the volume and intensity to elicit significant weight loss and improve cardiorespiratory fitness.

In addition, physical activity guidelines recommend that physical activity be performed bouts that are at least 10 min in duration. In fact, there is evidence to suggest that prescribing physical activity in multiple 10 min bouts each day may be particularly effective for overweight and obese adults. In addition to being effective for improving initial adoption of physical activity [23, 43], engagement in multiple 10 min bouts of daily activity can improve cardiorespiratory fitness [43–45] and may impact selected risk factors [45]. Thus, clinicians and other health-fitness professionals are encouraged to recommend this strategy as a viable alternative to more traditional physical activity prescriptions that include continuous exercise for periods ranging from 20 to 60 min/session. Moreover, the use of pedometers (step counters) that facilitate

adding an additional 2,000 steps per day has been shown to have modest, yet significant, effects on body weight [13].

Alternative Forms of Physical Activity

An alternative form of activity that may be recommended is resistance exercise. This form of exercise may be appealing for the treatment of obesity because of its potential to maintain or increase lean mass, increase total daily energy expenditure, or increase strength that may facilitate engagement in physical activity [13]. However, despite these potential benefits in overweight or obese adults, the majority of the scientific evidence shows only a modest effect of resistance exercise on weight loss [13, 46]. The modest weight loss produced by adding resistance exercise to a weight loss program is not due to the gain in lean mass offsetting the reduction fat mass in the majority of studies [47–50]. In addition, there are limited data from long-term intervention trials [13, 46]. However, rather than affecting total adiposity, resistance exercise may reduce subcutaneous abdominal adiposity [51], which has been shown to impact comorbidities associated with obesity. Thus, rather than prescribing resistance exercise for its effect on total adiposity, it should be considered an important modality for its potential effects on abdominal adiposity and consistent effects on strength gains [52, 53], which may influence physical function of overweight and obesity adults [54]. Thus, consistent with current clinical guidelines, resistance exercise should be prescribed as a component of a comprehensive physical activity program for overweight and obese adults [8, 55].

Overweight and obese adults may have functional limitations that hamper engagement in more traditional weight-bearing forms of physical activity. An alternative, and popular, form of physical activity is yoga because of its potential to improve range of motion and physical function, while reducing pain [56, 57]. Despite these potential benefits, there is insufficient data from well-designed research studies to suggest yoga as a form of physical activity that will reduce body weight. Because of functional limitations, another common physical activity recommendation for overweight and obese adults is to engage in aquatic forms of physical activity. However, data are also lacking to support that aquatic activity is more effective for weight loss than other forms of physical activity [58].

Additional Guidance for Clinicians Prescribing Physical Activity

Additional guidance on a progressive prescription and an intervention model that can be used with overweight and obese adults has previously been published [59]. These guidelines may facilitate the appropriate focus of counseling sessions with a participant and appropriate prescription of physical activity in the initial stages of a weight management and activity program. Moreover, physical activity is relatively safe for many individuals. Clinicians may need to conduct appropriate screening of overweight and obese patients prior to clearing them for physical activity participation. Clinicians are encouraged to refer to pre-participation screening tools and risk stratification guidelines that are recommended by the American College of Sports Medicine [60].

Summary

Overweight or obesity has been linked to significant health risks for numerous chronic conditions. A continuing challenge for healthcare providers and health-fitness professionals is to provide effective interventions to facilitate weight loss and to prevent weight gain in patients for whom weight loss is indicated. It appears that physical activity is an important component of any intervention to promote and sustain weight loss. It is important to acknowledge that physical activity alone will result in modest, yet beneficial, weight loss. However, the combination of physical activity and a prescription to reduce energy intake appears to be the most effective lifestyle treatment for achieving weight loss. More importantly is the consistent finding that

engagement in >250 min/week of MVPA is associated with improved long-term weight loss and potentially prevention of weight regain. This may be a result of this amount of physical activity directly increasing total energy expenditure. However, engagement in this amount of physical activity may also facilitate changes in dietary intake that reduce energy intake, and engagement in more light-intensity physical activity that further increases energy expenditure, resulting in improved long-term weight loss. Therefore, clinicians should encourage patients seeking weight loss to progressively increase engagement in moderate-intensity physical activity to a level that is consistent with >250 min/week. This may require tailoring of these physical activity recommendations to the individual needs and conditions of the patient to enhance both weight control and health-related outcomes in overweight and obese adults.

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Drugs for Weight Loss and Maintenance: Present and Future

16

Magdalena Pasarica and Steven R. Smith

How and When to Choose Obesity Pharmacotherapy

Obesity pharmacotherapy is only one tool in a practitioner's toolkit. In general, pharmacotherapy should only be used as an adjunct to lifestyle intervention and after other approaches have failed or met with less success than desired. There are a few areas where pharmacotherapy may be employed without both diet and physical activity components of lifestyle intervention; specifically, in persons who cannot exercise because of cardiovascular or orthopedic limitations, pharmacotherapy can be employed. Firstly, wheelchair bound persons should not be denied pharmacotherapy because they cannot exercise. Secondly, there is a common notion, unfortunately without strong supporting data, that weight loss might be beneficial to increase mobility and ease of exercise in obese persons. A trial of weight loss pharmacotherapy may be tried with subsequent efforts to increase physical activity after weight is lost. More research is needed in this area. In a similar vein, patients who have poor diets or crave for unhealthy foods may find they are more able to adhere to a diet plan when taking a weight loss medication than without. The larger concept is that weight loss drugs may assist patients in adhering to a lifestyle intervention and lifestyle may help people adhere to a drug. Again, more research is needed in this area.

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Drugs Approved by the FDA for Weight Loss

Phentermine

Phentermine was approved by Food and Drug Administration (FDA) in 1959. It is a modified amphetamine, which was designed to have lower central nervous system stimulation but still maintain the anorectic effects.

Indications

Phentermine is indicated as a short-term adjunct for weight loss management with exercise and caloric restriction in patients with body mass index (BMI) ≥ 30 kg/m^2 or 27 kg/m^2 with at least one weight related comorbidity (e.g. controlled hypertension, diabetes, and hyperlipidemia). Laws vary state to state regarding acceptable duration and extent of treatment and local guidance should be sought before prescribing.

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Mechanism of Action

Phentermine is a sympathomimetic amine with anorectic effects, probably due to the stimulatory effects on hypothalamus to release norepinephrine [1].

Efficacy

Phentermine is currently the most popular drug prescribed and used for weight loss [2]. This is probably due to the low cost, physician experience, efficacy, and a paucity of medical alternatives prior to 2013. The efficacy of Phentermine for weight loss has been evaluated in a meta-analysis of nine randomized controlled trials published between 1975 and 1999 [3] that used Phentermine short term. These studies involved mostly women (more than 80 %) treated with Phentermine for 2–24 weeks in addition to lifestyle modification (more than 80 % of the participants). Overall there was 3.6 kg (CI, 0.6–6.0 kg) additional weight loss compared to placebo in the subjects treated with Phentermine 15–30 mg daily [3]. Due to concerns around tachyphylaxis and the lack of data on long-term safety, Phentermine 30 mg daily was administered either continuously, or intermittent (4 weeks on, 4 weeks off) in a double-blinded placebo-controlled study with healthy overweight and obese subjects treated for 36 weeks in addition to a calorie restriction diet [4]. Munro et al. showed that there was no significant difference in amount of weight loss with intermittent Phentermine vs. continuous Phentermine treatment (13 kg vs. 12.2 kg, respectively), but there was a significant difference compared to placebo group weight loss (4.8 kg) [4] (Fig. 16.1a). A recent retrospective study of patients treated with Phentermine for 12 weeks to 12 years in addition to calorie restricted diet showed that the patients on Phentermine lost significantly more weight compared to the no Phentermine group [5]. Importantly, some patients in the Phentermine group continued to maintain more than 10 % weight loss for as long as 8 years [3]. The latter study is limited by the small number of patients in the long-term follow-up period. As part of the clinical development of Phentermine/Topiramate, Phentermine was studied as a monotherapy [5]. On a background of a lifestyle intervention (weight loss of 4.1 ± 7.5 kg), Phentermine produced greater weight loss (10.2 ± 6.9 kg) over 156 weeks [5].

Side Effects/Tolerability

Like all sympathomimetic amines, Phentermine has been reported to have cardiovascular side effects (palpitations, tachycardia, elevated blood pressure, ischemic events); central nervous system side effects (overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis); gastrointestinal side effects (dryness of mouth, unpleasant taste, diarrhea, constipation); allergic side effects such as urticaria; and endocrine side effects including impotence and changes in libido. Valvular heart disease and primary pulmonary hypertension have been reported in only rare cases of patients taking Phentermine alone [1] (Table 16.1). These cases probably represent the background of cardiac valvulopathy in the general population as several studies have not found evidence for valvular heart disease or primary pulmonary hypertension in patients using Phentermine as monotherapy [3, 5].

Contraindications

Phentermine is contraindicated in patients with a history of cardiovascular disease (defined as uncontrolled hypertension, stroke, arrhythmia, coronary artery disease, heart failure), during or within 14 days of treatment with monoamine oxidase inhibitor, in hyperthyroidism, in glaucoma, in agitated states, with a history of drug abuse, in pregnancy, during nursing or with known idiosyncratic reactions to the sympathomimetic amines [1].

Drug Interaction

The concomitant use of Phentermine should be avoided with: monoamine oxidase inhibitors, alcohol, and adrenergic neuron blocking drugs [1].

Monitoring

Blood sugar should be monitored carefully in patients with diabetes, particularly during the initiation of therapy so that insulin and oral glucose lowering medications can be adjusted as needed to prevent hypoglycemia. In patients with tight glucose control, and depending on the antihyperglycemic agents used, down titration of those medications should be considered when initiating

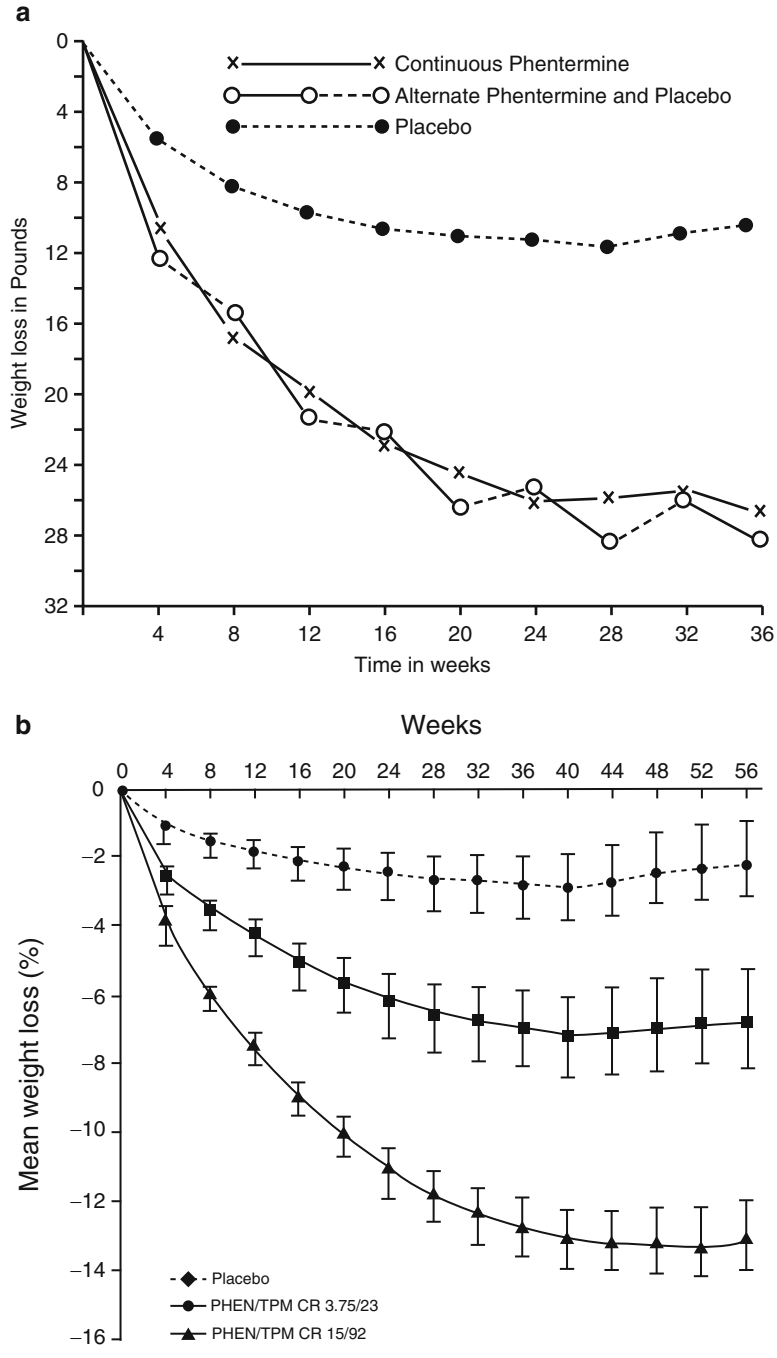

Fig. 16.1 Weight loss effects of the FDA approved weight loss drugs. (**a**) The effect of *Phentermine* 30 mg once daily on body weight during continuous or intermittent administration (1 week on, 1 week off) for 36 weeks during a randomized controlled clinical trial. Both treatment groups lost significantly more weight than the placebo group, but there was no significant difference between the two treatment groups. Data presented as mean. Adapted from Munro JF, MacCuish AC, Wilson EM, Duncan LJ. Comparison of continuous and intermittent anorectic therapy in obesity. British Medical Journal. Feb 10 1968;1(5588):352–354 with permission from BMJ Publishing Group Ltd. (**b**) The effect of *Phentermine/Topiramate* 3.75 mg/92 mg or 15 mg/92 mg once daily on body weight in a 56-week randomized controlled clinical trial. Both treatment groups resulted in significantly more

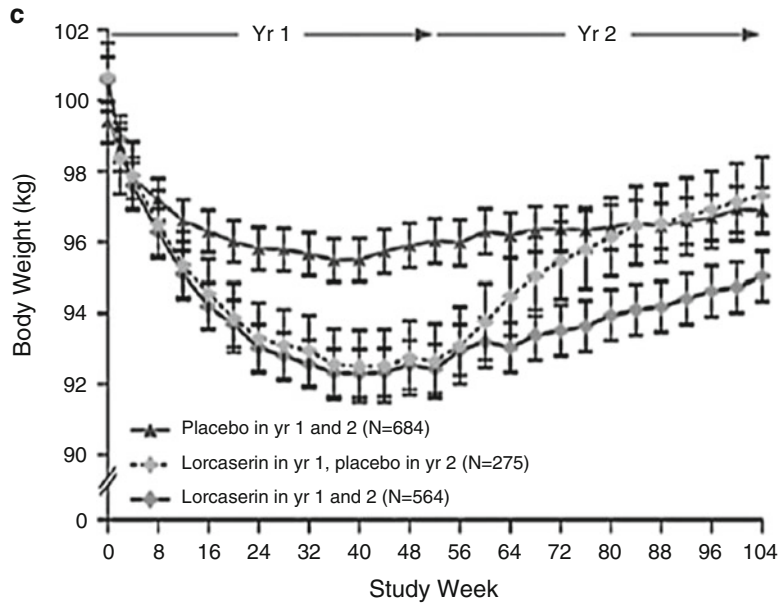

Fig. 16.1 (continued) weight loss compared with placebo group, with the bigger dose reaching significantly more weight loss. Data shown from the intention-to-treat population and represented as mean ±95%CI. *Abbreviations*: Phen/TPM (CR 3.75/23), Phentermine (3.75 mg/Topiramate 23 mg). Phen/TPM (CR 15/92) Phentermine (15 mg)/Topiramate (92 mg). Adapted from Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity. Feb 2012;20(2):330–342 with permission from John Wiley and Sons. (**c**) The effect of *Lorcaserin* 10 mg twice daily for 52 weeks followed by 52 weeks of placebo or 104 weeks of Lorcaserin alone in a randomized controlled clinical trial. During the first 52 weeks, the treatment group lost significantly more weight than placebo group. At 104 weeks, all groups gained weight compared to 52 weeks, although the subjects maintained on Lorcaserin for 104 weeks had significantly more weight loss compared to baseline and compared to patients on placebo for 104 weeks or Lorcaserin for 52 weeks switched to placebo for 52 weeks. Data presented as mean ± standard errors. Adapted from Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. The New England Journal of Medicine. Jul 15 2010;363(3):245–256 with permission from Massachusetts Medical Society

treatment with a weight loss drug. Blood pressure and heart rate should be monitored, especially in patients with hypertension [1].

Safety

Phentermine is pregnancy category X. Phentermine is not recommended in lactating mothers or children (less than 16 years old) due to potential side effects. Phentermine should be used with caution in elderly patients and patients with renal impairment due to potential of excessive accumulation. Because Phentermine is related to amphetamine (which has high abuse potential) Phentermine is a controlled substance and there is a warning of abuse potential in the drug insert [1]. However, Hendricks et al. [6, 7] showed that Phentermine does not induce psychological dependence and abrupt cessation does not induce Phentermine cravings. Symptoms experienced after abrupt cessation represent loss of therapeutic effects, not amphetamine-like withdrawal symptoms [6, 7].

Black Box Warnings

There are no black box warnings for Phentermine [1].

Phentermine/Topiramate

Early studies on the use of Topiramate [8] for weight loss led to the logical next step combining Phentermine with Topiramate. The combination was approved by the FDA in July 2012. Topiramate has been used for the treatment of seizure disorder since 1996; weight loss was noted as a side effect.

Table 16.1 Common side effects and serious side effects of the drugs used/studied for weight loss

Drug name	Common side effects	Serious side effects
Phentermine	Palpitations, tachycardia, elevated blood pressure; overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis; dryness of mouth, unpleasant taste, diarrhea, constipation; allergic side effects like urticaria and endocrine side effects like impotence and changes in libido	Valvular heart disease; primary pulmonary hypertension
Phentermine/topiramate	Paresthesias, dizziness, dysgeusia, insomnia, constipation, and dry mouth	Fetal oral clefts, seizures
Lorcaserin hydrochloride	Headache, dizziness, nausea, fatigue, dry mouth and hypoglycemia, back pain, cough and fatigue	Serotonin syndrome, valvular heart disease, psychiatric disorders, prolactin elevation
Bupropion	Agitation, insomnia, anxiety, dry mouth, headache, dizziness	Suicidal ideation, psychiatric disorders, hallucination, tachycardia and hypertension
Topiramate	Flushing, loss of appetite, altered taste sense, confusion, impaired memory and psychomotor performance, paresthesias	Liver failure, metabolic acidosis, glaucoma, depression, diplopia, speech and language disorder
Metformin	Diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, headache	Lactic acidosis and megaloblastic anemia
Exenatide	Nausea, hypoglycemia, vomiting, diarrhea, dizziness, headache, dyspepsia	Pancreatitis, nephrotoxicity and hypersensitivity reaction
Zonisamide	Somnolence, dizziness, anorexia, nausea, fatigue	Agranulocytosis, toxic epidermal necrolysis, aplastic anemia, hyperthermia, oligohidrosis, and depression
Liraglutide	Headache, nausea, diarrhea, anti-Liraglutide antibody formation, urticaria	Pancreatitis, renal failure, hypersensitivity reaction, and thyroid cancer

Side effects of the described drugs are taken from the respective drug inserts

Indications

Phentermine and Topiramate extended release (trade name Qsymia™) is indicated for chronic weight management in adults with a BMI ≥ 30 kg/m^2 or 27 kg/m^2 with at least one weight related comorbidity (for example: type 2 diabetes, hypertension, hyperlipidemia) [9]. Of note, Phentermine/Topiramate has not been studied in conjunction with other weight loss treatments and long-term safety, specifically regarding cardiovascular morbidity and mortality is not known at this time.

Mechanism of Action

The mechanism of action for Topiramate is unknown. However, the effect of Phentermine is likely mediated by catecholamine release that reduces appetite and decreases food intake. The effect of Topiramate may be due to increased activity of the neurotransmitter gamma-aminobutyrate, modulation of voltage-gated ion channels, inhibition of AMPA/kainite excitatory glutamate receptors, or inhibition of carbonic anhydrase, which decreases appetite and increases satiety [9].

Efficacy

Pivotal studies of Phentermine/Topiramate extended release included a broad range of patients both with and without weight related comorbid conditions. Specifically, the efficacy of Phentermine/Topiramate was studied in a randomized, double-blinded, placebo-controlled study in obese patients with BMI more than 35 kg/m^2 without diabetes (EQUIP study) [10]. Subjects (N=514) were 18–71 years old, mostly women (83 %) and mostly Caucasian (80 %) with baseline weight of 116 kg. Treatment consisted of two doses of Phentermine/Topiramate (3.75 mg/92 mg and 15 mg/92 mg) or placebo in addition to nutrition/lifestyle modification counseling and a 500 kcal/day decrease in

caloric intake with a balanced diet for 1 year. Both treatment dosages resulted in increased weight loss as compared with placebo (3.5 and 9.4 kg). The percentage of subjects losing greater than or equal to 5 % weight at the two doses was 27.6 % and 49.4 % or 10 % weight was 11.4 % and 39.4 % in the 3.75 mg/25 mg and 15 mg/92 mg Phentermine/Topiramate groups respectively [10] (Fig. 16.1b).

Subsequently, Phentermine/Topiramate efficacy was studied in 994 obese (BMI ≥ 30 kg/m^2) and overweight subjects (BMI ≥ 27 kg/m^2) with two or more significant comorbidities including hypertension, dyslipidemia, diabetes, prediabetes, or abdominal obesity (CONQUER study) [11]. Treatment dosage was either 7.5 mg/92 mg or 15 mg/92 mg. Subjects were between 18 and 70 years old, mostly women (70 %) and mostly Caucasian (86 %) with a baseline weight of 103 kg. In both studies, a substantial fraction of subjects withdrew from the study: 40 % in the EQUIP study with only obese subjects and 31 % in the CONQUER study with obese or overweight subjects with one or more comorbidity. Both treatment dosages resulted in increased weight loss as compared with placebo (6.6 and 8.6 kg). The percentage of subjects losing more than 5 % weight was 41.3 % and 49.2 %, or 10 % weight (29.9 % and 40.3 %) in the 7.5 mg/46 mg and 15 mg/92 mg Phentermine/Topiramate groups respectively.

The effect on weight maintenance was studied in a non-randomized extension of the overweight and obese SEQUEL trial for 52 more weeks in 676 subjects [12]. Phentermine/Topiramate 7.5 mg/46 mg and 15 mg/92 mg were found to be effective in maintaining weight loss for up to 108 weeks compared to baseline vs. placebo, respectively (7.5, 8.7 %). Phentermine/Topiramate significantly decreased waist circumference [10, 11]. Heart rate, systolic and diastolic blood pressure, cholesterol, and fasting glucose significantly improved with the 15 mg/92 mg dosage in the EQUIP trial [10] and CONQUER trial [11] and with 7.5 mg/46 mg Phentermine/Topiramate in the overweight and obese CONQUER trial [11]. In patients with and without diabetes, HbA1C significantly improved with both doses used in the CONQUER trial [11]. The development of new cases of diabetes was also decreased suggesting utility in diabetes prevention and treatment. Please note that Phentermine/Topiramate is not approved for use in the treatment of diabetes per se but is approved for use to manage weight in patients with diabetes.

Side Effects/Tolerability

The most common side effects associated with Phentermine/Topiramate use are paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth. If used in the first trimester of pregnancy, there is a higher risk for fetal oral clefts from the Topiramate. If Phentermine/Topiramate is discontinued abruptly, seizures may occur [9]. There is a known potential for abuse and dependence due to the Phentermine component [9] (Table 16.1). See the note on the addiction potential of Phentermine, as described in the Phentermine section.

Contraindications

Phentermine/Topiramate should not be used in pregnant patients, patients diagnosed with glaucoma, hyperthyroidism, recent/unstable cardiac or cerebrovascular disease, patients taking monoamine oxidase inhibitors or within 14 days of treatment, patients with known hypersensitivity or idiosyncrasy to sympathomimetic amines [9]. Caution should be used in women of childbearing potential [9].

Drug Interactions

Phentermine/Topiramate interacts with: (1) oral contraceptives and may produce irregular vaginal bleeding without an increase in pregnancy risk (discontinuation of oral contraceptives is not indicated); (2) CNS depressants including alcohol by potentiating CNS depressant effects (instruct to avoid concomitant use of alcohol); (3) potassium sparing diuretics by potentiating hypokalemia (monitor potassium before and during treatment); (4) antiepileptic drugs may decrease Topiramate concentration, increase blood ammonia, or produce hypothermia [9].

Monitoring

The absence of pregnancy should be confirmed in women of childbearing age by pregnancy

testing before initiating therapy and monthly during treatment, due to potential for teratogenic side effects. In all patients, heart rate, suicidal behavior and ideation, acute myopia, secondary angle closure glaucoma, mood and sleep disorder, cognitive impairment, electrolytes, and creatinine should be monitored. Glucose control and diabetic medication adjustments should be performed in patients with diabetes. See note above on initiation of weight loss drugs in patients with diabetes. In patients with renal or hepatic impairment, the maximum dose used should not exceed 7.5 mg/46 mg [9].

Safety

Phentermine/Topiramate is pregnancy category X and therefore contraindicated due to increase in fetal oral clefts. Safety and effectiveness have not been established and therefore use is not recommended in nursing mothers, labor, and pediatric/geriatric patients [9]. A cardiovascular safety trial is anticipated to establish long-term safety.

Black Box Warnings

There are no black box warnings for Phentermine/Topiramate extended release [9].

Lorcaserin Hydrochloride

Serotonergic agents have been known to be effective for weight loss for more than 40 years. In the 1990s Fenfluramine was used to treat obesity. Subsequently, the D-isomer of Fenfluramine (dexfenfluramine) was approved by the FDA in 2013 for weight loss. Practically, most of the Fenfluramine prescribed was combined with Phentermine off label and the phrase Fen/Phen was coined to describe this use. Unfortunately, cardiac complications, specifically, cardiac valvulopathy was discovered in patients taking this combination. Later, in vitro studies implicated Fenfluramine and dexfenfluramine, not Phentermine, as agonists of the 5-HT_{2B} serotonin receptors expressed on the interstitial cardiac valve cells. Agonists of the 5-HT_{2B} serotonin receptors stimulate the growth of the interstitial cells with subsequent valvular incompetence also known as valvulopathy. Valvulopathy is a condition that occurs with many serotonergic drugs and with serotonin producing carcinoid tumors that metastasize to the lungs (reviewed in [13]). At about the same time, preclinical data identified the 5-HT_{2C} serotonin receptor in the hypothalamus as critical for the weight loss effects of serotonergic agents. This led to the search, for 5-HT_{2C} specific serotonin receptor agonists, which has proven to be very difficult. Lorcaserin was designed to be a selective agonist for the 5-HT_{2C} serotonin receptor to retain weight loss efficacy without causing cardiac valvulopathy.

Indication

Lorcaserin is indicated as an adjunct to diet and exercise for weight loss and maintenance in obese patients (BMI $\geq$ 30 kg/m^2) or overweight subjects (BMI $\geq$ 27 kg/m^2) with at least one weight related comorbidity (for example: glucose intolerance, type 2 diabetes, hypertension, hyperlipidemia, and sleep apnea). Importantly, the FDA approved prescribing information mandates that Lorcaserin should be discontinued if less than 5 % weight loss has been achieved following 12 weeks of treatment [14].

Mechanism of Action

Lorcaserin decreases weight by reducing food consumption [15]. These effects are mediated through the activation of the 5-HT_{2C} serotonin receptor located throughout the central nervous system. Serotonin acts in the hypothalamus to release αMSH and decrease AgRP release, which modulate appetite by increasing satiety and decreasing hunger [14]. Lorcaserin is thought to activate these same hypothalamic appetite control systems [13].

Efficacy

The efficacy of Lorcaserin as a weight loss drug in conjunction with behavior modification was demonstrated in three pivotal phase 3 studies. The 2 year BLOOM study [16] and the 1 year BLOSSOM study [17] included obese (BMI $\geq$ 30 kg/m^2) or overweight subjects (BMI $\geq$ 27 kg/m^2) with at least one weight related comorbidity. The BLOOM-DM study included patients with type 2 diabetes [18] treated for 1 year.

Lorcaserin produced significant body weight loss as early as 2 weeks after starting the treatment compared to placebo, and resulted in weight loss of approximately 5.8 % vs. 2.5 % in the BLOOM [16] and BLOSSOM [17] studies, respectively. In patients with diabetes in the BLOOM-DM weight loss averaged 5 % vs. 1.5 % in placebo-treated patients [18]. As with most other weight loss drugs, Lorcaserin was more effective in nondiabetic patients. After 1 year of treatment, Lorcaserin 10 mg orally twice daily led to at least 5 % weight loss in twice as many subjects compared with placebo (47 % vs. 23 % in pooled BLOOM [16] and BLOSSOM [17]; and 37 % vs. 16 % in BLOOM-DM [18]). Lorcaserin led to more than 10 % weight loss in 22 % vs. 9 % of control subjects in the pooled BLOOM [16] and BLOSSOM [17]. In BLOOM-DM, 10 % weight loss was achieved in 16 % of Lorcaserin-treated patients vs. 4 % in placebo-treated patients [18]. In the BLOSSOM and BLOOM Lorcaserin 10 mg orally twice daily was superior to once daily dosing therefore the Lorcaserin is recommended as 10 mg twice daily. Interestingly, in BLOOM-DM, once daily was almost as efficacious as twice daily dosing [18].

The efficacy of Lorcaserin 10 mg orally twice daily as a *weight maintenance* drug was demonstrated in the BLOOM [16] phase 3 study. After 1 year patients randomized to the placebo group remained in the placebo group, while patients assigned to Lorcaserin were randomized at the end of 1 year to either placebo or continued on Lorcaserin. As shown in Fig. 16.1c the patients who were maintained on Lorcaserin for 2 years were better able to maintain weight loss.

Side Effects/Tolerability

Common side effects reported with Lorcaserin include: headache, dizziness, nausea, fatigue, dry mouth and hypoglycemia, back pain, cough, and fatigue in type 2 diabetic patients. These are self-limited and once resolved did not re-occur [14] (Table 16.1). Lorcaserin has less selectivity for the 5-HT_{2A} serotonin receptor than the 5-HT_{2C} receptor which may explain some of these side effects [13].

Serious adverse events were rare and occurred in a similar number of patients in treatment vs. placebo in the phase 3 trials. An echocardiographic safety monitoring program showed no evidence for an increase in the risk of clinically significant valvulopathy [19]. Lorcaserin did not prolong QT_C interval and did not increase heart rate or blood pressure. Psychiatric effects were evaluated in the phase 3 program. These studies showed a low potential for abuse, no increase in depression, anxiety, suicidal ideation or other mood disorders, and no cognitive adverse effects. Serum prolactin levels were moderately elevated [14].

Contraindications

Lorcaserin should not be used in patients with severe renal impairment (defined as a creatinine clearance <30 mL/min) due to potential accumulation of Lorcaserin metabolites. Lorcaserin should not be used in pregnancy [14].

Drug Interaction

Lorcaserin is a weak to moderate inhibitor of CYP2D6; however, clinical studies demonstrate a weak interaction with other CYP2D6 substrates, therefore no recommendation for dose adjustment is made. Caution should be used when combining Lorcaserin with serotonergic drugs [14].

Monitoring

Serum glucose should be monitored in type 2 diabetes patients [14].

Safety

Lorcaserin is contraindicated in pregnancy (Category X). Lorcaserin should not be used during lactation, or lactation should be discontinued prior to starting Lorcaserin. Pediatric use has not been studied, and therefore is not recommended [14].

Black Box Warnings

There are no black box warnings for Lorcaserin [14].

Off Label Use of Drugs for Weight Loss

Bupropion

Bupropion was approved by FDA for treatment of depression in 1985 and smoking cessation in 1997. An anorectic effect was reported from a series of clinical observations [20] and Bupropion was further studied for weight loss as monotherapy or in combination with other drugs.

Indications

Bupropion is approved for use in depression and smoking cessation [21] and is sometimes used off label for weight loss in obese patients due to the anorectic effect.

Mechanism of Action

The exact mechanism of action for Bupropion is unknown, but it is thought to act through the inhibition of the neuronal reuptake of norepinephrine and dopamine [21].

Efficacy

The first report of Bupropion use for weight loss in subjects without depression was a short (8 weeks) randomized double-blinded, placebo-controlled trial in 50 overweight and obese subjects [20]. Subjects were treated with either placebo or Bupropion 100 mg/day and gradually increased to 200 mg/day in addition to a low-calorie diet (1,600 kcal/day). In 8 weeks, the net weight loss in the Bupropion group was 4.4 kg from baseline. The study was continued for 16 more weeks in responders (subjects who lost more than 5 % of baseline weight in 8 weeks) and they lost an additional 12 kg, from which fat loss was 73 % [20].

A longer study of Bupropion was reported in 2002, where 327 subjects were enrolled in a multicenter double-blinded, placebo-controlled study with Bupropion SR 300 or 400 mg/day in addition to calorie restriction, meal replacements, and exercise [22]. Subjects weighed an average of 100 kg at baseline, and were mostly middle aged women. After 24 weeks there was a significant dose dependent net weight loss in the Bupropion 300 mg/day (2.2 %) vs. Bupropion 400 mg/day (5.1 %). In a 24-week extension, subjects taking Bupropion 300 mg/day lost a total of 7.5 % of initial body weight vs. 8.6 % in the Bupropion 400 mg/day arm [22].

In a double-blinded placebo-controlled randomized clinical trial of 419 patients with uncomplicated obesity, the effect of sustained-release Bupropion SR 400 mg/day monotherapy, immediate release Naltrexone monotherapy (48 mg/day), and the combination of both drugs was studied for 24 weeks [23]. In contrast to the study by Anderson, monotherapy with Bupropion sustained-release 400 mg/day led to a net weight loss of only 2 % as compared to placebo [23]. The effects of Naltrexone and the combination will be discussed in more detail below.

A meta-analysis on the effect of Bupropion in depressed patients [24] included 13 studies published from 1982 to 2006. Serretti et al. concluded that Bupropion produced a significant net weight change of −1.13 kg (95%CI −1.41 to −0.84, $p<0.0001$) during acute treatment (4–12 weeks) and −1.87 kg (95%CI −2.37 to −1.37, $p<0.0001$) during medium and long-term treatment (more than 4 months) [24].

Of all antidepressants with weight loss effects (imipramine, nortriptyline, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, mirtazapine) Bupropion was the only one to demonstrate weight loss maintenance in long-term treatment [24]. Of note, most of these other agents act on the serotonin system [24].

Side Effects/Tolerability

Common side effects of Bupropion include: agitation, insomnia, anxiety, dry mouth, headache, dizziness. Serious side effects include suicidal ideation, psychiatric disorders, hallucination, tachycardia, and hypertension [21] (Table 16.1). There are no long-term cardiovascular outcome trials of Bupropion. Given a mechanism of action that is similar to sibutramine, the authors recommend caution in using this agent in patients with a history of or high risk for cardiovascular disease.

Contraindications

Bupropion is contraindicated in patients with seizure disorder, eating disorders, patients undergo-

ing abrupt cessation of alcohol or sedatives or within 14 days of treatment with monoamine oxidase inhibitors [21].

Drug Interaction

Bupropion is metabolized in liver by the CYP2B6 isoenzyme, therefore may interact with other drugs that inhibit or induce CYP2B6 including: MAO inhibitors, amantadine, levodopa, tramadol, warfarin, clopidogrel, olanzapine, and systemic corticosteroids. Bupropion should be avoided with drugs that lower seizure threshold (like antipsychotics or other antidepressants) [21].

Monitoring

While on Bupropion therapy, monitor for seizures and suicidal ideation [21].

Safety

Bupropion is pregnancy category C, therefore should be used only if risks of discontinuation outweigh the benefits. It is possibly unsafe in lactation due to its secretion in human milk; therefore, Bupropion should be discontinued in these cases. Bupropion is not approved for use in children and should be used with caution in the elderly, due to probable impaired renal function [21].

Black Box Warnings

Bupropion has a black box warning of increasing suicidal ideation, especially in children and young adults; their close clinical monitoring is recommended especially in the beginning of therapy [21].

Topiramate

Topiramate was initially studied as an antidiabetic drug to inhibit gluconeogenesis. In the process of research an anticonvulsant effect was observed and subsequently Topiramate was FDA approved in 1996 for this indication. Later on, an effect on appetite was observed [25] and Topiramate was further tested for weight loss in mono or combination therapy.

Indications

Topiramate is approved for treatment of seizures and for migraine prophylaxis [26] and has been used off label for weight loss.

Mechanism of Action

The exact mechanism of action is unknown, but there is some evidence for voltage dependent sodium channel blockade, augmentation of gamma-aminobutyrate (GABA) activity, antagonizing the glutamate receptor, and inhibition of carbonic anhydrase [26].

Efficacy

The effects of Topiramate on weight was studied first in obese subjects or overweight subjects with BMI $\geq$ 27 kg/m^2 with hyperlipidemia or/and hypertension [27]. This randomized double-blinded, placebo-controlled dose-ranging trial studied the effect of Topiramate 64, 96, 192, or 384 mg/daily for 6 months on weight in addition to low-calorie diet and exercise counseling/monitoring. The study enrolled 385 subjects, and at the end of 6 months there were 242 completers. Net placebo adjusted weight loss at the end of study was 2.1 kg, 2.9 kg, 4.4 kg, 5 kg in the 64 mg/day, 96 mg/day, 192 mg/day or 384 mg/daily, respectively. Interestingly, weight loss started at 4 weeks and continued to 6 months without reaching a plateau. The responder rate (those losing more than 5 % body weight) was significantly higher in Topiramate in the 64 mg/day (49 %, $p=0.03$), 96 mg/day (59 %, $p=0.02$), 192 mg/day (70 %, $p=0.001$) or 384 mg/daily (61 %, $p=0.007$) groups as compared to placebo (29 %) [27].

Subsequently, the effect of Topiramate monotherapy in doses of 96, 192, and 256 mg/day was studied over 60 weeks in conjunction to the "Pathway to change" lifestyle intervention [28]. Subjects were obese or overweight with a BMI $\geq$ 27 kg/m^2 and had hyperlipidemia and/or hypertension. This randomized, placebo-controlled, double-blind study enrolled 1,289 subjects and 709 completed the 60-week trial. Topiramate induced a net weight loss compared to placebo of 5.9 kg ($p<0.001$), 7.9 kg ($p<0.001$), 8.4 kg ($p<0.001$) in the 96 mg/day, 192 mg/day, and 256 mg/day, respectively. Among the

Topiramate groups, weight loss in the 96 mg/day vs. 192 mg/day Topiramate was significantly different, but similar between 196 mg/day and 256 mg/day Topiramate. Responders (losing more than 5 % body weight) in the placebo and 96 mg/day, 192 mg/day, and 256 mg/day Topiramate groups were 18 %, 54 %, 61 %, and 67 % respectively. Weight loss was accompanied by a significant improvement in blood pressure, fasting glucose, 2 h glucose and insulin in all groups. Only the 96 and 256 mg/day Topiramate significantly improved LDL in this predominately normo-lipidemic population [28].

The effects of Topiramate on weight loss were summarized in a 2011 meta-analysis [29] which included 11 randomized, controlled trials published between 2003 and 2007. The analysis included 3,320 individuals treated with Topiramate for at least 16 weeks. Topiramate induced a 5.34 kg net weight loss (95%CI −6.12, −4.56) compared to placebo. This analysis also concluded that weight loss did not reach a plateau by 28 weeks [29].

Side Effects/Tolerability

Common side effects of Topiramate are flushing, loss of appetite, altered taste, confusion, impaired memory and psychomotor performance, and paresthesias. Serious side effects include liver failure, metabolic acidosis, glaucoma, depression, diplopia, and speech and language disorders [26].

Contraindications

Topiramate should be used with caution in patients with renal and hepatic impairment, patients that consume alcohol, patients that use other CNS depressant medications, or drugs that are associated with metabolic acidosis [26]. As noted above, Topiramate may cause oral clefts in children born to women who use this medication in pregnancy and so it is contraindicated in pregnant women [26].

Drug Interaction

Topiramate may increase levels of phenytoin, and decrease levels of digoxin. The concomitant use of citalopram may prolong QT interval [26].

Monitoring

Renal function, bicarbonate and depression symptoms should be actively monitored [26].

Safety

Topiramate is a pregnancy category D and safety in lactation is unknown. It is approved for use in adults and pediatrics older than 2 years of age [26]. While not specifically mentioned in the package insert, clinical judgment suggests that when using Topiramate off label for weight loss, the absence of pregnancy should be confirmed in women of childbearing age by pregnancy testing before initiating therapy and monthly during treatment, due to potential for teratogenic side effects.

Black Box Warnings

There was no black box warnings for Topiramate [26].

Metformin

Metformin was approved in 1994 for the treatment of type 2 diabetes. Weight loss was shown to be a side effect [30], and this led to clinical trials as a weight loss drug.

Indications

Metformin is indicated for the treatment of type 2 diabetes [31] and is used off label for weight loss as described below.

Mechanism of Action

Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization [31]. There is also some evidence that Metformin is an AMP kinase activator. In T2DM, a genetic polymorphism in the OCT1 gene [32] alters the glycemic effects of Metformin. The polymorphism's effects on weight loss are unknown.

Efficacy

The Diabetes Prevention Study [33] was a randomized, placebo-controlled, multicenter clinical trial to study the effects of placebo vs. lifestyle

intervention vs. Metformin in preventing diabetes and weight loss in subjects at risk for diabetes. Subjects ($N=3234$) had elevated fasting and post-load plasma glucose but not diabetes. Participants were on average 51 years old, with a mean BMI of 34 kg/m^2, mostly women (68 %) and of various races. The lifestyle intervention consisted of low-fat, low-calorie diet, and physical activity for at least 150 min/week. The participants were followed for an average of 2.8 years, and at the end of the study the net weight loss compared to placebo was 2 kg in the Metformin group and 5.5 kg in the lifestyle intervention group ($p<0.001$) [33]. This trial was followed by a 7–8 year open-label extension of Metformin and placebo [34]. At the end of the study Metformin induced a net weight loss compared with placebo of 1.8 % from baseline body weight ($p<0.001$). As expected, the weight loss was significantly dependent on adherence to treatment in the Metformin group ($p<0.001$) [34]. In addition to the weight loss effect, compared to placebo Metformin reduced the incidence of type 2 diabetes by 31 %, compared to lifestyle intervention by 58 % in the 2.8 year double-blinded study [33]. Taken together with the extension study, in the 10 years of the study, Metformin reduced the incidence of diabetes by 18 % while the lifestyle intervention reduced the incidence by 34 % [35].

The effect of Metformin was studied in children in a double-blinded, randomized, placebo-controlled trial of Metformin 1,000 mg twice daily in addition to a lifestyle modification program consisting of a 500 kcal/day deficit diet and 30 min of aerobic exercise daily [36]. The study was double blinded for 6 months followed by an open-label extension with Metformin for 6 months. Participants were obese (BMI range 23–57 with mean BMI = 34.6 kg/m^2), aged 6–12 years old, boys and girls, and of diverse races. In the first 6 months of the double-blinded trial, Metformin induced a net weight loss compared with placebo of 3.38 kg ($p<0.001$), and BMI–Z score decreased by 0.07 ($p=0.02$) [36]. Interestingly, in the next 6 months of the trial with Metformin open-label patients who were previously on placebo and were switched to Metformin significantly decreased their BMI–Z score, but the patients on Metformin initially did not reduce the BMI–Z score any further illustrating the weight loss plateau seen with most weight loss drugs. In addition to the weight loss effect, fasting plasma glucose ($p<0.007$) and homeostasis model assessment of insulin resistance index ($p<0.006$) decreased significantly with Metformin vs. placebo [36].

Side Effects/Tolerability

Metformin has the following common adverse reactions: diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, headache. Serious adverse reactions occurring with Metformin include lactic acidosis and megaloblastic anemia [31] (Table 16.1).

Contraindications

Metformin is contraindicated in patients with impaired renal function, congestive heart failure requiring treatment and metabolic acidosis. Metformin should be discontinued in patients undergoing radiologic investigations that require intravascular administration of iodinated contrast materials [31].

Drug Interaction

Metformin interacts with furosemide, nifedipine, and cationic drugs that increase Metformin blood levels [31].

Monitoring

While on Metformin, it is advised that patients have creatinine, hemoglobin, hematocrit, and vitamin B12 monitored [31].

Safety

Metformin is labeled as pregnancy category B. Metformin is excreted in milk, and studies have not been conducted in nursing mothers, therefore effects are unknown. Metformin produced by Bristol-Myers Squibb is approved in children beyond 10 years old [31].

Importantly, Metformin may increase lifespan with evidence for reduced overall and cardiovas-

cular mortality [37]. This increases confidence for use in lower risk persons with obesity.

Black Box Warnings

Metformin has a black box warning for metabolic acidosis, especially in patients with significant renal impairment [31].

Exenatide

Exenatide is a GLP-1 receptor agonist (an analog of GLP-1) and was approved in 2005 by the FDA as an adjunct to diet and exercise for the treatment of type 2 diabetes in adults. A side effect of decreased appetite was discovered [38], which led to weight loss trials.

Indications

Exenatide is indicated as an adjunct to diet and exercise for the treatment of type 2 diabetes in adults [39], and is used for weight loss off label.

Mechanism of Action

Exenatide is a GLP-1 receptor agonist, which induces weight loss probably by delaying gastric empting and decreasing food intake by increasing satiety [39]. There is also evidence that the GLP-1 receptor connects to key body weight regulating circuits in the hindbrain and hypothalamus although penetration of GLP-1 receptor agonists into the hypothalamus is controversial.

Efficacy

Exenatide was studied for weight loss in 152 obese subjects with normal glucose tolerance, impaired fasting glucose or impaired glucose tolerance, but without a diagnosis of type 2 diabetes [40]. In this double-blinded, randomized, placebo-controlled trial, subjects were treated with Exenatide or placebo administered as a subcutaneous injection twice daily along with a structured program of diet and physical activity for 24 weeks. Subjects were mostly women (82 %), of mean age 46 years old, and mean weight 108.6 kg. Exenatide induced significantly more weight loss compared to placebo starting at 4 weeks ($p<0.001$), and continued to decrease weight without a plateau until the end of the study at 24 weeks when weight loss in the Exenatide group was 5.1 ± 0.5 kg vs. placebo 1.6 ± 0.5 kg ($p<0.001$) [40].

A recent meta-analysis of type 2 diabetes patients compared treatment with Exenatide vs. active control (other antidiabetic drug therapy or lifestyle intervention, $N=14$ studies) vs. placebo ($N=6$) for a minimum of 12 weeks. Overall, Exenatide decreased body weight by 1.36 kg compared to active control ($p<0.0007$) but only 0.88 kg compared to placebo ($p=0.2$) [41].

Another double-blinded, placebo-controlled, crossover trial studied 41 obese women without diabetes treated with Exenatide or placebo twice daily for 16 weeks with a 3 week washout period; importantly, there was no lifestyle intervention [42]. Subjects had a mean age of 48 years and mean weight of 89 kg. When treated with Exenatide, subjects lost 2.49 kg compared to gaining 0.43 kg in the placebo period ($p<0.01$) [42].

The weight loss effect of Exenatide was also studied in patients with a diagnosis of type 2 diabetes. This 30-week study of Exenatide or placebo twice daily added to insulin glargine treatment showed that Exenatide induced significantly more weight loss especially in patients with a longer duration of diabetes (LS mean difference at end point −3.9 kg, $p<0.001$) [43]. The long-term effect of Exenatide was studied in an open-label extension of this same trial with Exenatide once daily or twice weekly for 30 weeks, followed by 1.5 years of treatment with Exenatide once weekly, for a total of 2 years of Exenatide treatment [44]. At the end of the study, the completers lost 2.6 kg compared to baseline ($p<0.05$) [44]. Exenatide once weekly was compared with Exenatide twice daily in a dose comparator controlled, randomized, open-label trial [45] of 295 obese subjects with type 2 diabetes. Subjects treated with Exenatide once weekly lost 3.7 kg compared to baseline, while subjects treated with Exenatide twice daily lost 3.6 kg compared to baseline (no

significant difference between groups $p<0.89$, but significantly different compared to baseline, $p<0.05$) [45]. Importantly, this degree of weight loss did not meet FDA guidance which requires 5 % placebo adjusted weight loss or a doubling of the proportion of patients achieving 5 % weight loss.

The effect of Exenatide or placebo twice daily was studied in adolescents (aged 12–19) with severe obesity (BMI > 35 kg/m^2) in addition to lifestyle modification canceling [46]. This was a 3-month randomized double-blinded placebo-controlled trial followed by a 3-month open-label extension involving 26 obese adolescents without diabetes. During the first 3 months of double-blinded study, Exenatide twice daily led to a net decrease in body weight of 3.26 kg ($p<0.02$) which continued in the next 3 months of open label [46].

Side Effects/Tolerability

Common adverse reactions with Exenatide are: nausea, hypoglycemia, vomiting, diarrhea, dizziness, headache, dyspepsia. Serious side effects include: pancreatitis, nephrotoxicity, and hypersensitivity reaction [39]. The role of Exenatide and other GLP-1 receptor agonists to increase the risk of pancreatitis is controversial and not conclusive; however, because it is listed in the prescribing information we include that risk herein.

Contraindications

Exenatide is contraindicated in subjects with history of hypersensitivity to Exenatide or any product component [39].

Drug Interaction

Exenatide interacts with warfarin to increase INR [39].

Monitoring

While on Exenatide, monitoring of renal function is recommended [39].

Safety

Exenatide is pregnancy category C, and safety in pregnancy is unknown, therefore caution is advised. Exenatide is not currently approved for use in the pediatric population [39].

Black Box Warnings

There are no black box warnings for Exenatide [39].

Liraglutide

Liraglutide was approved by FDA in 2010 for the treatment of type 2 diabetes in adults, in combination with weight loss and exercise. Weight loss is a side effect of Liraglutide [47], thus it was pursued further for treatment of obesity.

Indications

Liraglutide is approved for treatment of diabetes [48] and is in development and used off label for obesity.

Mechanism of Action

Liraglutide activates the glucagon-like-peptide 1 (GLP-1) receptor, increases insulin secretion, decreases glucagon secretion and delays gastric emptying [48]. Liraglutide also decreases appetite and reduces food intake [49]. The effect of Liraglutide on weight loss is probably through a combined gastrointestinal (delaying gastric emptying) and brain effects in the hindbrain and possibly the hypothalamus.

Efficacy

In 2009, four doses of Liraglutide were studied for the treatment of obesity without diabetes, defined as BMI $\geq$ 30 kg/m^2 with concomitant lifestyle change intervention [50]. This was a multicenter, double-blinded, placebo-controlled, open-label orlistat comparator trial that enrolled 564 subjects (mostly women), from which 472 completed the trial. After 20 weeks, subjects taking Liraglutide had a significant net weight loss of 2.1 kg ($p<0.003$), 2.8 kg ($p<0.0001$), 3.5 kg ($p<0.0001$), 4.4 kg ($p<0.0001$) in the 1.2 mg group, 1.8 mg group, 2.4 mg group and 3.0 mg group, respectively (Fig. 16.2b). The proportion of responders (weight loss more than 5 % from baseline body weight) was significantly higher

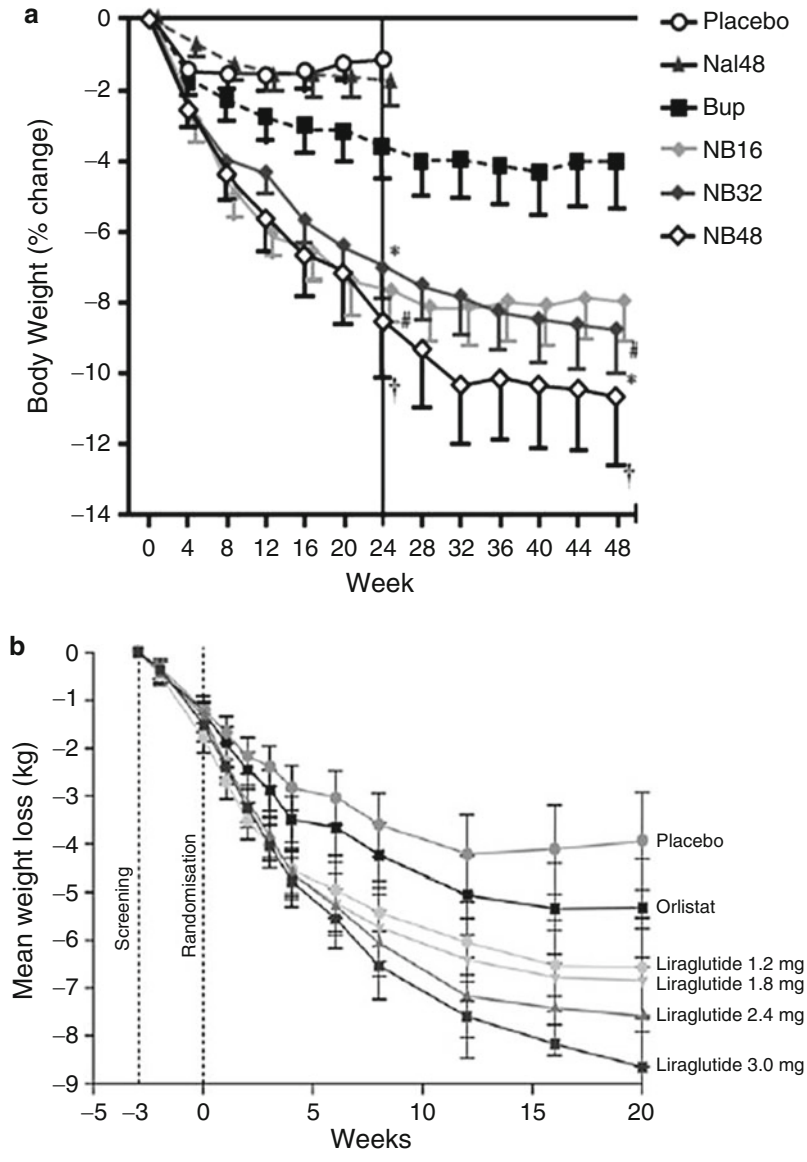

Fig. 16.2 Weight loss effect of drugs in development for weight loss. (**a**) The effect of *Naltrexone* and *Bupropion* alone or in combination on body weight for 24 weeks followed by a 24-week extension period of the combination therapy and Bupropion alone in a randomized controlled clinical trial. After 24 weeks, the combination therapy Bupropion SR (400 mg/day) and Naltrexone 16, 32, and 48 mg/day produced significantly more weight loss compared to placebo. The weight loss continued in the next 24 weeks of the study extension for the Bupropion/Naltrexone combination 400 mg/32 mg/day and 400 mg/48 mg/day. #$p<0.05$ for NB16 vs. placebo, Nal 48 and Bup. *$p<0.05$ for NB32 vs. placebo, Nal 48 and Bup. +$p<0.05$ for NB48 vs. placebo, Nal 48 and Bup. Statistical significance indicated in figure for week 24 and week 48 only. Abbreviations: Nal 48 (Naltrexone 48 mg/day). Bup (Bupropion 400 mg/day). NB16 (Naltrexone 16 mg/day, Bupropion 400 mg/day). NB32 (Naltrexone 32 mg/day, Bupropion 400 mg/day). NB48 (Naltrexone 48 mg/day, Bupropion 400 mg/day. Redrawn from Greenway FL, Dunayevich E, Tollefson G, et al. Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. The Journal of clinical endocrinology and metabolism. Dec 2009;94(12):4898-4906. (**b**) The effect of *Liraglutide* 1.2, 8, 2.4 or 3.0 mg subcutaneous once daily vs. orlistat and placebo on body weight in a 20-week randomized controlled study. At the end of the trial, all four Liraglutide treatment groups had significantly more weight loss compared with placebo or Orlistat treatment groups. Data are mean (95%CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward. Adapted from Astrup A, Rossner S, Van Gaal L, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet. Nov 7 2009;374(9701):1606–1616 with permission from Elsevier Limited

in the Liraglutide 1.2 mg group (52.1 %, $p=0.002$), 1.8 mg group (53.3 %, $p=0.002$), 2.4 mg group (60.8 %, $p<0.0001$) and 3.0 mg group (76.1 %, $p=0.0001$) compared to placebo control (29.6 %). The change in proportion of subjects with metabolic syndrome was not significant. However, there was a significant decrease in proportion of prediabetics patients in all Liraglutide groups. Mean HbA1C decreased with Liraglutide in a dose dependent manner that ranged from 0.14 to 0.24 % [50].

The long-term effects of Liraglutide were studied in an 84 week extension of the above described study [51]. The Liraglutide group participants stayed in the trial for one more year on the dose they were initially started on then transitioned to 2.4 then 3.0 mg/day for 1 more year. The placebo group participants were left on placebo. There were 398 subjects enrolled 268 subjects completed the study. After 1 year, the Liraglutide 1.2 mg group, 1.8 mg group, 2.4 mg group and 3.0 mg per day group subjects had a net weight loss of 1.8 kg ($p=$NS), 3.4 kg ($p<0.001$), 4.1 kg ($p<0.0001$), 5.8 kg ($p<0.0001$) compared to placebo, respectively. After 2 years the Liraglutide completers group (pooled 2.4/3 mg/day) had a net weight loss of 7.8 kg from screening. In the 3.0 mg/day Liraglutide group, subjects maintained a 10.3 kg weight loss over 2 years. After 2 years, 52 % of subjects maintained more than a 5 % weight loss compared with baseline weight. The composition of weight loss was measured after 20 weeks in the 3.0 mg/day Liraglutide group and showed that the majority of weight lost (15.4 % decrease vs. baseline) was fat compared to lean tissue (2 % decrease vs. baseline) [51].

Side Effects/Tolerability

Common side effects with Liraglutide are: headache, nausea, diarrhea, anti-Liraglutide antibody formation, and urticaria. Serious adverse events included in the prescribing information include: pancreatitis, renal failure, hypersensitivity reaction, and thyroid cancer [48].

Contraindications

Liraglutide is contraindicated in patients with family history of medullary thyroid carcinoma, or in patients with multiple endocrine neoplasia syndrome type 2 [48].

Drug Interaction

Because Liraglutide decreases gastric emptying, it may impact the absorption of oral medications [48].

Monitoring

Liraglutide increases the risk for hypoglycemia when administered concomitantly with insulin or an insulin secretagogue, therefore glucose levels should be monitored [48].

Safety

Liraglutide is labeled as pregnancy category C and is not recommended during lactation. Liraglutide should not be used in the pediatric population due to insufficient data [48].

Black Box Warnings

Liraglutide has a black box warning for increased risk of thyroid C-cell tumor risk [48].

Zonisamide

Indications

Zonisamide is an antiepileptic drug approved by FDA in 2000. It was shown to also decrease weight as a side effect. Therefore Zonisamide has been tested for weight loss in monotherapy or combination therapy with Bupropion.

Mechanism of Action

The exact mechanism of Zonisamide is not known, but it is believed to be through sodium and calcium channel blockade, and/or through increased dopaminergic and serotonergic activity [52].

Efficacy

In a randomized, placebo-controlled double-blinded clinical trial of 60 obese subjects, the effect of Zonisamide 100 mg/day, titrated up to 600 mg/day if tolerated, was studied in addition to low-calorie diet instruction [53]. Subjects were mostly women, averaged 37 years old, and weighed on average 98 kg. After 16 weeks of treatment, a net weight loss of 5 kg compared to pla-

cebo was observed [53]. Subjects that entered the 16 week extension arm of the treatment lost a significant net weight of 7.7 kg compared to baseline [53]. There was no significant added benefit for increasing the dose to 600 mg/day [53].

Another clinical trial studied the effect of Zonisamide 200 and 400 mg/day vs. placebo for 1 year [54]. This is a randomized, placebo-controlled, double-blinded study with diet and lifestyle counseling for 1 year of 225 obese subjects without diabetes. Study participants were on average 43 years old, 59 % were women and weighed on average 109–111 kg. After 1 year, Zonisamide 200 mg/day led to a net weight loss vs. placebo of 0.4 kg ($p=0.79$) and Zonisamide 400 mg/day of 3.3 kg ($p=0.009$). However, side effects (specifically gastrointestinal, nervous system, and psychiatric) increased as the dose was increased [54].

A 2013 meta-analysis showed a higher proportion of weight loss (0.242 %; 99%CI 0.021–0.462) as side effect in patients treated with Zonisamide for seizures [55].

Side Effects/Tolerability

The common side effects of Zonisamide are: somnolence, dizziness, anorexia, nausea, fatigue. Serious side effects including agranulocytosis, toxic epidermal necrolysis, aplastic anemia, hyperthermia, oligohidrosis, and depression have been reported [52].

Contraindications

Zonisamide is contraindicated in patients with hypersensitivity to sulfonamide. Zonisamide should be used with caution in renal and hepatic impairment, and nephrolithiasis [52].

Drug Interactions

Avoid concomitant use of carbonic anhydrase inhibitors. Plasma concentration of Zonisamide is decreased by concomitant use of other antiepileptic drugs [52].

Monitoring

While on Zonisamide, patients should be monitored for depression symptoms, renal function, and blood count [52].

Safety

Zonisamide is labeled as pregnancy category C. The effect of Zonisamide has not been studied sufficiently therefore should only be used if benefits outweigh the risks. Zonisamide is contraindicated in the pediatric population below 16 years old [52].

Black Box Warnings

There are no black box warnings for Zonisamide [52].

Drugs that Are in Development for Weight Loss

Naltrexone/Bupropion

Liraglutide (Fig. 16.2b)

Indications

Naltrexone is an opioid receptor antagonist FDA approved for narcotic and alcohol dependence. Bupropion is a dopamine and norepinephrine reuptake inhibitor FDA approved for depression and smoking cessation. The combination of these two agents is thought to stimulate pro-opiomelanocortin neuronal firing and decrease food craving by acting on reward pathways [56] .

Efficacy

In a phase 2 clinical trial in 2009, Greenway et al. showed that the combination of Naltrexone extended release (ER) with Bupropion sustained-release (SR) had greater efficacy for weight loss as compared to the monotherapy of either Naltrexone or Bupropion alone [23]. This was a randomized, placebo and monotherapy-controlled double-blinded study of 419 subjects with uncomplicated obesity. Patients were advised on diet and exercise in addition to receiving the medication(s). At 24 weeks, Bupropion SR (400 mg/day) and Naltrexone ER 16 mg/day, 32 mg/day, and 48 mg/day induced significant placebo subtracted weight losses of −4.62 % ($p<0.001$), −4.65 % ($p<0.001$) and −3.53 % ($p<0.001$) respectively [23]. The weight loss continued over the next 24 weeks in an extension for the Bupropion/

Naltrexone combination 400/32 and 400/48 [23] (Fig. 16.2a). The weight loss produced a reduction in body fat and visceral adipose tissue mass, consistent with the degree of weight loss [57]. The most common side effect was nausea and this was higher in the 400/48 group [23].

The combination of Naltrexone/Bupropion was next studied in four phase 3 clinical weight loss placebo-controlled, randomized, double-blinded trials in a total of 4,500 subjects, in conjunction with behavior modification for 56 weeks [56].

In the COR-I study [58], 1,742 participants were enrolled and randomized to placebo, Naltrexone 360 mg/Bupropion 16 mg/day (NB16) or Naltrexone 360 mg/Bupropion 32 mg/day (NB32). Subjects were obese without complications (such as diabetes) and were instructed in a mild hypocaloric diet and exercise. After 56 weeks, NB16 induced a significant 3.7 % net weight loss vs. 4.8 % net weight loss in the NB32 group. The percentage of subjects considered responders (more than 5 % weight loss) was significantly higher in the NB32 and NB16 vs. placebo (48 %, 39 %, 16 %, respectively, $p<0.0001$) [58].

In the COR-BMOD trial [59] an intensive behavior modification program in addition to placebo or Naltrexone 32 mg/Bupropion 360 mg/day was studied in 793 obese subjects. After 56 weeks, subjects who completed achieved 11.5 % vs. 7.3 % weight loss in the Naltrexone/Bupropion vs. placebo group respectively ($p<0.0001$) [59]. Significantly more subjects who completed the study achieved more than 5 % weight loss in the Naltrexone/Bupropion group vs. placebo (80 % vs. 60 % respectively, $p<0.001$). The treatment group had significant improvements in cardiovascular disease markers (waist circumference, triglycerides, fasting insulin) and quality of life [59].

In the COR-II trial [60] 1,496 subjects were randomized to either placebo or Naltrexone 32 mg/Bupropion 360 mg/day. Subjects were either obese or overweight with dyslipidemia and/or hypertension. After 28 and 56 weeks, Naltrexone/Bupropion induced a significantly greater net weight loss compared to placebo (−4.6 %, −5.2 % respectively, $p<0.001$) [60]. Significantly more subjects lost more than 5 % of initial body weight in the Naltrexone/Bupropion vs. placebo group (51 % vs. 17 %, respectively, $p<0.001$). Subjects in the treatment group significantly improved cardiovascular disease markers (waist circumference, triglycerides, HDL-Cholesterol, LDL-Cholesterol, fasting insulin) and quality of life [60].

In the COR-Diabetes trial, obese type 2 diabetes patients lost a net 3.2 % body weight ($p<0.001$ vs. placebo) [56]. Subjects that lost more than 5 % of baseline body weight were significantly more than in the placebo group (44.5 % vs. 18.9 %, respectively, $p<0.001$). Naltrexone 32 mg/Bupropion 360 mg/day induced an improvement in diabetes control as shown by the net decrease in HbA1C of 0.5 % [56].

Side Effects/Tolerability

Pooled analysis from the phase 2 and phase 3 trials showed that Naltrexone/Bupropion is generally well tolerated [56]. The most common side effects were nausea, followed by urticaria and anxiety. There was no effect on depression symptoms or suicidality, blood pressure, or electrocardiographic findings [56]. There were two serious adverse events of cholecystitis in the treated subjects [56] (Table 16.1).

Zonisamide/Bupropion

Indication

A combination of Zonisamide and Bupropion has been proposed for weight loss in order to: minimize side effects through dose reduction of each individual agent, to reduce seizure risk of Bupropion and to reduce somnolence, fatigue, and depression effects of Zonisamide. This combination acts on the three major neurotransmitters that regulate appetite and therefore may have additive effects.

Efficacy and Side Effects/Tolerability

A 12-week randomized, open-label clinical trial studied the effect of Zonisamide (starting at 100 mg/day and titrated up to 400 mg/day) and Bupropion (started at 100 mg/day and titrated to 200 mg/day) in 18 obese women with an average

BMI of 37 kg/m^2 in addition to a low-calorie diet. After 12 weeks, patients on Zonisamide/Bupropion lost 8.1 kg vs. 3.3 kg with Zonisamide monotherapy ($p=0.004$). This study did show better tolerability with the combination therapy as compared to Zonisamide alone [61].

Summary and the Future of Weight Loss Drugs

After the challenges of the initial approval of the two most recent drugs there has been a resurgence of interest in the discovery and development of obesity pharmacotherapy. There are clear challenges in the approval of obesity drugs including uncertainties around the potential for a requirement for expensive pre-marketing cardiovascular outcomes studies, an apparently higher bar set by European regulators, and modest coverage by private insurance and no coverage by federal programs like Medicare and Medicaid. Encouragingly, since March of 2014, federal employees are covered for obesity pharmacotherapy. This is balanced by the ever increasing number of patients with obesity worldwide and increasing awareness of the risks associated with not treating persons with obesity. More data on cost-effectiveness, reductions in concomitant drug use, and long-term safety as well as a change in the perception at Centers for Medicare & Medicaid Services will be needed to drive access to obesity treatments including pharmacotherapy forward. The pandemic will continue to drive demand; however, and given the richness of the pipeline it is likely that patients will have access to several new obesity pharmacotherapies in the decade to come.

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Surgical Approaches and Outcome in the Treatment of the Obese Patients

17

Bruce M. Wolfe, George L. Blackburn, and Vivian M. Sanchez

Introduction

Candidates for bariatric surgery include those who experience severe obesity with a BMI $\geq$ 40 kg/m^2 or those with a BMI $\geq$ 35 with significant comorbidities [1]. In the United States an estimated 10–15 million people suffer from severe obesity [2]. While the prevalence of obesity in the United States appears to be somewhat at a plateau, the number with severe obesity (BMI $\geq$ 40) continues to increase progressively [3]. Following a period of rapid increase in the number of bariatric operations performed in the United States per year, the number appears to have stabilized [4]. It is estimated that less than 2 % of potential adult bariatric surgery candidates in fact undergo surgery per year in the United States [5].

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Obesity Pathology

Obesity is now recognized as a disease due to its association with a substantial increased risk of morbidity and all cause of mortality from numerous comorbidities. An obesity related comorbidity is a condition in which the cause of the condition is related at least in part to obesity and is expected to improve or remit in the presence of effective weight loss. It is appropriate to refer to remission of these comorbid conditions rather than resolution or cure, as the condition may recur should weight be regained. These comorbid conditions include type-2 diabetes, hypertension, dyslipidemia, cardiovascular disease (including stroke), obstructive sleep apnea, asthma, gall bladder disease, obesity related liver disease, degenerative arthritis, and several forms of cancer. In addition, impaired quality of life including low self-esteem and depression are common to a variable extent among the severely obese.

In the Look AHEAD trial, intensive behavior modification among patients with type 2 diabetes and obesity achieved a mean of 8 % weight loss at 1 year and 4.8 % at 4 years [6]. The positive effects on the control of diabetes, hypertension, and other comorbid conditions were demonstrated. Over a period of 8 years, however, recidivism of diabetes and obesity commonly recurs [7]. New medications may offer improved weight loss, but the sustainability of medication induced weight loss remains uncertain [8].

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The greater weight loss achieved by bariatric surgery (discussed below) leads to a greater impact on obesity related comorbid conditions [1].

Response to Bariatric Surgery

Bariatric surgical procedures achieve substantially greater and longer lasting weight loss than does usual care or intense behavior modification with or without medication. Sustained (>5 years) weight loss of 20 % or more on average is reported for most bariatric surgical procedures [9, 10]. However, the weight loss is highly variable within a population that undergoes seemingly identical operative procedures [11]. This substantial variation of weight loss has been under emphasized in most reports of postoperative outcomes and requires further examination. Factors involved in this variation include choice of procedure, pre- and postoperative care as well as patient derived factors. Further research is needed, however, to more accurately identify predictors of outcome for specific patients. The establishment of such predictors would facilitate identification of the best candidates for surgical intervention from the risk to benefit standpoint [12].

Associated with this weight loss is the expected response of comorbid conditions. The induction of remission among as many as 80 % of patients with type-2 diabetes has been reported with 1–2 year follow-up. A recent study utilizing rigorous methodology and definitions reported partial remission of diabetes 3 years after gastric bypass [11]. Induction of remission of hypertension, dyslipidemia, obstructive sleep apnea, functional capacity, and psychosocial impairment has also been reported in the majority of bariatric surgical patients, although the sustainability of these responses remain to be further defined [13, 14].

Mechanisms of Action of Bariatric Surgery

The traditional construct described bariatric surgical procedures as restrictive in which a small gastric pouch is created thereby limiting the amount of nutrients that can be consumed and/or malabsorptive in which ingested energy containing nutrients are incompletely absorbed. This construct has been demonstrated to be a substantial oversimplification if not inaccurate. Complex neuroendocrine signaling systems have been identified that are critical to the accomplishment of a reduction of nutrient intake. Evidence that malabsorption of nutrients plays an important role in accomplishing weight loss, is lacking [14].

Specific Procedures

The first bariatric surgical procedure to gain popularity was the jejunoileal or intestinal bypass in which a surgical short gut syndrome was created. While effective in accomplishing weight loss, this procedure was abandoned due to unacceptable short- and long-term complication rates. A variety of gastric stapling producers followed, mostly reinforced with a fixed gastric banding. The complications related to malabsorption were avoided, but unsatisfactory long-term weight loss as well as a low but definite incidence of complications that led to replacement of this procedure with the procedures described below (Fig. 17.1).

Roux-en-Y Gastric Bypass (RYGB)

In this procedure a small gastric pouch is created. The jejunium is divided and a Roux-en-Y jejunal limb anastomosis to the small gastric pouch is done. The Roux-en-Y configuration is done to avoid the potential complication of bile reflux gastritis and/or esophagitis associated with loop gastrojejunostomy. The loop gastrojejunostomy has been used in the performance of a gastric bypass known as “mini-gastric bypass”. Long-term outcomes of this procedure remain to be defined. There are three components to a gastric bypass which contribute to its success as a bariatric surgical procedure.

(1) Gastric restriction due to the small gastric pouch and bypass of at least 90 % body of the stomach. This results in diminished ghrelin

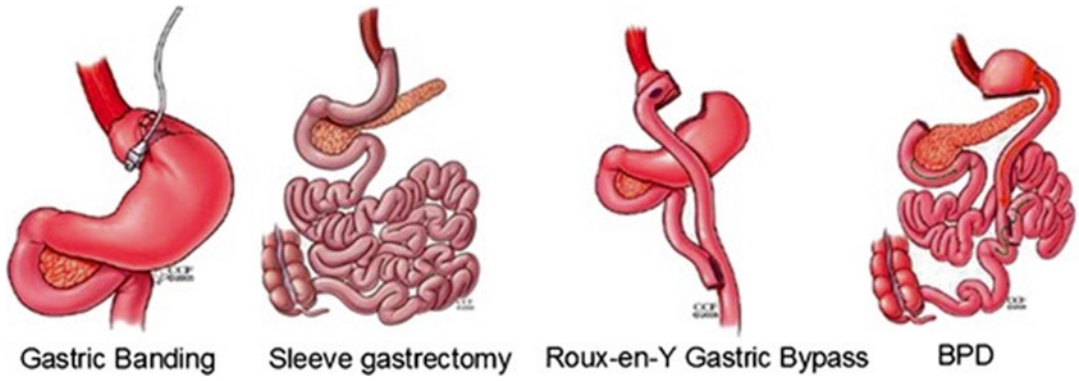

Fig. 17.1 Anatomic modifications of the four most commonly performed bariatric surgery procedures. More recently, purely restrictive operations such as adjustable gastric banding and sleeve gastrectomy have been widely adopted, although it is acknowledged that these procedures attain less weight loss and fewer metabolic benefits than bypass operations. From Heneghan HM, Nissen S, Schauer PR. Gastrointestinal surgery for obesity and diabetes: weight loss and control of hyperglycemia. Curr Atheroscler Rep. 2012 Dec;14(6):579-87. Reprinted with permission from Springer Science+Business Media

secretion [15]. (2) Bypass of the duodenum and proximal jejunum. Neuroendocrine phenomena, particularly with regard to stimulation of gastrointestinal peptide (GIP) occurs [16]. (3) Creation of an alimentary limb in which there is no proximal mixing of bile and pancreatic secretions to facilitate digestion. This procedure leads to relocation of the digestion and absorption of the nutrients more distally in the small intestine, presumably responsible for release of neuroendocrine signaling including gastrointestinal glucagon-like peptide 1 (GLP-1) and peptide YY secretion (PYY) [17]. These hormones are known to inhibit food intake. This procedure has proved durable with weight loss of 20–30 % persisting for 10 or more years [17].

Laparoscopic Adjustable Gastric Banding (LAGB)

Adjustable gastric banding was developed to address what was believed to be a primary limitation of the vertical banding gastroplasty. A small gastric pouch above the band and variable tightness of the band restrict the rate of gastric emptying. Tightening of the band may affect appetite and satiety apart from its role in restricting the amount of nutrients consumed. Weight loss following adjustable gastric banding was initially reported to approach that of gastric bypass, but more recent studies in the United States have indicated that 3 or more years following gastric banding, weight loss is approximately half of that seen with gastric bypass [2].

Biliopancreatic Diversion With our Without Duodenal Switch (BPD)

This procedure as initially described involved a partial gastrectomy with reconstruction of the small intestine to limit exposure of ingested nutrients, pancreatic secretion and bile to a short segment of distal small intestine, thereby creating a degree of malabsorption. In the duodenal switch modification of this procedure a gastric tube is created by resection of approximately 80 % of the stomach and anastomosis distal to the pylorus to the small intestine. Weight loss following this procedure is similar or superior to the weight loss following gastric bypass, as is the effect in ameliorating type in ameliorating type-2 diabetes. An increased rate of early and late complications particularly secondary to malabsorption, however, has limited application of this procedure.

Sleeve Gastrectomy (SG)

The application of the duodenal switch procedure to a subset of patients with severe obesity (generally BMI > 60) was associated with a problematic perioperative complication rate. As a modification the gastric component of the procedure was done as an initial procedure to be followed by the malabsorptive component in a later time. Careful observation of these patients demonstrated that many achieve satisfactory weight loss as the result of the partial gastrectomy component. As a result, sleeve gastrectomy became an independent procedure intended to be a definitive bariatric surgical procedure. This procedure has achieved considerable popularity, presently second to gastric bypass in application in the United States. Weight loss is generally reported as intermediate between that following gastric bypass and adjustable gastric banding [19, 20]. Long-term weight loss results remain to be determined. The impact on obesity related comorbid conditions also appears intermediate although more closely approximate the response seen following gastric bypass, thus accounting for much of this recent popularity.

Investigational Procedures

A number of procedures have been and continue to be developed to identify procedures which may offer satisfactory weight loss with less risk and/or cost. One such procedure is gastric plication in which a gastric tube similar to that achieved in sleeve gastrectomy is accomplished by imbrication of the greater curvature of the stomach. A number of devices are also under investigation. These include: intragastric balloon, devices to accomplish intermittent vagal blocking, an intraluminal sleeve to extend from the pylorus distally into the jejunum, and other devices which may serve to restrict nutrient intake. All of these investigational procedures in early studies have shown efficacy and acceptable safety. The sustainability of clinical outcomes will require further investigations [21–23].

Bariatric Surgery Outcomes: Complications

As with all surgical procedures, complications following bariatric surgery may occur and may be an important consideration. The relative safety of bariatric surgery has been substantially improved in recent years. For example, an expected mortality of 2 % in the past has been reduced to 0.3 % or less at 30 days [24]. The most common complications leading to perioperative mortality are anastomotic leak and secondary abdominal sepsis (procedures involving a gastrointestinal anastomosis), venous thromboembolism, and acute cardiac events (Table 17.1). Factors associated with nonfatal postoperative complications vary with variable definitions. Complications judged to be serious or requiring some type of intervention occurs in approximately 4 % of patients [24]. Several analyses of the predictors of increased perioperative risk have yielded inconsistent results making predictions of perioperative risk and risk adjustment difficult. Factors involved in the improved safety

Table 17.1 Longer-term complications of bariatric surgery

Surgical/Abdominal
– Hernia
– Intestinal obstruction
– Cholelithiasis
Metabolic
– Hypoglycemia
– Nephrolithiases
– Renal/Hepatic impairment
– Nutrient deficiency
Psychosocial
Procedure specific
Gastric bypass
– Anastomotic stricture
– Ulcer
– Gastrogastric fistula
Gastric banding
– Gastric erosion
– Gastric slippage
– Mechanical failure

Complications one or more years following bariatric surgery occur, but their incidence has not been well defined

of bariatric surgery include, but are not limited to the application of bariatric surgery to lower risk patients, establishment of care protocols, and increased operative experience for surgeons as well as the establishment of high volume bariatric surgery centers. Such centers may be accredited by a combined program of the American College of Surgeons and the American Society for Metabolic & Bariatric Surgery which is focused on the quality of care [25].

Bariatric/Metabolic Surgery and Type-2 Diabetes

Pories et al. made an important clinical observation that type-2 diabetes appears to go into remission very soon following RYGB, well before weight loss occurs [9]. The short- and long-term response to gastric bypass compared to gastric banding leads to greater weight loss and clinical response to diabetes [11]. This has led to the application of "metabolic" surgery to less severely obese patients with diabetes with remarkable induction of diabetes remission rates. Taken together, two main mechanisms seem to be responsible for the early improvement in glycemic control after RYGB: (1) an increase in hepatic insulin sensitivity induced, at least in part, by energy restriction and (2) improved beta cell function associated with an exaggerated postprandial glucagon-like peptide 1 secretion owing to the altered transit of nutrients. Later a weight loss induced improvement in peripheral sensitivity follows. In mild to moderately obese patients with type 2 diabetes, adding gastric bypass surgery to lifestyle and medical management was associated with greater likelihood of achieving the composite goal. Potential benefits of adding gastric bypass surgery to the best lifestyle and medical management strategies of diabetes must be weighed against the risk of serious adverse events. Further research is needed to determine the durability of this amelioration of type-2 diabetes by bariatric and/or metabolic surgery as well as the involved mechanisms [14, 27].

Bariatric Surgery and Cancer

Although the association of increasingly severe obesity with multiple cancers has been known for a number of years, the potential impact of weight loss on the incidence of cancer was not appreciated until long-term follow-up of bariatric surgery patients demonstrated a reduction in the incidence of cancer as well as cancer mortality ranging from 40 to 60 % 10 or more years following bariatric surgery [29]. The mechanism(s) of this cancer reduction remains to be defined. The cancer reduction in the Swedish Obese Subjects (SOS) study occurred in women, but not men. Specifically a reduced incidence of breast cancer was progressively noted as the duration of follow-up extended 10 years and beyond [29].

Decision to Perform Bariatric Surgery/Specific Procedure

Despite the multiple benefits of bariatric surgery on obesity and its comorbid conditions including quality of life, the number of individuals who in fact undergo bariatric surgery per year is a remarkably small proportion of the potentially eligible candidates. Factors involved include fear of complication and limited third party coverage for the cost and therefore access to surgical care. Further research to refine prediction of the potential surgical candidates most likely to achieve successful weight loss with minimal risk of complication will improve the benefit to risk ratio and potentially lead to greater application of surgical intervention to obesity and its complications. Continued definition of the pros and cons of these specific procedures their risks and role in addressing specific comorbidities such as diabetes will also facilitate future optimal identification of candidates for specific procedures. As less invasive procedures, particularly those performed by luminal endoscopy are developed the options will be expanded. Careful consideration of the risk and benefits of each procedure for each specific patient will be critical. An example is the superior response to diabetes following gastric bypass as opposed to gastric banding.

Bariatric Surgery Cost

There is definite upfront cost associated with the preparation for and accomplishment of bariatric surgical procedures. The induction of remission of comorbid conditions has the potential to reduce future healthcare cost by reduction of medication cost and complications associated with chronic comorbid conditions. These savings may be offset, however, by the increased application of procedures such as joint replacement for those severely obese patients who were denied joint replacement prior to weight loss as well as treatment of complications. Reported studies of long-term bariatric surgical cost/savings have yielded variable results [30].

Conclusion

Weight-loss surgery is fundamentally different from dieting. Changes in physiology resulting from the surgery reset energy equilibrium [31], affect the complex weight-regulatory system at multiple levels, inhibit environmental influences on weight regulation, and defeat powerful mechanisms that are inappropriately active in obesity. Gastric bypass procedures in particular induce physiological and neuroendocrine changes that appear to affect the weight regulatory centers in the brain, suggesting alteration of the reward pathways in the central nervous system.

Researchers have begun to explore the molecular pathways responsible for these changes. As they identify those pathways and ascertain the differences between surgical and nonsurgical treatments, new therapeutic options will become available. In the interim, bariatric surgery has taken its place as a first-line treatment option for the rapidly increasing population of patients who suffer from life-threatening severe obesity.

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18 Managing Micronutrient Deficiencies in the Bariatric Surgical Patient

Robert F. Kushner

Introduction

Bariatric surgery has been endorsed as an acceptable weight loss option for patients with severe (also called extreme, morbid or class III) obesity or those with moderate obesity who have comorbid conditions by several authoritative guidelines and conferences [1–6]. The exponential growth in procedures is due to several factors including improved surgical techniques, reduction in the postoperative mortality rate, significant improvement in obesity-related comorbid conditions [7], increased media attention, and profitability. The upsurge in surgical procedures also reflects the increasing prevalence of severe obesity in the United States. Approximately 6 % of adult Americans are considered severely obese (body mass index $\geq$40 kg/m^2) with prevalence figures reaching 18 % for non-Hispanic black women [8]. It is therefore likely that healthcare professionals from all disciplines will encounter patients who have undergone a bariatric surgical procedure. Similarly, primary care physicians and specialists will be expected to monitor and manage their patients on a long-term basis. Although physicians are trained to manage chronic diseases commonly associated with severe obesity, such as type 2 diabetes, obstructive sleep apnea, hypertension, mixed hyperlipidemia, and arthritis among others, nutritional management following bariatric surgery is not routinely taught. The combined restrictive-malabsorptive surgical procedures—Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD), and biliopancreatic diversion with duodenal switch (BPDDS), place patients at high risk for development of both macro- and micronutrient deficiencies unless they are properly counseled and supplemented. Since most of the deficiencies can be identified early at a preclinical stage, early treatment will prevent or reduce symptoms and deficiency syndromes. This chapter will review the identification and management of the most common micronutrient deficiencies that may occur following restrictive-malabsorptive bariatric surgeries.

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Bariatric Surgery-Related Micronutrient Deficiencies

By definition, micronutrients are essential nutrients that are required in only small quantities (mg or micrograms) such as minerals, trace elements, and vitamins. Deficiencies of micronutrients following bariatric surgery can arise from several mechanisms that include (1) preoperative deficiency, (2) reduced dietary intake, (3) malabsorption, and (4) inadequate supplementation. Bariatric surgery is unique in that the RYGB, LGS, BPD,

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and BPDDS procedures surgically alter the gastrointestinal anatomy in known ways. By bypassing the stomach, duodenum, and varying portions of the jejunum and ileum, malabsorption of four vitamins (thiamine, folate, vitamin B_{12}, and vitamin D) and two minerals (calcium and iron) may occur. Although less common, deficiencies of other vitamins and minerals have also been described, including vitamin A and copper. In general, the greater the malabsorption, the higher the risk for developing nutritional deficiencies. The prevalence of these deficiencies varies widely in the literature due to differences in surgical technique, patient population, definition of deficiency, supplementation protocols, and length and completion of patient follow-up. For example, iron deficiency is reported to range from 20 to 49 % and vitamin B_{12} deficiency from 26 to 70 % [9–17]. In the following section, 'at-risk' micronutrients will be each reviewed considering pathophysiology, clinical presentation, screening tests, and treatment. Table 18.1 provides a summary of the assessment and treatment of micronutrient deficiencies. Other recent review articles address the general topic of nutritional and metabolic problems following bariatric surgery [18–24].

Micronutrient Deficiency

Thiamine

Thiamine (vitamin B_1) is a coenzyme for the essential enzymes transketolase, pyruvate dehydrogenase, and pyruvate carboxylase, in the early stages of the tricarboxylic acid cycle and in the pentose phosphate pathway [25]. Thiamine is mainly absorbed in the jejunum by both active and passive diffusion. Since the biological half-life of the vitamin is rather short (in the range of 9–18 days) and only a small percentage of a high dose is absorbed [26], patients are at risk of developing deficiency syndromes after bariatric surgery. Over the past 3 decades, numerous case reports of thiamine deficiency have been reported following both restrictive and restrictive-malabsorptive surgeries [27–44]. An acute deficiency of thiamine associated with rapidly progressing clinical symptoms appears to most commonly result from a combination of restricted food intake and persistent intractable vomiting. Symptoms commonly occur 1–3 months postoperatively although may occur later. The clinical presentation varies but three conditions have been reported. Classical Wernicke's encephalopathy is the most common presentation and consists of double vision, nystagmus, ataxia, and a global confusion manifested by apathy, impaired awareness of the immediate situation, disorientation, inattention, and an inability to concentrate. Dry beriberi presents as bilateral, symmetric, lower extremity paresthesia, while wet beriberi manifests as high output congestive heart failure, edema, and metabolic acidosis.

Several recent reviews of neurologic complications following bariatric surgery have been published [45–50]. These authors describe a constellation of symptoms including mono- and polyneuropathy with weakness and/or paresthesias, burning feet syndrome, and hyporeflexia. Chang et al. [51] coined the acronym APGARS (Acute post-gastric reduction surgery neuropathy) to describe conditions with features of weakness, hyporeflexia, and vomiting. Since all symptoms did not improve with thiamine treatment, the authors suggest that additional nutritional deficiencies may be involved in the etiology of this syndrome.

Thiamine status is best assessed by determining erythrocyte transketolase activity. Magnetic resonance imaging (MRI) is useful in confirming the diagnosis of acute Wernicke's encephalopathy with a sensitivity of 53 % and specificity of 93 % [52]. With this test, increased T2 signal of paraventricular regions of the thalamus and increased T2 signal of periaqueductal regions of the midbrain are seen. However, treatment should not be delayed if a thiamine deficiency syndrome is suspected. Treatment with thiamine 100 mg IV every 8 h for 7–14 days followed by 50–100 mg po daily is recommended for these syndromes until the patient fully recovers. To avoid deficiency, patients should be routinely discharged from the hospital receiving a chewable multiple vitamin-mineral supplement that contains between 1.5 and 1.8 mg thiamine.

Table 18.1 Assessment and treatment of micronutrient deficiencies

Nutrient	Etiology	Deficiency conditions	Assessment/Monitoring	Treatment
Thiamine (vitamin B_1)	Precipitated after 1–3 months of intractable persistent vomiting	Wernicke's syndrome (double vision, nystagmus)	Diagnosis typically made by clinical presentation	Acute deficiency
		Acute polyneuropathy	Laboratory confirmation:	Thiamin 100 mg IV or IM × 7–14 days, then 10 mg/day orally until patient fully recovers
		Korsakoff encephalopathy (mental confusion)	Low basal erythrocyte transketolase activity (ETKA), enhanced response after TPP addition	Prophylaxis
		Dry beriberi (paresthesia)	Increased T2 signal on MRI of brain in thalamus and midbrain	1.5–1.8 mg po qd
		Wet beriberi (high output CHF)		
Iron	Diminished consumption of iron-rich foods (meats) due to intolerance	Iron deficiency is asymptomatic	Serum ferritin (reflects size of the storage of iron compartments (normal >12 μg/L)	All patients should take a multivitamin/mineral supplement containing 28–40 mg iron/day
	Achlorhydria—acid needed to reduce ferric to ferrous state	Iron deficiency Anemia (IDA)—fatigue, poor exercise tolerance, pale conjunctiva, spoon nails		Iron supplementation with ferrous iron 40-65 mg orally TID (+vitamin C)
	Bypassed site for absorption	Pica (pagophagia)	Increased total iron-binding capacity (TIBC), reduced transferrin saturation, microcytosis, microcytic anemia	Parenteral iron with iron dextran, sucrose or gluconate, ferumoxytol
	Iron losses in menstruating women			
Vitamin B_{12}	Decreased acid and pepsin digestion of protein-bound B_{12} from foods	Asymptomatic until development of anemia	Serum vitamin B_{12}	Vitamin B_{12} 350–1,000 μg orally or sublingually or
	Achlorhydria—acid needed to convert pepsinogen to pepsin	With advanced deficiency, development of polyneuropathy, paresthesias, and permanent neural impairment	<200 pg/mL	Nasal spray (Nascobal) 500 μg q weekly or
	Inadequate release of intrinsic factor (IF)		Macrocytic anemia, hypersegmented polymorphonuclear leukocytes	Intramuscular injection
	Incomplete release of B_{12} from R binders		Elevated serum homocysteine and methylmalonic acid (MMA) levels	100 μg monthly
Calcium		Tetany	Low serum calcium	Prophylaxis
		Osteoporosis	Elevated parathyroid hormone (PTH) level	Calcium citrate 1,200–2,000 mg q daily

(continued)

Table 18.1 (continued)

Nutrient	Etiology	Deficiency conditions	Assessment/Monitoring	Treatment
Calcium and Vitamin D	Reduced intake of calcium and vitamin D-containing foods	Asymptomatic until development of osteoporosis or	Increased alkaline phosphatase	All patients should take 1,200–2,000 mg calcium and ~3,000 IU vitamin D daily
	Malabsorption/ decreased absorption due to bypassed intestine and poor mixing of pancreatic and biliary secretions	Osteomalacia. May present as a bone fracture	Serum 25(OH)D level <30 ng/ mL	If deficiency, 50,000 IU vitamin D orally three times weekly; repeat 25(OH) D and PTH in several months
	Dark skin pigmentation, poor sun exposure, and obesity		Increased parathyroid hormone (PTH)—secondary hyperparathyroidism	

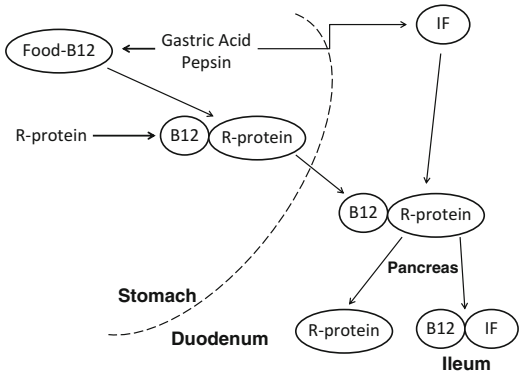

Fig. 18.1 Vitamin B_{12} absorption. See text for individual metabolic steps in absorptive process

Vitamin B_{12}

Vitamin B_{12} (cobalamin) is a cofactor in the biosynthesis of succinyl-coenzyme A and methionine and is important for the functioning of hemopoetic and neural cells [25]. Vitamin B_{12} absorption requires a complex sequence of orchestrated metabolic steps within the gastrointestinal tract (Fig. 18.1). In the stomach, food-bound B_{12} is first dissociated from animal proteins by acid and peptic hydrolysis to liberate free vitamin B_{12}. Once released, the vitamin is avidly bound to R proteins, which are glycoproteins secreted by the salivary glands and the gastric mucosa. In the intestine, pancreatic proteases then degrade R proteins and permit vitamin B_{12} to associate with intrinsic factor (IF), a glycoprotein that the parietal cells of the stomach secrete after being stimulated by food. The resulting IF-vitamin B_{12} complex is then bound to specific receptors in the distal ileum, where absorption occurs [26].

The restrictive-malabsorptive procedures disrupt several of these key steps. Vitamin B_{12} deficiency may occur due to decreased acid and pepsin digestion of protein-bound cobalamins from food, incomplete release of vitamin B_{12} from R proteins, and decreased availability of IF to form IF-vitamin B_{12} complexes. Because the parietal cells which secrete acid and IF, and chief cells which secrete pepsinogen, are located primarily in the fundus and body of the stomach, the LGS and RYGB procedures essentially excludes food from the normal gastric digestive process. Acid secretion has been demonstrated to be virtually absent in the small pouch constructed from the gastric cardia [53, 54]. Consequently, cobalamins are not liberated from protein and are not available for intestinal absorption. In all three restrictive-malabsorptive procedures, pancreatic secretions are diverted distally to mix with nutrients in a shortened common channel, thus affecting the vitamin's binding to IF and subsequent attachment to ileal IF-vitamin B_{12} receptors.

Although B_{12} deficiency is predictable, onset of signs and symptoms are typically delayed for months to years due to prolonged hepatic storage of the vitamin. When they do occur, clinical effects of deficiency are similar to those of pernicious anemia—hematological and neurological. Hypersegmented polymorphonuclear leukocytes and macrocytic erythrocytes can be seen on peripheral blood smear along with a macrocytic anemia. Neurological manifestations include sensory disturbances in the lower extremities (tingling and numbness); motor disturbances including abnormalities in gait; and cognitive changes ranging from loss of concentration to memory loss and disorientation [26].

Vitamin B_{12} status is most commonly and easily assessed by serum or plasma vitamin levels. The concentration of B_{12} in the serum or plasma reflects both the B_{12} intake and stores. The lower limit is considered to be approximately 120–180 pmol/L (170–250 pg/mL). However, a more sensitive biochemical indicator of deficiency is elevation of serum homocysteine and methylmalonic acid (MMA), levels which rise when the supply of B_{12} is low and virtually confirms the diagnosis.

All patients who undergo restrictive-malabsorptive procedures should receive prophylactic vitamin B_{12} supplementation to prevent deficiency. In contrast to the disruption of food-bound B_{12} absorption, crystalline vitamin B_{12} (the form found in vitamin supplements) can be absorbed in the surgical patient since approximately 1 % of orally administered crystalline cobalamin is absorbed by passive diffusion [55, 56]. An oral dose of at least 200 times the recommended dietary allowance (RDA) was shown to normalize mild vitamin B_{12} deficiency in older people assessed by reduction in plasma MMA concentration [57]. Oral treatment has also been effective in patients with pernicious anemia [58]. As a practical matter, patients should receive at least 500 μg B_{12} daily as a dietary supplement delivered orally as a tablet or liquid or sublingually; as a once weekly nasal spray 500 μg cyanocobalamin gel (Nascobal®), or by intramuscular injection (100 μg monthly to 3,000 μg every 6 months). The route of delivery is based on patient preference and monitoring of vitamin B_{12} status.

Folate

Folate deficiency occurs with lower frequency than vitamin B_{12} deficiency; however, it should be considered when evaluating a patient who develops anemia. Folate is a cofactor in the biosynthesis of methionine, thymidine, and purine nucleotides, and for the synthesis of the coenzyme tetrahydrofolate [25]. Folate is absorbed primarily from the proximal third of the small intestine after food folate polyglutamates are hydrolyzed to monoglutamates by intestinal brush border conjugases. Folate deficiency presents with many features similar to vitamin B_{12} deficiency, including hypersegmentation of the neutrophils, increased mean cell volume (MCV), and macrocytic anemia. Inadequate folate intake first leads to a decrease in serum folate concentration, then a decrease in erythrocyte folate concentration, a rise in homocysteine concentration, followed by clinical hematological changes as mentioned above [26]. A serum folate concentration of less than 7 nmol/L (3 ng/mL) indicates negative folate balance. All patients undergoing a restrictive-malabsorptive bariatric operation should receive supplemental doses of folate to prevent deficiency. Supplements of folic acid are nearly 100 % bioavailable. Typically, the amount of folate present in a general (400 μg) or prenatal multivitamin supplement (800–1,000 μg) is adequate to prevent deficiency.

Iron

Patients who undergo restrictive-malabsorptive procedures are at particular risk for developing iron deficiency and iron deficiency anemia (IDA) due to reduced iron absorption, decreased iron intake, and for menstruating women, increased iron losses. Surgical bypass of the duodenum and proximal jejunum decreases total iron uptake because the majority of iron absorption occurs across the apical and basolateral membrane of duodenal enterocytes [59]. Furthermore, acid secretion is nearly absent in the small gastric pouch [53, 54] or remnant gastric sleeve due to the paucity of parietal cells. Hypoacidity exacerbates

iron deficiency because both heme (found only in animal products) and nonheme (found in cereals and green leafy vegetables) iron depend upon the acidic environment of the stomach for efficient absorption [60]. Specifically, nonheme iron requires an acidic pH to reduce it from the ferric (Fe^{3+}) to the ferrous (Fe^{2+}) state, before it can be transported across the brush border membrane by divalent metal ion transporter 1 (DMT 1) in the alkaline duodenum. Although heme iron is more soluble and readily absorbed than nonheme iron, it must be released from its protein structure by the acid and proteases present in gastric juice before absorption can occur [61]. If iron is required by the body, it will cross the basolateral membrane through iron export protein ferroportin and enter the circulation in which is binds to plasma transferrin [62]. Iron absorption from the diet or from supplementation has been shown to decrease significantly after 6 months following RYGB to 33 % and 40 % of their initial values, respectively [63].

In addition to decreased iron absorption, bariatric surgical patients typically consume less heme iron due to an intolerance of meat products (which is full of hemoglobin and myoglobin) [64]. Women with menorrhagia are particularly prone to develop iron deficiency and IDA due to excessive menstrual blood loss. Menstrual iron losses range from 1.5 to 2.1 mg/day, bringing the RDA for females between 19 and 50 years old to 18 mg/day compared to 8 mg/day for males [65]. Due to the combination of these factors, IDA occurs postoperatively in 33–50 % of patients, with a higher incidence in menstruating women [66–68].

Iron deficiency may also be exacerbated in these patients as a result of a nutrient–nutrient inhibitory absorptive interaction between iron and calcium, another mineral that is routinely supplemented during the postoperative period. Most [69–74] but not all [75, 76] studies show that nonheme- and heme-iron absorption is inhibited up to 50–60 % when consumed in the presence of calcium supplements or with dairy products. Calcium at doses of 300–600 mg has a direct dose-related inhibiting effect on iron absorption. This has been seen with calcium carbonate, calcium citrate, and calcium phosphate. Studies by Hallberg et al. [70, 72] suggest that the inhibitory effect is situated within the intestinal mucosal cells. These observations are particularly important for bariatric surgical patients who are routinely prescribed calcium supplements and advised to consume dairy foods high in calcium, such as milk, cheese, and yogurt. In these patients, it appears prudent to recommend that iron and calcium supplementation be separated by several hours to avoid inhibitory interaction.

Early functional symptoms of iron deficiency include fatigue, poor exercise tolerance, and decreased work performance [77]. Signs on physical examination include pale conjunctiva and spoon nails. Serum ferritin is the most sensitive indicator of iron status (normal values usually fall in the range of 20–300 μg/L) and is recommended for diagnosing early iron deficiency [78]. The concentration of serum ferritin reflects the size of the storage iron compartment, with each μg/L representing 8–10 mg of storage iron [60]. However, caution is needed in interpreting ferritin concentration levels in the presence of acute and chronic inflammation since ferritin is also an acute phase reactant. Thus, serum ferritin concentrations may fall within normal range in individuals who have diminished iron stores. The concentration of liver-derived peptide hepcidin reflects body iron requirements and may be useful in the future as a biomarker for monitoring iron status [62]. Hepcidin regulates iron homeostasis by regulating ferroportin-mediated release of iron from enterocytes and macrophages. After the iron storage pool is depleted, there is an increase in total iron-binding capacity (TIBC), decreased serum transferrin saturation (serum iron concentration divided by TIBC × 100), followed by microcytosis (reduced mean corpuscular volume or MCV), hypochromia (reduced mean corpuscular hemoglobin concentration or MCHC), and anemia.

An unusual and fascinating symptom that is particularly associated with IDA is ice eating, or pagophagia, one of the most commonly reported forms of pica. Pica has been previously reported to occur with IDA of pregnancy [79, 80], gastrointestinal blood loss [81], and sickle cell disease [82].

Our group previously reported the first five cases of pagophagia associated with RYGB surgery [83, 84]. All patients were women between 34 and 45 years old with menorrhagia. Onset of pica symptoms ranged from 1 to 23 months post-surgery. Three of the patients described symptoms suggestive of pica when they were children and one during a previous pregnancy.

In order to prevent iron deficiency, all patients undergoing restrictive-malabsorptive surgeries should be prescribed a daily multivitamin–mineral supplement containing elemental iron. Supplementation with one prenatal vitamin and mineral tablet, which typically contains 28–40 mg elemental iron, is often sufficient. High-risk individuals, for example, those who have preoperative iron deficiency or excessive blood loss or those who develop iron deficiency or any degree of anemia, require additional supplementation with an iron salt preparation. Only ferrous iron formulations should be used such as ferrous sulfate, gluconate, or fumarate, since they are more readily absorbed [85]. However, it is important to note that a tablet of the sulfate salt contains twice the amount of elemental iron (65 mg) as a tablet of the other two salts. Therefore, twice as many ferrous gluconate or ferrous fumarate tablets are required to provide the amount of elemental iron in ferrous sulfate tablets [86]. Typical dosing of iron therapy is 150–200 mg/day po given in 2–3 divided doses for several months or until the serum ferritin reaches 50 μg/L. Patients who are responsive to treatment should develop reticulocytosis followed by an increase in hemoglobin. Co-administration with ascorbic acid (vitamin C), the best known reducing agent, is recommended to increase iron absorption [87]. In the presence of ascorbic acid, ferrous iron forms a soluble iron-ascorbic acid complex. Patients who were anemic may require long-term daily supplementation in addition to their other nutritional supplements. In patients with profound iron deficits and severe anemia unresponsive to oral iron supplementation, intravenous administration of iron dextran (InFed), ferric gluconate (Ferrlecit), ferric sucrose (Venofer), or ferumoxytol (Feraheme) will be required.

Calcium and Vitamin D

Calcium and vitamin D are considered together since deficiency of both nutrients may result in metabolic bone disease and their metabolism is interrelated. A negative calcium balance may result from limited intake of calcium- and vitamin D-containing dairy products, reduced fractional intestinal absorption due to surgical bypass of the absorptive sites, and vitamin D deficiency. The latter factor is important since calcium is absorbed by an active transport process dependent on the action of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) which binds with high affinity to the vitamin D receptor (VDR) to enhance calcium absorption primarily in the duodenum and jejunum [88] although most of the absorption occurs in the lower segment of the small intestine, the ileum [89]. Calcium is also absorbed by passive diffusion across the intestinal mucosa which becomes important at high calcium intakes such as supplemental calcium [90]. In a prospective study of women who underwent RYGB, fractional radiolabeled calcium absorption in milk was reduced 33 % 6 months after surgery [91].

Vitamin D deficiency may occur for the same reasons listed above for calcium deficiency, that is, reduced intake of vitamin D fortified dairy products and malabsorption of vitamin D due to mismixing of pancreatic and biliary secretions in the distal small intestine. Since vitamin D is fat soluble, it must be incorporated into the intestinal micelle along with bile salts for absorption. However, the major source of vitamin D for most people comes from casual exposure to sunlight. Unlike any other vitamin, vitamin D_3, or cholecalciferol is photosynthesized by the skin by UVB irradiation, converting 7-dehydrocholesterol (provitamin D) to previtamin D_3 in the plasma membrane of skin keratinocytes. Once formed in the skin, previtamin D_3 is rapidly converted to vitamin D_3 [90]. In the liver, vitamin D undergoes hydroxylation at the 25-carbon position to form 25-hydroxy vitamin D (25(OH)D) and subsequently transported to the kidney for additional hydroxylation at the 1-carbon position to form $1,25(OH)_2D$, the biological active form of the

vitamin. Several factors will impede the initial photosynthetic process including living at northern latitudes, wearing sunscreen lotion, limited sun exposure, dark skin pigmentation [92], aging, and obesity itself [93–96]. Melanin skin pigmentation is an effective natural sunscreen that greatly reduces UVB-mediated cutaneous synthesis of vitamin D_3. Thus dark-skinned individuals need longer UVB exposure to generate the same 25(OH)D stores compared with fair-skinned individuals. Several studies have demonstrated an inverse correlation between vitamin D concentrations and BMI or body fat percentage, suggesting decreased bioavailability of skin-derived vitamin D in obese individuals [97]. Thus, severely obese individuals are predisposed to vitamin D insufficiency or deficiency prior to undergoing bariatric surgery.

Clinical deficiency of calcium or vitamin D due to bariatric surgery cannot be detected on a routine chemistry panel, although an elevated alkaline phosphatase level and low calcium or phosphorus level may be seen. Symptoms of vitamin D deficiency are commonly nonspecific such fatigue or easy tiring, muscular weakness predominantly of the proximal limb muscles, and chronic musculoskeletal pain [98]. Unless specifically monitored, the first indication of deficiency is likely to be a vertebral or wrist fracture secondary to development of osteoporosis or osteomalacia. Physiologically, chronic calcium deficiency causes the circulating ionized calcium concentration to decline, which triggers an increase in parathyroid hormone (PTH) synthesis and release. In turn, PTH acts on three organs to restore the circulating calcium concentration to normal. At the kidney, PTH promotes the reabsorption of calcium in the distal tubule. PTH affects the intestine indirectly by stimulating the production of $1,25(OH)_2D$. PTH also induces bone resorption, thereby releasing calcium into the blood [88]. Chronic vitamin D deficiency can result in secondary hyperparathyroidism, increased bone turnover, enhanced bone loss, and increased risk of fragility fracture [99]. Secondary hyperparathyroidism is diagnosed by an elevated PTH level in the setting of low or normal serum calcium [92]. Therefore, detection of subclinical calcium and/or vitamin D deficiency requires measurement of several nutrients, hormone levels, and biochemical markers of bone turnover that are not routinely assessed.

Serum 25(OH) vitamin D is the best indicator for determining adequacy of vitamin D intake since it represents the combination of cutaneous production of vitamin D and the oral ingestion of both vitamin D_2 (ergocalciferol or plant-based vitamin D) and vitamin D_3. 25(OH)D is not only the transport form of the vitamin D but a direct measure of stores [100]. In the current literature, severe vitamin D deficiency is identified as a 25(OH)D level of less than 5–8 ng/mL (12.5–20 nmol/mL) and mild deficiency or insufficiency as a serum level less than 20 ng/mL (50 nmol/mL) [101]. However, there is debate about the exact cutoff values defining 'deficiency' and 'insufficiency' since these are static rather than functional definitions. When elevated PTH levels (secondary hyperparathyroidism) are used as a functional indicator of vitamin D deficiency, circulating levels of 25(OH)D of at least 30 ng/mL appear optimal [102, 103]. Biochemical monitoring of bone turnover includes measurement of bone formation markers—serum osteocalcin and bone-specific alkaline phosphatase, and the bone resorption marker—serum and urine peptide-bound N-telopeptide crosslinks of type 1 collagen (NTX) [104]. Assessment of bone mineral density (BMD) and bone mineral content (BMC) by dual energy X-ray absorptiometry (DXA) remains the gold standard for the diagnosis of osteoporosis [105].

Abnormalities in vitamin D and bone metabolism among patients undergoing restrictive-malabsorptive bariatric operations have been reported in numerous case series, case reports, and recent reviews [106–118]. Although the studies are primarily observational, contain few patients, and uncontrolled for diet and vitamin mineral supplementation, most studies document the occurrence of hypovitaminosis D and elevated PTH over the first 1–3 postoperative years, with a prevalence ranging from 30 [98] to 80 % [119]. Many of the studies also show a corresponding elevation in alkaline phosphatase levels and biochemical markers of bone turnover. There are multiple factors involved in post-surgical bone mass loss that includes nutritional

deficiencies, rapid weight loss, and possibly changes in adipokines and gut-derived appetite regulatory hormones [118]. In a prospective study of 73 patients who underwent either a restrictive or restrictive-malabsorptive bariatric surgical procedure, both urinary NTX and osteocalcin increased significantly by 3 months after surgery and remained significantly elevated through 18 months [120]. Median serum PTH levels at 9 and 12 months were higher in patients who underwent a restrictive-malabsorptive procedure compared to those who underwent LAGB. PTH levels were associated with increased serum $1,25(OH)_2D$.

It is important to prospectively monitor patients preoperatively and postoperatively since many obese patients present to surgical centers with underlying vitamin and mineral deficiencies, including D deficiency and some with secondary hyperparathyroidism [121–125]. Several cases of severe secondary hyperparathyroidism with osteomalacia have been reported to occur from 9 to 17 years post-surgery [112, 126]. However, since weight reduction itself is associated with reduced BMD and BMC [127, 128], it is important to distinguish between the weight loss and malabsorptive effects of bariatric surgery. Pugnale et al. [129] showed that BMD of the cortical bone decreased significantly among 31 women who underwent a restrictive banding procedure without evidence of secondary hyperparathyroidism. In a 1-year prospective study among 23 obese men and women who underwent RYGB, there was a significant decrease in BMD at the femoral neck and total hip by 9.2 % and 8 %, respectively, associated with a significant increase in urinary NTX and serum osteocalcin [130]. Similarly, Guney et al. demonstrated that weight reduction causes bone loss among both diet treated patients and those who underwent a restrictive vertical banded gastroplasty without a significant change in PTH levels [131]. In another study, six obese control patients were compared to four patients who underwent an RYGB and nine patients who received gastric banding [111]. The RYGB operation resulted in significant net loss of bone mass in comparison to the banding and obese control group. In the study by El-Kadre et al. [109], 10 % of patient had elevated PTH levels preoperatively, whereas the prevalence was 22 % and 25 % in the series by Johnson et al. [114] and Hamoui et al. [110], respectively.

Inclusion of calcium- and vitamin D-containing dairy products in the postoperative diet is important. One serving of milk contains approximately 300 mg calcium. However, many patients will avoid or limit dairy foods due to lactose intolerance or lack of an acquired taste. Choosing lactaid milk or adding lactase to dairy products will address the former problem. To avoid deficiency and supplement the diet, all patients should receive calcium supplements of at least 1,200–2,000 mg/day in divided doses, depending on the adequacy of dietary calcium. Postmenopausal, lactating or pregnant women may require higher ranges due to increased needs. Calcium citrate + vitamin D is the preferred preparation because it is more soluble than calcium carbonate in the absence of gastric acid production [132]. The optimal dose for vitamin D is more controversial since some studies have shown continued deficiency despite high dose supplementation [116, 120, 121]. General guidelines recommend 3,000–5,000 IU per day. Since multivitamin–mineral tablet typically contains 400 IU and calcium + Vitamin D tablets typically contain 500 IU, many patients will require additional vitamin D.

If vitamin D deficiency is detected, measurement of PTH should be obtained to provide a functional assessment. Treatment may involve recommending higher supplemental doses of calcium and vitamin D and reassessing in about 3 months. In patients with severe vitamin D deficiency, initial repletion of stores should be treated with vitamin D 50,000 IU 1–3 times weekly for 8 weeks, then checking 25(OH)D levels [111]. Monitoring of the alkaline phosphatase level and serum and urinary calcium should also be performed.

Other Deficiencies

Micronutrient deficiencies of vitamin A and copper have been reported following bariatric surgery, although less often that the aforementioned nutrients. They will briefly be reviewed.

Vitamin A

Vitamin A, whether ingested as preformed vitamin A (retinyl esters) or as provitamin A carotenoids, requires processing in the intestine to release the nutrients in an absorbable form [25]. Since vitamin A is a fat-soluble vitamin, any condition that interferes with emulsification is likely to reduce intestinal absorption of retinol. Thus vitamin A dietary compounds are more likely to be malabsorbed with the BPD and BPDDS procedures which limit the exposure of food with biliopancreatic digestive secretions within a shortened common channel. Subsequently, deficiency of vitamin A has been more frequently reported among patients who have undergone a BPD or BPDSS procedure compared to RYGB [16], although deficiency has been reported following RYGB as well [133–135]. Slater et al. [136] observed an incidence of vitamin A deficiency of 52 % at 1 year which increased to 69 % by year 4. Similarly elevated incidence rates of vitamin A deficiency were seen by Dolan et al. [137] at 12–18 months after BPD or BPDDS. In a retrospective chart review among 122 patients who underwent RYGB, 35 % and 18 % of patients were vitamin A deficient at 6 weeks and 1 year, respectively [135]. Several cases of symptomatic vitamin A deficiency have been reported following bariatric surgery, occurring 18 and 24 months postoperatively [138, 139]. Patients presented with night blindness (nyctalopia) while one developed diffuse conjunctival xerosis with a Bitot's spot, and diffuse punctuate keratitis of both corneas. In another study of 64 RYGB patients who completed a postoperative survey, reported ocular symptoms potentially related to vitamin A deficiency included xerosis (38 %), night vision changes (68 %), and eye pain/foreign body sensation (23 %) [133].

Preformed vitamin A is found in foods from animal sources, including dairy products, fish, and meat (especially liver). By far the most important provitamin A carotenoid is beta-carotene. Good sources of carotenoids include spinach, sweet potato, carrots, and cantaloupe. Routine screening for vitamin A is recommended for the BPD and BPDDS malabsorptive procedures. To prevent deficiency, a daily dose of at least 10,000 IU is recommended. For patients who undergo RYGB, a prenatal multiple vitamin-mineral supplement containing at least 5,000 IU vitamin A should be provided on a daily basis

Copper

Copper deficiency has emerged as a cause of an array of neurological symptoms that may occur among patients who have undergone bariatric surgery. Reported symptoms include unsteady gait, extremity numbness, paresthesias, or paralysis occurring as long as 10 years following the procedure [140–142]. Other accompanying presentations may include anemia, neutropenia, and pancytopenia. Copper is absorbed primarily in the small intestine with a small amount absorbed in the stomach through a saturable, active transport process [25]. Iron and zinc have been shown to interfere with copper absorption, a particularly important fact since bariatric surgical patients are often asked to take multiple mineral supplements. Copper is required for the formation and maintenance of myelin and in iron metabolism. Most of the copper in blood is bound to ceruloplasmin which is the most reliable index of copper status. The incidence of copper deficiency is uncertain since the micronutrient is not commonly measured.

Copper administration of 2 mg/day should be included as part of routine multivitamin–mineral supplementation. Routine copper screening is not recommended for bariatric surgery patients. However, patients presenting with signs and symptoms of myelopathy or myeloneuropathy should have serum copper and ceruloplasmin values measured. In severe deficiency, treatment can be initiated with IV copper (2–4 mg/day) for 6 days, followed by oral administration [23].

Prophylactic Management and Monitoring for Nutritional Deficiencies

Nutritional management of the bariatric surgical patient must include prophylactic administration of vitamins and minerals to avoid deficiencies.

Table 18.2 Vitamin and mineral supplementation products (selected 'at-risk' micronutrients)

Nutrient	DRI[a]	Flintstones complete chewable	Centrum adults	One-A-Day women's prenatal	Bariatric advantage	Bari Life
Serving size		1 Tablet	1 Tablet	1 Tablet	2 Tablets	3 Tablets
Vitamin A	900	3,000	3,500	4,000	7,500	5,000
Vitamin D (IU)	800	600	400	400	1,000	3,000
Thiamine (mg)	1.2	1.5	1.5	1.7	6.0	3.0
Folate (μg)	400	400	400	800	800	200
Vitamin B_{12} (μg)	2.4	6	6	8	100	500
Calcium (mg)	1,200	100	200	300	200	1,000
Iron (mg)	18	18	18	28	–	22.5
Copper (mg)	0.9	2.0	2.0	2.0	2.0	1.0

Products included in the table are intended to provide examples of commercially available products. Patients and providers should review the specific supplement facts label for the product chosen for clinical use

[a]Dietary Reference Intake, highest value per individual micronutrient for male or female adult ≥18 years old

As a practical manner, all patients should be discharged from the hospital receiving a chewable multiple vitamin-mineral supplement. After the first postoperative month, patients can be switched to a prescribed or over-the-counter supplement. Examples of products with nutrient content are shown in Table 18.2. Since the calcium, vitamin D, and vitamin B_{12} contents of the supplements are inadequate to meet postsurgical needs, all patients should receive additional calcium citrate 1,200–2,000 mg daily depending on dairy calcium along with at least 500 μg vitamin B_{12}.

Monitoring of nutritional status should begin preoperatively. Table 18.3 displays a list of routine laboratory and micronutrient tests and procedures. Once detected, deficiencies should be treated and monitored carefully. Patients at particularly high risk, such as women with menorrhagia, will likely require additional supplementation of selected nutrients.

Table 18.3 Postoperative checklist for nutritional supplementation and monitoring for bariatric surgery

Early postoperative care
Multivitamin–mineral tablet
Calcium citrate, 1,200–2,000 mg/day
Vitamin D, at least 3,000 IU/day
Vitamin B_{12} 500–1,000 μg/day orally or sublingually
Maintain adequate hydration (usually >1.5 L/d)
Monitoring (preoperatively and at follow up ~3, 6, and 12 months, then annually)
CBC, chemistry profile
Vitamin B_{12} (if deficient, supplement and assess q 3–6 months)
Folic acid
Iron studies (iron, TIBC, transferrin saturation, ferritin)
25(OH)D and iPTH
Bone density (DXA) at 2 years
Vitamin A (for BPD and BPDDS procedures)
Copper, zinc, and selenium evaluation with specific findings
Thiamine evaluation with specific findings

Adapted from Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: American Association of Clinical Endocrinologists, The Obesity Society, and the American Society for Metabolic & Bariatric Surgery. Obesity 2013;21:S1-S27

Conclusion

The restrictive-malabsorptive bariatric surgeries are associated with an increased risk of developing several micronutrient deficiencies. With judicious monitoring and adequate supplementation, these deficiencies are largely avoidable and treatable. However, the long-term sequela of calcium and vitamin D malabsorption and development of metabolic bone disease remains a major concern. It is recommended that patients be screened preoperatively and at periodic intervals postoperatively. Identification of micronutrient deficiencies should be aggressively treated.

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Evaluation and Treatment of Obesity in Primary Care

19

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Primary care physicians (PCPs) and other providers are in a unique position to evaluate and treat obesity in their patients. As the physicians who see patients longitudinally, they can intervene on obesity as a chronic condition, one that can be treated, but usually not cured. Given the number of conditions treated in primary care that are partly or mostly a result of overweight and obesity [1], it is logical for PCPs to initiate the conversation about obesity, if not to provide treatment.

Historically, treatment for obesity has been reimbursed inconsistently, if at all. However, in 2011, the Center for Medicare and Medicaid Services (CMS) began to reimburse PCPs and other providers for intensive treatment of obesity [2]. Specifically, CMS will pay for weekly visits in the first month, every other week visits through month 6, and if the patient loses at least 3 kg, monthly visits during months 7–12 (up to 20 visits total in 1 year; the same schedule of visits may be repeated annually). The visits are expected to be 15 min long and must be delivered in the physical setting of the primary care office.

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This decision by CMS is important, given the high prevalence of obesity in the United States [3] and the benefits of weight loss in improving health and reducing risk factors for cardiovascular disease (CVD) [4–7]. In the long run, the CMS decision is likely to be an important turning point in the incorporation of obesity treatment into routine settings of medical care. The decision occurs in the context of the recommendation from the US Preventive Services Task Force (USPSTF) that "clinicians screen all adults for obesity and offer intensive multicomponent behavioral interventions to affected individuals", either by providing such treatment themselves or referring patients to appropriate interventions [8]. This recommendation received a "B" rating from the USPSTF (B rating = high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial) and was an update of its initial recommendation from 2003 [9].

This chapter reviews the evidence for PCPs who wish to treat obesity in their own practices and/or to refer patients to other interventions for intensive treatment. What follows is not a systematic review of the literature, but a review of key studies in the field, the results of which can guide PCPs in their efforts to counsel patients about weight [10, 11]. We review the general principles of behavioral treatment for obesity, followed by a description of models for treating obesity in practice (including remotely delivered counseling), and the evidence for these models. We end with options to refer patients for treatment outside of the practice.

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Treatment of Obesity with Lifestyle Modification

Lifestyle modification for treatment of obesity has three components, whether delivered in the primary care setting or in another setting. These three components are diet, physical activity, and behavior modification [4, 12]. The National Heart Lung and Blood algorithm for treatment of obesity recommends a comprehensive program of lifestyle modification for all individuals with BMI ≥ 30 kg/m^2 and for those with a BMI ≥ 25 kg/m^2 who have risk factors for CVD [4]. Diet typically consists of a prescription for a calorie-restricted diet, following federal dietary guidelines with respect to macronutrient content (approximately 50–60 % of calories from carbohydrate, mostly whole grains), and with a deficit of 500–1,000 cal/day. This is often translated into a target of 1,200–1,500 kcal/day for individuals <250 lbs and a target of 1,500–1,800 kcal/day for individuals ≥250 lbs [7]. Physical activity usually involves advice to exercise at least 30 min/day on most or all days of the week, with aerobic activities on most days and 2 days/week of muscle strengthening activity [13]. This amount of exercise is considered the minimum for general health and preventing weight gain, while greater amounts of exercise (45–60 min/day) are thought to be required for maintaining weight loss [14]. Behavior modification provides a set of principles and techniques, such as goal setting and record keeping, to help patients adhere to their diet and activity recommendations.

Comprehensive lifestyle modification for the treatment of obesity was developed in academic medical centers. Treatment is typically provided in a group format, with weekly meetings for the first several months. Treatment providers usually include registered dietitians, behavioral psychologists, exercise experts, or other professionals with formal training in patient counseling and obesity treatment. Weight losses after 4–6 months of treatment average 7–10 % of starting weight [7, 15].

As mentioned, the USPSTF recommendation is for intensive programs, defined as 12–26 sessions during the first year [8]. The recommendation for intensive programs is true whether or not the treatment is delivered in the primary care setting. This recommendation was reinforced by a 2011 systematic review of obesity treatment interventions, sponsored by the Task Force [16]. The review found that interventions that provided 12–26 treatment sessions in the first year produced weight losses of 4–7 kg, while those interventions that provided fewer than 12 sessions induced a weight loss of 1.5–4 kg (an amount not likely to be clinically important for most individuals).

The CMS decision memo stipulates that the obesity counseling visits take place in the physical setting of the primary care practice. However, the studies that formed the basis of the 2011 review by LeBlanc [16], as well as of the 2012 update by the Task Force, were mostly conducted in academic medical centers, using experienced staff as treatment providers (e.g., RDs, psychologists). Most primary care practices do not have a full time dietitian or health educator working in the practice. Thus, it remains unclear how the recommendations of the USPSTF can actually be implemented in a busy primary practice. Primary care practices are under significant pressure from multiple directions to improve quality and coordination of care, manage population health, and control costs. Whether PCPs, most of whom have no formal training in weight management [17], can successfully implement the CMS guidelines and produce weight loss in their patients, is an unanswered question.

The 5A Approach to Treating Obesity

CMS, in its decision to reimburse obesity treatment, recommended a 5A approach to counseling patients about their weight [18–20]. The 5A approach is: Assess; Advise; Agree; Assist; Arrange.

Assess: PCPs should assess weight and related health risk. For example, a 55-year-old obese man with dyslipidemia and pre-diabetes is at much higher risk of CVD, as compared to a

30-year-old obese woman with normal lab values. *Advise*: PCPs should recommend weight loss, personalizing the recommendation to the patient. "Mr. Smith, I know it's not easy to wear the CPAP mask. If we could help you lose at least 10 % of your current weight, you would likely have an improvement in the sleep apnea, and possibly not even need the mask any longer". *Agree*: Patients and PCPs should agree on a specific target for behavior change. For example, they might agree that the patient will try to cut out desserts or sugar-sweetened drinks. *Assist*: PCPs should assist in offering their patients intensive treatment, as recommended by the USPSTF, or assist by referring them to a program that offers intensive treatment. *Arrange*: PCPs should arrange follow-up in the primary care office, to check in with the patient in a few months and assess progress towards goals.

Models for Behavioral Treatment of Obesity in Primary Care

A model for the treatment of obesity in primary care, developed by Tsai and Wadden [21], proposes that the PCP has a critical role to play in both the initiation and follow-up of treatment of obesity (Fig. 19.1). PCPs, if they choose, can also provide or supervise the active phase of obesity treatment. PCPs diagnose and treat most of the common weight-related medical conditions, not

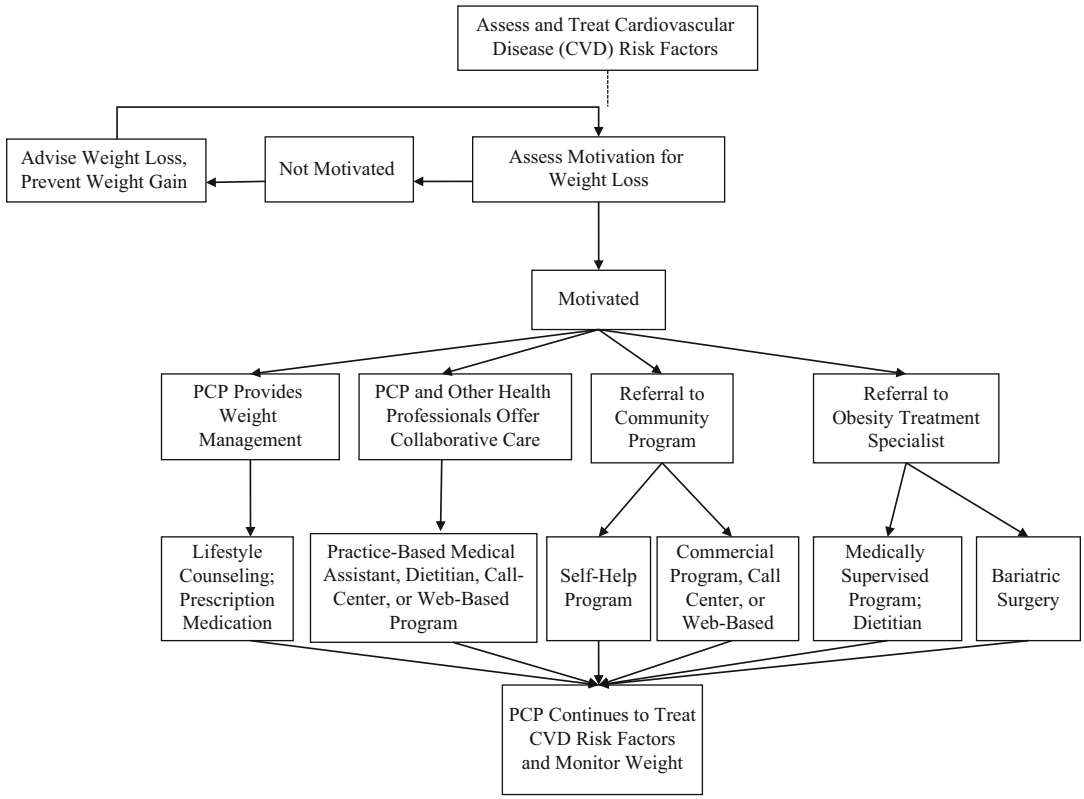

Fig. 19.1 An algorithm for identifying an appropriate weight loss option. After treating cardiovascular disease (CVD) risk factors and assessing patients' activation for weight loss, primary care providers (PCPs) may elect to offer behavioral counseling themselves (with or without pharmacotherapy) or to provide collaborative care with other health professionals. Alternatively, PCPs may refer patients to community programs (e.g., Weight Watchers) or to obesity treatment specialists (e.g., medically supervised programs, bariatric surgery). From Tsai AG, Wadden TA. Treatment of obesity in primary care practice in the United States: a systematic review. J Gen Intern Med. 2009;24(9):1073–1079. Reprinted with permission from Springer

limited to but including diabetes, hypertension, hyperlipidemia, CVD, sleep apnea, and osteoarthritis. Because of this, PCPs are in a unique position to explain to patients, using personalized language as described above, how their weight is related to their current medical conditions, and how moderate weight loss can have significant health benefits. PCPs can also assess patients' "readiness" (i.e., motivation) for weight loss, and with appropriate patients, develop a specific weight loss plan. A practical method to assess motivation for weight loss is to ask the patient to self-monitor diet and physical activity for at least 1 week [22]. (Such an approach may be more useful than asking the patient to self-assess their readiness for weight loss [23].) An assessment of patients' weight and weight loss history is very helpful, with a particular focus on successful weight loss attempts (i.e., that resulted in at least a 5 % loss of initial weight) [24]. If the patient does not seem "ready" for weight loss, PCPs can explore reasons for hesitance, discuss the importance of preventing weight gain, and continue to monitor and treat comorbid conditions, with a goal of returning to the topic of weight at a later time.

PCPs should consider what they and their practice are able to offer patients in terms of options for obesity treatment. As shown in Fig. 19.1, they have the option to provide behavioral treatment to patients in their offices (e.g., as outlined by the new CMS benefit). Behavioral treatment can be provided in combination with pharmacotherapy, which approximately doubles the weight loss achieved [25–27]. PCPs can also enlist other staff in the practice to provide counseling. These individuals may include nurses, medical assistants, or even well trained clerical staff [28, 29]. If treating obesity is not feasible for the providers or their practice staff, practices can contract to enlist outside clinicians to provide counseling, such as registered dietitians (RDs) or behavioral psychologists. In a 2009 review [21], Tsai and Wadden referred to this model (PCP supervising treatment, other practice staff providing counseling) as "collaborative obesity treatment within primary care." Regardless of who does the counseling, patients are treated at their usual site of care, which has the advantage of integrating obesity treatment with other primary health care services. Due to limitations of space, costs of additional staff, or increased patient visits, provision of care in the practice itself may not be feasible, even with a RD or psychologist brought in as a consultant. PCPs who practice in larger, integrated health systems (e.g., accountable care organizations [ACOs]) are likely to have options to refer their patients for treatment outside of the practice (but within the same health system).

If treatment in the practice or in the larger health system is not an option, providers should consider referrals to obesity treatment programs in the community, or to obesity treatment specialists. Community treatment programs include nonprofit and commercial programs such as TOPS (Take Off Pounds Sensibly), Weight Watchers, Jenny Craig, and Nutrisystem. Alternatively, they may refer patients to obesity treatment specialists, such as dietitians in private practice, internists who specialize in prescribing new weight loss agents or who direct medically supervised weight loss programs (e.g., liquid meal replacement diets), or bariatric surgeons. Wherever a patient pursues treatment, the PCP's role is to encourage continued efforts at long-term behavior change and participation in treatment, and to monitor the status of co-morbid conditions.

Supporting Evidence for Models of Intervention

Each section below examines several key studies that describe the efficacy of a specific model of treatment. The discussion is mostly limited to studies that recruited patients from primary care, using providers who were mostly naïve to treating obesity, or to studies that were modeled directly after a typical primary care environment (e.g., short duration of visits). We believe that the studies described below provide the most realistic estimate of the weight losses that can be achieved in busy primary care settings. We do not discuss trials of high-intensity treatment that were conducted in academic medical centers or community settings, as these have been reviewed previously [7, 16, 30, 31].

Table 19.1 Studies of brief primary care provider (PCP) counseling and PCP counseling plus pharmacotherapy

Study	*N*	Interventions	Number of visits	Months	Weight change (kg)	Attrition (%)*
Brief PCP counseling						
Martin et al. [35]	144	(1) Usual care	0	18	+0.1[a]	23
		(2) Usual care + PCP counseling	6	18	−0.5[a]	44
Christian et al. [36]	310	(1) Quarterly PCP visits	4	12	+0.6[a]	15
		(2) Quarterly PCP visits + PCP counseling	4	12	−0.1[a]	9
Christian et al. [37]	279	(1) Usual care	1	12	+0.15[a]	5
		(2) Usual care + PCP counseling	2	12	−1.5[b]	6.5
Ockene et al. [34]	1,162	(1) Usual care	3.4	12	0.0[a]	42
		(2) PCP training	3.1	12	−1.0[a,b]	42
		(3) PCP training + office support	3.6	12	−2.3[b]	37
Cohen et al. [33]	30	(1) Usual care	5.2	12	+1.3[a]	Not stated
		(2) Usual care + PCP counseling	9.7	12	−0.9[a]	
ter Bogt et al. [32]	457	(1) Usual care	2	36	−0.5	20
		(2) Usual care + PCP counseling	13	36	−1.1	24
Ashley et al. [39]	113	(1) RD counseling	26	12	−3.4[a]	38
		(2) RD counseling + meal replacements	26	12	−7.7[b]	32
		(3) PCP/RN counseling + meal replacements	26	12	−3.5[a]	34
Brief PCP counseling + pharmacotherapy						
Hauptman et al. [43]	635	(1) PCP guidance + placebo	10	24	−1.7[a]	57
		(2) PCP guidance + orlistat, 60 mg TID	10	24	−4.5[b]	44
		(3) PCP guidance + orlistat, 120 mg TID	10	24	−5.0[b]	44
Poston et al. [44]	250	(1) RD/RN counseling	13	12	+1.7[a]	67
		(2) Orlistat, 120 mg TID	13	12	−1.7[b]	35
		(3) RD/RN counseling + orlistat, 120 mg TID	13	12	−1.7[b]	34
Wadden et al. [27]†	106	(1) Sibutramine, 10–15 mg/day	8	12	−5.0[a]	18
		(2) Sibutramine, 10–15 mg/day + PCP counseling	8	12	−7.5[a]	19

Note: For each study, under "weight change," values labeled with different letters (a,b) are significantly different from each other at $p<0.05$; *RD* registered dietitian, *RN* registered nurse, *TID* three times per day

*Attrition is defined as the percentage of participants who did not contribute an in-person weight at the end of the study. An intention-to-treat analysis was used in most studies, except for three that used a completers' analysis [33, 34, 39]

†This study included two additional groups, both of which included intensive group lifestyle modification. The results of these groups are not displayed here

Studies of Weight Loss Counseling Conducted by PCPs

At least six randomized trials [32–37] have tested the effects of PCPs themselves delivering behavior weight loss counseling to their own patients. In one study, Martin and colleagues studied the effect of providing brief monthly counseling to patients in two primary care internal medicine practices [35]. Study participants were mainly African-American, low-income women, with a mean age of 41.7 years and BMI of 38.8 kg/m^2. Counseling visits were brief (15 min each). After 6 months, patients randomized to counseling lost more weight than those assigned to the control condition (1.4 vs. 0.3 kg; $p=0.01$). However, after 18 months, the difference in weight was no longer significant (see Table 19.1).

In two studies, Christian et al. tested the effectiveness of weight loss counseling for patients with type 2 diabetes or metabolic syndrome. The majority of patients in both studies were Latino and low-income. Providers in both studies received 3 h of training, and patients in both studies completed a computer-based assessment of motivation for (and barriers to) weight change. The computer program produced a personalized report with recommendations for the patient, and

the provider received a copy. In the first study of patients with type 2 diabetes (mean age 53.2 years, BMI 35.1 kg/m^2), patients received quarterly visits. After 12 months, the intervention group lost 0.1 kg, while the control group gained 0.6 kg ($p=0.23$) [36]. In the second study of patients with metabolic syndrome (mean age 49.6 years, BMI 34.2 kg/m^2), patients were seen at baseline, 6 months, and 12 months. After 12 months, weight changes in the intervention and control groups were −1.5 kg and +0.15 kg ($p=0.002$ for difference) [37].

In two other studies, Ockene et al. and Cohen et al. tested the effect of brief weight loss counseling by PCPs for patients with overweight/obesity and comorbidity (hyperlipidemia and hypertension, respectively). In both studies, randomization was done at the level of the PCP, rather than at the patient level. In the study by Ockene [34], patients had a mean age of 49.3 years and BMI of 28.7 kg/m^2. PCPs ($n=45$) were randomized to: (1) usual care; (2) brief counseling; or (3) brief counseling with in-office support. Visits were brief (8–10 min). The office support program provided prompts to the PCPs, as well as counseling algorithms and handouts. Patients had an average of 3.1–3.6 visits during the year of the study. Patients receiving the in-office support intervention lost more weight than those in the control group (2.3 vs. 0.0 kg, $p<0.001$). Weight loss in the brief counseling group (1.0 kg) was not significantly different than the other two groups. In the study by Cohen [33], family medicine residents ($n=18$) were randomly assigned to provide brief monthly counseling to their patients (mean age 59.5 years, BMI 34.1 kg/m^2) or to provide usual care. Patients were seen an average of 9.7 and 5.2 times, respectively, over the year of the study. Residents in the intervention group were instructed on how to counsel patients on calorie restriction and healthy eating. After 1 year, patients of intervention PCPs lost 0.9 kg, while patients of usual care PCPs gained 1.3 kg ($p>0.05$; exact p value not provided). Finally, ter Bogt et al. assessed the effect of counseling by nurse practitioners (NPs, mid-level primary care providers) [32]. Patients (age 56.1 years, BMI 29.6 kg/m^2) received either quarterly telephone visits (plus one in-person visit), with NPs following computerized treatment guidelines, or usual care. After 1 year, weight losses were 2.0 and 0.6 kg in the intervention and control groups, respectively ($p=0.002$). After 3 years, weight losses were similar in the two groups (1.1 vs. 0.5 kg, $p=0.34$).

The results of these six studies indicate that low- to moderate-intensity counseling, provided by PCPs to their own patients, is not likely to produce clinically significant weight loss. While even 1 kg of weight loss may have detectable health benefit [38], the average amount of weight loss achieved in the above studies is not likely to produce substantial health benefits [5]. The low intensity of treatment and brief duration of visits are likely factors that explain the small weight losses. If patients had been seen more frequently, as recommended, by the USPSTF, weight losses might have been larger.

The possibility of greater weight loss with more frequent visits is suggested by results of a study by Ashley et al., in which both PCP counseling and "collaborative care" were tested in the same study [39]. (Note: participants in this study were volunteers from the local area, rather than patients in the practice where the study took place.) Study participants (mean age 40.4 years, BMI 30.0 kg/m^2) were randomized to: (1) group behavioral counseling, 1 h visits, every 2 weeks, delivered by RDs; (2) group behavioral counseling with provision of meal replacements (Slim-Fast); or (3) individual counseling by PCPs, 10–15 min visits, every 2 weeks, with provision of meal replacements. Study participants received the LEARN Manual [40], a behavioral weight loss workbook, which was used for counseling sessions. After 1 year, weight losses in the three groups were 3.4, 7.7, and 3.5 kg, respectively ($p=0.03$ for group 2, compared to groups 1 and 3). The results of this study (and of a meta-analysis of randomized trials [41] which included the study by Ashley et al.) suggest that provision of meal replacements increases weight loss, compared to a diet of self-selected food with the same calorie target. The results also suggest that RDs are at least as effective as PCPs as weight loss counselors, although this study did not do a direct comparison.

Studies of PCP Weight Loss Counseling Plus Pharmacotherapy

Randomized trials conducted in academic center or research clinics have demonstrated that adding weight loss medication to lifestyle counseling increases weight loss [26, 42]. Three randomized trials tested the effect of adding weight loss medications, simulating brief primary care office visits with PCPs providing weight loss counseling [27, 43, 44]. In the first study, Hauptman and colleagues [43] tested brief dietary counseling with placebo, orlistat 60 mg 3×/day (over-the-counter dose), or orlistat 120 mg 3×/day (prescription dose). Study participants (mean age 42.5 years, BMI 36 kg/m^2) received quarterly videotapes and written materials in addition to dietary counseling. Weight losses after 2 years were 1.7, 4.5, and 5.0 kg, respectively ($p=0.001$ for the orlistat groups combined, compared to placebo).

In another study of orlistat [44], Poston et al. assigned patients (mean age of 41.0 years, BMI 36.1 kg/m^2) to brief counseling (15–20 min monthly visits), orlistat 120 mg 3×/day, or brief counseling plus orlistat. Counseling was provided by nurses or RDs, using the LEARN Manual. After 1 year, both orlistat groups lost 1.7 kg, while the counseling group gained 1.7 kg ($p<0.001$ for orlistat groups combined, compared to counseling).

In the third study [27], Wadden et al. randomized patients (mean age 43.6 years, BMI 37.9 kg/m^2) to sibutramine, 10–15 mg/day, with eight brief visits that included lifestyle counseling provided by PCPs, or sibutramine with eight brief visits that included only weigh-in and monitoring of blood pressure and pulse. Counseling visits lasted 10–15 min each and used the LEARN Manual. Weight losses after 18 weeks were 8.4 and 6.2 kg, respectively ($p=0.05$), but weight losses at 1 year were not significantly different. (Note: sibutramine was removed from European and US markets in 2010 after the publication of a study indicating that it increased the risk of cardiovascular events [45].)

The results of these three studies show that medication, when added to brief counseling visits meant to simulate a primary care office environment, does increase weight loss. Sibutramine is no longer available, and orlistat, although still available both over-the-counter and as a prescription agent, is prescribed infrequently. Trials will be needed in primary care settings of two new medications approved by the FDA in 2012, phentermine–topiramate and lorcaserin [46, 47], as well of generic phentermine, which remains the most commonly prescribed weight loss agent in the United States.

Studies of the Collaborative Model of Obesity Treatment

At least four randomized trials have tested the effect of weight loss counseling conducted in the practice [28, 48–50]. Three of these studies used medical assistants or other non-PCP practice staff as counselors [28, 48, 49], and the fourth study used a RD and a fitness instructor who contracted with the practice to deliver counseling [50].

In the first study, Tsai et al. [28] trained medical assistants at two primary care practices to serve as weight loss coaches. Patients (mean age 49.5 years, BMI 36.5 kg/m^2) were randomized to: (1) quarterly PCP visits and printed weight loss handouts; or (2) PCP visits plus handouts, plus eight brief counseling sessions (15–20 min each) with a weight loss coach. The written materials used for the counseling sessions were adapted from the Diabetes Prevention Program [39]. After 6 months, weight losses were 0.9 and 4.4 kg, respectively ($p<0.001$), but as shown in Table 19.2, differences at 1 year were no longer significant. (Treatment was provided only during the first 6 months.)

Two larger trials have expanded the model of using medical assistants from the practice as weight loss counselors. In the first study, Wadden et al. [48] recruited 390 patients with abdominal obesity and at least 1 other component of the metabolic syndrome from six primary care practices. Study participants (mean age of 51.5 years and BMI of 38.5 kg/m^2) were randomized to: (1) quarterly PCP visits and printed materials; (2) quarterly PCP visits, printed materials, plus brief

Table 19.2 Studies of collaborative obesity care that included auxiliary professionals in the primary care practice

Study	*N*	Interventions	Number of visits	Months	Weight change (kg)	Attrition (%)*
Tsai et al. [28]	50	(1) Quarterly PCP visits	4	12	−1.1[a]	4
		(2) Quarterly PCP visits + MA counseling	12	12	−2.3[a]	8
Wadden et al. [48]	390	(1) Usual care	4	24	−1.7[a]	15
		(2) Brief lifestyle counseling (quarterly PCP visits + MA counseling)	28	24	−2.9[a,b]	15
		(3) Enhanced brief lifestyle counseling (quarterly PCP visits + MA counseling + meal replacements/medication)	28	24	−4.6[b]	12
Kumanyika et al. [49]	261	(1) Brief PCP counseling	4	12	−0.6[a]	28
		(2) Brief PCP counseling + MA counseling	16	12	−1.6[a]	28
Ma et al. [50]	160	(1) Usual care	3	15	−2.4[a]	8.6
		(2) Adapted DPP†	12	15	−6.3[b]	8.9
		(3) Adapted DPP, self-directed	3	15	−4.5[c]	7.4
Ryan et al. [51]	390	(1) Usual care	2	24	0.0[a**]	55
		(2) Counseling†† + meal replacements + medication	46	24	−8.3[b**]	49

Note: For each study, under "weight change," values labeled with different letters (a,b) are significantly different from each other at $p < 0.05$; *PCP* primary care provider, *MA* medical assistant, *NP* nurse practitioner, *DPP* Diabetes Prevention Program

*Attrition is defined as the percentage of participants who did not contribute an in-person weight at the end of the study. An intention-to-treat analysis was used in these studies

†In this study, counseling was delivered by a registered dietitian who contracted with the practice, along with a fitness instructor

††In this study, lifestyle counseling was provided by a registered dietitian, social worker, professional counselor, or marriage and family therapist

**Weight losses represent percentage weight change, as determined by a last-observation carried forward analysis

monthly weight loss counseling visits, provided by a weight loss coach from the practice; or (3) all of the above interventions, plus a choice of either meal replacements or weight loss medication (orlistat or sibutramine). Weight loss coaches used written materials adapted from the Diabetes Prevention Program. After 6 months, weight losses in the three groups were 2.0, 3.5, and 6.6 kg (all significantly different from each other). After 2 years, group 3 had lost more weight than group 1 (4.6 vs. 1.7 kg, $p = 0.003$), but weight loss in group 2 (2.9 kg) was not significantly different from the other groups. In the second larger trial, Kumanyika et al. [49] tested the effect of using weight loss coaches from primary care practices that served primarily ethnic minority patients. Similar to the study by Wadden et al., weight loss coaches were mainly medical assistants, and they used materials adapted from the Diabetes Prevention Program. Study participants (mean age 47.2 years, BMI of 37.2 kg/m^2) were randomized to PCP visits every 4 months or to PCP visits, plus brief (15–20 min) monthly visits with a weight loss coach. After 1 year, weight losses in the two groups were 0.6 and 1.6 kg, respectively ($p = 0.15$).

In the last of the collaborative treatment studies, Ma et al. [50] recruited patients from a single large primary care practice, all of whom had prediabetes by lab measurement. Study participants (mean age 59.4 years, BMI 32.0 kg/m^2) were randomized to: (1) a group behavioral intervention [12 sessions], based on an adapted version of the Diabetes Prevention Program and led by a weight loss coach; (2) a self-directed intervention, using a DVD that taught patients the same curriculum in their homes; or (3) usual care. The weight loss coaches were a registered dietitian contracted to provide counseling to study participants and an exercise instructor hired to lead some groups; these two individuals were not employees of the practice. The study included a 3 month

intensive intervention phase and a 12 month weight maintenance phase, during which participants in both intervention groups did not have classes but continued to receive e-mails with advice and motivational messages. After 6 months, weight losses in the three groups were 6.6, 4.3, and 0.7 kg ($p<0.001$ for each comparison between groups). After 15 months, weight losses were 6.3, 4.5, and 2.4 kg, with usual care participants losing more weight and participants in the two intervention groups maintaining their weight loss ($p<0.05$ for all comparisons, $p<0.001$ for group behavioral intervention vs. usual care).

Together, the results of these trials suggest that obesity treatment provided by weight loss coaches from the practice (e.g., medical assistants) produces modestly greater weight loss after 1–2 years, compared to usual care. As with studies of PCP counseling, the greater weight losses in the active treatment arms of these studies are likely attributable to the greater frequency of visits (monthly with weight loss coaches, vs. approximately quarterly with PCPs). In the trial by Wadden [48], the combination of monthly counseling with a weight loss "enhancement" (meal replacements or medication) increased average weight loss to a clinically significant amount. The study by Ma et al. [50] additionally suggests the benefits of using registered dietitians, rather than medical assistants. However, controlled trials are needed to directly test this hypothesis.

The benefit of combining modalities for treatment (as was done by Wadden et al. [48]) was further highlighted by a study conducted by Ryan and colleagues [51]. They recruited patients from 7 primary care practices, where patients were covered by the same health insurance plan. Study participants (mean age 47.2 years, median BMI 46.1 kg/m^2) were assigned to usual care (instruction to use a weight loss website) or to an intensive, multimodality intervention. In the intervention group, participants were offered a 3-month liquid very-low-calorie diet, followed by 4 months of high-intensity group weight loss counseling (ten sessions) combined with medication (orlistat, sibutramine, or diethylpropion), and then during months 8–24, continuing group treatment along with medication and one meal replacement per day. Weight loss counselors included staff from the practices, RDs, and social workers. After 2 years, weight losses were 0.2 and 4.9 % of starting weight, using baseline carried forward analysis and 0.0 and 8.3 %, using last-observation carried forward analysis. (The true weight loss average for the intervention group is likely somewhere between these two values.) Attrition in the study was 49 %. This study shows that, with multimodal, high-intensity therapy, clinically significant weight loss can be produced in primary care settings. Whether such an intervention can be broadly disseminated will depend on cost and whether similar results could be produced at lower cost by other programs [52].

Studies of Collaborative Obesity Treatment Delivered by Telephone or Internet

Weight loss counseling can be delivered remotely (i.e., via telephone [53–55] or through smart phone [56] or Internet [57, 58]). Counseling delivered remotely appears to produce less weight loss than interventions delivered face-to-face [58]. However, remote counseling has the advantages of being less costly, more convenient for patients (no travel time), as well as having greater reach (e.g., for patients living in rural areas). Telephonic or web-based delivery of weight loss programs could also be attractive to integrated health systems, especially if the obesity program and primary care office can share information about patients via an electronic medical record.

At least six randomized trials [29, 55, 59–62] and one uncontrolled study [63] have tested the use of telephonic or web-based counseling for the treatment of obesity for patients from primary care practices. In one study [55], Appel and colleagues randomized patients from primary care (mean age 54.0 years, BMI 36.6 kg/m^2) to a behavioral weight loss intervention, delivered either remotely or in-person, or to usual care. (The interventionists worked for a free-standing company that was not affiliated with the health system.) Those in the telephone arm were offered

up to 33 contacts total, while those in the in-person arm were offered up to 57 contacts. Weight loss counselors in the telephone arm were trained coaches but not RDs, while those in the in-person group were RDs and psychologists. After 2 years, weight losses in the usual care, telephone, and in-person groups were 0.8, 4.6, and 5.1 kg. Both intervention groups lost more weight than usual care ($p<0.001$). In a similar study [29], Weinstock et al. recruited patients with metabolic syndrome from five primary care practices; study participants were mostly white but had a range of incomes. Participants (mean age 51.7 years, BMI 39.3 kg/m^2) were randomized to receive the 16 session curriculum of the Diabetes Prevention Program, either in-person or by group conference call. Interventionists included four licensed practical nurses, five registered nurses, two nurse practitioners, and one front desk office staff. The interventionists had assistance from RDs, who assisted with some in-person sessions and also made every other month phone calls, alternating with the primary interventionists. Weight losses after 1 year were similar in the telephone and in-person groups (4.5 and 4.2 % of initial weight), but after 2 years, weight losses were greater in the telephone arm (5.6 % vs. 1.8 %, $p=0.016$).

Two studies examined the treatment of obesity with telephonic interventions, both using behavioral models designed to induce patients to progress through inaction to behavior change [59, 60]. Logue et al. [59] carried out a 2-year obesity treatment intervention. Overweight and obese patients from primary care, ages 40–60 and BMI $\geq$ 27 kg/m^2, were randomized to: (1) augmented usual care [10 min counseling with a RD]; or (2) transtheoretical model (TTM) chronic disease care, which included the brief RD visits, plus monthly telephone calls (15 min each) with a weight loss coach who counseled patients using the stages of change model, including tailored written materials. After 2 years, weight losses were 0.2 kg (augmented usual care) vs. 0.4 kg (TTM); $p=0.5$ for difference. In a similar study, Ely et al. [60] tested a telephone intervention in a rural primary care setting. Patients (mean age 49.5, BMI 36 kg/m^2) were randomized to: (1) usual care [written materials]; or (2) telephonic intervention that included eight sessions using motivational interviewing. The interventionist was a masters-level counselor. PCPs of patients in both groups received obesity treatment guidelines and updates on their patients' progress. After 6 months, weight losses in the usual care and intervention groups were 1.0 and 4.3 kg, respectively ($p=0.01$).

Bennett and colleagues have conducted two randomized trials that included a web-based component [61, 62]. In the first study [61], patients (mean age 54.5 years, BMI 34.6 kg/m^2) with hypertension and who were mostly low-income were randomized to: (1) usual care; or (2) a behavioral intervention for weight loss and hypertension. The intervention arm included a study website and an interactive voice response system, both of which provided individually tailored feedback to patients. Patients in the intervention arm also were offered 12 group sessions in-person and 18 telephone calls from trained community health educators. After 2 years, weight losses in the usual care and intervention groups were 0.5 and 1.5 kg ($p<0.05$ for difference). In the second study [62], a web-based intervention was tested in primary care patients with hypertension. Patients (mean age 54.4 years, BMI 34.6 kg/m^2) were randomized to: (1) usual care (printed materials); or (2) a weight loss website designed to encourage behavior change. Intervention patients also were offered four coaching sessions (two in-person, two by phone) from a RD, using motivational interviewing. After 12 weeks, the intervention group lost 2.3 kg, while the usual care group gained 0.3 kg ($p<0.05$). Table 19.3.

The results of trials of remote intervention show that primary care patients can achieve clinically significant weight loss if they are offered high-intensity interventions (as recommended by the USPSTF). The studies by Appel, Ely, and Weinstock are the most encouraging in terms of demonstrating weight loss, but the study by Appel also included a web-based component. Thus, the efficacy of telephonic intervention alone cannot be determined from that study. The study by Weinstock, which delivered the

Table 19.3 Studies of collaborative obesity care supported by remotely delivered counseling

Study	*N*	Interventions	Number of visits	Months	Weight change (kg)	Attrition (%)*
Appel et al. [55]	415	(1) Control (self-directed)	2	24	−0.8[a]	7
		(2) Remote support only (telephone + electronic-based counseling)	33	24	−4.6[b]	5
		(3) In-person support (telephone + electronic-based + in-person counseling)	57	24	−5.1[b]	4
Weinstock et al. [29]	257	(1) DPP in-person (individual)	28	24	2.2[a]	32.1
		(2) DPP group-based (telephone)	28	24	6.2[b]	34.4
Logue et al. [59]	665	(1) Brief RD counseling	4	24	−0.2[a]	31
		(2) Brief RD counseling + telephone counseling	28	24	−0.4[a]	38
Ely et al. [60]	101	(1) Patient education	0	6	−1.0[a]	52
		(2) Patient education + telephone counseling	8	6	−4.3[b]	48
Bennett et al. [61]	101	(1) Usual care	0	12	+0.3[a]	16
		(2) Web-based + brief RD counseling	2	12	−2.3[b]	16
Bennett et al. [62]	365	(1) Usual care	0	24	−0.5[a]	10
		(2) Telephone + electronic-based + group counseling	30	24	−1.5[b]	18

Note: For each study, under "weight change," values labeled with different letters (a,b) are significantly different from each other at $p < 0.05$; *RD* registered dietitian, *DPP* Diabetes Prevention Program

*Attrition is defined as the percentage of participants who did not contribute an in-person weight at the end of the study. An intention-to-treat analysis was used in most studies, except for one that used a completers' analysis [52]

highest intensity of treatment, produced the largest weight loss at 2 years. The study by Weinstock also confirms the results of earlier research, suggesting that group-based intervention is more effective than individual intervention [64]. Overall, the results of remote intervention are encouraging, and should be subjected to trials that include cost-effectiveness analysis, comparing them to traditional, in-person programs.

Obesity Treatment Options in the Community

Figure 19.1 also shows referral options for PCPs and their patients when treatment cannot be offered in the practice or the larger health system. Options include organized self-help programs, commercial weight loss programs that offer in-person, telephone, and web-based/email counseling. PCPs can also refer to clinicians who specialize in obesity treatment. These include RDs, psychologists, bariatric medical physicians, or bariatric surgeons. The next two sections briefly summarize these options. Interested readers are referred to more detailed review articles on each topic (referenced below).

Commercial and Nonprofit Programs

The largest commercial weight loss programs in the United States are Weight Watchers, Jenny Craig, and Nutrisystem. A systematic review of commercial weight loss programs published in 2005 [65] concluded that Weight Watchers was the only program with randomized-trial evidence of its efficacy. Since that time, both Jenny Craig and Nutrisystem have sponsored randomized trials [66–68]. Although none of the patients in any of these studies were recruited from primary care, the results of published trials of all these programs were positive, and suggest that these programs are a viable option for patients and their PCPs as a tool for weight loss. Programs that require the purchase of food are substantially more expensive, although it is important to keep in mind usual food costs and weigh these against the costs of programs. Most recently, the nonprofit program TOPS was evaluated in a retrospective

analysis [69]. The results, while not a randomized trial, were based on national data, and suggest that TOPS may be a reasonable option for patients who need a low-cost option for group behavioral treatment.

Two studies, both from the UK, have tested the effectiveness of commercial programs among patients referred from primary care practice [70, 71]. In the first study, Jebb et al. [70] recruited patients ($n=772$) from primary care practices (mean age 47.4 years, BMI 31.4 kg/m^2) and randomized them to: (1) usual care; or (2) a voucher to attend Weight Watchers for 1 year, at no cost to the patient. After 1 year, weight losses were 2.3 and 5.1 kg in the two groups ($p<0.001$). In the second study, Jolly et al. [71] conducted an eight-arm randomized trial ($n=740$) to test several weight loss programs in the UK. Study participants were randomized to Weight Watchers, one of three other UK weight loss programs, general practice counseling, pharmacy-based counseling, an arm in which patients could choose their own program, or an exercise-only group. Using last-observation carried forward analysis, weight losses after 1 year were 4.4 kg (Weight Watchers), 1.1 kg (general practice counseling), 3.0 kg (choice of intervention), and 1.3 kg (exercise-only group). Weight Watchers was significantly more effective than general practice counseling or exercise-only, but not significantly more effective than self-selection of program.

Obesity Specialists

For patients needing more intensive intervention than commercial programs, PCPs can refer their patients to obesity specialists, who can provide more targeted and/or intensive treatment options. (Sometimes, these specialists practice in the same health system as the PCP.) As outlined above, specialists may include dietitians, psychologists, medical physicians, or surgeons. The Academy of Nutrition and Dietetics (formerly the American Dietetic Association) has developed a certification program for RDs to treat obesity. Obesity specialists in the community can also provide more targeted evaluation and additional options for treatment. Medical physicians (both pediatric and adult) can certify under the newly created American Board of Obesity Medicine (http://www.abom.org). These physicians may prescribe and supervise low-calorie diet programs, or prescribe weight loss medication (e.g., phentermine–topiramate, lorcaserin). In the past, physicians offered very-low-calorie diet programs (<800 cal/day), but as long-term differences in weight loss between very-low-calorie and more moderate calorie restriction (1,000–1,800 kcal/day) are minimal [72], most programs have moved to medically supervised low-calorie diets of at least 1,000–1,200 kcal/ day.

The most aggressive intervention that can be offered to patients is bariatric surgery. PCPs should consider referring patients to surgery if they have severe obesity (BMI >40 or >35 kg/m^2 in the presence of comorbid conditions) and if they have not been successful with sustained attempts at lifestyle modification (diet, exercise, and behavior modification) and/or pharmacotherapy [4]. The most common surgical procedures done in the United States are Roux-en-Y gastric bypass, gastric banding, and most recently, sleeve gastrectomy. Gastric bypass produces the greatest weight losses (25–30 % of initial weight), gastric banding the smallest (15–20 % of initial weight), and sleeve gastrectomy intermediate weight losses (20–25 % of initial weight) [73–76]. Roux-en-Y gastric bypass, in addition to producing the largest weight loss, appears to produce improvements in glycemic control that are mediated by mechanisms other than weight loss [77]. Gastric bypass also is associated with the highest risks of any of the surgical procedures, including anastomotic complications, as well as the long-term risk of nutritional deficiencies. However, all types of bariatric surgery have become safer in recent years [78]. Some data suggest that bariatric surgery is safer in centers of excellence and/or centers with high volume [79].

Summary and Future Directions

Most trials of weight loss counseling by PCPs and practice staff have produced only modest weight loss (1–3 kg, over a period of 6–24 months). These modest results are likely a result of low- to

moderate-intensity intervention (one or fewer contacts per month). Trials in primary care that provided high-intensity counseling or that combined counseling with another modality (meal replacements or medication) were able to produce clinically significant weight loss. However, the feasibility of these interventions in most primary care settings in the United States is unclear. While obesity is a major problem in primary care settings, there are many other issues that compete for attention (e.g., smoking cessation, medication adherence, depression, cancer screening, etc.), as well as broader issues of chronic disease management and quality measurement that more directly affect reimbursement. However, there are several notably successful examples of efforts to disseminate the results of trials conducted in academic medical centers (i.e., trials that provided weekly, high-intensity treatment using weight loss specialists such as dietitians and psychologists). One of the most notable efforts at dissemination is the collaboration between the Centers for Disease Control and Prevention (CDC) with YMCAs and other organizations across the country to deliver the Diabetes Prevention Program, in both community and health care settings [80].

Given the more favorable results of trials that provided high-intensity treatment, the mandate from CMS to offer weekly and then biweekly visits during the first 6 months seems justified. The schedule of 14 visits stipulated by CMS during the first 6 months approximates the 16 visits offered in the Diabetes Prevention Program during the first 6 months. However, the effectiveness of brief 15 min visits (compared to 30–60 min visits in the Diabetes Prevention Program) is unknown. The requirement for the visits to be conducted in the physical setting of the primary care office also is limiting, as most PCPs do not have a dietitian or trained weight loss counselor who works in their office, and most PCPs are not trained in management of obesity. Finally, it is unclear how many PCPs will want to conduct these visits for the relatively low reimbursement rate (approximately $30 per visit), and whether patients will be willing to travel back and forth to their PCP's office 14 times in 6 months for brief visits. For all these reasons, the schedule of visits reimbursed by CMS needs further validation.

The study that comes closest to the CMS treatment paradigm is the trial by Ashley and colleagues [39], in which patients had brief visits every other week with a PCP, using a behavioral weight loss workbook (the LEARN Manual [40]), and were provided with meal replacements free of charge. Patients in that group lost only 3.5 kg after 1 year, while patients who had the same frequency of visits and meal replacements, provided by a dietitian, lost 7.7 kg (more than twice as much weight). The results of the study by Ashley suggest that dietitians would be the preferred provider to deliver the schedule of visits reimbursed by CMS. Primary care providers (physicians, nurse practitioners, and physician assistants) could certainly be trained to provide weight loss counseling. However, dietitians are already trained for this task, and are able to do it at a lower cost than a primary care clinician. In addition, the certificate program in obesity treatment ensures that dietitians have a broad scope of knowledge in treating obesity, not simply in providing nutrition advice but in understanding the broader context of behavioral treatment.

In the long-term, PCPs and/or their employers will have to decide whether it makes financial and clinical sense for PCPs to be the providers of obesity treatment, or whether dietitians or other providers should take the lead in providing this care. Integrated health systems in the United States, such as Kaiser Permanente and the Veterans Health Administration, have mostly chosen the latter course. (No published evaluations on a national level from either system exist, to our knowledge.) In contrast, at least one national health system (that of the UK) has instead chosen to train as many of its PCPs as possible to improve the management of obesity in the primary care office [81].

While intensive in-person intervention has been demonstrated to be effective, remotely delivered weight loss counseling may have greater reach. As the US health system moves more towards integrated systems (e.g., ACOs), clinicians and health system leaders will need to manage population health. For this reason, remotely delivered counseling, if high-intensity as provided in the trials by Appel [55] and Weinstock [29], has the potential to offer care to a substantially greater

number of individuals than could be treated in-person. These two trials, as well as two trials of proprietary weight loss programs [53, 66] (not delivered in primary care) suggest that counseling by phone is at least equivalent to counseling in-person. Remotely delivered lifestyle counseling would seem to be an attractive option for patients who have difficulty in attending in-person sessions, and would help to support PCPs in their efforts to offer intensive counseling, as recommended by the USPSTF. Ultimately, reimbursement by CMS of remotely delivered counseling, conducted by dietitians or other trained weight loss counselors, may serve patients and their PCPs more effectively than a requirement for in-person office visits.

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Thomas Wadden serves on advisory boards for Novo Nordisk and Orexigen Therapeutics, each of which is developing weight loss medications. None of the other authors has any potential conflicts of interest to disclose.

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Assessment of the Obese Child or Adolescent

20

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Introduction

Extra weight or body fat in childhood is not an isolated problem but one that is accompanied by many health risks. Following identification of extra weight, a comprehensive evaluation should examine three core aspects of good health: physical, psychosocial, and behavioral. First, a comprehensive medical evaluation is aimed at identifying underlying causes of obesity as well as the medical conditions, both common and uncommon, that potentially accompany obesity. Such conditions include cardiovascular disease risk factors, which may be asymptomatic, musculoskeletal issues, and sleep disorders. Discovery of these and other conditions provides an opportunity to address them; although interventions usually include weight control, conditions may require other treatments as well. Second, a health evaluation should aim to uncover obesity-related psychosocial conditions so patients and families can get appropriate support. Finally, an assessment of food intake and eating patterns as well as physical activity is needed. The foundation of weight intervention is behavior change, and improvement in health behaviors begins with recognition of the problem behaviors for an individual. Because of their role, positive and negative, in shaping lifestyle and influencing psychosocial health, parents must be part of the assessment. A thorough assessment is complex. A specialist will need to set aside adequate visit time and coordinate with other specialists like nutritionists. A primary care provider may have a baseline knowledge of the family situation and associated health risks and could fill in missing information over several visits.

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Anthropometric Measures

Clinical evaluation of body weight for children starts by measurement of body mass index (BMI), which adjusts the weight for height and indirectly assesses body fat. BMI is defined as weight in kilograms divided by the square of height in meters.

$$\mathrm{kg/m^2\,(metric)\ or\ lb/in^2 \times 703\,(English\ units)}$$

Although BMI is not a precise measure of body fat, weights and heights can be assessed accurately,

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quickly, and inexpensively, and BMI correlates with body fat measures [1] and also with medical risks and conditions, including cardiovascular risk factors [2]. In contrast to adults where the same BMI values define categories of healthy weight, overweight, and obesity across genders and ages, the distribution of BMI among children changes; a BMI of 20 kg/m^2 is healthy in a 13-year-old, overweight in a 9-year-old, and obese in a 4-year-old. Therefore, percentiles specific for age and gender, developed from a reference population, define weight categories in children [3]. BMI 5th–84.9th percentile is healthy, BMI 85th–94.9th percentile is overweight, and BMI ≥ 95th percentile is obese. These cut points correspond to adult cut points of 18–25, 25–29.9, and ≥30 kg/m^2. Severe obesity in children has been defined as a BMI ≥ 99th percentile or as a BMI value that is ≥20 % above the obesity cut point (BMI of 95th percentile) [4]. For a given child, these two values are very similar. Studies that apply either of these definitions to national prevalence data indicate a 4–6 % prevalence of severe obesity among children across age groups [4, 5]. Unfortunately, these studies illustrate that severe obesity is not rare among children and does confer greater health risk [2].

Appropriate assessment of a child's growth in weight and height requires:

1. Annual measure of weight and height.
2. Annual plot of weight and height on NCHS gender-specific weight-for-age and height-for-age growth charts.
3. Annual calculation of body mass index and then plot on gender-specific BMI-for-age growth charts available for age 2–20 years.
4. When children are under 2 years of age, BMI is not calculated, but weight and height values should be plotted on weight-for-height charts, also available from NCHS. Overweight is defined as weight-for-height ≥95th percentile.

The plotting of BMI over time is essential to categorize the BMI as healthy, overweight, or obese, and to identify an early rise in BMI that may put the child at risk of overweight or obesity. Although calculations and plotting are cumbersome when done by hand, electronic health records generally perform these functions automatically.

Because BMI is an imperfect measure of body fat and may reflect high lean body mass, especially in the overweight category, assessment of health risk from high BMI requires other clinical information such as family history, risk factors, and lifestyle behaviors.

Communication of Weight Status to Patients and Families

Despite the high prevalence of childhood obesity, the condition is stigmatized, and patients and parents often feel ashamed and defensive. The chronicity and refractoriness of obesity mean providers need to be empathic and supportive because when the stigma occurs in the healthcare setting, families could avoid care or give up the efforts to be healthy, as occurs in obese adults [6]. In addition, parents frequently are unaware that their child is overweight or obese [7]. Thus, providers must identify excess weight but introduce the subject carefully. Terms parents prefer (and find more motivating for change) include "weight," "unhealthy weight," "high BMI," and "weight problem," while "chubby," "heavy," "obesity," and of course "fat" are considered derogatory [8]. Thus providers may identify "obesity" in a medical sense as BMI above the 95th percentile but use different terminology when speaking with patients and families. Providers can introduce the topic by asking whether a patient or parent has any concern about the child's weight. This approach allows the patient/parent to respond before feeling judged by provider, and the provider can ally with concerned families or begin a discussion with unconcerned families about potential health risks.

Assessment of Medical Conditions Associated with Childhood Obesity

Hypertension

Average blood pressures have risen along with BMI in the last 3 decades. The prevalence of hypertension in obese patients is difficult to assess in the current literature as most studies are

Table 20.1 Normal and elevated ranges of cardiovascular screening evaluations in children and adolescents

	Healthy range	Increased risk	Abnormal	Urgent
Blood pressure [13] (3 measures over several weeks)	Normal	Pre-hypertension	Stage 1 hypertension	Stage 2 hypertension
Systolic	<90th percentile	>90th% but <95th percentile Adolescents: >120 mmHg but <95th percentile	>95th percentile + 5 mmHg	>99th percentile + 5 mmHg
Diastolic	<90th percentile	>90th% but <95th percentile Adolescents: >80 mmHg but <95th percentile	>95th% + 5 mmHg	>99th% + 5 mmHg
Lipid [17]	Normal	Borderline	Abnormal	
Total cholesterol mg/dL	<170	170–199	≥200	
LDL mg/dL	<110	110–129	≥130	
Triglycerides mg/dL 0–9 years (>9 years)	<75 (<90)	75–99 (90–129)	≥100 (≥130)	
HDL mg/dL	>45	40–45	≤40	
Diabetes [99]	Normal	Prediabetes	Diabetes	
Fasting glucose mg/dL	<100	100–125	≥126	
Random glucose mg/dL			≥200	
2 h glucose tolerance mg/dL	<140	140–199	≥200	
Hgb A1c	<5.7 %	5.7–6.4 %	≥6.5 %	

cross sectional and do not follow recommendations for diagnosing hypertension. Recent studies that follow more rigorous diagnosis protocols suggest that only 0.3–3.4 % are hypertensive [9, 10]. Risk factors for developing hypertension includes African-American or Mexican-American background, male gender, overweight or obese BMI, and family history of hypertension.

Blood pressure measurements should be a routine part of medical visits. Correct measurement requires that the patient be seated for 5 min, the cuff is the correct size, and the patient's right arm is supported at heart level when the measurement is taken. A small cuff will falsely elevate the reading as will a pressure taken with the patient talking or without adequate rest [11]. A proper cuff size is one in which the bladder width covers 40 % of the arm circumference and the length covers 80–100 % of the arm circumference [12].

Classification of BP is determined by using the American Heart Association (AHA) charts for pediatric blood pressure ranges and is described as normal, pre-hypertensive, Stage 1 and Stage 2 hypertension (see Table 20.1) [13]. Any blood pressures that are >90 percentile should be repeated manually at the end of the visit. A diagnosis of hypertension requires three separate readings done over days or weeks.

Further evaluation differentiates secondary from essential hypertension. Secondary causes are more common in younger children and include renal disease, medication side effects, obstructive sleep apnea, and rarer causes such as pheochromocytoma, Cushing's syndrome, and congenital adrenal hyperplasia. It is important to evaluate renal function with renal ultrasound with Doppler, renal panel, complete blood count, and urinalysis [13]. Those with Stage 2 hypertension require a more detailed evaluation; in such cases, consider referral to a pediatric hypertension specialist.

Dyslipidemia

Abnormal lipid values in childhood are risk factors for subsequent heart disease [14], and improvements can be achieved through dietary changes [15] as well as with medication [16]. Recent recommendations from NHLBI propose universal screening, regardless of family history,

weight, or other risk factors, at two different age periods: 9–11 years and 17–21 years. Screening from age 2 to 8 years should occur when BMI ≥ 95th percentile or in the presence of other risk factors. Screening between ages 17–21 years should be done when BMI ≥ 85th percentile or in the presence of other risk factors. An abnormality in a fasting lipid panel (see Table 20.1 for cut points) should be confirmed with a second panel 2 week–3 months after the first, with results averaged. A non-fasting lipid panel can be performed as a prescreen. If total cholesterol minus HDL is >145 mg/dL, the fasting lipid panel should be evaluated and repeated if any values on that panel are abnormal [17].

Common patterns of dyslipidemia in obesity include combined hyperlipidemia (elevated triglyceride, depressed HDL, and normal or mildly elevated LDL) or elevated LDL alone. Both patterns are associated with initiation and progression of atherosclerotic lesions in children. Both show improvement with diet and activity changes and weight control, which should be the first line of treatment. More aggressive intervention may be needed in severe triglyceride elevation (>500 mg/dL) or severe LDL elevation (>169 mg/dL).

Insulin Resistance and Glucose

Altered glucose metabolism in the obese patient begins with insulin resistance (IR) and can progress to prediabetes and then diabetes. Current best practices do not recommend routine laboratory screening for IR in obese children. Fasting insulin is not an accurate marker of whole body impairment of glucose metabolism although it may identify compensatory hyperinsulinemia. Physical signs of insulin resistance will be discussed further in the skin subsection. Factors associated with insulin resistance include puberty (a time when insulin sensitivity is lower), Hispanic, and African-American race (blunted compensatory increase in insulin levels), visceral adiposity, polycystic ovary syndrome, and fatty liver disease [18].

The incidence of newly diagnosed Type 2 diabetes mellitus has risen and now accounts for 46 %, 57.8 % of, 69.7 % and 86.2 % of newly diagnosed diabetes cases in Hispanic, African-American, Asian/pacific Islander, and American Indian youth ages 10–19 years, respectively, [10]. Indications for screening include elevated BMI, acanthosis nigricans, and family history of diabetes. Four screening methods are available for screening: random blood glucose, fasting blood glucose, 2-h oral glucose tolerance test, and glycosylated hemoglobin [19]. Per American Diabetes Association guidelines, unless there is "unequivocal hyperglycemia," one abnormal screening test should be confirmed with repeat testing. Hemoglobin A1C may not be an ideal test in those with anemia or conditions that alter the rate of red blood cell turnover.

Metabolic Syndrome

Metabolic syndrome (MetS) is a constellation of symptoms that are known to increase the risk of developing cardiovascular disease in adulthood [20]. Other terms for MetS are Syndrome X and cardiometabolic syndrome. Currently recognized components of MetS include elevated blood pressure, impaired glucose metabolism as noted by insulin resistance or glucose intolerance, dyslipidemia noted by low HDL and elevated triglycerides, high waist circumference, and obese BMI. Metabolic syndrome is defined as three abnormal components, but the criteria for abnormal values vary based on patient age and which of the more than eight existing sets of criteria is used [21]. Prevalence of the syndrome ranges from 2 to 39 % depending on the definition used [21–23]. Caution is needed when diagnosing MetS due to instability of the individual components during childhood and adolescence [17, 23]. In addition, cut points considered abnormal in MetS definitions may fall within the normal range on laboratory reports.

Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is a silent and serious condition that is challenging to

diagnose and treat. NAFLD is the accumulation of triglycerides in liver cells, not related to alcohol or other toxins or metabolic conditions. Simple fat accumulation (steatosis) can progress to inflammation (nonalcoholic steatohepatitis or NASH), which in turn can progress to fibrosis and ultimately cirrhosis. Risk factors are obesity, diabetes or family history of diabetes, and Latino background. Relative to white patients, African-American patients have a low risk despite a high population prevalence of obesity and diabetes. Currently, confirmation and staging of NAFLD require a liver biopsy. An autopsy study found that prevalence among children of all weight categories is low until age 10 years, when it is 11 %, and rises further by mid-teen years. About 25 % of children with NAFLD have NASH, and about 10 % with NAFLD have advanced fibrosis or cirrhosis. Obesity greatly increases the risk [24]. Weight loss can reverse the condition, but effective pharmaceutical treatment has not yet been identified. There is debate about the use of serum alanine aminotransferase (ALT) as a screening tool. Although ALT elevation of 1.5–3 times normal in a high risk patient is suggestive of NAFLD, it is not specific for NAFLD and the degree of elevation does not correlate with stage of NAFLD. Patients with normal ALT can have advanced NAFLD. Those who oppose its use cite its low sensitivity and the lack of treatment options other than weight loss, which generally should be recommended in the presence of obesity. Those who support its use point to NAFLD's high prevalence and potential severity and to the change in monitoring and management when cirrhosis is identified. Recommendations by an Expert Panel on Child and Adolescent Obesity suggested screening with transaminases every 2 years, starting at approximately 10 years of age, to coincide with recommendations for screening for diabetes [25]. In the absence of underlying evidence, clinicians may use judgment given more recent information about low prevalence among African-American youth. When elevations are in the 1.5–3 times normal range, one approach is to counsel healthy lifestyle and weight control. If elevations persist for 6 months or more, refer to specialist for further management. Specialists will be best positioned to evaluate need for biopsy and also will be aware of emerging studies on medication.

Skin Conditions

Common skin conditions include acanthosis nigricans, striae distensae, skin infections, and acrochordon (skin tags) [26]. Many skin lesions found in obese patients are in part due to hyperinsulinemia and its effect on IGF-1 receptors in skin. The overgrowth of keratinocytes and fibroblasts results in increased cell growth, which leads to conditions such as acanthosis nigricans, acrochordons, and hidradenitis suppurativa [27]. Often, the lesions are found in intertriginous areas. A close examination of the skin folds of obese patients is important and can be done best when the patient is wearing a gown.

Striae distensae (stretch marks) represent a loss of elasticity in the skin, manifested by linear areas of thinned skin. They are often pink in color and become less pigmented with time. They occur during times of rapid growth, either linear or in girth, and are typically located on upper arms, buttocks, hips, abdomen, and breast. Wide purple striae may be a sign of Cushing's syndrome.

Acanthosis nigricans is lichenified, velvety, and hyperpigmented lesions of the skin. It is primarily located along the skin folds of the neck, axilla, and groin although it may be present in other areas of the body as well. In the development of acanthosis nigricans, the skin initially looks mildly hyperpigmented (parents may believe their child's skin is dirty) and then progresses to appear thickened and velvety. As it progresses further, the lesions may involve larger portions of the body. Involvement of the oral mucosa, palms, or soles may be a sign of malignancy or drug-induced acanthosis nigricans. A grading system for acanthosis nigricans located on the neck has been proposed: grade 1 lesions are present only on close observation, grade 2 lesions are at the base of the skull, <3 in. in breadth and do not extend to lateral neck, grade 3 lesions extend to lateral margins of neck but are not

visible from front, and grade 4 are visible from the front [28]. Use of a grading system assists with monitoring progression or resolution of lesions.

Acrochordons (skin tags) are commonly seen in obese adults though they may be present in older children and adolescents. They present as soft, flesh-colored, pedunculated growths in intertriginous areas such as the neck, axilla, and groin. If they are present in very young children or in those who are not obesity or insulin resistant, a dermatology referral should be made.

Intertrigo describes superficial skin infections within the skin folds. They appear as painful, moist, macerated areas usually along the abdominal pannus and groin. Common organisms include yeast, bacteria, and dermatophytes. Recurrent deep boils may be a sign of hidradenitis suppurativa.

Sleep Disorders

In obstructive sleep apnea (OSA), the consequences of oxygen desaturation and hypercapnea from the upper airway resistance include systemic hypertension, left ventricular dysfunction, and pulmonary hypertension. In addition, poor sleep compromises neurocognitive function. The incidence of OSA in children is estimated to be 3–4 % in population studies [29, 30]. Among severely obese children, prevalence seems to be much higher [31]. There is not a highly sensitive set of questions that screen for OSA. Most children with OSA snore, but many snorers do not have OSA. Daytime somnolence, assuming child is spending an appropriate amount of time in bed, can be a symptom, and also hyperactivity can reflect disrupted sleep, especially in younger children. A sleep study is a necessary tool to diagnose OSA [32]. Removal of enlarged tonsils and adenoids will improve airway function, but may not resolve the conditions, especially in the severely obese [33].

Sexual Maturation and Reproductive Health

Obesity impacts the development of secondary sexual characteristics and long-term reproductive health. Obese girls undergo thelarche and menarche earlier than their normal weight peers [34]. Data is conflicting regarding males but also suggests earlier onset of puberty [35]. Males may have exaggerated pubertal gynecomastia or pseudogynecomastia (fatty infiltration of the breast). Obesity is associated with a higher prevalence of true gynecomastia in children and adults, likely because of increased conversion of testosterone to estradiol in adipose tissue [36, 37]. Among males, the increased mons fat pad that surrounds the phallus may result in a buried penis although when extended and measured, the phallus is of normal length. True microphallus and undescended testes may be a sign of Prader–Willi syndrome.

Polycystic ovary syndrome (PCOS) should be given special consideration in adolescent girls with irregular cycles. It is the most common endocrine abnormality in women and a common cause of infertility. Women with PCOS are less successful at losing weight and are at increased risk of developing cardiometabolic comorbidities, regardless of obesity [38]. PCOS is characterized by amenorrhea or oligomenorrhea (fewer than 9 cycles per year in women who have been menstruating for at least 3 years or <6 cycles per year for those menstruating for less than 3 years, physical or biochemical signs of androgen excess and/or polycystic ovaries on ultrasound [39–41]. Physical signs of androgen excess are hirsutism, clitoromegaly, acne, and androgenic alopecia. PCOS is a diagnosis of exclusion; therefore a full evaluation must be done to rule out other causes of androgen excess and oligoamenorrhea including thyroid dysfunction, hyperprolactinemia, late onset congenital adrenal hyperplasia, premature ovarian failure, androgen-secreting tumor and Cushing's syndrome. Work-up includes free and total testosterone, sex hormone binding globin, thyroid stimulating hormone, prolactin, dehydroepiandrostenedione sulfate (DHEAS), 17-hydroxyprogesterone, and pelvic ultrasound [42, 43].

Orthopedic Conditions

Obese pediatric patients not only are prone to several specific musculoskeletal complications but also are at increased risk of fractures and have

more complaints of foot and ankle pain then their normal weight peers [44, 45]. Review of systems often notes ankle, knee, hip, groin, and lower back complaints. Physical exam will identify bow-legs, pes planus (flat feet), limb length discrepancies, limited range of motion, and antalgic gait. Special attention should be paid to possible Blount's disease (tibia vara) and slipped capital femoral epiphysis (SCFE). Blount's presents with bowing of the legs from tibial torsion in the setting of excessive weight placed on medial tibial growth plate which inhibits growth medially while lateral growth continues unopposed. Blount's is more common in African-American males [46]. Depending on the severity of obesity, bowing may not be as obvious though patient complains of knee or ankle pain. Diagnosis required X-rays of the lower extremities.

SCFE is the displacement of the femoral head off of the epiphyseal plate. Most cases occur in adolescents and an estimated 60 % of patients have BMI >90 percentile [47]. The incidence of SCFE has increased as BMIs have increased [48]. Chronic, dull hip pain and groin pain may be the presenting complaint. Diagnosis is made based on symptoms and hip radiographs. Anterior-posterior and lateral X-rays of the hips show a classic "ice cream falling off the cone" appearance. Both hips should be imaged because in a significant proportion of cases the condition is bilateral (20–40 %) [47]. Complications of SCFE include a vascular necrosis and loss of the particular cartilage.

Additional complaints include low back pain from an exaggerated lumbar lordosis secondary to weak core muscles and the strain of supporting large abdomens. Adolescent females may complain of shoulder and upper back pain due to heavy, poorly supported breasts. Having the patient walk without shoes will reveal pes planus and other foot deformities resulting from increased weight bearing on developing foot structures [49, 50].

Pseudotumor Cerebri

Pseudotumor cerebri is defined as elevated intracranial pressure without an underlying mass, central nervous system infections, or other direct causes of increased pressure. The condition presents with severe headache, often accompanied by nausea, vomiting, and sometimes by neurological symptoms including visual loss from papilledema and diplopia from cranial nerve VI impairment. Visual loss can be permanent. In addition to being associated with medications, including vitamin A, growth hormone, and steroid withdrawal as well as infections, the condition appears to be association with obesity. The evidence for this association is strong in late teens and adults, but the rarity of the condition and the likelihood of an ascertainment bias make incidence and prevalence estimates unreliable. One study estimated an incidence rate of less than 2 per 100,000 for children under age 15, regardless of weight status or gender, but rates increasing to 20 per 100,000 among obese women 15–44 years of age [19]. Not all symptoms may be present [51], but severe headache, visual impairment, abnormal neurological examination, and papilledema should prompt urgent referral to neurology for neuroimaging and lumbar puncture.

Genetic/Endocrine/Neurologic Causes of Obesity

Scientific understanding of influences on regulation of appetite, energy expenditure, and body composition is exploding. We now recognize the influences of adipocytes, the hypothalamus, gut and other hormones, and also a number of genes in the development of obesity. Clearly defined genetic syndromes or treatable endocrine disorders are small in number and their prevalence is low, and so the new scientific knowledge of physiologic "causes" for obesity have not yet led to specific treatment strategies. The role of the general clinician is to use the history and physical exam to identify those patients who need further evaluation.

Clinical hypothyroidism has an estimated prevalence of 2 in 1,000 in the US population 12 years and older [52] and is likely somewhat lower in children [53]. In contrast, about 300 of 1,000 children are overweight or obese. Thyroid screening should be limited to children with other

symptoms, particularly linear growth cessation or short statue, but also depression, hair thinning, cold intolerance, and other clinical signs and symptoms of low thyroid hormone levels. Primary Cushing's syndrome is very rare, less than 1 per 100,000 [54]. Screening for Cushing's syndrome should be limited to children with short stature, hirsutism, striae, and central adiposity with excess weight on back ("buffalo hump").

The presence of early severe obesity increases the likelihood of a genetic cause of obesity. Some well-recognized syndromes, like Prader–Willi or Bardet–Biedl, are associated with short stature and developmental delay. However, recently identified genetic variations are not uncommon among severely obese children, and they may have normal or accelerated linear growth and normal development. An excellent review article presents an algorithm for investigation of underlying causes of severe early obesity [55]. In contrast to the rarity of metabolic and genetic causes of obesity, medications, especially neuropsychiatric medications, are fairly common contributors to weight gain. If patients and prescribing physicians are aware of this risk and see weight gain, they can sometimes find less obesogenic alternatives. Table 20.2.

Table 20.2 Summary of visit components to evaluate obesity-associated medical conditions

a. Symptoms of obesity-related medical conditions

Review of systems	Possible condition(s)	Next diagnostic step
Double vision	Pseudotumor cerebri	Physical examination (see below) and possible neurology referral
Severe headaches	Pseudotumor cerebri	Fundoscopic exam
	Obstructive sleep apnea(OSA)	Assess for snoring
	Hypertension	Assess blood pressure
Snoring, especially with reported pauses, somnolence, or hyperactivity	Obstructive sleep apnea	Sleep study. Consider ENT referral
Infrequent or very irregular menses	Polycystic ovary syndrome	Laboratory testing to rule out non-PCOS causes of oligomenorrhea
	Immature hypothalamic–pituitary–ovary axis	Consider specialty referral
Pain of the pelvis, hip, knee, foot, or with walking	Slipped capital femoral epiphysis	Physical examination (see below)
	Pes planus	
Polyuria, polyphagia, and/ or polydipsia	Type 2 diabetes mellitus	Laboratory evaluation
Right upper quadrant abdominal pain	Fatty liver	Liver function tests. Consider ultrasound and/or referral to gastroenterology
	Cholelithiasis	

b. Signs of obesity-related medical conditions

Physical examination	Possible condition(s)	Next diagnostic step
Short stature, especially in relation to parental height	Low thyroid, other endocrine, or genetic disorders	Bone age
		Thyroid function tests
Early severe obesity, especially with short stature and/or developmental delay	Underlying genetic, endocrine, or neurologic disorder	Refer to genetics
Elevated blood pressure	Hypertension	Assess at least 3 times. Consider ambulatory monitoring to eliminate white coat hypertension. Assess for secondary hypertension if appropriate
Papilledema, CN VII palsy, in setting of headache	Pseudotumor cerebri	Refer emergently to neurology

(continued)

Table 20.2 (continued)

Tonsillar hypertrophy	Obstructive sleep apnea if other symptoms of OSA are present	Refer to ENT, consider sleep study
Acanthosis nigricans	Insulin resistance	Consider screen for altered glucose metabolism (see table: diabetes screening)
	Prediabetes although often AN precedes laboratory findings	
Skin rash	Intertrigo	Consider dermatology if diagnosis uncertain
	Keratosis pilaris	
Hirsutism	PCOS, Cushing	Consider laboratory investigation for PCOS or Cushing, depending on other signs and symptoms
Hepatomegaly	Nonalcoholic liver disease	Liver function tests
Micropenis	Penis hidden by fat	Measure length
Enlarged breasts in males	Gynecomastia	Palpate for actual breast tissue making note of the diameter;
		Monitor every 3 months;
		Surgery referral
Bowing of lower extremities	Blount's disease	Orthopedic referral
Limp and limited hip range of motion	Slipped capital femoral epiphysis	Urgent orthopedic referral

c. Laboratory evaluation for common but frequently silent conditions

Laboratory screening tests and schedule	Common conditions	Next steps
Abnormal lipids		
Fasting lipid panel	Combined hypercholesterolemia (elevated triglyceride, low HDL, ±elevated LDL)	Nutrition and physical activity counseling
2–8 years if BMI ≥ 95th percentile	Hypercholesterolemia (elevated LDL)	If TG > 500, or LDL > 160, review guidelines for intervention, including medication
9–11 years universal screen		
12–16 if BMI ≥ 85th percentile		
17–21 years universal screen		
Diabetes/prediabetes		
Fasting glucose or hemoglobin A1c	Prediabetes	Nutrition and physical activity counseling for prediabetes
10 years/onset of puberty when BMI ≥ 85th percentile and other risk factors	Diabetes	Urgent referral to pediatric endocrinology for diabetes
Nonalcoholic fatty liver disease		
ALT and AST can be considered (lack of consensus on utility of NAFLD screening)	Steatosis, steatohepatitis if 1.5–3 times normal in high risk patients	Nutrition and physical activity counseling
10 years/onset of puberty when BMI ≥ 85th percentile and other risk factors		Repeat testing in 6 months and consider gastroenterologist consult if persistent elevation

Non-fasting lipid panel can "prescreen" children if clinician has concerns about adherence to fasting assessment. If non-HDL cholesterol (total cholesterol minus the HDL value) is less than 145, then no further work-up is needed. If >145, then a fasting lipid panel is needed

Hemoglobin A1c is sometimes used in adolescents when adherence to fasting glucose assessment is a concern. The values used in adults to define prediabetes is 5.8–6.4, and 6.5 % or greater is likely to indicate diabetes

Assessment of Psychosocial, Environmental, and Obesity-Related Psychological Factors

Social Environment

Obesity is best considered as a chronic disease with social, environmental, and behavioral mitigators. A complete assessment of the obese child requires a review of these areas.

Past medical, social, and family history should focus on known contributors to the development and continuation of overweight and obesity and its comorbidities. Relevant features of the past medical history includes prematurity, small for gestational age, macrosomia, and gestational diabetes. A factor in the family history that influences the development of obesity is the presence of parental obesity. Parental obesity, especially maternal, increases the risk of childhood obesity; obesity in both parents further increases the likelihood, with the greatest impact being on children under 10 years of age [56, 57]. Obesity in grandparents also increases the risk of childhood overweight and obesity, even if parents are of normal weight [19].

A family history of overweight and obesity provides information regarding the child's risk for obesity as well as providing increased awareness of food and exercise attitudes held by the family. Assessment of parental weight status is objectively assessed by asking for parental heights and weights; actual measurement of parents is ideal. A family history of bariatric surgery may help identify how other family members have personally managed weight concerns as this example influences parent and patient expectations of the treatment course. Cultural perceptions of weight are also important to consider. Minority populations may see thinness as undesirable, preferring a larger body size as a marker of health and wealth [58]. Acknowledgement of cultural norms and reframing from a health belief perspective may allow a more culturally competent approach that is acceptable to the family.

When obtaining a social history, it is important to review access to parks, neighborhood safety, and closeness of grocery stores. Parents often cite the local built environment as a barrier to outdoor physical activity. Some neighborhoods do not have sidewalks that extend beyond the subdivision, parks are located across busy and dangerous highways, and parks may be areas for criminal activity. Questions such as "is there a park or playground nearby," "are you comfortable allowing your child to play there," and "is your neighborhood safe" will help identify these concerns and allow you to partner with the family to create a viable treatment plan. Food deserts are a problem in many cities, especially in lower income areas. In food deserts, there is a relative lack of supermarkets (compared to smaller convenience stores and independent grocers) that provide a wide array of healthy food options when compared to the population density. Smaller grocers typically have a reduced quantity and variety of produce and carry fewer recommended healthy foods such whole grains, lean meats, and low fat items [59–61]. Food deserts may have fast food restaurants making less healthy options more accessible to families with overweight or obese children. Healthcare providers should understand and consider the financial status of families and costs of food options when making treatment recommendations.

Psychological Conditions

Research suggests an association between childhood/adolescent obesity and several specific psychological symptoms. However, studies of these associations have reached mixed conclusions. In addition, the directionality of these relationships is not clear. In general, emotional consequences of obesity may be more powerful for younger children, females, and those who report a loss of control when eating [62]. This section outlines three psychological symptoms (depression, anxiety, disordered eating) that in their most severe form may warrant a formal psychological diagnosis and evaluation.

Clinical practice guidelines are less detailed for psychological comorbidities than for medical comorbidities. Many clinical practice guidelines do discuss behavioral interventions and important

psychosocial aspects (e.g., family environment, parenting style, access to calorically dense foods); however, specific psychological conditions (for example, depression and anxiety) are not always addressed in guidelines or are given limited attention. Identification of these potential psychological comorbidities will provide a more complete understand of the youth's challenges and quicker referral to necessary treatments, which in turn will increase success of the patient and family in treatment. Table 20.3 provides both a general guide for evaluating these aspects in a pediatric obesity screening and also specific screening measures that are available to more systematically identify symptoms of depression, anxiety, and disordered eating through self- or parent-report [63, 64].

Depression

When compared to non-obese children, the prevalence of symptoms of depression is often higher in treatment-seeking youth with obesity [65, 66]. Some studies have reported close to 25 % of treatment-seeking youth reporting some form of depressive symptoms [66]. In studies of severely obese adolescents seeking bariatric surgery, 13–27 % report moderate to severe depressive symptoms and 68 % have a history of a diagnosis of depression [67, 68].

However, research is inconsistent about the relation between obesity and depression, and the statistics above indicate that not all obese youth have a depressed mood. In fact, in studies of community cohorts, overweight and obese children and adolescents suffered from depression at the same rate as normal weight controls [69]. Reports of depressive symptoms are typically higher in treatment-seeking (clinical) youth compared to non-treatment-seeking youth (community samples) [65, 70–72]. Also, the symptoms of depression may be indirectly related to obesity with body dissatisfaction and experiences of bullying/teasing being more directly related to depressive symptoms than actual weight status [65, 69, 71]. Current research is attempting to understand moderators and mediators and to identify what conditions and which specific groups are most vulnerable to the link between weight status and depression.

Some research has suggested that early symptoms of depression may increase risk of obesity later in adolescence and adulthood, particularly for females. Therefore, prompt identification and treatment of depressive symptoms may be an obesity prevention strategy [66, 72–74].

Low self-esteem is related to symptoms of depression although is not required for the diagnosis. In treatment-seeking samples, overweight/obesity is often associated with lower self-esteem [62, 75]. This relationship is more consistent among females and adolescents and stronger when weight-based teasing is present [62, 65, 69].

Anxiety

Less research exists on the relationship between anxiety and obesity. Similar to depression, findings remain inconsistent across studies, with some but not all studies reporting symptoms of anxiety being more common among obese youth versus non-obese youth [65, 76]. One study showed that treatment-seeking obese youth were no more likely to report anxiety than non-treatment-seeking obese youth [77]. Like depression, anxiety may increase the risk of future weight gain and increased BMI. In contrast to depressive symptoms, anxiety seemed to increase the risk of obesity for both males and females [73]. One additional psychological symptom related to adolescent obesity is a loss of control over eating, which may be a way of avoiding negative feelings, including anxiety [70].

Disordered Eating and Body Dissatisfaction

Binge eating is defined as a discrete period of time during which one eats "a quantity of food that is definitely larger than what most individuals would eat in a similar period of time and circumstances." In addition, a binge is characterized by a feeling of lack of control over eating or a feeling like one cannot stop eating [78]. Eating disorder diagnoses entail not only disordered eating but also disordered body image. The reported prevalence of binge eating in pediatric obesity has ranged from as high as 60 % to as low as 9 % in treatment-seeking youth and is higher in females than males [68, 70, 79, 80]. Binge eating

Table 20.3 Guide to screening for psychological disorders among obese children and adolescents

Symptom	Sample questions/Prompts [100]	Indications for referral
Depressive symptoms	Inquire about severity, intensity, and frequency of sad or irritable mood	Irritability/depressed mood that interferes with daily activities or family functioning
	For parent:	Depressed or irritable mood for two weeks or greater
	"How often does your child seem sad, down or irritable for seemingly little or no reason?"	Known strong family history of depression
	For patient:	Concern for self-harm or suicidality
	"Tell me about the last time you felt sad"	Presence of weight-based teasing or bullying
	"Tell me about the last time you felt irritated or annoyed at little things"	
	"How often do people make negative comments about you and your weight?"	
Anxiety	Inquire about severity, intensity, and frequency of anxiety	Routine avoidance of age-typical activities (e.g., social events, school absences)
	For parent:	Anxiety interferes with daily activities or family functioning
	"Tell me about times when you notice your child may feel scared or anxious"	Reported difficulty with making friends or meeting new people
	"What does your child worry about most?"	Any known trauma which continues to cause distress to patient or family
	"What situations does your child routinely avoid? What kinds of situations does your child often ask to get out of?"	
	For patient:	
	"Tell me about the last time your felt scared or worried"	
Disordered eating	Inquire about severity, intensity, and frequency of disordered eating	Reported binge episodes (high caloric consumption in a discrete period of time with a reported feeling of loss of control when eating)
	If reported or suspected binge, consider asking for a dietary recall of the binge	Night eating (consumption of 50 % of calories following last meal of day or waking to eat in the middle of the night)
	For parent:	Secretive eating, preferring to eat alone
	"What is the most you've noticed your child eat in one setting?"	Report of repeated attempts to diet volleying between high restriction and binge/overeating experiences
	"Outside of mealtimes, what other times do you notice your child eating?"	Strong preoccupation or concern with weight; high body dissatisfaction that may interfere with daily functioning or social situations
	"How much do you think your child focuses on/thinks about his or her shape or weight?"	
	For patient:	
	"How many times have you felt like you have had 'eating attacks'? Or times when you have felt you can't stop eating?"	
	"Can you stop eating once you have started?"	
	"How often do you think about your weight?"	

Instruments to assist in diagnosis of these conditions
Depression screening measures: Patient Health Questionnaire Depression Screener (PHQ-2) [101], Beck Depression Inventory (BDI-II) [102], Beck Depression Inventory Primary Care (BDI-PC) [103], Center for Epidemiological Studies Depression Scale for Children (CES-DC) [104], Patient Health Questionnaire for Adolescents (PHQ-A) [81], Pediatric Symptom Checklist (PSC/PSC-17) [105, 106]
Anxiety screening measures: The Screen for Child Related Disorders (SCARED) [107], Pediatric Symptom Checklist (PSC/PSC-17) [105, 106]
Disordered Eating screening measures: The SCOFF Questionnaire [108, 109], Questionnaire of Eating and Weight Patterns (QEWP-A) [110], Eating Disorder Diagnostic Scale (EDDS) [111, 112], and Eating Attitudes Test (EAT) [113]

and depressive symptoms may go hand-in-hand; moods may trigger overeating/binge eating which increases the child's risk for overweight/obesity, and also a binge episode may fuel a negative mood [65, 72].

Disordered eating patterns other than binge eating have demonstrated a relationship with obesity, including emotional eating (increased caloric intake in response to negative mood), external eating (caloric intake following the sight or smell of food), night eating, secretive eating, objective overeating (high caloric intake in a discrete period without feeling loss of control), and active restraint or restriction in eating (extreme dieting). Studies suggest that girls display higher levels of emotional eating and boys display higher levels of external eating [65, 71, 79].

In community-based samples, body dissatisfaction is higher for overweight and obese children and adolescents, particularly females [69]. In fact, body dissatisfaction may be a key driver for psychological comorbid conditions. Some studies show that controlling for body image negates the relationship between psychological diagnoses (e.g., depression) and obesity status [75].

Nutrition and Diet Assessment

Although the factors that influence obesity in children are numerous, the mainstay of obesity prevention and intervention remains healthy eating behaviors. Today's obesogenic environment encourages increased access to energy dense foods, changes in family feeding practices, and more eating outside the home [81, 82]. Healthcare providers play an integral role in motivating behavior change through systematic obesity screening, yet less than half of children who see primary care providers receive prevention counseling about diet and exercise as recommended by the American Academy of Pediatrics [83, 84]. It is thought that obesity intervention efforts may be most beneficial in younger children who are still developing their eating preferences and that earlier intervention in general yields more successful outcomes [83, 85].

Table 20.4 lists evidence-based dietary behaviors which providers should assess and discuss with patients and families at risk for obesity [82, 86–89]. When discussing diet with patients/families, providers appear to struggle most with lack of attention or accurate recollection from parents, underreporting of intake, and reporting of only favorable intake [90]. Studies show that parents underestimate their children's consumption of sweetened beverages in comparison to child reports, and a greater percentage of African-American children eat large meals compared with Caucasian children [82, 90].

Provider confidence in obesity screening increases when tools for obesity counseling are available. However, the tools need to be brief, targeted, and effective [86]. The White House has partnered with the American Academy of Pediatrics to provide primary care providers with Internet resources for diet and activity screening as part of the "Let's Move" initiative [91]. Many groups around the country have developed toolkits to assist in obesity screening and intervention such as "Eat Smart, Move More," the "Hawaii Pediatric Weight Management Toolkit," the "Healthy Weight Toolkit," and the "Good Health Club Toolkit" [85, 86, 89]. The use of toolkits by providers supports their provision of anticipatory guidance, promotes positive dietary and physical activity changes, and improves parental recognition of child's weight status [85, 91]. Examples of types of tools that can help primary care providers better screen and treat obesity include color-coded growth charts, intake assessment forms, handouts for families on weight-related behaviors, monitoring tools, and motivational interviewing tools [86]. Motivational interviewing is thought to enhance the effects of obesity intervention but takes skill building and time to perform. This "pull rather than push" philosophy adopts a patient-centered approach promoting higher patient/parent satisfaction [86, 87].

Physical Activity and Sedentary Time

Adequate physical activity and minimizing sedentary time in children is also fundamental in the prevention and intervention of obesity. Unfortunately, the majority of children (6 in 10

Table 20.4 Guide to assessment of eating and physical activity

Targets of modifiable choices and behavior	Specific areas to assess
Food and drink choices	Sugar-sweetened beverages and juices
	Water and low fat milk
	Snack food and junk food (e.g., cookies, chips, candy)
	Fruits and vegetables
Eating behavior and environment	Portion size (www.choosemyplate.gov)
	Meal frequency and balance
	Frequency of eating outside the home, especially fast food
	Meal environment (table or living room, television on or off)
	Family participation in nutrition changes
Psychological influences on eating	Self-efficacy and readiness to change
	Family and cultural values related to eating
	Triggers for overeating
Physical activity	Time spent in moderate to vigorous aerobic physical activity
	Time spent in muscle-strengthening activity
	Time spent in bone-strengthening activity
	Time spend in routine activities, like walking to school or performing yard work
	Participation in organized physical activity, like sports or dance class
	For children 3–6 years of age, time spent playing or engaging in any physical activity regardless of intensity or structure
Physical activity environment	Areas that are safe for play (yard, parks, nearby schools)
	Parent and family support for casual and organized physical activity
Sedentary behavior	Hours spent watching television
	Hours spent on other sedentary electronic activity
	Presence of television in the bedroom
Psychological influences on physical activity	Self-efficacy and readiness to change
	Family and cultural values related to physical activity
	Preferred activities for child

younger children and 9 in 10 adolescents) do not meet federal guidelines for physical activity, and the average child who is 8–18 years old spends 7.5 h per day in total screen time [92, 93]. There is a clear association between sedentary behaviors and unhealthy dietary intake [94]. Almost half of school aged children exceed the 2 h American Academy of Pediatrics guideline for non-educational screen time (activities other than reading, homework, crafts) [95]. Table 20.4 lists the evidence-based physical activity and sedentary time behaviors which providers should assess and discuss with patients and families at risk for obesity [86, 89, 92, 93, 95–97].

It is particularly important to counsel children who do not get adequate physical activity on minimizing non-educational screen time. Male children (of any ethnicity), African-American children, and those of lower socioeconomic level have the highest amounts of screen time [93]. The likelihood of excess screen time increases with the presence of a television in the bedroom, lack of rules about television content, and the frequency of family meals [95]. The period of time after school represents a golden opportunity to reduce sedentary time and increase physical activity [94]. Television viewing, isolated from all other non-educational sedentary time, predicts overweight and is more detrimental than other sedentary behaviors in relation to cardiometabolic risk [82, 93, 98]. The combination of having a television in the bedroom and exceeding screen time recommendations is another strong predictor for obesity [93]. Interestingly, regardless

of duration or type of sedentary activity, a high level of moderate to vigorous physical activity is extremely protective and associated with less cardiometabolic risk [98]. Beyond television, video games, and computers there has been an increased use of smart phones in children over the last few years. There are few data to date of the effects on weight gain of this new type of screen time.

Conclusion

A thorough assessment of the child with obesity will lay out a clear picture of the age- and gender-adjusted degree of excess weight and the health risks, both physical and psychosocial. The assessment may lead to diagnoses of comorbidities or raise concerns about a problem that needs the evaluation of another medical specialist or a mental health professional. Early identification makes possible early intervention in obesity's many comorbidities. In addition, an assessment of current lifestyle behaviors provides a basis to identify problem areas and recommend changes appropriate for each family. Dietitians and behaviorists would be welcome additions to the assessment team, but they are often not available, and a healthcare office, especially a child's primary care office, has the tools necessary to do a comprehensive screening of the child or adolescent with obesity.

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Treatment of the Obese Child or Adolescent

21

Sonia Caprio and Mary Savoye

Introduction: Childhood Obesity—A Worldwide Growing Epidemic

Childhood overweight and obesity have reached epidemic proportions and are major public health concerns both nationally and globally [1]. Excess body weight is the sixth most important risk factor contributing to the overall burden of disease worldwide [2, 3]. The prevalence of overweight almost tripled among US preschoolers and adolescents and quadrupled among children aged 6–11 years. Depending on ethnicity, 17–22 % of children 2–19 years old were at or above the 95th percentile of Body Mass Index (BMI) in 2004 compared to 5–6 % in the 1970s [4]. Not only are ethnic differences obvious among childhood obesity, but socioeconomic differences persist with families of lower socioeconomic status having higher prevalence rates [5]. Developing countries, like Latin America, undergoing a rapid nutritional transition, are reporting increasing trends in childhood obesity. Ironically, in the developing countries in which underweight and poor growth were previously the main health concerns in children, overweight and obesity are now becoming significant problems as a consequence of an environment characterized by easily available, cheap, high-calorie foods combined with sedentary lifestyles [6].

Several collaborative efforts have been made to gather experts from all disciplines of treatment and to review the existing literature on childhood obesity treatment. This chapter will present some of the findings, as well as challenges identified while compiling such data. It will discuss what a typical health care visit entails at both the primary care and specialist settings, treatment goals for children and adolescents, and treatment options, including diet modification, exercise, behavior modification, and pharmacological and surgical approaches.

Collaborative Effort

In light of childhood obesity's presence as a major public health problem, numerous health organizations and foundations, including the Institutes of Medicine, American Academy of Pediatrics, American Medical Association, and the National Institute of Health, requested a working group be formed and organized into both a prevention and treatment panel. The Treatment Panel primarily focused on research priorities for treatment of obesity which had already developed in children and adolescents.

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The Office Visit: Role of the Pediatrician

Although pediatricians are concerned about the problem of obesity, most feel unprepared, ill equipped, and ineffective in addressing it. Many studies, as well as a survey of pediatricians, dietitians, and pediatric nurse practitioners, confirm that pediatricians do indeed face many challenges in treating childhood obesity [7]. Most pediatric primary care providers are not trained to provide the extensive counseling on nutrition, exercise, and lifestyle changes that are required to treat obesity, and most are pessimistic that treatment can be successful. Most also have insufficient time and attention to dedicate to the obese child, a problem compounded by the lack of reimbursement by third-party payers. Pediatricians also lack support services, especially access to mental health professionals, nutritionists, or exercise physiologists [8, 9]. Given the magnitude of the childhood obesity problem, however, pediatricians and other health care providers are going to have to step up and take a major role in the care and health of the obese child. Successfully treating obesity will require a major shift in pediatric care.

In 1998 the Maternal and Child Health Bureau, an agency of the U.S. Department of Health and Human Services, convened a committee of pediatric experts to develop recommendations to guide physicians, nurse practitioners, and nutritionists in evaluating and treating overweight children and adolescents [10]. A group of pediatricians, nurse practitioners, and nutritionists reviewed the recommendations and approved their appropriateness for practitioners. Although the document is not entirely evidence-based, it represents the consensus from experts in pediatric obesity and is the gold standard of care for all practitioners evaluating and treating the obese child.

Evaluating the obese child should begin with a detailed medical examination, together with an assessment of nutrition, physical activity, and behaviors that are linked to obesity, followed by an appraisal of the degree of obesity and its associated metabolic complications. The goals of the medical exam are to identify and treat diseases associated with childhood obesity, to rule out possible underlying causes of obesity, and to assess the child's readiness for change. The focus should be on the child's entire family and any other caregivers or role models living at home [11, 12]. The examination should include a family history of parental obesity, gestational diabetes, dyslipidemia, and cardiovascular disease, as well as type 2 diabetes [13]. It should also gather information about any medication the child uses, because so many common medicines, such as glucocorticoids and antipsychotic medications, influence weight [14]. A nutritional history should include the quality and portion size of the meals, when and where the child eats, and levels of satiety and fullness following a meal. It should also record the amount and quality of snacks and daily consumption of juice and soft drinks [15]. Finally, practitioners should inquire as to how often the child eats "fast food," because children who frequently eat at fast-food restaurants consume more total energy, more energy per gram of food, more total fat and carbohydrates, more added sugars, less fiber, and fewer fruits and vegetables than children who do not [16].

The child's activity level should also be assessed. Lack of physical activity in the lifestyle of children is directly linked to the rise of childhood obesity in the US [17, 18]. This is of particular concern for the pediatric population given that physical activity patterns track from childhood into adulthood [1]. Sedentary activities such as TV viewing, computer use, and video and other electronic games all contribute to the decrease in activity levels of our youth globally [2, 18]. In addition, television viewing increases consumption of foods while watching television and increases the purchasing of foods advertised on TV [19].

Assessment of Obesity: The Body Mass Index

The initial assessment should begin with an accurate measure of height and weight, which is used to calculate, record, and plot the child's age- and gender-specific body mass index (BMI) on the Centers for Disease Control and Prevention 2000 BMI charts [20]. BMI in children provides

a consistent measure of obesity across age groups, correlating with measures of body fatness in children and adolescents. Although there is some controversy about the use of BMI to assess obesity in children [21], the International Task Force on Obesity finds BMI a reasonable index of adiposity [22].

Early recognition of excessive weight gain relative to normal growth is an essential component of the physical examination and should be part of any visit in primary health care. In 2003, the American Academy of Pediatrics recommended that pediatricians calculate and plot BMI in all children and adolescents [23].

Despite the uncertainties and controversy surrounding BMI's use in pediatrics, assessing children's BMI and BMI percentiles beginning at age two can prompt health care providers to address weight-to- height ratios during well child visits and should be part of the routine physical exam.

Assessment of Obesity-Related Diseases

To identify the obesity-related diseases that are being seen increasingly in children, laboratory tests should include a fasting lipid profile, which measures cholesterol and triglyceride levels, a liver function test, and fasting glucose and insulin levels [24]. A consensus panel of the American Diabetes Association recommends that overweight children with two additional risk factors, such as a family history of type 2 diabetes, race or ethnicity (American Indian, African American, Hispanic, or Asian Pacific), signs of insulin insensitivity, or hypertension, be considered for further testing [25]. Another consensus report finds that patients with obesity-related diseases, such as type 2 diabetes, hypertension, polycystic ovarian syndrome, dyslipidemia, nonalcoholic steatohepatitis, and sleep apnea, will require the expertise of the pediatric endocrinologist, cardiologist, gastroenterologist, and pulmonologist [13]. Children with these conditions should be cared for within specialized obesity clinics. Another chapter in this volume addresses the assessment of the obese child in more detail.

Treatment Goals for Children and Adolescents

The objective of interventions in overweight and obese patients is the prevention or amelioration of obesity-related comorbidities, e.g., glucose intolerance and type 2 diabetes mellitus (T2DM), metabolic syndrome, dyslipidemia, and hypertension. Without existing comorbidities, weight management goals may range from discontinuation of further weight gain to a modest weight loss, particularly for a young child. BMI will decrease over time with a discontinuation of weight gain as the child grows.

Most of the effective treatment programs have been carried out in academic centers through an interdisciplinary approach. Epstein and his team [26] at the State University of New York at Buffalo have been in the forefront of developing multidisciplinary programs that reduce childhood adiposity and the most important finding of these interventions may be that relatively modest but sustainable changes in lifestyles may have more long-term impact on obesity than radical regimens that enable patients to lose weight rapidly but not to maintain their new weight.

Components of Childhood Obesity Treatment

Treatment of obesity in children and adolescents includes diet modification via nutrition education and consequent reduction in caloric intake, increased exercise and decreased sedentary behaviors, and behavior modification that changes obesity-causing behaviors and helps maintain a healthier lifestyle. Ideally, these treatment approaches include a family member or caregiver [27]. Although each of these components is described separately, a treatment plan that includes all components is highly recommended as a potential long-term solution.

When comorbidities exist and/or there is a greater degree of obesity, more robust approaches such as pharmacological and surgical methods may be appropriate. Again, each

component will be discussed separately, but in reality, many of these components are prescribed and used concurrently.

Diet Modification

The general goal of diet modification is to lower the typical caloric intake to promote weight maintenance or loss while providing adequate calories for growth. However, dieting is thought to be ineffective and harmful, and there are long-standing beliefs that it may contribute to obesity [28]. Using a structured meal plan with youth may have adverse effects on self-esteem and constitute risk behaviors for development of obesity by encouraging denial of hunger cues, discontinuation of eating while still hungry, and skipping meals [29].

It is helpful for parents to learn the caloric density of foods and overall calories needed to maintain weight and promote growth (Table 21.1), but this information should be used for meal planning and not for food restriction. A calorie count can be determined by keeping a food record and bringing it to a dietitian for calculation or by using a calorie app or calorie counter on the internet. Unlike the app or other computer-based resource, a trained registered dietitian (RD) sees much more than calories, however, when a food record is provided. Patterns in lifestyle that may be contributing to obesity are uncovered and these habits should be worked on verses trying to restrict calories to a specific amount by imposing a diet on the youth. Theoretically an excess of 3,500 cal will cause a one pound of weight gain. A 500 cal deficit that promotes a one pound loss after one week (500×7 days in a week) is inappropriate for a preschooler but may be appropriate for a teenager. Treatment strategies for obesity should be based on several considerations: the age and developmental stage of a child, the degree of obesity, and the underlying problem. Specific information is listed below by age group since approaches may differ based on both physical and emotional development.

Table 21.1 Daily calorie needs

Age (years)	Not active (calories)	Somewhat active (calories)	Very active (calories)
A. For boys			
2–3	1,000–1,200	1,000–1,400	1,000–1,400
4–8	1,200–1,400	1,400–1,600	1,600–2,000
9–13	1,600–2,000	1,800–2,200	2,000–2,600
14–18	2,000–2,400	2,400–2,800	2,800–3,200
B. For girls			
2–3	1,000–1,200	1,000–1,400	1,000–1,400
4–8	1,200–1,400	1,400–1,600	1,400–1,800
9–13	1,400–1,600	1,600–2,000	1,800–2,200
14–18	1,800	2,000	2,400

Source: Modified from HHS/USDA Dietary Guidelines for Americans, 2010

Preschool-Aged and Early Elementary School-Aged Children

Beverage modification should be the first line of intervention for the obese child and is a practical intervention for pediatricians to use given time constraints. Skim milk can safely replace whole milk after two years of age [30]. The overconsumption of juice has been linked to childhood obesity [15]. The Academy of Pediatrics suggests no more than 4–6 oz of juice per day for children under 6 and 8–12 oz for older children [31]. If a child is overweight, however, they should be "weaned off" the juice by adding water to a total of 4 oz per day until no juice is consumed. Water and skim-milk are the primary beverages suggested for this age group. A rule-of-thumb is to use water for thirst and snack, and to encourage milk consumption at meal times. There are 60 cal in 4 oz of most juices (apple, orange) and even more in others (grape, cranberry). The discontinuation of two four-ounces glasses of juice per day saves 120 cal a day and prevents a one pound weight gain/promotes a 1 lb weight loss each month. The elimination of juice may be the only major diet modification a parent may have to undertake to see a weight change in their child.

Although some literature recommends calorie counting and food restriction at this younger age [32], there is strong research that suggests the avoidance of food restriction because of the importance of early development in learning hunger and satiety cues [29, 33]. Over-restriction of food or allowing foods at specific times only

Table 21.2 Typical daily food guideline for ages 2–5 years old

			Approximate Portion size	Approximate Portion size
Food group	Servings per day	Food	Toddlers	Preschoolers
Bread, cereal, rice and pasta	6	Bread	¼–½ slice	½ slice
		Rice or pasta	¼ cup	1/3 cup
		Hot/cold cereal	¼ cup	1/3 cup
Vegetables	3	Cooked/raw Vegetables	2 Tbsp	¼ cup
Fruits	2	Fresh fruit	2 Tbsp	¼ cup
		Canned fruit	¼ cup	½ cup
		Fruit juice	¼ cup	½ cup
Milk, yogurt, and cheese	3–4	Milk or yogurt	½ cup	3/4 cup
		Cheese	1 oz	1½oz.
Meat, poultry, fish, beans, eggs, and nuts	2–3	Meat	1 oz	1½oz
		Cooked beans	2 Tbsp	¼ cup
		Egg	½	1
		Peanut butter	1 Tbsp	2 Tbsp

Source: The Yale Guide to Children's Nutrition; Yale University Press, 1994. Reprinted with permission from Yale University Press

(characteristic of dieting) impedes autonomy and self-regulation, natural skills learned at a very young age [23, 33]. Because of this, programs such as Head Start offer foods to children family-style so that the child can serve his or herself and develop independent habits [34]. Total energy intake in studies of preschool children who were allowed to serve themselves show mixed results however, so it is reasonable to suggest that some guidance or modeling is needed for 2–5-year-olds to select appropriate portion sizes at meal times [35].

Snacking is crucial for this age group since the young child has a smaller stomach and therefore needs to eat more often to meet his or her calorie needs. In addition, a preschool child can be quite active and so may need food more often. Calorie prescriptions should be used as guidance only for the parents and not a strict plan that provides no deviation. A typical daily food guideline for ages 2–5 is shown in Table 21.2.

The Stop Light or Traffic Light Diet is perhaps the most widely used diet modification approaches for young children. It was originated by Leonard Epstein, PhD, [36] but others have written books on the basis of it [37]. His original version has been the method most studied over the years and continues to be evaluated in different clinical settings [38]. In this method, foods from standard food exchange programs are separated into red, yellow, and green categories. Red foods are those that are high in sugar, fat, and calories and therefore should be eaten in limited amounts. Yellow foods are foods that are nutrient-dense and relatively low in fat; moderate portion sizes are advised in this food category. Green foods are low in calories and can be eaten in larger quantities. Calorie recommendation ranges from 900 to 1,400 per day. The Stop Light Diet has been studied most extensively in a family-based setting with other weight management components considered.

My Plate (Fig. 21.1) [39] is the US Department of Agriculture's (USDA's) nutrition guideline that replaced the Food Guide Pyramid. It has five major messages, including filling a child's plate halfway with vegetables and fruits. There is an interactive Web site that allows this tool to be used for weight management purposes for all age groups by indicating the child's age, height, and weight, and receiving a daily food group recommendation with portion sizes. This sophisticated method tracks progress as well, similar to adult methods (Fitness Pal, Lose It) available on smart phone apps.

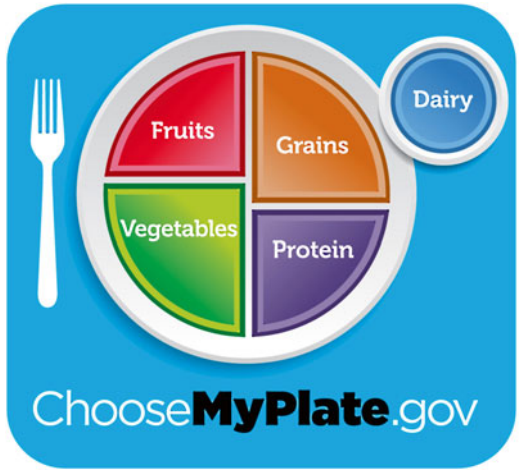

Fig 21.1 MyPlate is the current nutrition guide published by the United States Department of Agriculture. It depicts a place setting with a plate and glass, divided into five food groups. http://www.choosemyplate.gov

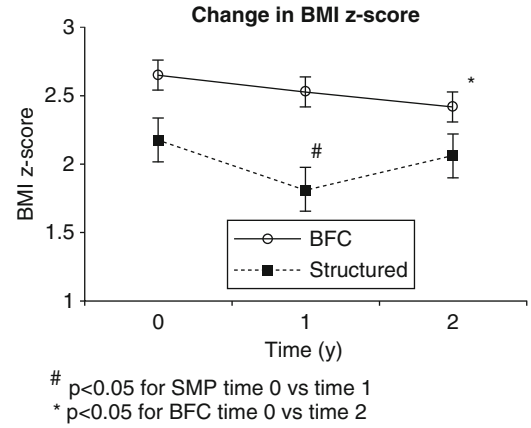

Fig 21.2 Dieting vs. Non-dieting Approach. Better food choices (non-diet approach) vs. structured meal plan (diet approach). Groups matched for age, gender, and motivational level. From Savoye M, et al. Anthropometric and psychosocial changes in obese adolescents enrolled in a Weight Management Program. J Am Diet Assoc. 2005; 105:364-370. Reprinted with permission

Adolescent-Aged Children

During early adolescence (10–14 years old) physical changes take place more rapidly than at any other time in the lifespan with the exception of infancy [40]. This age is characterized by a growth spurt that lasts approximately three years, usually beginning about 2 years earlier in girls than in boys [41]. While this growth spurt allows for a "window of opportunity" to decrease BMI with increased height, it is this exact period of time when there is a need for independence from parents. This age is a time when eating behavior should not be controlled too harshly by the parent because the child will eventually have to make his or her own choices when confronted with eating situations in the absence of the parent.

A non-diet approach that focuses on nutrient-dense, low-fat foods in moderate portions is strongly recommended for this age group. There is no calorie prescription but the concept of balanced meal planning is encouraged with the elimination of sugar sweetened drinks. Savoye and colleagues [42] followed a group of adolescent (mean age 13) dieters verses non-dieters for 2 years and found that those using a structured meal plan (dieters), rebounded back to baseline BMI at 2 years while the non-dieters (better food choice approach) continued to decrease BMI (Fig. 21.2).

Beverage choice continues to be the first-line intervention in this age group, particularly with high levels of soda consumption in adolescence. Soda and sports drinks typically take the place of juice during these years. Clinicians should make every effort to persuade the child to drink water in place of these sugar-laden beverages. Water can usually be purchased at school or brought from home, if acceptable to the school district.

As clinicians, it is important to dispel the misconception of the need for sports drinks while playing a sport. These fashionable drinks that provide nothing but carbohydrate in the form of sugar are not needed to replace electrolytes when a child's sport is limited to less than 2 hours and the temperature is cool. On the other hand, if a child is playing multiple games in the summer heat, there may be more indication for their consumption. Some drinks offer lower calorie versions (less sugar) with the same electrolyte value.

Mid-Late Adolescent-Aged Children

Mid-late adolescence serves as a stepping stone to the young adult world. The overweight child in

this age group (15–18 years old) has a very high chance of becoming an overweight adult if the problem is not rectified [43]. It is in this age group, if any, that caloric restriction may serve a better purpose if a non-dieting approach has not worked. A caloric restriction and/or energy expenditure totaling 500 cal per day is appropriate, if necessary. Family-based programs offer additional positive social benefits for adolescents such as building relationships and improving self-concept [42].

In contrast to this modest caloric restriction, a protein-sparing modified fast (PSMF) has been used in this older age group [44]. A PSMF is high in protein (2 g of protein per kilogram of ideal body weight per day) and extremely low in calories (600–900 kcal per day). Protein foods are low in fat (lean meats) and vitamin and mineral supplementation is used. Significant weight loss has been observed with this diet approach over the short-term (10 weeks and 6 months), however, when followed long-term (15months), no difference between PSMF and control groups were observed.

Increased Physical Activity and Decreased Sedentary Behavior

The Expert Committee recommends that overweight or obese children decrease television viewing (and other screen time) to ≤2 h per day as an initial step for treatment. If the child is <2years old, the goal is that they watch no television. To achieve this goal, a television should not be located in the room in which the child sleeps. Furthermore, the child should be physically active ≥1 h each day. This hour may consist of several shorter periods of activity over the course of the day. If necessary, the Expert Committee suggests there be an additional reduction of television/screen time to ≤ 1 h per day, a planned, supervised activity for 60 min per day, and the monitoring of such behavior through the use of logs (minutes spent on screen time and duration of physical activity [45].

Like the Expert Committee, the Centers for Disease Control and Prevention (CDC) recommends that children and adolescents complete 60 min or more of physical activity daily, with most of this exercise as aerobic, including walking, running, or swimming [46]. The US Department of Health classifies *aerobic activities* as activities in which people utilize their muscles. These activities should be performed at a vigorous pace (i.e. enough to produce a sweat) 3 days per week or more [47]. For children and adolescents, the CDC also recommends exercise that induces muscle and bone strengthening 3 days per week. *Muscle strengthening activities* make muscles do more work than activities of daily life, while *bone strengthening activities* produce a force on bones that fosters bone growth and strength. These activities may include push-ups, gymnastics, jump-roping or running [46].

Health care professionals often classify activity levels as light, moderate, and vigorous using METS (metabolic equivalents) or units that estimate metabolic cost or oxygen consumption. One MET is equal to the resting metabolic rate of 3.5 mL O_2/kg/min. *Light activity*, such as walking leisurely, is >1.5–3 METS; *moderate activity*, such as climbing stairs, is approximately 6 METS; and *vigorous activity*, such as jogging, requires >6 METS [48]. Conversely, a *sedentary behavior*, such as sitting or reclining, requires ≤1.5 METs [49].

Despite global and national guidelines, the effect of exercise alone on childhood obesity appears to be minimal or inconclusive, at best. There is agreement, however, that while weight loss is modest, there is an increase in lean body mass coupled with reductions in body fat, both of which increase metabolic rate [50, 51]. A major limitation of exercise studies appears to be their short-term nature, making it difficult to assess long-term benefits of exercise alone in obesity treatment. Exercise within the context of a comprehensive program, including other aspects of such as nutrition education and behavior modification, tends to be longer in duration and thus shows more beneficial results [52, 53]. As with dietary approaches, successful physical activity methods vary with age because of the physical and psychological development of the youth.

Preschool-Aged and Early Elementary School-Aged Children

Unstructured play is most appropriate for the young, overweight child. Long periods of free play are recommended, with frequent periods of adult-initiated moderate to vigorous activities, including parents, caregivers, and teachers [54]. Providing a safe environment for children to play outdoors is essential to increasing physical activity patterns of overweight children and, in many cases, is an obstacle for low socioeconomic populations [55]. Overcoming this obstacle may be accomplished through policy changes, improved environmental planning, and joint school and community efforts [54].

Few randomized controlled studies have been carried out in this young age group. Mo-suwan and colleagues [56] found that a 30-week preschool- and kindergarten-based exercise program prevented BMI gain in girls and induced a remission of obesity in both genders with just 15 min of walking in the morning and 20 min of dancing after afternoon nap three times per week. Currently, research is focusing on this age group to help fill this knowledge gap and to treat early and prevent obesity before unhealthy habits are established.

Elementary School-Aged Children

Activities that provide more structure such as sports, dance, and martial arts appeal to elementary school-aged and older children. The benefits of group sports include a sense of belonging and team building. Some children prefer activities they can engage in alone, particularly when at home (i.e. outside of school), such as shooting basketball hoops, jumping rope, bicycling, or walking. Parents and caregivers should respect the overweight child's choice as they may be more willing to continue with an activity of their own choice. In fact, even a hobby such as painting, stamp or card collecting, or theatre involvement, can be helpful to decrease screen time and avoid eating in response to boredom. Hobbies are often energy consuming and lead to improvements in self-confidence through achievement and, possibly, success with something others cannot do [57].

There is evidence to suggest that school-based physical activity interventions can be effective at increasing activity in children and, furthermore, can reduce the time spent watching television. A Cochrane review [58] analyzed several studies totaling over 36,000 children between 6 and 18 years of age and, although no two programs were alike in method (exercise intensity, duration, or frequency), children exposed to school-based activity programs were three times more likely to engage in moderate to vigorous exercise during the day than those not exposed. Interestingly, school-based interventions were not effective at increasing physical activity rates or decreasing television viewing among adolescents.

Policy change needs to take place to improve school-based activity as currently gym classes are offered infrequently, perhaps due to curriculum demands, and children are relatively inactive in them [59, 60]. Designing a school-based program to fit the needs of the overweight and obese population may be useful to curtail the obese child from feeling further stigmatized as overweight children have a harder time doing challenging exercises and will feel unfit in front of others. Additionally, changing their clothes in front of others also presents problems of embarrassment. These reasons may contribute to the lack of overall behavior change found in adolescents vs. younger children in school-based activity programs.

Adolescent and Teen-Aged Youth

Although it is generally beyond the resources of a primary care office, the use of a comprehensive multidisciplinary intervention that includes physical activity, with input from a physical therapist or exercise physiologist, is often recommended for the treatment of pediatric obesity. Obese children should have the support of an experienced professional team to develop a plan to minimize injuries during rapid growth and optimize the likelihood of long-term sustained weight loss [61].

The comprehensive Committed to Kids Program utilizes exercise physiologists and incorporates an increase in exercise frequency, duration, and intensity with a series of group sessions that promote increased physical activity

and improved body-movement awareness. The type of exercise is based on the level of overweight and physiologic function of the adolescent. Outcome data lacks randomized controlled study, but a prospective study of 56 participants showed a BMI reduction from 32.3 ± 1.3 kg/m^2 at baseline to 29.35 ± 1.9 kg/m^2 at 10 weeks and further reductions to 28.2 ± 1.2 kg/m^2 at 1 year [62].

Randomized controlled studies have been carried out with the Bright Bodies Weight Management Program (discussed later in this chapter) that includes instruction from exercise specialists and physical therapists. Anthropometric and metabolic improvements were achieved after 1 year [63, 64] and the treatment effects were sustained at 2 years [65].

Although it is important to increase physical activity in this age group, reinforcing a decrease in sedentary behavior can be equally important, particularly for those uninterested in sports or other vigorous activity. In fact, Epstein and colleagues demonstrated that a decrease in sedentary behavior resulted in greater weight loss than reinforcing an increase in physical activity or reinforcing both behaviors. This study found that encouraging children to spend less time playing computer games was more effective than encouraging them to participate in sports [66].

Behavioral Intervention

The behavioral treatment of childhood obesity is made up of a set of principles, theories, and techniques to help children and teens modify obesity-causing habits. The goal of behavior modification is to help the obese child and their family members identify problem behavior and modify their eating, activity, or thinking habits that are contributing to their weight problem [67]. To help an individual or family identify a problem behavior, a set of skills must be developed (self-monitoring and awareness). After the hard work of identification, the individual must also learn how to replace the obesity-causing habit with a positive one; this involves a different set of skills (cognitive behavior strategies, including relapse prevention, and solution-focused techniques).

Self-Monitoring/Increasing Awareness

Self-monitoring or recording one's behavior is the most fundamental component of behavioral weight loss treatment [68] and is typically initiated at the beginning of any weight management curriculum, for children and adults alike [69, 70]. If one does not monitor their habits, it is difficult to know what needs to be modified. Older children and parents can be taught how to look for patterns to determine the precipitants of inappropriate eating. Monitoring falls on the shoulders of the parent for the young child as this is too difficult for them cognitively. Patterns of inactivity (and reasons for inactivity) can also be determined by keeping a record or log. The help of a dietitian, psychologist, or other health care provider may be necessary to provide instruction on self-monitoring. In adults, several studies have demonstrated that self-monitoring is associated with long-term weight control [71, 72].

Cognitive Behavioral Strategies

Behavioral methods are based on the principles of B.F. Skinner's operant conditioning [73], in which one event—positive or negative—leads to another when done repeatedly. For example, if one eats in response to anger, he will continue to eat in response to anger. On the other hand, if socializing at parties leads to overeating, it is also a learned behavior and will be done repeatedly. Cognitive behavioral strategies attempt to "unlearn" this behavior or trigger by helping the individual change the automatic response. In the above example, anger leads to overeating and learning to manage anger is the key to avoid overeating.

Stress is similar to this end providers can teach techniques to minimize stress so that overweight individuals do not respond detrimentally to this stimulus.

Stress management is a cognitive behavioral strategy. Stress can both contribute and cause the maintenance of excessive weight for children. The inter-relatedness between weight gain and stress may be bi-directional, in that psychological distress might bring about weight gain and rapid weight gain may lead to psychosocial problems [74]. Stress reduction methods are frequently included in adult weight management programs

because of the relationship between stress and overeating. Stress reduction methods in youth, though relatively new, may provide a useful skill for overweight or at-risk for overweight youth.

Stimulus control techniques helps overweight individuals better manage triggers associated with overeating or in response to a stimuli [68]. For example, if seeing a cookie jar on the counter causes one to reach in for the cookie, the child or family can be taught not to keep a cookie jar on the counter where it is visible. Realizing the cooking jar is causing the problem is self-awareness. Moving the cookie jar out of sight is stimulus control or a problem solving skill.

Coping Skills Training (CST) is also a form of a cognitive behavioral intervention and is based on Bandura's social cognitive theory [75]. CST involves practicing and rehearsing new, constructive behaviors to cope with a problem situation and eventually retraining oneself from nonconstructive coping styles and behaviors. Berry and colleagues [76] used CST with parents of overweight children attending the Bright Bodies Weight Management Program and after 6 months parents in the experimental group had significant improvement in interpersonal relationships, behavior control, and stress management compared with those who received no coping skills training. These behavior modifications also accompanied significantly lower BMI and percent body fat, while children of these parents demonstrated trends towards decreased BMI and percent body fat. CST has been used successfully in other chronic conditions such as Type 1 diabetes to help replace negative coping strategies with more positive behaviors in both children [77] and parents of children with Type 1 diabetes [78].

Solution-Focused vs. Problem-Focused Approach

Solution-focused brief therapy (SFBT) is a strengths-based approach, based on Milton Erickson's work when he challenged the psychotherapeutic community in 1960s–1970s by moving away from analysis of client's problems to a strength-based partnership approach with clients where clients were encouraged to do more of what works. It focuses on strengths and "life without the problem" rather than an analysis of the problem. This approach is much shorter than problem solving and typically last for 1–3 sessions lasting an hour each [79]. Nowicka and colleagues [80] have used this approach with a multidisciplinary team to treat childhood obesity and outcomes included improved BMI-z score, self-esteem rating, psychological well-being, and family climate.

Relapse Prevention

A lapse is defined as a single event in which previous, poor behavior has occurred (e.g., binged on cookies while watching television), while a relapse is considered a full return of the target behavior to original or baseline behavior (e.g., regularly binging on cookies while in front of television as if no behavior modification had ever taken place) and is a central concept in the field of addiction [81]. Obesity programs use relapse prevention methods to help patients cope with setbacks and to get "back on track." This cognitive behavior approach includes assessing and reassessing motivation and outcome expectancies, assessing and reassessing high-risk situations and re-training clients in more effective planning and coping skills, and developing alternatives to the addictive behavior [75, 82].

Family Involvement

Because parents are the major agents of change, it is imperative to include parents or other caregivers in the pediatric obesity treatment process [10, 27, 83]. It is the caregiver who purchases the food, prepares the food, and acts as a role model in the home. The parent should foster a healthy eating environment as well as being instrumental in decreasing sedentary behaviors and increasing activity in the home.

Because the parent has control of resources and often serves as the support system for the child, it is important that the child not be targeted alone during nutrition education. Given the effort exerted in pediatric weight management programs, this is important for clinicians to know, particularly if they are planning after-school

models that meet too early for working parents to attend. Epstein et al. [84] reported that when children were targeted alone, an increase in percentage overweight was found vs. when children and parents were targeted together. More recently, however, Golan et al. found that when targeting the parent alone—without the child in the intervention at all—the most significant reduction in percent overweight occurred in the overweight children [27]. This study, carried out with young children (mean 8.7years of age), demonstrated that omitting the child from attendance in intervention sessions has a greater advantage.

Comprehensive Treatment Programs: Gold Standard of Treatment

Perhaps the best consensus in the treatment of childhood obesity is that a treatment program should include all components necessary to address each contributing factor to the child's weight issue: diet changes, increased activity, behavioral modification, and parent involvement. Thus, a comprehensive approach is the gold standard in the treatment of obesity in both the child and adolescent. When analyzing the efficacy of this type of program, a randomized controlled trial (RCT) is preferred and the longer the duration of follow up, the better, given the chronic nature of obesity [58].

Yale Bright Bodies Healthy Lifestyle Program

Our comprehensive family-based program has demonstrated sustained treatment effects of improved BMI and insulin resistance for up to 24 months when compared with a standard clinical care group in children 8–16 years old [65].

The Bright Bodies Program uses a non-diet approach and supervised activity with behavior modification directed at parent and child separately. The nutrition education component is directed at both the parent and child. The registered dietitians use the *Smart Moves Workbook* [69], which provides consistent structure for all nutrition and behavior modification class topics. Behavior modification techniques include self-awareness, stimulus control, coping skills training (CST), and other cognitive behavior strategies. Parent's classes primarily consist of CST and SFBT strategies, all described earlier in this chapter.

The exercise component is facilitated by an exercise physiologist or physical therapist and consists of typical children's games that have been modified to increase heart rate such as jumping jack tag, obstacle courses, flag football, basketball, sprinting games, and sports drills. Participants are encouraged to exercise three additional days per week at home and to decrease sedentary behaviors.

Long-Term Cochrane Review of Comprehensive Programs

There are a plethora of comprehensive weight management programs for youth. The Cochrane Review [58] embarked on the mission of systematically reviewing thousands of studies and found 54 lifestyle approaches that met the search criteria of a randomized controlled trial (RCT), similar primary outcomes (BMI and BMIz scores), and a minimum of 6 month outcomes. Once a 12-month outcome was imposed on the search, only five studies were included for meta-analysis. We will include a description of each program with 12-month outcomes in Table format separated by < 12 years old (Table 21.3A, BMI-SDS only) and ≥ 12 years old (Table 21.3B,C, BMI and BMI-SDS, respectively).

Golley and colleagues [85] compared a parent-skills training program with the addition of intensive lifestyle education vs. parenting-skills training alone with obese children 6–9 years of age. The study concluded that parenting-skills training combined with promoting a healthy family lifestyle may be an effective approach to weight management in prepubertal children. Kalavainen and colleagues [86] compared comprehensive, one-on-one appointments with children and parents for a total of two appointments (control) to 15 group sessions separate for children and parents (intervention), though parents were targeted as the main agents of change. The group sessions included nutrition and physical activity education, both highly solution-oriented, and behavioral therapy

Table 21.3 Comparison of lifestyle interventions in children

Study	*N*	Intervention Mean (SD)	*N*	Control Mean (SD)
A. Children <12years old. Change in BMI-SDS at 12 months				
Golley et al. [85]	31	−0.24 (0.43)	29	−0.15 (0.47)
Kalavainen et al. [86]	35	−0.2 (0.3)	35	−0.1 (0.3)
Hughes et al. [87]	69	−0.17 (0.34)	65	−0.18 (0.28)
B. Children ≥12years old. Change in BMI at 12 months				
Study	*N*	Intervention Mean (SD)	*N*	Control Mean (SD)
Savoye et al. [63]	105	−1.7 (0.31)	69	1.6 (0.38)
Williamson et al. [88]	28	0.11 (1.6)	29	1.47 (1.95)
C. Children ≥12 years old. Change in BMI-SDS at 12 months				
Study	*N*	Intervention Mean (SD)	*N*	Control Mean (SD)
Savoye et al. [63]	105	−0.21 (0.24)	69	0 (0.22)
Williamson et al. [88]	28	−0.08 (0.11)	29	−0.02 (0.1)

Tables excerpted from *Interventions for treating obesity in children* (*Review*). The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. 2009

using principles of behavioral therapy, all described earlier in this chapter. The group sessions meeting more often offered a more effective mode of therapy for the 7–9-year-olds. The third 12-month outcome study of Hughes and colleagues [87] analyzed in the Cochrane Review investigated a best-practice, individualized behavioral program to a standard care approach for 5–11-year-olds. The best-practice approach used a modified traffic light diet, a goal of increasing activity to 1 h per day, and a process whereby the child sets his or her own goals. Families met with the dietitian eight times during the 1 year intervention. This approach was compared to a control group that also received one-on-one counseling but met less often and the dietitians gave general healthy eating advice. Both the intervention and control groups improved (−0.5 vs.−0.2 BMI, respectively), but there were no significant between-group differences observed. The authors argue that the modest benefits observed suggest a more intensive approach to the treatment of pediatric overweight is needed.

The most intensive comprehensive program was studied by our group (Savoye and colleagues [63]) for 12–16-year-old obese adolescents. The Bright Bodies Program, (described earlier), met twice per week for the first 6 months of the study then twice per month for the second 6 months. The control group consisted of standard of care at a pediatric obesity specialty clinic, with visits at baseline, 6 months, and 12 months. The intervention group was much more effective than the standard of care at decreasing BMI and BMIz as depicted in Table 21.3B,C, respectively. Other improvements were found in percent body fat, fasting insulin, insulin resistance, and total cholesterol. The other 12-month study reported in the older group was launched by Williamson and colleagues [88] and involved 11–15-year-old African American girls who used an interactive behavioral Internet program (intervention) or an Internet health education program (control). The intervention included Internet counseling and was highly interactive, while the control was a passive educational program. Interestingly enough, participation in the program was measured by the number of "hits" on the Web site and this was associated with positive outcome such as percent body fat loss in adolescents and significantly more weight loss in parents. BMI and BMI-z differences between the intervention and control groups indicate that the intervention was superior to the control (Table 21.3B,C). The 12-month studies in the Cochrane Review suggest that the more intense and regular the intervention, the better the results.

Improved Sleep Patterns as an Innovative Lifestyle Approach

During the past century, there have been declines in the sleep duration of children and adolescents [89]. Increased television viewing, computer use, and video games (sedentary activities discussed earlier) may be delaying bedtime. Busier lifestyles and more demanding academics, particularly for adolescents, may also be reasons for less sleep [90]. Adequate sleep promotes increased concentration and energy levels. There may be a tri-directional relationship between sleep, healthy food choices, and physical activity in that better sleep fosters more mindful food choices and feeling well enough to obtain physical activity. Adult

studies show a link between obesity and lack of sleep [91, 92] and more recently pediatric studies are showing similar findings [93, 94]. Since a chronic lack of sleep appears to be associated with higher BMI in children, pediatric obesity treatment should include the innovative approach of assessing sleep patterns and suggesting strategies to obtain adequate sleep.

Pharmacological Approaches

The utility of pharmacotherapy in adolescents has been reviewed [95, 96], and the use of medication to treat severe obesity can be an additional treatment modality [97, 98]. Several limitations preclude physicians from early implementation of drug therapies. These include: (1) the lack of U.S. Food and Drug Administration (FDA) approval for medication use in preadolescents and younger adolescents; (2) reduced efficacy over time, with a plateau after 6 months of treatment due to reduced energy expenditure offsetting the decrease in energy intake—an effect also noted with hypocaloric diets [99]; (3) the existence of a limited number of well-controlled studies of the safety and efficacy of pharmacological intervention in obese children; and (4) the need to weigh the relative risk of severe adverse events in children against the long-term potential for obesity-related morbidity and mortality. Despite these concerns, the negative health impact of childhood obesity may justify long-term medication administration, but only in combination with lifestyle modification [97, 98].

Orlistat or Xenical is the only Food and Drug Administration (FDA) approved medication for obesity treatment in adolescents ≥12years [100]. Sibutramine was an obesity treatment agent that was taken off the market [101]. Metformin or Glucophage is commonly used to treat prediabetes and diabetes in children and adolescents and may facilitate an initial modest weight loss [102]. The data on pharmacologic treatment is limited. The studies target adolescents and therefore are not applicable to younger children. Furthermore, there is no data of maintenance treatment effect and safety past 1 year [100].

Orlistat works by inhibiting the action of gastrointestinal lipase which leads to decreased fat absorption up to 30 % [103]. Mild to moderate gastrointestinal side effects are common which included fecal incontinence and urgency, oily spotting, abdominal pain, or flatus with discharge [100, 101]. Chanoine et al. [103] showed that Orlistat in conjunction with behavioral change improves weight loss in obese adolescents after being treated for 1 year. In the Orlistat group, BMI decreased by 0.55 compared to an increase of 0.31 in the placebo group [$p=0.001$]. Both the control and intervention groups had similar LDL, HDL, triglycerides, fasting plasma glucose, and insulin. However, diastolic blood pressure significantly decreased in the Orlistat treated group (−0.51 mmHg) and increased in placebo group (+1.30 mmHg) [$p=0.04$] [100, 101].

Sibutramine or Meridia was an oral agent used for obesity treatment and works by inhibiting norepinephrine, serotonin, and dopamine reuptake [101]. Though significant weight loss was achieved with this drug, it was taken off the market by FDA for safety concerns in 2010 based on data from the Sibutramine Cardiovascular Outcomes Trial (SCOUT) [101].

Metformin or Glucophage is a medication traditionally used to treat type 2 diabetes in children at least 10 years of age [102]. The drug decreases hepatic glucose production and plasma insulin levels, and increases insulin sensitivity [104]. Freemark et al. [105] examined the effects of metformin in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes in a large randomized trial and showed it decreased BMI 0.5 kg/m^2 or -1.3 % [SD=0.12, $p<0.02$], and decreased fasting blood glucose (from a mean of 84.9 ± 2.2 mg% to 75.1 ± 1.6 mg%) [$p<0.01$] and insulin levels (from a mean of 31.5 ± 3.3μU/mL to 19.3 ± 1.5 μU/mL) [$p<0.01$]). Common side effects included abdominal pain or diarrhea.

Combined behavior and pharmacological trials lacked standardized interventions (some included dietary change only, exercise change only, or no lifestyle intervention with drug administration) making it difficult to compare outcomes [100]. One study by the Glaser Pediatric Research

Network Obesity Study Group [106] clearly demonstrated weight loss augmentation with pharmacological intervention by comparing metformin with placebo (lifestyle). This study showed BMI outcomes were more favorable in the metformin group than placebo [mean (SE) adjusted BMI −0.9(0.5) vs.−0.2(0.5), $p=0.03$, respectively]. This difference remained after metformin was discontinued for 3–6 months.

The FDA defines clinically significant weight loss for pharmacotherapy as 5 % of body weight in adults [107]. Treadwell and colleagues [107] reported that the 5–7 % weight loss corresponded to BMI reductions of 2.7 and 3.7 units, respectively. Therefore, weight loss generated by medications may not be clinically significant in adolescents.

Surgical Approaches

Bariatric surgery is being used as an option for treating serious obesity in adolescents. Laparascopic adjustable gastric banding (LAGB) and Roux-en-Y gastric bypass (RYGB) are the two most common surgical procedures in obese adolescents [108]. Treadwell and colleagues [107] conducted a pediatric meta-analysis of bariatric surgery and concluded that LAGB and RYGB had significant BMI reductions of −13.7 to −10.6 kg/m^2 and −17.8 to −22.3 kg/m^2, respectively. The analysis showed resolution of comorbidities like type 2 diabetes and hypertension. Though LAGB is perceived as safer than RYGB, the FDA has not approved LAGB in adolescents [107]. The risks associated with LAGB include band slippage and erosion, port/tubing problems, hiatal hernia, wound infection and pouch dilation [107, 108]. The more serious complications associated with RYGB include nutritional deficiencies, pulmonary embolism, postoperative bleeding, shock, and intestinal obstruction [108].

A majority of the data on bariatric surgery in adolescents is from observation, thus hindering the ability to make definitive conclusions. However one randomized control trial compared gastric banding to lifestyle modification program [109]. After 2 years, the mean change in BMI in the gastric banding group was 12.7 units (95%CI, 11.3–14.2) in comparison to the lifestyle group 1.3 units (95 % CI, 0.4–2.9) [$p<0.001$]. The gastric banding group was also noted to have improved quality of life and health outcomes [109].

Conclusions

Given the magnitude of the problem of childhood obesity, pediatricians and other health care providers should learn the components that have been shown to be effective in childhood obesity treatment. Diet modification, increased physical activity, decreased sedentary activity, and behavior modification with parental involvement are all critical to effect change. A non-diet approach with an elimination of sugar-laden beverages and moderate portion sizes seems to be a better long-term approach than restrictive dieting. Although exercise alone is not sufficient for the treatment of obesity, it creates a "win-win" situation in weight management for its role in calorie expenditure and the transition of adipose tissue to lean muscle which increases metabolic rate. Unlike increasing exercise, decreasing sedentary behavior will not burn calories and increase metabolic rate as efficiently as physical activity, however doing less sedentary behavior by way of less screen time and engaging in hobbies contributes to treatment goals by providing some calorie expenditure and avoiding the eating that generally accompanies screen time or eating out of boredom. Behavior modification techniques, available in comprehensive programs, can be effective for decreasing obesity-causing behaviors.

Many comprehensive programs exist, but only few have undergone rigorous, long-term randomized controlled trials. In contrast to pharmacological agents and bariatric surgery, lifestyle interventions pose no risk of harm to the patient and can offer valuable life skills. Thus, these approaches should be attempted before pharmacological or surgical measures are considered. The ease of medication may attract adolescents when compared to the commitment involved

with lifestyle intervention. However, the pharmacological agents available for pediatric obesity treatment are not superior when compared to lifestyle intervention when using BMI as a measure. In contrast, surgical options can achieve significant weight loss, but at the cost of potentially serious post-surgical health complications. More long-term data is needed from pharmacological studies and randomized controlled studies are lacking in surgical approaches in adolescents. Because of the pros and cons, obesity treatment approaches should be tailored to each child and their family. After serious commitment to lifestyle modification, one may consider pharmacological or surgical alternatives after contemplating side effects and health risks.

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