Chapter 1
Understanding Obesity and Setting the Stage for Comprehensive Treatment

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What is Obesity?

Obesity is a chronic, relapsing, multifactorial, neurobehavioral disease state characterized by excess unhealthy adipose tissue accumulation reflecting a disorder of the energy regulatory system (ERS). Under healthy homeostatic conditions, the ERS is designed to tightly maintain a desired amount of energy stored in the form of fat. This targeted amount of fat mass is called the "set point." Accordingly, in response to acute and chronic energy needs, peripheral and central feedback signals direct brain responses to increase or decrease energy intake and energy expenditure to maintain this desired body fat mass set point [1, 2]. Dysfunction of the complex ERS, via multiple and various injuries (genetics, epigenetics, environmental triggers, etc.) results in abnormal accumulation of fat mass (i.e., eating more even when energy stores are replete) and the maintenance of an abnormally high body fat mass set point [3]. This is obesity.

Unfortunately, public perception of obesity as a simple failure of will power permeates our society, including our medical system. This bias and stigma may, in turn, lead to the experience of shame by people who are living with obesity and, for many, their subsequent avoidance of medical care [4]. Providing *compassionate*, *accurate*, and *scientifically based* education about the complex causes and contributors to abnormal weight (adipose tissue) gain in children and adolescents is critical for building a therapeutic relationship between the health care provider and the patient with obesity and their family [5]. Explaining this to families in words they

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C. K. Fox (ed.), *Managing Pediatric Obesity Using Advanced Therapies*,
https://doi.org/10.1007/978-3-031-37380-0_1

can understand helps dispel myths about what obesity is and is not and helps ease the discomfort that some families may experience when confronting obesity treatment. By emphasizing that no one is to "blame" or is "at fault," defenses may be lessened and an openness to hearing about effective treatment options can be enhanced. Ongoing supportive conversations about the underlying biological causes of obesity are frequently needed as many parents/families hold tight to pervasive misperceptions that if they "try harder" to "eat less and move more" their weight status would improve.

In addition to gaining the trust and allegiance of the patient, understanding the physiological complexity of obesity is essential for effective management of the disease. Specifically, for many people with obesity, abnormal biological forces limit the effectiveness and durability of lifestyle therapy. Indeed only a small fraction of youth with obesity, especially severe obesity, will achieve clinically significant BMI reduction with lifestyle therapy alone [6–11]. For this reason, adjunct treatments that target the underlying pathophysiology of obesity, such as anti-obesity medications (AOMs) and/or metabolic and bariatric surgery (MBS), are often needed. This chapter will review the causes of and contributors to obesity and explain the role of intensive lifestyle therapy (ILT), pharmacotherapy, and MBS vis a vis these causes and contributors.

Fat Mass Regulation and Obesity

Obesity is the quintessential multifactorial disease with biological underpinnings that are expressed in the context of certain environmental and social exposures. These biological underpinnings are the causes of obesity and the environmental and social exposures further contribute to the development and intractable, relapsing nature of obesity [12]. Not only are these causes and contributors additive, but they are also interactive and multiplicative [13]. Arguably, the number and extent of obesogenic factors a person has is likely proportional to the degree of their obesity and subsequent need for more intensive, multipronged interventions.

Furthermore, it is important to recognize the normal physiological changes in relative adiposity that occur throughout a child's development. Adiposity increases from conception through birth and up to 1 year of age after which it decreases to a nadir around age 5–7 years and then increases to adolescence. There are critical periods of development that are especially vulnerable to insult or influence, which in turn may increase the odds of abnormal accumulation of adipose tissue and developing obesity [14] (see Fig. 1.1). These include:

- Gestation/early infancy, when for example, being large for gestational age and rapid weight gain increases the odds of childhood obesity.
- Early childhood when early adiposity rebounds before age 5–7 years increases the risk for future obesity.

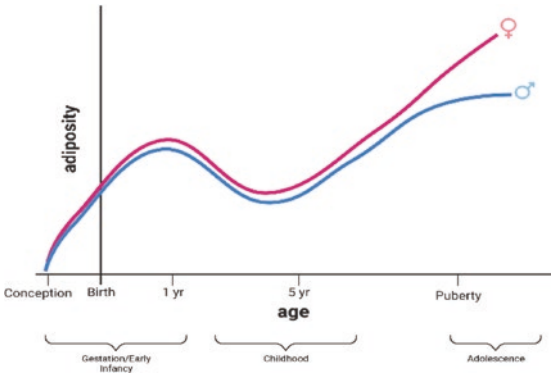


Fig. 1.1 Critical periods of development and changes in fat mass

- Adolescence is characterized by a rapid increase in adipocyte size and number and because adipocyte number is generally determined by the end of adolescence [15], this is another sensitive period of development.

Physiology of Appetite Regulation

Under normal, healthy circumstances, adiposity is controlled by homeostatic processes that are tightly regulated by central nervous system circuitry, which controls *food intake and energy expenditure* [3]. Peripheral signals from gustatory inputs, gastrointestinal tract, pancreas, liver, muscle, and adipose tissue all communicate bidirectionally with the brain, primarily the hypothalamus, via the autonomic nervous system, hormones, and metabolites. These peripheral signals relay short-term information on energy availability and long-term information on energy stores to direct appropriate energy intake or expenditure. Clearly, the degree of adiposity a person has is not under their volitional control [16].

Peripheral Signals

Hormones active in energy regulation can be classified as "orexigenic," which increases food intake or "anorexogenic," which decreases food intake. (see Table 1.1, Fig. 1.2) Ghrelin is the main orexigenic hormone, whereas there are multiple anorexigenic hormones including glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), cholecystokinin (CCK), peptide YY (PYY), amylin, insulin, glucagon, adiponectin, and leptin. At the onset of hunger, ghrelin, secreted by the fundus of the stomach, stimulates the hypothalamus and hippocampus to increase food intake and decrease energy expenditure. As eating proceeds, satiation, the feeling of fullness that leads to meal termination, is induced by multiple anorexogenic hormones [17–19].

Table 1.1 Energy regulation hormones

Hormone	Source	Site of action	Action
GLP-1 [20]	Enteroendocrine cells of small intestine	Pancreatic β cells Hypothalamus Brain reward centers Heart	Stimulates hypothalamus and brain reward center to increase satiety and reduce eating Slows gastric emptying Stimulates insulin secretion Postprandial GLP1 levels are low in obesity
GIP	Enteroendocrine cells of small intestine	Pancreatic β cells Adipocytes Brain Heart Bone	Stimulates insulin secretion Stimulates lipoprotein lipase in adipocytes Acts on bone remodeling
CCK	Enteroendocrine cells of small intestine	Stomach Pancreas Brain	Via efferent vagus, opposes ghrelin to increase satiety Inhibits gastric emptying and secretion of gastric acids Stimulates exocrine pancreas
PYY [21]	Enteroendocrine cells of small intestine	Hypothalamus via efferent vagus nerve	Decreases appetite Increases insulin secretion Slows gastric emptying May be attenuated in obesity
Amylin	Pancreatic β cells (co-secreted with insulin)	Brain: area postrema	Stimulates brain to increase satiety Slows gastric emptying Enhances CCK effects Decreases glucagon Affects bone metabolism via calcitonin receptor
Insulin	Pancreatic β cells	Hypothalamus Adipocytes Muscle Bone	Glucose homeostatic and anabolic actions Decreases food intake Increases energy expenditure Proportional to amount of fat mass
Glucagon	Pancreatic α cells	Liver	Decreases food intake and meal size Gluconeogenesis Glycogenolysis
Adiponectin [22]	White adipocytes	Liver Muscle Heart Vasculature	Increases mitochondrial mass and oxidative function in muscle Increases basal and insulin-stimulated glucose uptake Increases FFA update and oxidation Affects vasodilation, cardiac remodeling Anti-inflammatory properties
Leptin	White adipocytes	Hypothalamus	Decreases appetite Increases energy expenditure Effects reproductive axis and bone metabolism Proportional to amount of fat mass
Ghrelin 1	Stomach	Hypothalamus Hippocampus	Increases food intake Decreases energy expenditure High levels observed in sleep deprivation and people with Prader-Willi Syndrome

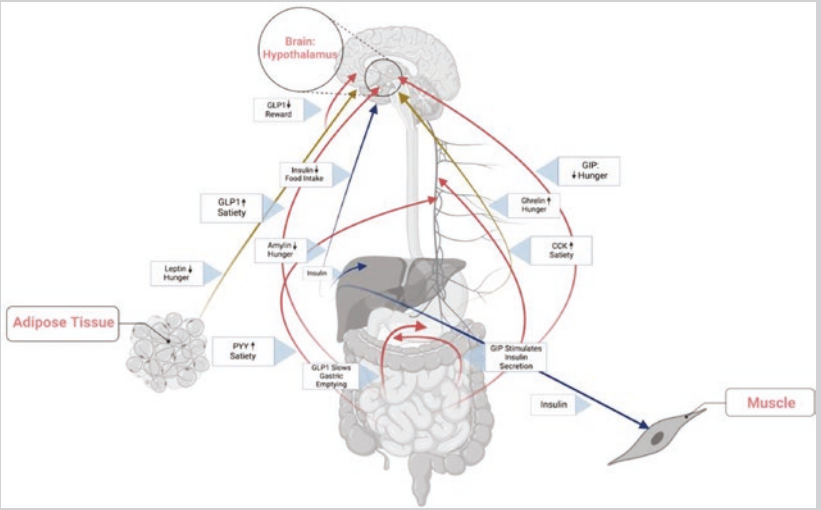


Fig. 1.2 Peripheral signals involved in energy regulation

A Word About Fat (Adipose Tissue): Adipose tissue is a highly active organ whose function extends beyond that of energy depot. It secretes not only pro-inflammatory molecules but also important adipokines, including leptin and adiponectin. Leptin, in particular, is integral to long-term energy regulation and circulates proportionately to the amount of adiposity. When the body's adipose tissue mass is low, as in starvation, leptin signaling at the hypothalamus is also proportionally low, which in turn leads to increased hunger and energy intake and reduced energy expenditure.

Central Signals

Peripheral signals from enteroendocrine cells, pancreas, liver, muscle, and adipose tissue relay the body's energy needs to the hypothalamus where these signals are integrated. The hypothalamus then directs the modulation of energy intake or expenditure. The first-order neurons located in the arcuate nucleus of the hypothalamus include AgRP/NPY (agouti-related peptide/neuropeptide Y) and the POMC/CART (pro-opiomelanocortin/cocaine-amphetamine regulated transcript) neurons. AgRP/NPY neurons are orexigenic; when stimulated, they promote food intake and decrease energy expenditure. POMC/CART neurons function in the opposite manner, when stimulated they decrease food intake and increase energy expenditure.

Leptin, an anorexigenic hormone, inhibits AgRP/NPY and stimulates POMC/CART cells. Ghrelin, an orexigenic hormone, works in the opposite fashion.

Signals from AgRP/NPY and POMC/CART then extend to second-order neurons in the periventricular nucleus of the hypothalamus to either increase food intake or decrease energy expenditure likely through stimulation or inhibition of the sympathetic nervous system (see Fig. 1.3).

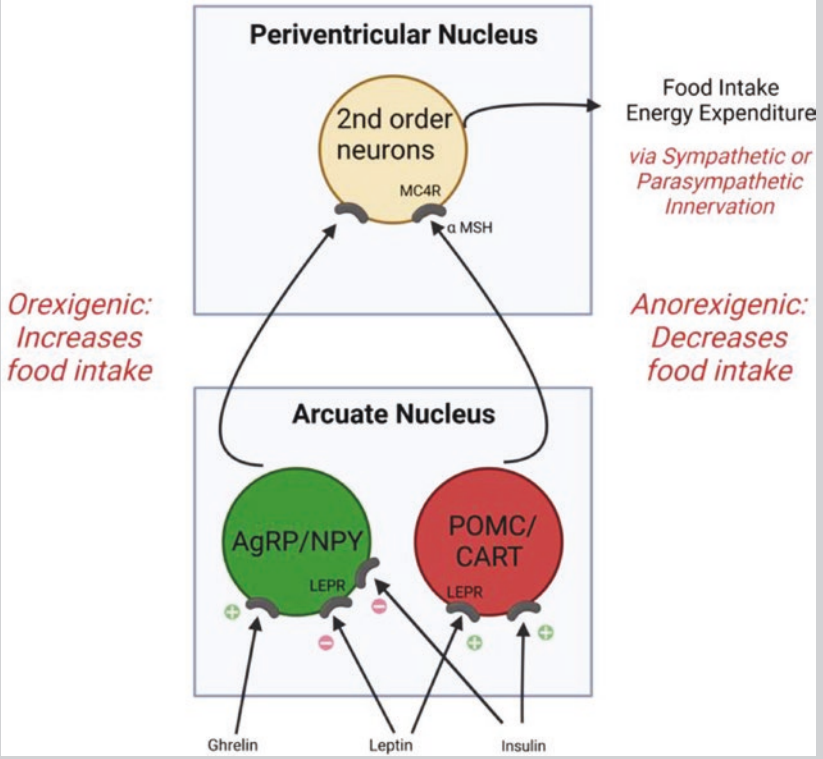


Fig. 1.3 Central signals involved in energy regulation

Reward

Humans do not eat only because they feel hungry or stop eating because they feel full. From a teleological perspective, it follows that because eating is vital for survival, it is also linked to the brain's control of pleasure and reward [23]. Ingesting food for energy becomes a pleasurable behavior [24]. The corticolimbic system is intimately connected to the hypothalamus and provides the emotional, cognitive, and executive support for ingestive behavior. The pleasure-reward system uses opioid and dopamine activity to convey liking and wanting of food [25, 26]. This complex hormonal crosstalk between the hypothalamus and reward centers like the nucleus accumbens, an area considered to be the neural interface of motivation and action, contributes to reinforcement of these pathways [27].

Energy Expenditure

Energy expenditure is also relevant to fat mass regulation. There are three main components of daily energy expenditure: resting energy expenditure (REE), physical activity expenditure, and thermic effect of food. In general, males compared to females have higher energy expenditure (because males compared to females have more fat-free mass) and individuals with obesity compared to those without obesity have higher energy expenditure [28] (see Table 1.2 and Fig. 1.4).

Table 1.2 Components of energy expenditure

Components of energy expenditure	Percent of total daily expenditure (%)	Description
Resting Energy Expenditure (REE)	50–80	• Energy needed for basic physiological processes when the body is not doing physical work • Generally higher, not lower, in individuals with obesity, as REE is determined primarily by the amount of fat-free mass, and individuals with obesity have greater amounts than people without obesity
Physical Activity Expenditure	10–40	• Most variable component • Consists of volitional exercise and activities of daily living/moving, known as non-exercise activity thermogenesis (NEAT) • The amount of energy expended in physical activity is proportional to overall body weight—while people with obesity may be less physically active, they may still have similar daily energy costs from PA as people without obesity [29]
Thermic Effect of Food (TEF)	10	• Energy used in digestion, absorption, and storage of food • Protein digestion expends the most energy and fat the least

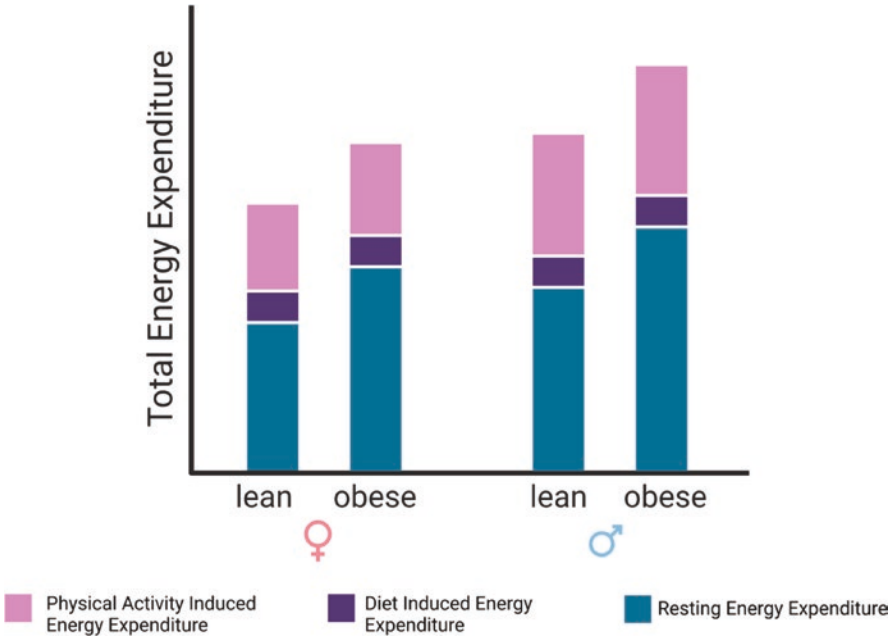


Fig. 1.4 Energy expenditure in males vs females who are lean vs have obesity

Pathophysiology of Obesity

Obesity is a pathophysiological state characterized by impairment of the energy regulatory system leading to excess accumulation and storage of adipose tissue. Abnormalities in the normal physiology of adiposity regulation, where peripheral and central signals do not appropriately decrease eating or increase energy expenditure when energy is replete (or even overflowing), lead to unhealthy adipose tissue accumulation. For instance, a notable characteristic of obesity is relative resistance to leptin signaling at the hypothalamus, which is thought to be related to a combination of genetic, epigenetic, social, and environmental factors such as pro-inflammatory diets or inflammation stemming from chronic stress. Leptin resistance leads to increased leptin levels but no subsequent decrease in appetite or increase in energy expenditure. Studies also suggest that obesity is associated with blunted postprandial response to satiety factors such as GLP1, PYY, and CCK and reduced postprandial suppression of ghrelin [19].

Just like diabetes is a disorder of glucose regulation and hypertension is a disorder of blood pressure regulation, obesity is a disorder of fat mass regulation. Further, just like edema is not caused by drinking too much water, obesity is not caused by eating too much food [12]. Impaired regulation of fluid balance leads to water retention and edema and impaired regulation of fat mass leads to adipose tissue accumulation.

Stated another way, overeating does not cause obesity. Rather, obesity causes overeating.

Causes of Obesity

What *causes* this disorder in the energy regulatory system? Like other bodily functions, genes direct physiological processes and are the primary determinant of obesity. Additionally, other disorders that affect the physiological processes of the energy regulatory system may also cause obesity.

Genetics

Genes are the main determinant of obesity. In fact, 40–70% of obesity is heritable, with significant variability in humans [30]. Genetic factors may influence both energy intake and expenditure and may account for the widely different responses in weight gain from identical positive energy balance [31, 32].

Polygenic Obesity

More than 100 genes related to the development of obesity have been identified, however, the exact mechanism by which these genes contribute to the disruption of the energy regulatory system is unclear. From genome-wide association studies, it appears that most obesity results from the additive effects of multiple single nucleotide polymorphisms (SNPs) that individually make small contributions to the overall effect [33]. There are hundreds of SNPs associated with BMI [34, 35]. The various constellation of SNPs in a given individual may account for the various phenotypic presentations and subsequent responses to treatments each person with obesity experiences. Multi-allelic obesity is sometimes referred to as "polygenic" obesity, in contrast to monogenic obesity, and is the most common "type" of obesity.

Informing patients and families about the predominant contribution of genetics to the development of obesity is extremely helpful for removing blame and may explain why some people can seemingly eat huge amounts of food and not develop obesity, while others with certain genetics, cannot. It is also worth stating explicitly to families that just because a person may have a genetic predisposition and risk for the development of obesity, obesity is not necessarily their destiny. As health care providers, we must balance reality with hope. A person's genetics may make it more difficult to achieve and maintain a healthy weight and there are treatments that can help mitigate the effects of their genetic profile.

Monogenic Obesity

Monogenic obesity most often results from a single gene mutation along the leptin-POMC-melanocortin pathway and typically presents early in a child's life with severe obesity and hyperphagia. Monogenic obesity may be present in as many as 7% of children with early onset (under age 5 years) severe obesity [36]. Examples include congenital leptin deficiency in which there is no leptin production (this is exceedingly rare), leptin receptor variants, POMC variants, and melanocortin-4 receptor (MC4R) variants. See Chap. 13 for more on monogenic obesity.

Syndromic Obesity

Syndromic obesity, such as Prader-Willi syndrome or Bardet-Biedl syndrome, also results from genetic variants, though their presentation usually has its onset after the first year of life and is usually associated with developmental delay and anomalies of large organs. See Chap. 13 for more on syndromic obesity.

Epigenetic Changes

Epigenetic changes can also affect the energy regulatory system. Rather than changes in the genetic code itself, epigenetic changes consist of changes in gene expression, as might be seen in certain prenatal environments such as maternal obesity or gestational diabetes or perhaps prenatal exposure to certain social determinants of health.

Endocrine Disorders

Endocrine causes of obesity, such as growth hormone deficiency, hypothyroidism, and Cushing's syndrome, are rare, accounting for less than 1% of childhood obesity. Most endocrine causes of obesity usually present with other symptoms and are associated with poor linear growth or short stature. This is in contrast to polygenic obesity in which case the child growth rate is usually normal or increased [37].

Growth Hormone Deficiency

Growth hormone (GH) deficiency, with onset during childhood, usually presents with slowing growth, delayed puberty, and increased body fat. GH is lipolytic and increasing GH leads to decreased fat mass. The opposite is also true [38].

Hypothyroidism

The most common cause of acquired hypothyroidism in children is autoimmune hypothyroidism (Hashimoto's thyroiditis), which usually presents with fatigue, cold intolerance, constipation, and menstrual irregularities [39]. A goiter is the most common sign and hypothyroidism can cause poor linear growth. It is not typically a cause of weight gain.

Up to 23% of children with obesity may have elevated TSH levels with normal T3 and T4 levels. Some studies indicate that with weight loss, TSH levels normalize. It has been hypothesized that elevated TSH in the context of obesity may stem from leptin resistance and subsequent elevated leptin levels, which increase production thyrotropin-releasing hormone. It has also been proposed that increased TSH and thyroid hormones may be an adaptive change to increase energy expenditure for the prevention of further weight gain [40].

Cushing Syndrome

Cushing syndrome is a state of glucocorticoid excess. In children, the most common cause is exogenous administration of corticosteroids, though endogenous causes (such as pituitary adenoma or adrenal tumor) should also be considered. Although oral corticosteroids are most often implicated, long-term use of inhaled and topical steroids can also cause Cushing syndrome [41]. Typical signs and symptoms include weight gain and growth failure. Additionally, acne, hirsutism, delayed puberty, and amenorrhea are common at presentation [42]. Violaceous striae, moon facies, and large dorsocervical fat pad of Cushing syndrome may be difficult to distinguish from exogenous, polygenic obesity, though striae of polygenic obesity tend to be more pink in color and thinner.

> Use the patient's growth chart to "look" for endocrine causes of obesity. Because polygenic obesity is usually associated with tall stature, poor linear growth is a red flag that warrants further evaluation.

Hypothalamic Obesity

Injury to the hypothalamus from a brain tumor, inflammation, trauma, or radiation may adversely affect its ability to maintain normal energy regulation. For instance, it has been suggested that children with hypothalamic obesity have more severe forms of leptin resistance than even those with polygenic obesity. Also, it has been observed that hypothalamic obesity is associated with decreased sympathetic tone which in turn may decrease metabolic rate [43].

Hedonic Obesity

Dysregulation of the reward pathway can lead to overconsumption, especially of highly palatable foods. When reward-based eating or hedonic eating behaviors overwhelm homeostatic processes and weight gain can no longer be autocorrected by homeostatic forces, some call this "hedonic obesity." This reward-based eating may also have a genetic component [44, 45].

Contributors to Obesity

Other factors contribute to energy imbalance. Some of these are related to eating and others to energy expenditure and yet others, like poor sleep, may be related to both.

Diet

Consumption of processed foods is associated with a greater risk of obesity [46]. Such diets may interfere with normal energy regulation potentially via their pro-inflammatory properties that are believed to contribute to gliosis in the hypothalamus and resultant interference with leptin signaling [47]. Additionally, foods high in fat and sugar may impair the reward system [48].

Physical Activity

Overall, children with obesity compared to their lean counterparts engage in somewhat less moderate to vigorous physical activity, but the differences are very small [49]. According to a systematic review of studies using accelerometer data, most demonstrated a difference of less than 10 min per day between youth with and without obesity [50]. These differences may be due to a variety of factors including musculoskeletal pain, gross motor delay (which may be especially prominent in young children with severe obesity) and environmental limitations such as lack of green space or poor neighborhood safety. Importantly, most studies support no difference in sedentary time between youth with and without obesity [51].

Sleep

Poor sleep quality and inadequate sleep duration in childhood are associated with increased risk of obesity [52] and there is some evidence that long sleep duration may be protective against obesity, particularly in toddlers and school-aged children [53] (see Table 1.3 for recommended sleep duration by age). Current theories posit that the association between sleep dysfunction and obesity is bidirectional. Sleep dysregulation/reduction is associated with changes in hormones controlling appetite and feeding behaviors. For instance, lack of sleep is associated with a decrease in leptin, which may in turn increase appetite. Ghrelin, which increases feeding behavior, is typically at its lowest during sleep and has been found to be elevated during times of sleep deprivation [54–56]. Sleep reduction has also been associated with increased sympathetic activation, elevated cortisol, and inflammatory markers which may contribute to insulin resistance and weight gain [57] (see Fig. 1.5). Finally, short sleep and accompanying fatigue may lead to decreased motivation to engage in vigorous physical activity. In regards to bidirectionality, obesity also increases a child's risk for

Table 1.3 Recommended sleep duration by age [59]

Age	Hours
4–12 mos	12–16
1–2 years	11–14
3–5 years	10–13
6–12 years	9–12
13–18 years	8–10

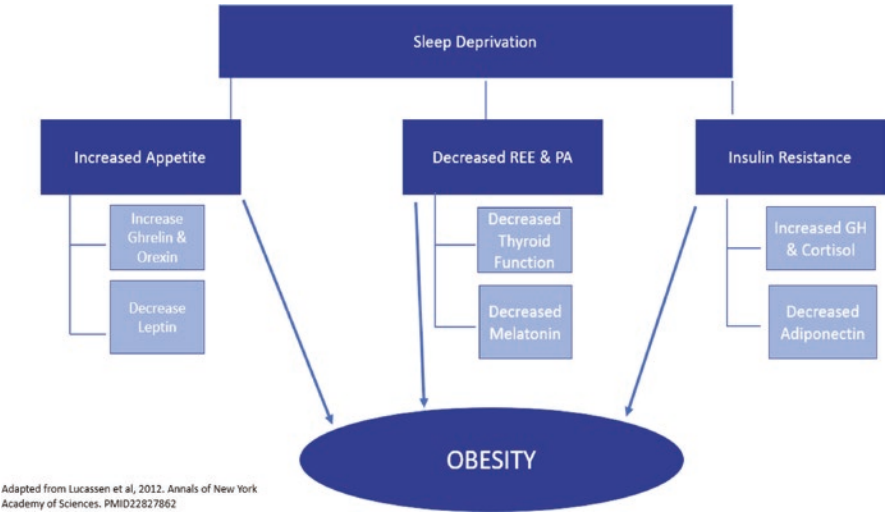


Fig. 1.5 Mechanisms by which sleep deprivation may increase risk for obesity

sleep-related breathing disruptions, including obstructive sleep apnea and obesity hypoventilation syndrome, thus adding to the ongoing dysregulation of appetite signaling hormones [58].

Psychological Factors

Depression, Anxiety, and Stress

Depression and obesity are commonly co-occurring diseases with a bidirectional association. This link may be due to shared biological, psychological, and behavioral factors. Some of the proposed biological mechanistic pathways include shared genetics, hyperactivation of the hypothalamic–pituitary–adrenal pathway, and inflammation. Behavioral links include poor sleep, increased consumption of highly palatable foods, and reduction of time spent in physical activity. Psychological factors may include emotional eating [60]. Although most research has been conducted in the area of depression linked with obesity, it is likely that much of the same proposed mechanisms could apply to the links between anxiety and obesity.

Separate from depression and anxiety, chronic stress (as from social determinants of health, such as weight stigma or racism, for example) may also contribute to obesity. Chronic stress may lead to increased cortisol which stimulates fat storage and may further lead to increased appetite and reward-based eating [61, 62].

Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) and obesity are commonly co-occurring diseases and the direction of causality is most likely bidirectional. These conditions share pathophysiologic pathways including genetics, binge eating/loss of control eating, and functional abnormalities in reward (via dopamine activity), response inhibition, and emotional processing and regulation [63–65].

Binge Eating and Loss of Control Eating

Binge eating is the consumption of a large amount of food accompanied by a perceived inability to stop eating. Repeated binge eating with associated distress surrounding the eating episodes are the hallmarks of binge eating disorder (BED), which is relatively uncommon in children. In contrast, the experience of subjective lack of control over eating, without necessarily consuming objectively large amounts of food, known as loss of control (LOC) eating, is present in up to 30% of youth with obesity. LOC eating is a predictor of full syndrome BED and is associated with greater risk of poor metabolic health [66].

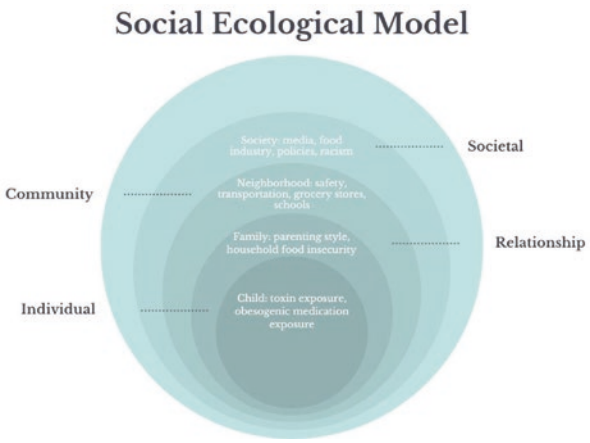


Fig. 1.6 Social and environmental factors that contribute to obesity

Environmental Factors

A comprehensive discussion of the environmental contributors to the development of obesity is beyond the scope of this book. Using the socio-ecological model, these factors may include features at the level of the individual child, family, community, and society (see Fig. 1.6).

Set Point

Excess food intake leads to obesity only when the energy regulatory system fails to compensate for the increased energy intake by either commensurately increasing energy expenditure or by reducing food intake at subsequent meals. A healthy regulatory system is one that is able to defend a person's body fat mass within narrow limits. This limit is often referred to as the "set point" [67, 68]. However, the set point is not static. Genetics, epigenetics, endocrinopathies, and a host of contributors (see Sect. "Contributors to Obesity") to obesity drive the set point up such that in the obesity state, the body is defending this new higher body fat mass set point [69].

The set point theory of obesity can be illustrated using an analogy to a home thermostat. The thermostat is designed to keep a house at an ambient temperature of say 72°F, whether it is hotter or colder outside. When working properly, the thermostat will turn on the air conditioner when the temperature outside exceeds 72°F and turn on the heater when the temperature dips below 72°F. Now imagine that the thermostat is broken and stuck at 85°F. Even if it is summer and hot outside, the heat will turn on inappropriately to raise the house temperature to 85°F. The thermostat is like the hypothalamus and the temperature setting is like the fat mass set point. A thermostat that is not working and stuck at an excessively high temperature is like obesity in which the body defends this higher body fat mass.

Implications of Energy Dysregulation in the Treatment of Obesity

Lifestyle Therapy

Like many biologically regulated systems in our bodies, such as body temperature or respiration, body fat/adipose tissue mass is also tightly regulated and is mostly controlled at the subconscious level. For instance, you can hold your breath for a few moments but after that, your brain seeks to maintain a specific blood oxygen level and forces you to inhale. Similarly, if a person tries to oppose their homeostatic mechanisms of energy regulation by dieting and exercising to lose weight, weight loss may be able to be sustained for a time, but for most, hunger increases and weight regain occurs. The result is only temporary weight loss. Clearly, this is not a failure of willpower.

When a person tries to lose weight via energy restriction (i.e., diet and exercise), they are in effect opposing their set point. Counter-regulatory processes ensue that resist weight loss to defend the set point. These processes include a decrease in daily energy expenditure that is often greater than what would be expected for the decrease in thermic effect of food (energy burned as a result of digestion of food) and changes in body composition. This decrease in "metabolism" is termed "metabolic adaptation" and may persist for years. It is believed that decreased leptin from decreased fat mass/adipose tissue and increased ghrelin underlie this decrease in metabolic state. Simultaneously, as adiposity decreases, food becomes more palatable and the desire to eat increases. The net result is weight regain.

Practically speaking, weight loss by caloric restriction alone is often not durable because of counter-regulatory signals that promote weight regain. These include a reduction in metabolic rate, greater hunger, and increased sense of food palatability. To experience further weight reduction, one must consume evermore fewer calories.

A minority of youth (about 2–15%) with obesity will be able to achieve and maintain a healthier body composition with lifestyle therapy alone [6, 8–11]. This population typically includes youth with BMI $<1.2 \times 95$th percentile and youth who may not have the same burden of genetic and epigenetic predisposition for the development of severe obesity. Further, this population may also be free of obesity-related comorbidities and psychopathology. Such patients likely represent a lower-risk phenotype with less dysfunction in their energy regulatory system, rendering them more responsive to lifestyle therapy.

Anti-Obesity Medications

Unlike lifestyle therapy, anti-obesity medications (AOMs) target the peripheral and central signals that are instrumental in the energy regulation system. For example, liraglutide and semaglutide are GLP-1 receptor agonists, tirzepatide is a combination GLP-1/GIP agonist, cagrilinitide is an amylin analogue, phentermine stimulates sympathetic output. However, AOMs do not alter the set point. For this reason, as soon as they are discontinued, obesity returns.

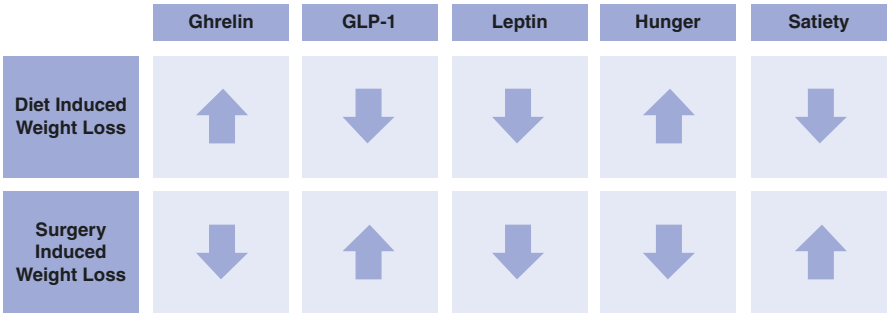
Metabolic and Bariatric Surgery

In contrast to lifestyle therapy, after metabolic and bariatric surgery (MBS), weight loss is more durable. This may be due to relatively more robust and/or permanent physiologic changes such as increased concentrations of GLP-1 and peptide YY and lower levels of ghrelin that occur after surgery [70] (see Table 1.4). Other mechanisms which may account for longer-term weight loss after MBS include alterations in bile acids which may modulate glucose and energy metabolism and changes in the gut microbiome. However, weight regain after MBS can happen, suggesting that set point mechanisms may still be operative.

Obesity is a Chronic Disease

Obesity is a chronic, progressive, and [71] relapsing disease that has no cure. Indeed 90% of 3-year olds with obesity will become adolescents with overweight or obesity [72] and virtually all 12-year olds with severe obesity will become adults with severe obesity [73]. We therefore manage obesity over the course of a lifetime rather than simply treat it like an acute process such as an ear infection. Framing obesity as a

Table 1.4 Changes in hormones, hunger, and satiety after dieting versus after metabolic and bariatric surgery



chronic condition for your patients and families will help them understand the rationale for the interventions and have realistic goals and expectations for the interventions. As with other chronic conditions, like diabetes, effective management of obesity requires daily attention at home (to nutrition, physical activity, mood, sleep, and medications) and regular interdisciplinary medical visits to assess health status and response to interventions. There will be weeks, months, or years when your patient's obesity will respond well to interventions and other times when the treatments will be less effective. The overall goal in managing pediatric obesity is to support the best physical, psychological, and social health for our patients now and for their future. This may not equate to normalization of their BMI percentile, though with newer AOMs this may soon be a realistic outcome. Note that most patients and their families are seeking improved health and quality of life, not a specific number on the scale.

Obesity is a Heterogeneous Disease

As illustrated by the numerous causes and contributors to obesity, it is apparent that obesity is a heterogeneous disease. For instance, one person may have a familial predisposition for obesity, depression, and a tendency toward binge eating, while another person may have early onset severe obesity with obstructive sleep apnea. These two individuals will likely need very different obesity treatment strategies. This heterogeneity of obesity likely accounts for the wide variability in response to given therapies, whether they are lifestyle therapy, anti-obesity medications, or surgery. By identifying the specific causes and contributors to a person's obesity, treatments can be tailored to optimize outcomes. This is the basis for a personalized or precision medicine approach to obesity management.

Frequently Asked Questions

What if a Patient has no Obesity-Related Co-morbidities? Is It Still a Disease?

Like most chronic conditions whose definitions depend on characteristics that fall on a continuum, the diagnosis of obesity is based on a specific cut point. Cut-points are established to provide consistency among the medical community when communicating about a condition. So while the difference between a BMI of the 94th and 95th percentile is not likely to be clinically significant, we still give the patient with a BMI at 95th percentile a diagnosis of obesity. Using BMI to define obesity, however, is a shortcut. It's like saying "edema" is a disease. In reality, edema is a sign of underlying fluid imbalance which may have a cardiac

or renal origins, for instance. Similarly, obesity is the manifestation of underlying disorder of the energy regulatory system. The apparent absence of obesity-driven complications in some individuals with excess adiposity may just be a matter of time. Therefore, the notion of metabolically healthy obesity (having obesity but no cardiometabolic risk factors) likely represents only a transitory state [74, 75]. Eventually, most bodies decompensate when exposed to the chronic stress of obesity, whether in 5 years or in 50 years.

It is also critically important to recognize that our standard of using BMI to define obesity has major limitations. BMI is used only as a proxy of adiposity. Better, easy to use, inexpensive, and reproducible techniques that can quantify adiposity are needed.

If Obesity Is Primarily a Genetic Disease, Why Is the Prevalence of Obesity So High Only in Recent Years? Genes Don't Change That Fast

It is true that genes do not change that fast. However, our environment has changed considerably in ways that facilitate excess energy intake and reduced energy expenditure. People who have a genetic predisposition to carrying extra weight have been around for decades, as have people who are genetically relatively resistant to obesity. It is those with a genetic predisposition to develop obesity who, when exposed to our modern obesogenic environment, will gain weight. From a renowned obesity advocate, "genes set the table and the environment serves it up."

Additionally, while genes do not change from generation to generation, gene expression can change more acutely in response to certain exposures such as gestational diabetes. These changes in gene expression are called epigenetic changes. The implication of this is that youth with obesity who become young adults with obesity can pass epigenetic changes to their offspring, which increases the likelihood of developing obesity in the next generation [76].

Why Can't I Stop Taking My Anti-obesity Medications After I've Lost Weight?

Remember that obesity is a chronic disease. AOMs may help normalize the pathophysiology that is driving obesity, but they do not permanently fix it or cure it. Obesity is like hypertension, for example, in that if the anti-hypertensive agent is stopped, blood pressure will go back up to its pre-treatment level.

My Child Exercises a Lot and They Still Carry Extra Weight. How Do You Explain That?

Exercise accounts for only a small portion of a person's energy expenditure, approximately 20%. Furthermore, at least for adults, exercise interventions that are consistent with public health recommendations for physical activity are unlikely to result in weight loss without caloric restriction. It appears that, in general, it takes A LOT of aerobic exercise in order to produce clinically significant weight loss [77]. Individuals who lose less weight than expected based on their exercise are termed "weight compensators." Identified explanations for this include dietary compensation and low aerobic exercise training dose. Other factors that may also be relevant and continue to be researched include compensatory changes in non-exercise physical activity or resting metabolic rate, among others [78]. Importantly:

- Like response to dietary strategies, anti-obesity medications, and surgery, outcomes of physical activity interventions are variable. Some people lose a lot of weight with a given exercise program while others may not lose any weight.
- Physical activity improves cardiometabolic health, including insulin sensitivity, independent of changes in BMI [79, 80]. Physical activity also has positive effects on mood, sleep, and academic performance.

My Child's Metabolism Must Be Slow, So There Is Nothing I Can Do, Right?

People with obesity do not have slower metabolisms than people without obesity. The primary determinant of a person's metabolism is their resting energy expenditure and this is proportional to the amount of lean body mass. People with obesity have relatively more fat mass and similar to higher lean body mass compared to normal-weight individuals. *However, in the weight reduced state,* i.e., after a person has lost weight, resting energy expenditure decreases in an attempt to regain weight toward the body fat mass set point. Thus, metabolism is lower than expected in the weight reduced state. It is possible that increasing lean body mass through physical activity may counteract slowing metabolism. Using indirect calorimetry to measure a patient's resting energy expenditure may be a useful demonstration for families and patients.

My Child's Dad Was Heavy When He Was a Boy and He Grew Out of His Extra Weight. Why Should I Worry?

This may be a reflection of different environments. Dad may have a genetic predisposition to carrying extra weight but perhaps he did not have the same environmental pressures that increased his set point such as those present in today's obesogenic world.

Will You Check My Child's Thyroid?

Endocrinopathies are a very rare cause of obesity in children and adolescents, accounting for <1% of cases. However, hypothyroidism may exist concurrently with obesity and sometimes symptoms overlap (fatigue, constipation). If there is evidence of hypothyroidism such as poor linear growth or short stature given mid-parental height or strong family history of thyroid disease or symptoms, it may be prudent to check thyroid function tests. Recognize, however, that obesity may cause elevation of TRH (thyrotropin-releasing hormone), which in turn may elevate TSH, giving a "false" diagnosis of true hypothyroidism.

How Much Should My Child Weigh?

Often this is a tricky question to navigate. Most children and adolescents with severe obesity will not achieve a normal BMI, even with metabolic and bariatric surgery (MBS). Stating this directly may be viewed as being hopeless. An alternative approach may be to emphasize that the goal of obesity treatment is to help the child achieve their best physical and psychological health. Physical health means that the patient is free of obesity-driven comorbidities and is not limited by their obesity (or "body size") to do whatever they want. Psychological health means that the patient feels comfortable in their body and is generally content. The weight at which a child achieves physical and psychological health varies from patient to patient. If pressed by the family, indicating that because a 5% BMI reduction is often associated with improved cardiometabolic outcomes, this is a good initial goal of treatment.

On the other hand, sometimes families do not recognize just how far from normal their child's BMI status is. This may be especially true of parents of school-age children. In these situations, it may be helpful to describe their current status in terms of the average weight of an older child; for example, "Your 7 year old boy has the average weight of an 11 year old boy, which places him at increased risk for many complications."

Final words: As reflected by one 19-year old patient who receives care for obesity, "If you are going to provide obesity care, make sure it is accurate, comes from the heart and reflects the complexity of the disease of obesity."

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