Chapter 8
Obesity: Understanding and Achieving a Healthy Weight

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Key Points

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

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

Introduction

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

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

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

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

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

Definition and Prevalence of Obesity

Body Mass Index

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

Central Adiposity

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

Prevalence

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

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

Cost of Obesity

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

Etiology

Energy Imbalance

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

Epidemiologic Model

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

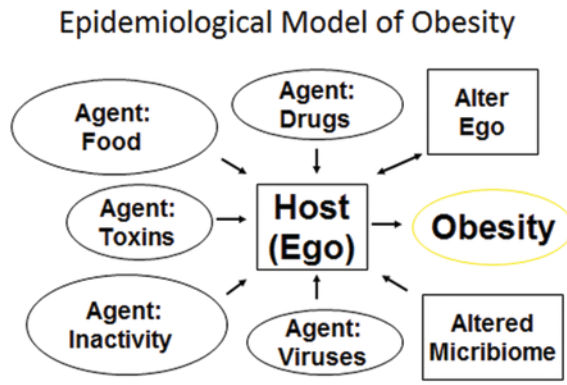

Fig. 8.1 An epidemiological model of obesity. The host at the center receives inputs from various environmental agents. Depending on the constitution of the host, obesity is one of the consequences [Adapted from Bray [3]]

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

Environmental Agents

Intrauterine Factors

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

Drug-Induced Weight Gain

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

Table 8.1 Drugs that produce weight gain and alternatives

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

Diet

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

Infant and Child Environment

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

Fat Intake

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

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

Glycemic Index

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

Calcium Intake

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

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

Frequency of Eating

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

Restrained Eating

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

Physical Activity

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

Smoking

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

Host Agents

Genetic Causes

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

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

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

Physiologic Factors

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

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

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

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

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

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

Pathology and Pathophysiology of Obesity

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

Fat as an Endocrine and Inflammatory Organ

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

Visceral Fat

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

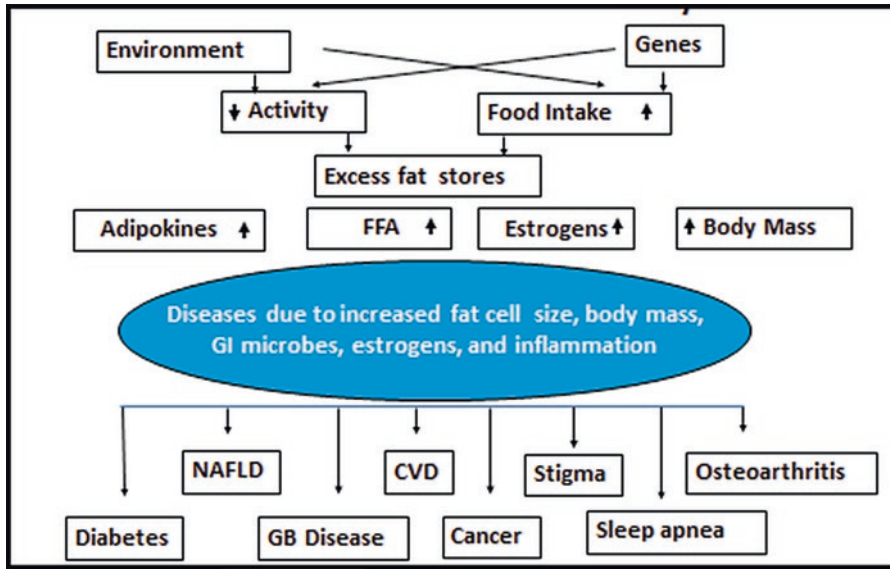

Fig. 8.2 Pathogenesis of health problems associated with obesity. The mass of fat and the responses to products produced by fat cells can explain most of the diseases that result from prolonged obesity. *NAFLD* nonalcoholic fatty liver disease, *CVD* cardiovascular disease, *GB* gall bladder. Adapted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

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

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

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

Complications of Obesity

Death

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

Diseases

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

Prevention

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

Treatment

Realities of Treatment

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

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

Diet

Diets Low in Fat, Carbohydrate, or Energy Density

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

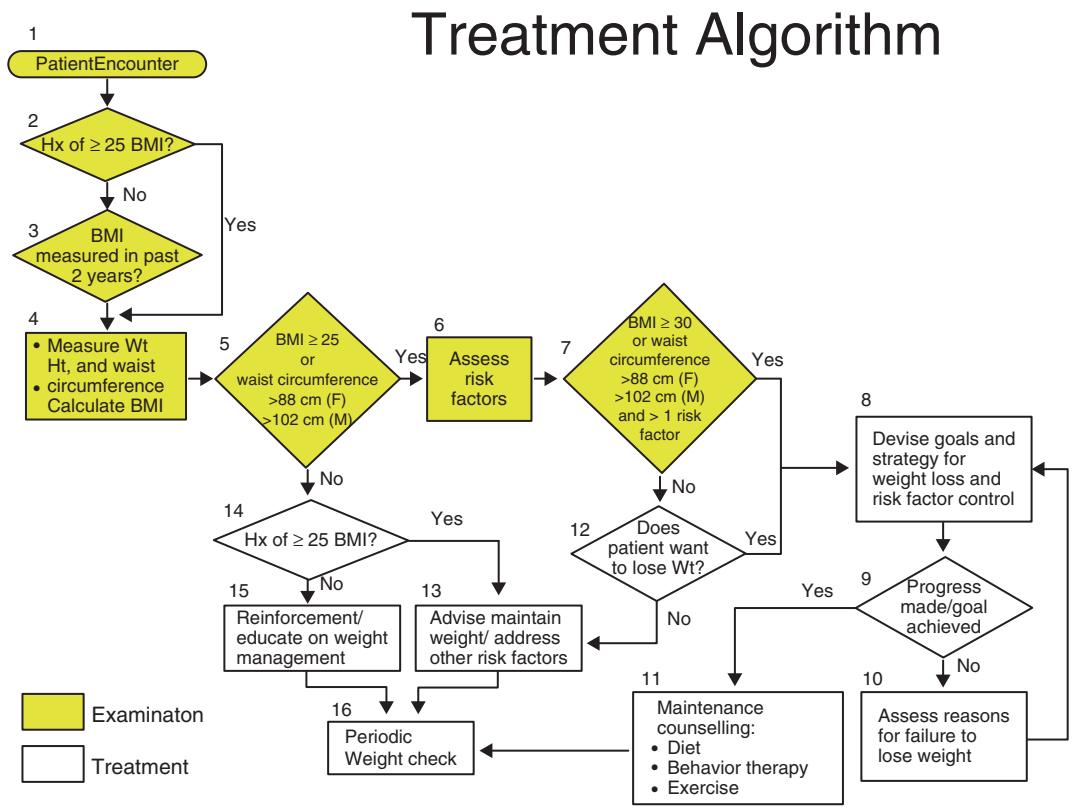

Fig. 8.3 Algorithm for diagnosis and treatment of obesity. Adapted from [22]

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

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

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

Portion-Controlled Diets

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

Table 8.3 Comparison of diet programs and eating plans compared to the typical American diet

Type of diet	Example	General dietary characteristics	Comments	AHA/ACC/TOS evaluation
Typical American diet		Carb: 50% Protein: 15% Fat: 35% Average of 2200 kcal/day	Low in fruits and vegetables, dairy, and whole grains High in saturated fat and unrefined carbohydrates	
Balanced nutrient, moderate-calorie approach	DASH Diet or diet based on MyPyramid food guide; commercial plans such as Diet Center, Jenny Craig, NutriSystem, physician's weight loss, Shapedown Pediatric Program, Weight Watchers, Setpoint Diet, Sonoma Diet, volumetrics	Carb: 55–60% Protein: 15–20% Fat: 20–30% Usually 1200–1800 kcal/day	Based on set pattern of selections from food lists using regular grocery store foods or prepackaged foods supplemented by fresh food items Low in saturated fat and ample in fruits, vegetables, and fiber Recommended reasonable weight-loss goal of 0.5–2.0 lb/week Prepackaged plans may limit food choices Most recommend exercise plan Many encourage dietary record keeping Some offer weight-maintenance plans/support	
Low and very low-fat, high-carbohydrate approach	Ornish diet (eat more, weigh less), Pritikin diet, T-factor diet, choose to lose, fit or fat	Carb: 65% Protein: 10–20% Fat: ≤10–19% Limited intake of animal protein, nuts, seeds, other fats	Long-term compliance with some plans may be difficult because of low level of fat Can be low in calcium. Some plans restrict healthful foods (seafood, low-fat dairy, poultry) Some encourage exercise and techniques for stress management	Same weight loss at 6 months comparing <30% fat to >40% fat Strength of evidence—moderate
Low energy density	Volumetrics	Carb: 55% Protein: 10–25% Fat: 20–35% Focus on fruits, vegetables, and soups	Four food categories: 1. Very low energy density—non-starchy fruits and veggies, nonfat milk, broth-based soups 2. Low energy density—starchy fruits/veggies, grains, breakfast cereal, low-fat meats and mixed dishes 3. Medium energy density—meat, cheese, pizza, fries, dressings, bread, etc. 4. High energy density—desserts, nuts, butter, oils Focus on categories 1 and 2, some from 3, minimum from 4	More weight loss at 6 months with low energy dense diet: RCT
Portion-controlled	Use of meal replacements, both liquid and solid meals			Weight loss at 1 year in the Look AHEAD trial related to frequency of consuming portion-controlled meals

Mediterranean style diets		Carb: 35–40% Protein: 12–20% Fat: 40–50% – Approximately 25–30% of energy from mono-unsaturated fat	Eat primarily plant-based foods (fruits, vegetables, whole grains, legumes, and nuts) Healthy oils (olive) instead of saturated fats Limit red meat to a few times a month Eat fish and poultry at least twice a week Red wine in moderation, if you choose to drink alcohol Be active and enjoy meals with family and friends	Meta-analysis showed more weight loss with Mediterranean diet than low-fat diets (weighted-mean difference = 2.2 kg)
Low-carbohydrate, high-protein, high-fat approach	Atkins New Diet Revolution, Protein Power, Stillman Diet (The Doctor's Quick Weight Loss Diet), the Carbohydrate Addict's Diet, Scarsdale Diet	Carb: ≤20% Protein: 25–40% Fat: ≥55–65% Strictly limits carb to less than 100–125 g/day	Promotes quick weight loss (much is water loss rather than fat) Ketosis causes loss of appetite Can be too high in saturated fat Low in carbohydrates, vitamins, minerals, and fiber Not practical for long term because of rigid diet or restricted food choices	Same weight loss at 6 months comparing <30 g/day vs. 55% carb—15% protein OR 40% carb and 30% protein Strength of evidence—low
Higher protein, moderate-carbohydrate, moderate-fat approach	The Zone Diet, Sugar Busters, South Beach Diet	Carb: 40–50% Protein: 25–40% Fat: 30–40%	Diet rigid and difficult to maintain Enough carbohydrates to avoid ketosis Low in carb; can be low in vitamins and minerals	Same weight loss at 6 months comparing 25–30% vs. 15% protein Strength of evidence—high
Glycemic Load (GL)	The Glycemic-Load Diet—Rob Thompson	Carb: 40–55% Protein: 15–30% Fat: 30% (note that I attached an abstract below)	Focus on low-GL foods	Same weight loss at 6 months comparing high vs. low GL Strength of evidence—low
Low or no sugar-sweetened beverages (SSBs)	Not really a diet but just a call to reduce SSB intake as a preventive strategy	No recommendations other than to reduce/remove SSBs from the overall diet plan	Meta-analyses show that consumption of SSBs is related to risk of obesity, diabetes, and heart disease	In sustained intervention studies, low-energy beverages showed lower energy intake and less weight gain than sugar-containing beverages
Novelty diets	Immune Power Diet, Rotation Diet, Cabbage Soup Diet, Beverly Hills Diet, Dr. Phil	Most promote certain foods, or combinations of foods, or nutrients as having allegedly magical qualities	No scientific basis for recommendations	
Very low-calorie diets	Health Management Resources (HMR), Medifast, Optifast	Less than 800 kcal/day	Requires medical supervision For clients with BMI ≥ 30 or BMI ≥ 27 with other risk factors; may be difficult to transition to regular meals	
Weight-loss online diets	Cyberdiet, DietWatch, eDiets, Nutrio.com	Meal plans and other tools available online	Recommend reasonable weight loss of 0.5–2.0 lb/week Most encourage exercise Some offer weight-maintenance plans/support	

Behavior Modification and Lifestyle Interventions

Behavioral modification in lifestyle programs has been an important part of programs for weight loss for more than a quarter of a century [27, 28]. Weight losses have been in the 5–10% range. Behavior modification has a number of components. First, it is a strategy designed to help people understand their eating behavior, from the triggers that start it to the location, speed, and type of eating, through the consequences of eating and the rewards that can change it. In addition, it consists of strategies to help people develop assertive behavior, learn cognitive techniques for handling their internal discussions, and ways of dealing with stress. The newest innovation in the use of lifestyle intervention is to implement it over the Internet. This has shown promising results [29].

Exercise

Exercise is important for maintaining weight loss, but when used alone does not generally produce much weight loss [30]. Comparisons of people who successfully maintain weight loss and those who do not show a critical role of exercise. More than 200 min/week provides greater likelihood of maintaining weight loss than lower levels of exercise. Using a pedometer allows counting of steps. Working toward 10,000 steps per day is a good goal.

Medications

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

Noradrenergic Drugs

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

Orlistat

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

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

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

Lorcaserin

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

Liraglutide

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

Combination of Phentermine and Topiramate: Extended Release

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

Combination of Naltrexone-Bupropion: Sustained Release

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

Surgery

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

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

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

Conclusion

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

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Suggested Further Reading

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

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

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