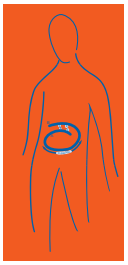
XI

Chapter 60



Obesity

Osama Hamdy and Robert J. Smith

Definition and Assessment of Obesity

Obesity is usually defined as a body mass index (BMI) higher than 30 kg/m^2 (weight [kg]/(height [m])^2). A person with a BMI of 25 to 29 is considered overweight. Severe obesity is defined as a BMI of more than 40. The old term *morbid obesity* refers to individuals weighing 45 kg more than desirable body weight (about 100 lb or about 60% above ideal body weight). There is increasing recognition of limitations to the interpretation of BMI, especially in individuals who are muscular or have a low BMI. Many clinicians prefer, at least conceptually, to define obesity not strictly by BMI but as an excess of body fat sufficient to confer risk. However, the BMI value is still useful for estimating overall health risks of obesity and comparing outcomes between clinical trials.

Population data in the United States indicate that adverse health consequences increase progressively with a BMI at or above 27 kg/m^2. In considering the cardiometabolic risk of obesity, individuals who accumulate visceral fat and have higher waist circumferences are at much higher risk for cardiovascular disease than those with the same BMI or a similar percentage of body fat but lower waist circumferences. The National Cholesterol Education Program Adult Treatment Panel III (ATP III) has included a waist circumference greater than 40 inches (102 cm) in American men and 35 inches (88 cm) in American women among five criteria that define the cardiometabolic syndrome. As an alternative mode of assessment, central and probably visceral obesity is likely with a waist-to-hip circumference ratio greater than 1 in men and 0.6 in women. Dual-energy x-ray absorptiometry and abdominal computed tomography or magnetic resonance imaging can be used to quantify visceral obesity, but these measurements typically are used in research studies and are not routine in clinical care.

Epidemiology of Obesity

During the past 20 years, the prevalence of overweight and obesity has increased sharply for both adults and children in the United States. Comparison of data from two National Health and Nutrition Examination Survey (NHANES) reports shows that among adults aged 20 to 74 years, the prevalence of obesity increased from 15% in the 1976-1980 survey to 32.9% in 2003-2004. According to the U.S. Centers for Disease Control and Prevention, after a quarter century of increases, obesity prevalence has stabilized, but levels are still high at 34% of U.S. adults older than 20 years in 2007. Because the adverse consequences of obesity develop over multiple years, it can be expected that the complications of obesity will continue to increase in prevalence. Overweight and obesity and their associated health problems have a significant economic impact on the U.S. health care system, accounting for about 9% of total medical expenditures. An epidemic of obesity and its complications similar to that in the United States is occurring throughout the world.

Pathogenesis of Obesity

Obesity exemplifies a genetic-environment interaction in which genetically prone individuals who lead a sedentary lifestyle and consume a larger amount of food are particularly at risk. Children of obese parents are 80% more likely to become obese through the combined effects of genetic and shared environmental factors.

In considering genetic factors, obesity may result from the effects of a single gene or the effects of multiple genes acting in concert. An example of a single gene defect is leptin deficiency. Leptin is a hormone produced in fat cells and is a potent inducer of satiety. Rare individuals with inactivating leptin mutations have been identified. They are characterized by increased food seeking and marked obesity, which can be substantially ameliorated by the administration of leptin. Mutations in a number of other genes that encode appetite regulatory proteins also have been identified as causes of obesity. However, these monogenic causes of obesity are rare, and the genes that contribute to common forms of human obesity have not yet been clearly identified. In addition to appetite regulation, there appears to be a heritable component associated with metabolic rate, spontaneous physical

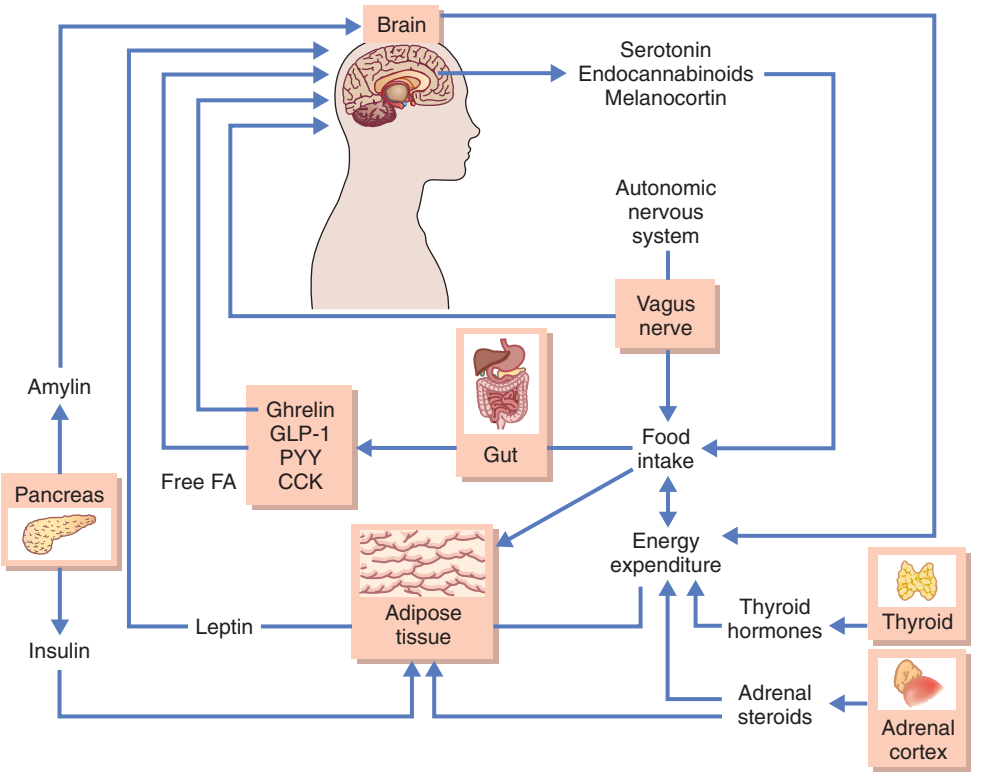


Figure 60-1 Hormonal and neurogenic control of appetite and food intake. CCK, cholecystokinin; FA, fatty acid; GLP-1, glucagon-like peptide-1; PYY, peptide YY.

activity, and thermal responses to food. Polymorphisms in several candidate genes, including the melanocortin-4 receptor, the β_3-adrenergic receptor, and peroxisome proliferator–activated receptor-γ2 (PPAR-γ2), have been linked in population studies to obesity. Genome-wide association scans recently have identified additional genes linked to obesity, and it is thought that genetic risk in most individuals derives from the synergistic or additive effects of multiple genes. Although the specific genetic factors still are not well understood, the heritability of obesity clearly is evident in twin and adoptee studies, in which obese individuals generally follow the weight pattern of their identical twins and biologic parents even when raised apart.

Many hormones, neurotransmitters, and neurogenic signals affect appetite and food intake, as shown in Figure 60-1. Endocannabinoids increase appetite, enhance nutrient absorption, and stimulate lipogenesis. Melanocortin hormone, through its effect on several receptors, modifies appetite. Multiple gut hormones play significant roles in inducing satiety, including glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and cholecystokinin. Leptin and pancreatic amylin are other potent satiety hormones. On the other hand, ghrelin, which is secreted from the stomach fundus, functions as an orexigenic or hunger-inducing hormone.

Although the genetic determinants of obesity clearly are significant, it is important to recognize the equal influence of environmental and socioeconomic factors. Lower socioeconomic status, lower education level, cessation of smoking, and consumption of high glycemic index carbohydrates all are associated with increased prevalence of obesity. The current worldwide epidemic of obesity undoubtedly is driven by changes in environmental and socioeconomic factors operating on a relatively stable background of genetic influences within a given population.

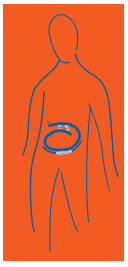
Pathogenesis of Obesity-Associated Risk

Recent evidence indicates that adipocytes in fat tissue function as an endocrine organ, producing secretory products with a major role in whole-body metabolism. The relationship of obesity to insulin resistance and endothelial dysfunction (the early stage of atherosclerosis) is mediated through the release of several hormones from adipose tissue. These hormones, designated adipocytokines or adipokines, include adiponectin, leptin, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), resistin, plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, and monocyte chemoattractant protein-1 (MCP-1). Many of these factors have actions that are proinflammatory or alter blood coagulation. Their production is influenced by both the overall amount of adipose tissue and its distribution between central and peripheral body regions. The differences in adipokine gene expression between visceral and subcutaneous fat likely have an important role in the high cardiometabolic risk of visceral obesity.

Risks Associated with Obesity

Overweight and obese individuals are at increased risk for multiple clinical disorders. A partial list of obesity-related

conditions is provided in Table 60-1. Obese individuals often manifest more than one of these disorders, and such secondary consequences of obesity account for much of the morbidity and mortality of the obese state. The "metabolic syndrome" as defined by a National Cholesterol Education Program Expert Panel refers to a state of particularly high cardiometabolic risk that characterizes individuals with at least three of five individual risk factors: abdominal obesity (waist circumference >40 inches in men and >35 inches in women), glucose intolerance (fasting plasma glucose ≥100 mg/dL), hypertension (≥130/≥85 mm Hg), elevated plasma triglycerides (≥150 mg/dL), and low high-density lipoprotein (HDL) cholesterol (<40 mg/dL in men and <50 mg/dL in women). Even modest weight loss (7% to 10% of body weight) can result in substantial reduction in many if not all of these risks.



Treatment of Obesity

Current guidelines for treatment approaches to obesity are summarized in Table 60-2. The major options are lifestyle modification (diet and exercise), behavior modification, pharmacologic intervention, and bariatric surgery. In general, a combination of approaches is more effective than a single modality.

LIFESTYLE MODIFICATION

Managing overweight and obesity by lifestyle modification requires a multidisciplinary strategy and teamwork. Key components include a structured dietary intervention and a physical activity program. Evidence-based dietary guidelines should be used to design individualized patient plans in consultation with a registered dietitian. As a general approach, daily caloric intake initially should be reduced by a modest 250 to 500 calories. Calories from carbohydrate should be decreased to about 40 percent of total calories, with a daily intake of no less than 130 g carbohydrate. Except in patients with renal impairment (creatinine clearance <60 mL per minute) or significant microalbuminuria, protein may represent 20% to 30% of daily caloric intake to minimize lean mass loss during weight reduction. The remaining 30% of calories should come from fat. *Trans*-fats should be eliminated, and saturated fat should be reduced to 7% to 10% of total fat calories. Meal plans should also include increased soluble fiber (e.g., from fresh fruits and vegetables) and healthy carbohydrate consumption, especially foods with a low glycemic index. Caloric intake should be adjusted progressively as needed until weight loss is achieved. Underlying all these steps should be the goal of designing individualized plans that can be maintained over the long term. Many patients find it helpful to receive a structured dietary intervention that includes specific suggestions for daily meals. This may increase adherence and can be easier to follow than a list of general guidelines. Nutritionally complete meal replacement (e.g., in the form of shakes or bars) can be useful for some patients at the start of the weight reduction program.

Patients should meet with an exercise physiologist to construct an individualized plan that is responsive to their capabilities and lifestyle. A balanced exercise plan will incorporate a mix of cardiovascular, stretching, and strength exercises, and it should be graded to increase gradually in both duration and intensity. Patients can start with 10 to 20 minutes of daily stretching and aerobic exercise, with a gradual increase as tolerated. Any exercise should be preceded by a warm-up period to minimize injuries. Cardiovascular evaluation and oversight during implementation of exercise (e.g., through a cardiac rehabilitation program) should be considered based on individual risk. Current guidelines recommend an ultimate goal of 60 to 90 minutes of daily exercise, with a minimum of 150 to 175 minutes per week for weight loss benefits to be realized. Emphasis should be placed on moderate-intensity exercise, such as walking 20-minute miles, rather than strenuous exercise. Because patients who are not accustomed to exercising may find it difficult to incorporate physical activity into daily practice, it is also important to emphasize variety of exercises to avoid boredom.

Table 60-1 Clinical Conditions Associated with Obesity

Diabetes mellitus
Dyslipidemia
Hypertension
Ischemic heart disease
Stroke
Reproductive dysfunction
Cholelithiasis
Gastroesophageal reflux disease
Sleep apnea
Degenerative arthritis
Cancer (endometrial, breast, prostate)
Incontinence (women)

Table 60-2 Guide to Selecting Treatment Based on Body Mass Index

	Body Mass Index				
Treatment	**25-26.9**	**27-29.9**	**30-34.9**	**35-39.9**	**≥40**
Diet, physical activity, behavior therapy	Yes with comorbidities	Yes with comorbidities	Yes	Yes	Yes
Pharmacotherapy		Yes with comorbidities	Yes	Yes	Yes
Weight-loss surgery				Yes with comorbidities	Yes

"Yes" indicates that the treatment is indicated regardless of comorbidities.
Data from NIH/NHLBI/NAASO. October 2000, NIH Publication No. 00-4084.

BEHAVIOR MODIFICATION AND PATIENT EDUCATION

Cognitive-behavioral intervention and patient education are important components of successful weight loss programs. Whenever possible, cognitive-behavioral intervention should be conducted by an experienced psychologist. The fundamental principals of intervention should include behavioral goal setting, stimulus control techniques, cognitive restructuring, assertive communication skills, stress management, and relapse prevention. Cognitive behavioral support conducted in a group setting with weekly meetings is frequently successful. Patients should learn how to set realistic goals for weight loss over a specific period of time. They also should receive guidance and support in dealing with specific challenges, such as social eating, coping with craving, and managing relapses.

PHARMACOLOGIC OPTIONS

Three antiobesity drugs—sibutramine, orlistat, and phentermine—are approved for use in the United States. Only sibutramine and orlistat are approved for long-term use. Rimonabant, an endocannabinoid receptor antagonist, is used in many countries but has not been approved in the United States because of concern about its common psychiatric side effect of depression. A recent meta-analysis of 30 placebo-controlled trials of 1 to 4 years' duration has provided evidence for significant weight loss with sibutramine (4.2 kg average weight loss, 10 studies, 2623 participants), orlistat (2.9 kg, 16 studies, 10,631 participants), and rimonabant (4.7 kg, 4 studies, 6365 participants).

Sibutramine

Sibutramine is an oral serotonin- and noradrenaline-reuptake inhibitor that controls appetite by inducing satiety. Sibutramine-assisted weight loss has been accompanied by improved serum concentrations of triglycerides, but adverse effects of lowered concentrations of HDL cholesterol and increased blood pressure and pulse rate. It therefore is recommended that blood pressure be monitored during sibutramine treatment. There typically is a gradual rebound of weight gain on discontinuation of sibutramine.

Orlistat

Orlistat limits caloric intake through inhibition of the lipase-mediated breakdown of fat in the gastrointestinal tract. This typically decreases fat absorption by about 30% and increases fecal fat content. In addition to its weight loss effect, there is evidence that orlistat can decrease the incidence of diabetes, improve concentrations of total and low-density lipoprotein (LDL) cholesterol, and improve blood pressure and glycemic control in patients with diabetes. Conversely, HDL cholesterol may be slightly lowered by orlistat, and there is an increased risk for cholelithiasis. Most patients develop some degree of side effects that range from diarrhea, flatulence, oily stools, and fecal urgency to fecal incontinence (rare). Gastrointestinal side effects are usually proportional to the amount of fat intake. Possible deficiency of fat-soluble vitamins A, D, E, and K mandates their routine supplementation in patients on orlistat. The usual dose of orlistat is 120 mg before each meal. A 60-mg dose is currently available over-the-counter. This dose is less effective but is associated with fewer adverse side effects.

Phentermine

Phentermine is approved for the short-term treatment of obesity. In addition to appetite suppression, it can cause elevated blood pressure, increased heart rate, and insomnia, owing to its sympathomimetic properties. Combining phentermine with tricyclic antidepressants or monoamine oxidase inhibitors may result in a marked increase in blood pressure and other serious side effects because of elevated serotonin levels.

BARIATRIC SURGERY

Bariatric surgery involves the use of one of several different techniques to modify the gastrointestinal tract in a manner that results in a decrease in calorie intake or absorption. The most common bariatric surgical procedures in the United States at present are Roux-en-Y gastric bypass (RYGB) and laparoscopic placement of an adjustable gastric band (LAGB) (Fig. 60-2). The number of bariatric procedures performed in the United States has increased about 15-fold over the past 10 years to nearly 200,000 in 2007. Bariatric surgery is indicated for individuals with a BMI of more than 40 kg/m^2 or with a BMI of more than 35 kg/m^2 plus high-risk comorbid conditions, such as severe sleep apnea, obesity-related cardiomyopathy, or uncontrolled type 2 diabetes. Bariatric surgery is not uniformly a low-risk procedure, and judicious patient selection and diligent perioperative care are mandatory. Contraindications include high operative risk (e.g., severe congestive heart failure or unstable angina), active substance abuse, and significant psychopathology.

LAGB is associated with substantially better maintenance of weight loss than lifestyle intervention alone and carries a very low operative mortality rate (0.1%). As a less invasive procedure than RYGB, it may be preferred in patients older than 55 years. LAGB is associated with significantly less loss of fat-free mass, but less excess weight loss than RYGB at 5 and 10 years. Complications associated with LAGB include band slippage, band erosion, balloon failure, port malposition, band and port infections, and esophageal dilation. Overall, complication and mortality rates are much lower for LAGB than those observed with RYGB.

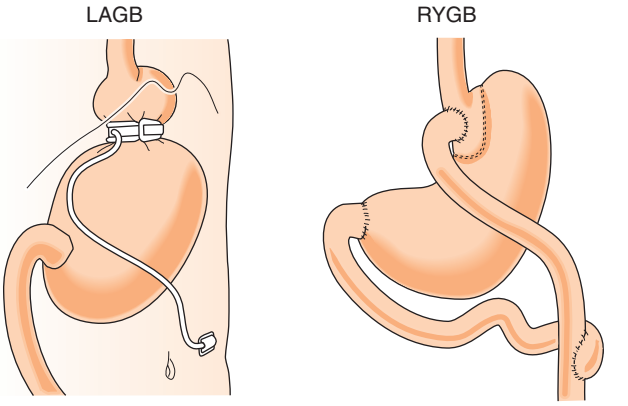
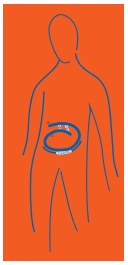


Figure 60-2 Common bariatric procedures. LAGB, laparoscopic adjustable gastric band; RYGB, Roux-en-Y gastric bypass.



RYGB is currently the most commonly performed bariatric procedure in the United States. In RYGB, the upper stomach is transected, creating a very small proximal gastric pouch with a capacity of 10 to 30 mL. The gastric pouch is anastomosed to a Roux-en-Y proximal jejunal segment, bypassing the remaining stomach, duodenum, and a small portion of jejunum. The operative mortality rate for RYGB is 0.5%. The resulting foregut bypass appears to have benefits beyond just calorie intake reduction and weight loss. These include improvement in the physiologic responses of gut hormones involved in glucose regulation and appetite control, such as ghrelin, GLP-1, and PYY. Mechanical improvements from decreased adiposity include less weight bearing by lower extremity joints and improved lung compliance and reduced fatty tissue around the neck, which relieves obstruction to breathing and sleep apnea.

A meta-analysis of 22,000 bariatric surgery patients demonstrated an average excess body weight loss of 61% accompanied by significant improvements in type 2 diabetes, hypertension, sleep apnea, and dyslipidemia. The beneficial effect of obesity surgery on type 2 diabetes is one of the most important outcomes, with resolution of diabetes in most patients (range, 40% to 100% of patients in various studies). Independent predictors of diabetes reversal following bariatric surgery include selection of RYGB as the bariatric procedure, a shorter duration of diabetes, and greater weight loss after surgery. Insulin-treated patients usually experience significant decreases in insulin requirements, and improvements in fasting blood glucose levels often occur before significant weight loss. Most type 2 diabetic patients are able to discontinue insulin therapy by 6 weeks after surgery, and euglycemia has been maintained up to 14 years after RYGB.

It is important to recognize that the altered gastrointestinal dynamics of gastric bypass surgery result in substantial risk for developing deficiencies of vitamins and minerals, including iron, calcium, vitamin B_{12}, vitamin D, and other fat-soluble vitamins. Supplements of multivitamins, iron, and calcium should be provided postoperatively, and there should be periodic screening for acquired deficiencies. Inadequate protein intake and absorption may occur after RYGB and lead to protein malnutrition. An infrequent but serious complication of RYGB that recently has been recognized is hyperinsulinemic hypoglycemia, which appears to result from induced changes in pancreatic β-cell mass and insulin secretion. This requires careful diagnostic evaluation to confirm hyperinsulinemia and rule out insulinoma. Affected patients may be responsive to diet modifications (frequent, low carbohydrate feedings), but when symptoms are severe, patients may require partial or total pancreatectomy.

Prognosis

Although a small percentage of obese individuals are able to achieve and maintain weight loss for a long period after nonsurgical intervention, most regain weight over the following months or years. Weight regain even after bariatric surgery is not uncommon, with regain occurring typically after reaching maximum weight loss about 2 years after surgery. Weight reduction of 10% to 20% in an obese individual from any intervention results in a decrease in total and resting energy expenditure, and this may prevent further weight loss at a given level of reduced calorie intake. In considering the underlying causes of obesity, there currently is substantial support for the concept of a biologic set point or control mechanism that may target a body weight in the overweight or obese range. Whether the set point is determined by genetic or environmental factors, this concept lends support to the theory that behavior is not the sole determinant of obesity. Further understanding of the genetic and hormonal regulation of obesity and their roles in establishing a functional set point may help in creating long-lasting and effective treatment strategies.

Prospectus for the Future

- The fundamental behavioral, environmental, and genetic determinants of appetite, satiety, and obesity will be better understood.
- New medications will be developed that more effectively modulate appetite and satiety control mechanisms, likely with a greater emphasis on the use of multiple medications in combination.
- The environmental factors promoting obesity, including influences on food choice and total calorie intake, will be better understood and will need to be addressed as population-level determinants of obesity.

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