

Obesity

(See also *Harrison's Principles of Internal Medicine*, 17th Edition, Chapters 74 and 75)

Definition

- Characterized by a relative excess of adipose tissue mass
- Body mass index (BMI) ≥ 30 kg/m² defines obesity.
 - BMI = weight/height² (in kg/m²)
- See Classification for BMI classification.

Epidemiology

- Prevalence
 - Prevalence of medically significant obesity is increasing worldwide.
 - Estimates of prevalence in U.S. adults >20 years of age
 - Overweight (BMI >25 kg/m²): 64%
 - Obesity (BMI >30 kg/m²): 30.5%
 - Extreme obesity (BMI >40 kg/m²): 4.7%
- Sex
 - More common among women
- Socioeconomic status
 - More common among poor populations
 - In industrial societies, obesity is more common among poor women.
 - In underdeveloped countries, wealthier women are more often obese.
- Age
 - Prevalence is increasing in children.

Risk Factors

- Poor-quality diet
- Chronic ingestion of excess calories
- Sedentary lifestyle
- Family history of obesity
- Smoking cessation

Etiology

- Obesity has a multifactorial etiology.
 - Genetic influences
 - Genetic susceptibility to obesity is polygenic.
 - Approximately 135 different candidate genes have been associated and/or linked with obesity-related phenotypes.
 - Monogenic causes of obesity are rare and cause early-onset severe obesity.

- Mutations in approximately 10 different genes have been associated with an obese phenotype (see Table 1).
 - Environmental influences
 - Availability and high caloric composition of the diet
 - Sedentary lifestyle
 - Sleep deprivation
 - Socioeconomic/cultural influence
 - Lower socioeconomic status is associated with obesity in the U.S. and other developed countries.
- Recent increase in the prevalence of obesity worldwide is largely due to lifestyle factors (changes in diet, physical activity), as it has been too rapid to be caused by changes in the gene pool.
- Physiologically, obesity results from an imbalance between energy intake and energy expenditure.
 - Increased energy intake
 - Decreased energy expenditure
 - Combination of the 2 factors

Table 1: Some Obesity Genes in Humans and Mice

Gene	Gene Product	Mechanism of Obesity	In Human	In Rodent
<i>Lep</i> (<i>ob</i>)	Leptin, a fat-derived hormone	Mutation prevents leptin from delivering satiety signal; brain perceives starvation	Yes	Yes
<i>LepR</i> (<i>db</i>)	Leptin receptor	Same as above	Yes	Yes
<i>POMC</i>	Proopiomelanocortin, a precursor of several hormones and neuropeptides	Mutation prevents synthesis of melanocyte-stimulating hormone (MSH), a satiety signal	Yes	Yes
<i>MC4R</i>	Type 4 receptor for MSH	Mutation prevents reception of satiety signal from MSH	Yes	Yes
<i>AgRP</i>	Agouti-related peptide, a neuropeptide expressed in the hypothalamus	Overexpression inhibits signal through MC4R	No	Yes
<i>PC-1</i>	Prohormone convertase 1, a processing enzyme	Mutation prevents synthesis of neuropeptide, probably MSH	Yes	No
<i>Fat</i>	Carboxypeptidase E, a processing enzyme	Same as above	No	Yes
<i>Tub</i>	Tub, a hypothalamic protein of unknown function	Hypothalamic dysfunction	No	Yes

Associated Conditions

- Diseases associated with obesity
 - Cushing's syndrome
 - Hypothyroidism
 - Insulinoma
 - Male hypogonadism
 - Growth hormone deficiency
 - Craniopharyngioma and other disorders involving the hypothalamus

- Genetic syndromes associated with obesity (See Table 2)
 - Prader-Willi syndrome
 - Laurence-Moon-Biedl syndrome
 - Ahlström syndrome
 - Cohen syndrome
 - Carpenter syndrome
 - Fragile X syndrome
 - Wilson-Turner syndrome
 - Albright's hereditary osteodystrophy
- Associated conditions
 - Type 2 diabetes mellitus
 - Up to 80% of patients with type 2 diabetes mellitus are obese.
 - Polycystic ovarian syndrome (PCOS)
 - Hypertension
 - Hyperlipidemia
 - Coronary artery disease
 - Stroke
 - Congestive heart failure
 - Obstructive sleep apnea
 - Steatohepatitis
 - Gallstones

Table 2: A Comparison of Syndromes of Obesity--Hypogonadism and Mental Retardation

Feature	Syndrome				
	Prader-Willi	Laurence-Moon-Biedl	Ahlstrom	Cohen	Carpenter
Inheritance	Sporadic; two-thirds have defect	Autosomal recessive	Autosomal recessive	Probably autosomal recessive	Autosomal recessive
Stature	Short	Normal; infrequently short	Normal; infrequently short	Short or tall	Normal
Obesity	Generalized Moderate to severe Onset 1-3 yrs	Generalized Early onset, 1-2 yrs	Truncal Early onset, 2-5 yrs	Truncal Mid-childhood, age 5	Truncal, gluteal
Craniofacies	Narrow bifrontal diameter Almond-shaped eyes Strabismus V-shaped mouth High-arched palate	Not distinctive	Not distinctive	High nasal bridge Arched palate Open mouth Short philtrum	Acrocephaly Flat nasal bridge High-arched palate
Limbs	Small hands and feet Hypotonia	Polydactyly	No abnormalities	Hypotonia Narrow hands and feet	Polydactyly Syndactyly Genu valgum
Reproductive status	1° Hypogonadism	1° Hypogonadism	Hypogonadism in males but not in females	Normal gonadal function or hypogonadotrophic hypogonadism	2° Hypogonadism
Other features	Enamel hypoplasia Hyperphagia Temper tantrums Nasal speech			Dysplastic ears Delayed puberty	
Mental retardation	Mild to moderate		Normal intelligence	Mild	Slight

Symptoms & Signs

- BMI classification
 - Overweight: 25–29.9 kg/m²
 - Obesity (class I): 30–34.9 kg/m²
 - Obesity (class II): 35–39.9 kg/m²
 - Obesity (class III or morbid obesity): >40 kg/m²
- Regional fat distribution
 - Abdominal obesity is defined by measurement of waist circumference >102 cm (40 in) in men and >88 cm (35 in) in women.

Differential Diagnosis

- Cushing's syndrome (see Cushing's Syndrome.)
 - Central obesity, hypertension, and glucose intolerance may be present in simple obesity, but specific stigmata of Cushing's syndrome are absent.
 - Cortisol production and urinary metabolite levels (17-hydroxysteroids) may be increased in simple obesity.
 - Overnight 1-mg dexamethasone suppression test is normal in 90% of obese patients without Cushing's syndrome; standard 2-day low-dose dexamethasone suppression test is normal in the remaining 10%.
- Hypothyroidism (see Hypothyroidism.)
 - Uncommon cause of obesity
 - Excluded by measuring thyroid-stimulating hormone
 - Weight gain in hypothyroidism is predominantly due to myxedema.
- Male hypogonadism
 - May result in increased adiposity and decreased lean tissue
 - Excluded by history and laboratory investigation, when appropriate
- Growth hormone deficiency (see Hypopituitarism.)
 - Results in an increased in body fat (especially abdominal fat) and decrease in lean tissue
 - Should only be suspected when accompanied by other evidence of pituitary disease
- Insulinoma (see Hypoglycemia.)
 - Weight gain results from overeating to prevent hypoglycemia.
- Craniopharyngioma and other disorders of hypothalamic dysfunction
 - Hypothalamic dysfunction of systems controlling satiety, hunger, and energy expenditure (due to central nervous system tumors, trauma, or inflammatory disorders) can cause varying degrees of obesity.
 - Uncommon to identify a discrete anatomic basis for these disorders.

Diagnostic Approach

- Calculate body mass index and measure waist circumference.
- Determine degree and rate of acquisition of obesity.
- Exclude identifiable causes of obesity.
- Assess comorbid conditions, presence of cardiovascular risk factors, and absolute risk status.
 - Conditions that indicate high absolute risk for obesity-related disorders
 - Established coronary artery disease
 - Other atherosclerotic disease
 - Type 2 diabetes mellitus
 - Sleep apnea
 - ≥3 of the following indicate high absolute risk for obesity related disorders.
 - Hypertension
 - Cigarette smoking
 - High low-density lipoprotein cholesterol level (>160 mg/dL)
 - Low high-density lipoprotein cholesterol level (<35 mg/dL)

- Impaired fasting glucose
- Family history of early coronary artery disease
- Age >45 years in men and >55 years in women

Laboratory Tests

- Fasting lipid profile
- Fasting plasma glucose and electrolyte measurement
- Liver function tests
- Serum TSH measurement
- Additional laboratory testing should be performed on the basis of presentation of symptoms and risk factors.

Imaging

- Not indicated

Diagnostic Procedures

- Review of electrocardiogram

Classification

- BMI classification
 - Overweight: 25–29.9 kg/m²
 - Obesity (class I): 30–34.9 kg/m²
 - Obesity (class II): 35–39.9 kg/m²
 - Obesity (class III or morbid obesity): >40 kg/m²

Treatment Approach

- Patients who meet the following criteria should be considered for treatment.
 - BMI >30 mg/kg²
 - BMI 25–29.9 mg/kg² and presence of ≥2 risk factors
 - BMI 25–29.9 mg/kg² and waist circumference >102 cm (40 in) in men or >88 cm (35 in) in women
- Combined therapy with a low-calorie diet, increased physical activity, and behavior therapy provide the most successful intervention for weight loss and weight maintenance.
- All patients should be counseled on lifestyle and behavioral modifications (appropriate diet and physical activity), and weight loss goals should be individualized.
- Treatment goals should be guided by the health risks of obesity in any given person.

Specific Treatments

Behavior modification

- The principles of behavior modification provide the underpinnings for many current programs of weight reduction.
- Goal of behavior modification is to modify maladaptive behaviors, including eating habits and physical activity.
- Patient is asked to monitor and record the circumstances related to eating and physical activity.
- Patients may benefit from counseling offered in a stable group setting for extended periods of time, including after weight loss.

Dietary therapy

- Reduced caloric intake is the cornerstone of obesity treatment.
- There is no scientific evidence to validate the utility of specific "fad diets."
- General facts relevant to food intake and weight loss
 - Deficit of 7,500 kcal will produce a weight loss of ~1 kg.
 - Consuming 100 kcal/d less for 1 year should cause a 5-kg weight loss.
 - Consuming 1,000 kcal/d less should cause a loss of ~1 kg per week.
 - Rate of weight loss on a given caloric intake is related to rate of energy expenditure.
 - Obese persons have a higher metabolic rate than lean persons.
 - Men have a higher metabolic rate than women (due to their greater lean body mass); thus, the rate of weight loss is greater among more obese and among men.
 - With chronic caloric restriction, the metabolic rate decreases.
 - With total starvation or diets restricted to < 600 kcal/d, initial weight loss over the first week results predominantly from natriuresis and the loss of fluids.

Very-low-calorie diets (400–600 kcal/d)

- May be appropriate for short-term treatment of obesity in selected patients.
 - Use should be restricted to patients >130% of ideal body weight.
 - Most commonly used for 1–2 months to initiate more rapid weight loss, improve comorbid conditions, and provide patients with positive feedback
 - Safe in selected patients under medical supervision
- Daily diet composition
 - 45–70 g high-quality protein
 - 30–50 g carbohydrate
 - ~2 g fat
 - Supplements of vitamins, minerals, and trace elements
- Advantages
 - Greater rate of weight loss compared with less restrictive diets
 - Possible beneficial effect of hunger suppression from production of ketones
 - Blood pressure and blood glucose, cholesterol, and triglyceride levels decrease.
 - Pulmonary function and exercise tolerance improve.
 - Sleep apnea may improve within a few weeks.
- Complications
 - Minor
 - Fatigue, constipation or diarrhea
 - Dry skin
 - Hair loss
 - Menstrual irregularities
 - Orthostatic dizziness
 - Difficulty concentrating
 - Cholelithiasis and pancreatitis may occur when a very-low-calorie diet is interrupted by binge eating.
 - Gallstones develop in up to 25% of patients on a very-low-calorie diet.
- Close supervision is required in patients with diabetes who are receiving insulin or oral agents.
- Contraindications
 - Pregnancy
 - Cancer
 - Recent myocardial infarction
 - Cerebrovascular disease
 - Hepatic disease
 - Untreated psychiatric disease

Low-calorie diets (>800 kcal/d)

- Are applicable to most patients and have fewer restrictions than very-low-calorie diets.
- Considerable controversy surrounds the question of what constitutes the best diet composition for promoting weight loss.
- Low-fat diets
 - Commonly recommended, but benefits to obesity reduction from very-low-fat diets are modest at best
 - Health effects aside from weight reduction may be important.
 - Large amounts of simple carbohydrates are substituted for fats but may actually promote obesity.
- Diets rich in fruits, vegetables, whole grains, and other low-glycemic index carbohydrates may promote weight loss and are preferable to low-fat diets.
- Diets with protein replacement of simple carbohydrates aim to minimize insulin production.
 - Efficacy of this strategy, aside from overall calorie reduction, is unknown.
- Very-low-carbohydrate "Atkins" style diets
 - More effective for short-term weight loss when compared to standard caloric restriction, but have not been shown to be more effective in maintaining weight loss
 - Consequences of maintaining a lower body weight at the expense of consuming more saturated fat are unknown.
- Diet therapy education is important to prevent weight regain.
 - Patients should be counseled on the caloric content of specific portions to promote weight loss and maintenance.

Exercise

- Physical activity is an important component of the overall approach to weight reduction and maintenance.
- The effect of an exercise regimen as a sole therapy for obesity is not established, but exercise is a valuable means to sustain diet therapy.
- Additional benefits
 - Improves cardiovascular tone and reduce blood pressure, independent of weight loss
 - Helps reduce appetite
 - Increases the likelihood of weight maintenance once targets are achieved
 - Reduces intra-abdominal fat
 - Reduces risk of glucose intolerance
- Many obese persons have not exercised on a regular basis and may have cardiovascular risk factors.
 - Exercise should be introduced gradually under medical supervision, especially in the most obese patients.
- Minimal physical activity recommendations
 - Adults should engage in moderate-intensity physical activities for ≥ 30 minutes on ≥ 5 days of the week **or**
 - Adults should engage in vigorous-intensity physical activity ≥ 3 days per week for ≥ 20 minutes per occasion.

Pharmacotherapy

- May be considered as adjunctive therapy in patients with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with other risk factors or diseases who fail to achieve weight loss goals through nonpharmacologic approaches
- Limitations
 - Medication-induced weight loss is not a cure despite modest short-term benefits from several agents.
 - Safety and efficacy of weight loss agents beyond 2 years has not been established.

- Rebound weight gain after the cessation of drug use is common.
- Most agents are associated with substantial side effects, and some have potential for abuse.
- Phentermine is approved for short-term use (<12 weeks).
 - Mechanism of action: increases the release of norepinephrine and dopamine from nerve terminals and inhibits their reuptake
 - Dosing: 15 mg–30 mg/d
 - Efficacy: modest (10 versus 4.4 kg of weight loss over 24 weeks in a well-controlled study)
 - Side effects (numerous): insomnia, dry mouth, constipation, palpitations, hypertension
- Sibutramine is approved for long-term use.
 - Mechanism of action: central reuptake inhibitor of both norepinephrine and serotonin
 - Dosing: 10 mg/d
 - Efficacy: Once-daily dose over 24 weeks produced a 7% weight loss and decreased cholesterol and triglyceride levels in a double-blind, placebo-controlled trial.
 - Adverse effects: increases pulse by an average of 4–5 beats/min and blood pressure by 1–3 mmHg
- Orlistat is approved for long-term use.
 - Mechanism of action: inhibitor of pancreatic lipase with no systemic availability; causes modest weight loss due to drug-induced fat malabsorption
 - Dosing: 120 mg 3 times daily, before meals, taken with a multivitamin
 - Efficacy: 2-year randomized, double-blind trial revealed modest weight loss (8.7 kg for 120 mg of orlistat versus 5.8 kg from diet alone) during first year and better maintenance of weight loss in second year compared with the placebo group (3.2 kg regained vs. 5.6 kg regained for placebo)
 - Adverse effects
 - GI side effects include oily stools, flatulence, and fecal urgency; these usually diminish as patients limit fat intake to avoid symptoms.
 - Absorption of fat-soluble vitamins is decreased.
- Metformin tends to decrease body weight in patients with obesity and type 2 diabetes mellitus.
- Recombinant leptin is highly effective in rare cases of leptin deficiency caused by mutations of the leptin gene.
 - Regulates hunger and induces loss of fat mass while preserving lean body mass.
 - Response to leptin is limited or absent in common obesity, which is associated with hyperleptinemia and leptin resistance.

Surgery

- Bariatric surgery should be considered for patients meeting the following criteria.
 - BMI >35 kg/m² with an associated comorbid condition or BMI >40 kg/m²
 - Repeated failure of other therapeutic approaches
 - At eligible weight for 3–5 years
 - Capable of tolerating surgery
 - Absence of alcoholism, other addictions, or major psychopathology
 - Prior clearance by a psychiatrist
- Vertical-banded gastroplasty
 - Purely restrictive procedure
- Roux-en-Y gastric bypass
 - Combines restriction with slight malabsorption
 - May also reduce appetite via suppression of gastric hormone ghrelin
 - Most often performed via laparotomy, but may be performed laparoscopically
 - May be associated with risk of islet hyperplasia and hypoglycemia
- Laparoscopic adjustable gastric banding
 - Widely used in Europe and Australia and is being introduced in the U.S.

- Potential benefits
 - Significant, sustained weight loss (10–159 kg over 1–5 years)
 - Improvements in hypertension, diabetes, sleep apnea, congestive heart failure, angina, hyperlipidemia, and venous disease
- Short-term complications
 - Pulmonary embolus
 - Anastomotic leak
 - Bleeding
 - Wound infection
- Long-term complications depend on the specific surgical procedure but include:
 - Dumping syndrome
 - Stomal stenosis
 - Marginal ulcers
 - Hernias
- Lifelong medical monitoring after surgery is necessary.
- Lifelong supplementation with vitamin B₁₂, iron, folate, and calcium is recommended.

Monitoring

- For dieting patients
 - Monitor weight loss and general health.
 - Set appropriate goals and expectations.
 - Offer education on relationship of diet and exercise.

Complications

Insulin resistance and type 2 diabetes mellitus

- Hyperinsulinemia and insulin resistance increase with weight gain and diminish with weight loss.
- Insulin resistance is more strongly linked to intra-abdominal fat than to fat elsewhere.
- Despite nearly universal insulin resistance, most obese persons do not develop diabetes; however, obesity is a major risk factor for diabetes.
- Up to 80% of patients with type 2 diabetes mellitus are obese.
- Weight loss and exercise, even of modest degree, are associated with increased insulin sensitivity and improved glucose control in diabetes.

Reproductive disorders

- Men
 - Male hypogonadism can contribute to increased adiposity and decreased lean tissue.
 - Hypogonadal men often develop a distribution of adipose tissue with a pattern more typical of women.
 - Total plasma testosterone and sex hormone-binding globulin (SHBG) levels are often reduced, and estrogen levels are increased when weight exceeds 160% of ideal body weight in simple obesity.
 - Free testosterone may be decreased when weight exceeds 200% ideal body weight in simple obesity.
 - Gynecomastia may be observed, but masculinization, libido, potency, and spermatogenesis are preserved in most cases.
- Women
 - Menstrual abnormalities are common, particularly in women with upper body obesity.
 - Increased androgen production, decreased SHBG level, and increased peripheral conversion of androgen to estrogen

- Most obese women with oligomenorrhea have PCOS.
 - 40% of women with PCOS are obese.
- Increased incidence of uterine cancer in postmenopausal obese women

Cardiovascular disease

- Obesity is an independent risk factor for cardiovascular disease in men and women, including coronary disease, stroke, and congestive heart failure.
- Effect of obesity on cardiovascular mortality in women may be seen at BMI as low as 25 kg/m².
- Atherogenic lipid profile
 - Increased low-density lipoprotein cholesterol level
 - Elevated very-low-density lipoprotein and triglyceride levels
 - Decreased high-density lipoprotein cholesterol level
- Hypertension
 - Increased peripheral resistance and cardiac output
 - Increased sympathetic nervous system tone
 - Increased salt sensitivity
 - Insulin-mediated salt retention

Pulmonary disease

- Reduced chest-wall compliance
- Increased work of breathing
- Increased minute ventilation due to increased metabolic rate
- Decreased total lung capacity and functional residual capacity↓
- Severe obesity may be associated with obstructive sleep apnea and "obesity hypoventilation syndrome."
 - Weight loss (10–20 kg) can lead to substantial improvement.

Nonalcoholic steatohepatitis

- Obesity is associated with excess hepatic triglycerides.
- Occurs in about two-thirds of obese people
- Usually asymptomatic with mildly increased values on liver function tests
- Can lead to inflammation and fibrosis
- Increased risk of cirrhosis, particularly when associated with other liver diseases, such as hepatitis C

Gallstones

- >50% above ideal body weight is associated with 6-fold increased incidence of symptomatic gallstones.
- Fasting-induced cholecystitis is a complication of extreme diets.

Cancer

- Men: higher mortality rate from cancer
 - Esophagus
 - Colon
 - Rectum
 - Pancreas
 - Liver
 - Prostate
 - Obesity accounts for 14% of cancer deaths for men in the U.S.

- Women: higher mortality from cancer
 - Gallbladder
 - Bile duct
 - Breast
 - Endometrium
 - Cervix
 - Ovary
 - Increased incidence of uterine cancer in postmenopausal women with obesity
 - Obesity accounts for 20% of cancer deaths in women in the U.S.

Bone, joint, and cutaneous disease

- Osteoarthritis, partly from trauma of added weight bearing and joint malalignment
- Gout
- Acanthosis nigricans
 - Reflects the severity of underlying insulin resistance and diminishes with weight loss
- Cutaneous fungal and yeast infections due to friability of skin, especially in skin folds
- Venous stasis

Prognosis

- Morbidity
 - Distribution of adipose tissue has substantial implications for morbidity.
 - Elevated abdominal–gluteal ratio (men, 1.0; women, 0.9) is associated with many of the most important complications of obesity.
 - Insulin resistance
 - Diabetes mellitus
 - Hypertension
 - Hyperlipidemia
 - Hyperandrogenism in women
- Mortality
 - Mortality rates increase with obesity, particularly when obesity is associated with increased intra-abdominal fat.
 - Morbidly obese persons (BMI >40 kg/m²; >200% ideal body weight)
 - 12-fold increase in mortality rate in men 25–34 years of age
 - 6-fold increase in mortality rate in men 35–45 years of age

Prevention

- Maintain a healthy, balanced diet.
- Exercise regularly.

ICD-9-CM

- 278.00 Obesity, unspecified
- 278.01 Morbid obesity
- 278.02 Overweight

See Also

- Cardiovascular Complications of Diabetes Mellitus
- Carpal Tunnel Syndrome and Other Entrapment Neuropathies
- Cushing's Syndrome
- Essential Hypertension
- Gallstones

- Health Care Screening and Disease Prevention
- Hyperlipidemia
- Hypothyroidism
- Ischemic Stroke
- Male Hypogonadism
- Obstructive Sleep Apnea
- Type 2 Diabetes Mellitus

Internet Sites

- Professionals
 - The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults
National Heart, Lung, and Blood Institute Obesity Education Initiative
- Patients
 - Obesity
MedlinePlus

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PEARLS

- Reductions of 500–1,000 kcal/d will produce a recommended weight loss of 1–2 lb per week.

- A 10% reduction in body weight reduces disease risk factors.
- Moderate exercise increases energy expenditure but also reduces disease risk factors, including glucose intolerance.
- Increased waist circumference is associated with a high risk for type 2 diabetes, dyslipidemia, hypertension, and cardiovascular disease in patients with a BMI of 25–34.9 kg/m².
- Bariatric surgery is most effective for morbid obesity (BMI >40 kg/m²) or BMI >35 kg/m² in the presence of comorbid conditions.