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In This Issue…

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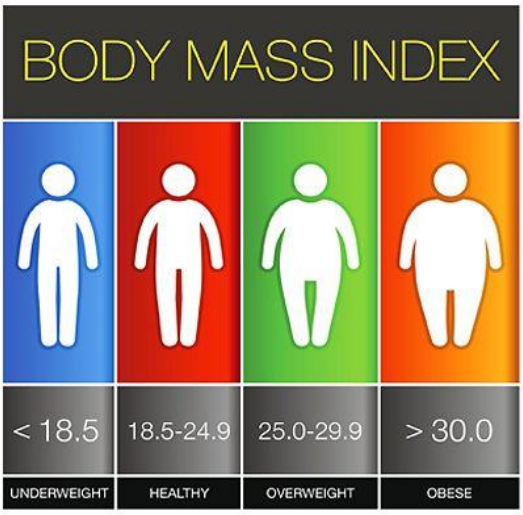
Overweight and Obesity



Obesity rates have increased at an alarming rate since the mid1970s.Overweight and obesity are significant because they are associated with increased morbidity and mortality from various conditions. Obesity is excess body weight, defined as a body mass index (BMI) of≥30 kg/m^2. Complications include cardiovascular (CV) disorders (particularly in people with excess abdominal fat), diabetes mellitus, certain cancers, cholelithiasis, fatty liver, cirrhosis, osteoarthritis, reproductive disorders in men and women, psychologic disorders, and, for people with BMI ≥35, premature death. Overweight but not obese is BMI ≥ 25 but less than 30.

In the US, obesity and its complications cause as many as 300,000 premature deaths each year, making it second only to cigarette smoking as a preventable cause of death.

Etiology

Causes of obesity are probably multifactorial and include genetic predisposition. Ultimately, obesity results from a long-standing imbalance between energy intake and energy expenditure, including energy utilization for basic metabolic processes and energy expenditure from physical activity:

Genetic factors

Heritability of BMI is about 66%. Genetic factors may affect the many signaling molecules and receptors used by parts of the hypothalamus and GI tract to regulate food intake. Genetic factors can be inherited or result from conditions in utero (called genetic imprinting). Rarely, obesity results from abnormal levels of peptides that regulate food intake (eg, leptin) or abnormalities in their receptors (eg, melanocortin-4 receptor).

Genetic factors also regulate energy expenditure, including basal metabolic rate (BMR), diet-induced thermogenesis, and nonvoluntary activity–associated thermogenesis. Genetic factors may have a greater effect on the distribution of body fat, particularly abdominal fat (which increases the risk of metabolic syndrome), than on the amount of body fat.

Environmental factors

Weight is gained when caloric intake exceeds energy needs. Important determinants of energy intake include portion sizes and the energy density of the food.

High-calorie foods (eg, processed foods), diets high in refined carbohydrates, and consumption of soft drinks, fruit juices, and alcohol promote weight gain. Diets high in fresh fruit and vegetables, fiber, complex carbohydrates, and lean proteins, with water as the main fluid consumed, minimize weight gain. A sedentary lifestyle promotes weight gain.

Regulatory factors

Prenatal maternal obesity, prenatal maternal smoking, and intrauterine growth restriction can disturb weight regulation and contribute to weight gain during childhood and later. Obesity that persists beyond early childhood makes weight loss in later life more difficult.

The composition of the gut microbiome also appears to be an important factor; early use of antibiotics and other factors that alter the composition of the gut microbiome may promote weight gain and obesity later in life.

Early exposure to obesogens, a type of endocrine-disrupting chemical (eg cigarette smoke, bisphenol A, air pollution, flame retardants, phthalates, and polychlorinated biphenyls) can alter metabolic set points through epigenetics or nuclear activation, increasing the propensity of developing obesity.

About 15% of women permanently gain ≥ 20 lb with each pregnancy.

Insufficient sleep (usually considered < 6 to 8 h/night) can result in weight gain by changing the levels of satiety hormones that promote hunger.

Drugs, including corticosteroids, lithium, traditional antidepressants (tricyclics, tetracyclics, monoamine oxidase inhibitors [MAOIs]), benzodiazepines, anticonvulsants, thiazolidinediones (eg, rosiglitazone, pioglitazone), beta-blockers, and antipsychotic drugs, can cause weight gain.

Uncommonly, weight gain is caused by one of the following disorders:

- Brain damage caused by a tumor (especially a craniopharyngioma) or an infection (particularly those affecting the hypothalamus), which can stimulate consumption of excess calories.
- Hyperinsulinism due to pancreatic tumors.
- Hypercortisolism due to Cushing syndrome, which causes predominantly abdominal obesity.
- Hypothyroidism (rarely a cause of substantial weight gain).

Eating disorders

At least 2 pathologic eating patterns may be associated with obesity:

- **Binge eating disorder** is consumption of large amounts of food quickly with a subjective sense of loss of control during the binge and distress after it. This disorder does not include compensatory behaviors, such as vomiting. Binge eating disorder occurs in about 3.5% of women and 2% of men during their lifetime and in about 10 to 20% of people entering weight reduction programs. Obesity is usually severe, large amounts of weight are frequently gained or lost, and pronounced psychologic disturbances are present.
- **Night-eating syndrome** consists of morning anorexia, evening hyperphagia, and insomnia, with eating in the middle of the night. At least 25 to 50% of daily intake occurs after the evening meal. About 10% of people seeking treatment for severe obesity may have this disorder. Rarely, a similar disorder is induced by use of a hypnotic such as zolpidem.

Similar but less extreme patterns probably contribute to excess weight gain in more people. For example, eating after the evening meal contributes to excess weight gain in many people who do not have night-eating syndrome.

Diagnosis

BMI

In adults, BMI, defined as weight (kg) divided by the square of the height (m^2), is used to screen for overweight or obesity. However, BMI is a crude screening tool and has limitations in many subpopulations. Some experts think that BMI cutoffs should vary based on ethnicity, sex, and age. For example, in certain nonwhite populations, complications of obesity develop at a much lower BMI than in whites.

Asians and many aboriginal populations have a lower cut-off (23 kg/m^2) for overweight. In addition, BMI may be high in muscular athletes, who lack excess body fat, and may be normal or low in formerly overweight people who have lost muscle mass.

Waist circumference

Waist circumference and the presence of metabolic syndrome appear to predict risk of metabolic and CV complications better than BMI does.

Body composition analysis

Body composition—the percentage of body fat and muscle—is also considered when obesity is diagnosed. Although probably unnecessary in routine clinical practice, body composition analysis can be helpful if clinicians question whether elevated BMI is due to muscle or excessive fat.

The percentage of body fat can be estimated by measuring skin fold thickness (usually over the triceps) or determining mid upper arm muscle area.

Other testing

Obese patients should be screened for common comorbid disorders, such as obstructive sleep apnea, diabetes, dyslipidemia, hypertension, fatty liver, and depression. Obstructive sleep apnea is often under diagnosed, and obesity increases the risk.

Treatment

Weight loss of even 5 to 10% improves overall health, helps reduce risk of developing CV complications (eg, hypertension, dyslipidemia, insulin resistance) and helps lessen their severity, and may lessen the severity of other complications and comorbid disorders such as obstructive sleep apnea, fatty liver, infertility, and depression.

Diet

Balanced eating is important for weight loss and maintenance. Strategies include:

- Eating small meals and avoiding or carefully choosing snacks
- Substituting fresh fruits and vegetables and salads for refined carbohydrates and processed food
- Substituting water for soft drinks or juices
- Including no- or low-fat dairy products, which are part of a healthy diet and help provide an adequate amount of vitamin D.

Low-calorie, high-fiber diets that modestly restrict calories (by 600 kcal/day) and that incorporate lean protein appear to have the best long-term outcome. Foods with a low glycemic index and marine fish oils or monounsaturated fats derived from plants (eg, olive oil) reduce the risk of CV disorders and diabetes.

Diets that are overly restrictive are unlikely to be maintained or to result in long-term weight loss. Diets that limit caloric intake to < 50% of basal energy expenditure (BEE), described as very low calorie diets, can have as few as 800 kcal/day. A very low calorie diet may be indicated for obese patients; however, such diets must be supervised by a physician, and after weight is lost, intake must be increased gradually to prevent patients from regaining weight.

Physical activity

Exercise increases energy expenditure, BMR, and diet-induced thermogenesis. Exercise also seems to regulate appetite to more closely match caloric needs. Other benefits associated with physical activity include: increased insulin sensitivity, improved lipid profile, lower BP, better aerobic fitness, improved psychologic well-being, decreased risk of breast and colon cancer and increased life expectancy. Exercise, including strengthening (resistance) exercises, increases muscle mass. Because muscle tissue burns more calories at rest than does fat tissue, increasing muscle mass produces lasting increases in BMR. Exercise that is interesting and enjoyable is more likely to be sustained. A combination of aerobic and resistance exercise is better than either alone. Guidelines suggest physical activity of 150 min/wk for health benefits and 300 to 360 min/wk for weight loss and maintenance.

Behavioral interventions

Clinicians can recommend various behavioral interventions to help patients lose weight. Support from health care practitioners, peers, and family members and various structured programs can help with weight loss and weight maintenance.

Drugs

Drugs may be used if BMI is ≥ 30 or if BMI is ≥ 27 in patients who have complications (eg, hypertension, insulin resistance). Usually, drug treatment results in modest (5 to 10%) weight loss.

Orlistat inhibits intestinal lipase, decreasing fat absorption and improving blood glucose and lipids. Because orlistat is not absorbed, systemic effects are rare. Flatus, oily stools, and diarrhea are common but tend to resolve during the 2nd yr of treatment. A dose of 120 mg po tid should be taken with meals that include fat. A vitamin supplement should be taken at least 2 h before or after taking orlistat. Malabsorption and cholestasis are contraindications; irritable bowel syndrome and other GI disorders may make orlistat difficult to tolerate. Orlistat is available OTC.

Phentermine is a centrally acting appetite suppressant for short-term use (≤ 3 mo). Usual starting dose is 15 mg once/day, and dose may be increased to 30 mg once/day, 37.5 mg once/day, 15 mg bid, or 8 mg tid before meals. Common side effects include elevated BP and heart rate, insomnia, anxiety, and constipation. Phentermine should not be used in patients with preexisting CV disorders, poorly controlled hypertension, hyperthyroidism, or a history of drug abuse or addiction. Twice/day dosing may help control appetite better throughout the day.

The combination of **phentermine and topiramate** (used to treat seizures and migraines) is approved for long-term use. This combination drug results in weight loss for up to 2 yr. The starting dose of the extended-release form (phentermine 3.75 mg/topiramate 23 mg) should be increased to 7.5 mg/46 mg after 2 wk; then the dose can be gradually increased to a maximum of 15 mg/92 mg if needed to maintain weight loss. Because birth defects are a risk, the combination should be given to women of reproductive age only if they are using contraception and are tested monthly for pregnancy. Other potential adverse effects include sleep problems, cognitive impairment, and increased heart rate. Long-term CV effects are unknown, and postmarketing studies are ongoing.

Lorcaserin suppresses appetite via selective agonism of serotonin 2C (5-HT_{2c}) brain receptors. Unlike serotonergic drugs previously used for weight loss, lorcaserin selectively targets 5-HT_{2c} receptors in the hypothalamus, which, when targeted, result in hypophagia; it does not stimulate the 5-HT_{2b} receptors on heart valves. The usual and maximum dose of lorcaserin is 10 mg po q 12 h. The most common adverse effects in patients without diabetes are headache, nausea, dizziness, fatigue, dry mouth, and constipation; these effects are usually self-limited. Lorcaserin should not be used with serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or MAOIs, because serotonin syndrome is a risk.

Naltrexone/bupropion extended-release tablets can be used as a weight-loss adjunct. Naltrexone (used to aid in alcohol cessation) is an opioid antagonist and is thought to block negative feedback on satiety pathways in the brain. Bupropion (used to treat depression and aid in smoking cessation) can induce hypophagia by adrenergic and dopaminergic activity in the hypothalamus. The starting dose is a single tablet of naltrexone 8 mg/bupropion 90 mg; dose is titrated over 4 wk to the maximum dose of 2 tablets bid. The most common adverse effects include nausea, vomiting, headache, and increases in systolic and diastolic BP of 1 to 3 mm Hg. Contraindications to this drug include uncontrolled hypertension and a history of or risk factors for seizures because bupropion reduces the seizure threshold.

Liraglutide is a GLP-1 agonist used initially in the treatment of type 2 diabetes. Liraglutide augments glucose-mediated insulin release from the pancreas to induce glycemic control; liraglutide also stimulates satiety and reduces food intake. Studies have shown that liraglutide 3 mg daily results in a 12.2% weight loss after 56 wk. The initial dose is 0.6 mg once/day; the dose is increased 0.6 mg/wk to the maximum dose of 3 mg once/day. Liraglutide must be given by injection. Adverse effects include nausea and vomiting; liraglutide has warnings that include acute pancreatitis and risk of thyroid C-cell tumors.

Weight loss drugs should be **stopped** if patients do not have documented weight loss after 12 wk of treatment. Most OTC weight-loss drugs are not recommended because they have not been shown to be effective. Examples of such drugs are brindleberry, l-carnitine, chitosan, pectin, grapeseed extract, horse chestnut, chromium picolinate, fucusvesiculosus, and ginkgo biloba. Some (eg, caffeine, ephedrine, guarana, phenylpropanolamine) have adverse effects that outweigh their advantages. Also, some of these drugs are adulterated or contain harmful substances banned by the FDA (eg, ephedra, bitter orange, sibutramine).

Surgery

Bariatric surgery is the most effective treatment for extremely obese patients. It may be considered for patients with a BMI of 40 or higher or a BMI of 35 or higher with comorbid conditions, including hypertension, hyperlipidemia, and type 2 DM. This surgery is effective for helping achieve weight loss for many patients, although success following surgery also requires lifestyle changes. The procedures carry their own significant risks. Many chronic diseases and conditions improve with weight loss. However, weight loss goals set by many individuals are unrealistic and based on cosmetic rather than health benefit. Weight loss (and maintenance of that loss) of 5%10% of initial weight can have positive benefits in individuals with hypertension and type 2 DM. The American Heart Association/American College of Cardiology/The Obesity Society (AHA/ACC/TOS) guidelines state that the initial goal of weight loss is to reduce body weight by about 5%10% over 6 months. If this goal is achieved and further weight loss is indicated, it can be attempted. The first 10% loss carries the greatest health benefits and is easiest to attain, given that weight loss often plateaus after 6 months because of decreased basal metabolic rate. It is more important to maintain the 10% weight loss than to pursue further weight loss in many patients, and most patients find the weight maintenance to be harder than the initial modest weight loss.

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2) National Heart Lung and Blood Institute of the National Institutes of Health.*Overweight and Obesity*. [Internet];[cited April 15, 2019]. Available from: www.nhlbi.nih.gov/health-topics/overweight-and-obesity
3) Krinsky DL. Overweight and Obesity. In: Krinsky DL. Handbook of Nonprescription Drugs: An Interactive Approach to Self-care. 18th ed. Washington, DC: American Pharmacists Association; 2014. pp: 510-530.

Surgery with Ultrasound Treats Hypertension in Trial

A minimally invasive surgical procedure that targets nerves leading to the kidneys could one day offer a safe way for some people to reduce their blood pressure medications.

Scientists find a new way to optimize blood pressure control. Investigators have announced the 6-month results of an international clinical trial on the safety and effectiveness of renal denervation by ultrasound as a treatment for mild to moderate hypertension. The findings featured recently at the American College of Cardiology Conference in New Orleans and in a study paper in the journal Circulation.

Surgeons carry out the procedure, which takes about 1 hour, under local anesthetic. It decreases activity in nerves that link the brain to the kidneys and carry signals that regulate blood pressure.

The 2-month results from the randomized, controlled trial had already shown that the procedure resulted in a more significant reduction in blood pressure, compared with a "sham operation."

None of the people in the trial took their blood pressure drugs during the first 2 months. They then resumed blood pressure medication in a managed way, as necessary.
Now, the more recent results reveal that the participants who underwent the ultrasound surgery maintained their reduced blood pressure for 6 months.

Compared with those who had the sham operation, fewer participants who had the surgery needed to resume blood pressure medication, and those who did required fewer drugs at lower doses. These results point towards an exciting future for this new technology.

Hypertension and kidney nerves

Hypertension is a growing global health issue. According to a report in *The Lancet*, between 1975 and 2015, the number of adults living with hypertension rose from 594 million to 1.13 billion.

Having hypertension increases the risk of heart disease, heart failure, and other conditions. Some people can keep their blood pressure under control by watching their weight, doing plenty of exercise, and maintaining a healthy diet. Others may need to supplement these measures with medication. However, some people struggle to control hypertension even with lifestyle changes and medication.

The kidneys have a rich system of nerves for sending and receiving messages.
Scientists have discovered that overactivity in this system can raise blood pressure through its interaction with the body's sympathetic nervous system.

Renal denervation by ultrasound is a treatment that aims to relieve hypertension by disrupting the nerves leading to the kidneys. The procedure involves inserting a device through a catheter in the groin to reach up into the artery of a kidney. The device emits ultrasound waves that then heat up and damage some of the nerve fibers that surround the artery.

Source:Paddock C. *Surgery with ultrasound treats high blood pressure in trial* [Internet]; March 22, 2019 [cited March 25, 2019]. Available from:www.medicalnewstoday.com/articles/324779.php

Weight Loss Tea

Uses: Sugar Addiction, Cigarette Addiction
Ingredients:
1 tsp. Alfalfa leaf
1 tsp. Hawthorn Berry
1 tsp. Guggulu
1 tsp. Dandelion root
1/2 tsp Gymnema
1/2 tsp. Fennel seed

Place the herbs and 4 cups of water in a pot and bring to a boil, then turn the heat off. Allow to stand for 10 -15 minutes. Strain off the herbs and drink the beverage throughout the day, preferably with meals.

Test Your Knowledge

1) Alteplase (Activase) is an example of a tissue plasminogen activator. Which of the following describes the characteristics of this drug?

I. administered orally II) stimulates erythrocyte production III) produced by recombinant DNA technology

a) I only b) III only c) I and II only d) II and III only e) I, II, and III

2) Prolonged use of organic nitrates (eg, nitroglycerin) is likely to result in the development of:

a) hepatotoxicity b) tolerance c) aplastic anemia
d) nephrotoxicity e) pseudomembranous enterocolitis

3) What is the approximate maximum volume of fluid that should be administered daily by intravenous infusion to a stabilized patient?

a) 1 L b) 4 L c) 8 L d)12 L e) 16 L

Real Enquiries

At the "Drug Information Center", we respond to enquiries from the professional healthteam as well as from others. Here's one of the enquiries received at the center:

Enquiry received from: R. R. - *Faculty of Pharmacy,Assiut University*
Enquiry: Is metformin safe and effective for weight loss?

Summary of the answer:

Metformin is the first-line pharmacologic treatment for patients with type 2 diabetes (T2D) and can be useful in preventing or delaying diabetes in patients with prediabetes, defined as glycated hemoglobin (A1c) from 5.7% to 6.4%. Metformin is a valuable treatment for the majority of patients with T2D due its high rate of efficacy, low risk for hypoglycemia, few side effects, ease of use, and low cost.
Additionally, metformin has beneficial effects on weight loss in T2D and possibly in polycystic ovary syndrome (PCOS) and obesity without diabetes. The only approved indication for metformin is T2D; thus, most of the understanding of the effect of metformin on weight loss has been gained from research in patients with T2D.

The mechanism of action for metformin is unique compared with other antihyperglycemic agents. Metformin decreases the production of glucose in the liver, decreases the absorption of glucose in the intestine, and improves insulin sensitivity through increasing muscle glucose uptake and use.

Metformin induces weight loss most likely through a loss of adipose tissue rather than a change in energy expenditure, as is seen with exercise. Women with PCOS have a higher risk of developing diabetes compared with women of similar age and weight. Metformin has been used off label in PCOS to prevent diabetes and increase ovulation through weight loss.

In conclusion, metformin does have a modest effect on weight loss in patients with T2D, PCOS, and possibly in overweight and obese euglycemic patients. More studies, especially randomized controlled trials, are needed to determine the duration and dose of metformin and potential long-term adverse effects in patients without T2D. Patients should be advised that metformin is unlikely to cause a drastic decrease in weight, and lifestyle modifications should be recommended. Renal function and blood glucose should be monitored in patients receiving metformin.

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2. C. Seifarth, B. Schehler and H. J. Schneider. Effectiveness of Metformin on Weight Loss in Non-Diabetic Individuals with Obesity. *Exp Clin Endocrinol Diabetes*. 2013; 121: 27–31.
3. Al-qallaf S.M. Efficacy and Safety of Metformin in Weight Loss in Bahraini Population. *Journal of Applied Pharmaceutical Science*. 6(06); 2016:091-095.

Placebo and Nocebo

The term ***placebo*** is derived from the Latin for “I will please.” The term *placebo* is the name given to the sham treatment, be it pill, injection, surgery, etc., that the patient perceives as therapeutic. The placebo response is the patient's psychological and behavioral response of analgesia following the administration of the sham treatment. It has been stated that approximately one third of patients receiving a placebo will exhibit a positive placebo response. Although this number has been more recently called into question, suffice to say that the phenomenon of placebo response is frequently encountered in clinical practice and is real.

The concept of the placebo and placebo response is hundreds of years old, but the complex neurobiologic mechanisms responsible for this phenomenon remain elusive. Although there is no doubt that the patient's belief that an effective treatment has been administered and that treatment will be beneficial can produce in the patient the perception of pain relief, it must be understood that often other variables that may be responsible for the patient's placebo response are at play. These include the normal waxing and waning of the patient's perception of pain, the patient's interaction with the practitioner administering the placebo, the patient's expectancy of pain relief, and so on.

The concept of the **nocebo** response is essentially the opposite of the placebo response. With the nocebo response, the patient’s belief that the treatment administered is ineffective and will produce harm, will result in the patient perceiving that the pain is worse following the sham treatment. As with the placebo response, variables other than the administration of the sham treatment may be responsible for the patient perceiving that the pain is worse.

Source:Waldman SD. Chapter 214 - Placebo and Nocebo. In: Waldman SD, editor. Pain Review. Philadelphia: W.B. Saunders; 2009. pp. 358-9.

Answers:

1. b) Alteplase (Activase) and reteplase (Retavase) are tissue plasminogen activators prepared by recombinant DNA technology. They are administered intravenously in order to lyse thrombi in patients with acute myocardial infarction.
2. b) The development of tolerance to the action of nitroglycerin and other nitrates may occur with repeated use. Sensitivity to the action of nitroglycerin is generally restored after several hours of withdrawal from the drug.
3. b) Although the maximum volume will vary depending on the condition of the patient, the normal daily water requirement is approximately 25 to 40 mL/kg of body weight or 2000 mL per square meter of body weight. Daily volumes greater than 3 to 4 L in normal (non dehydrated) patients may cause a fluid overload. A dehydrated patient will require larger quantities. Water replacement therapy (hydration therapy) in an adult may be 70 mL/kg. Thus, a 50-kg patient will need 3500 mL (replacement) plus 2400 mL (maintenance).