МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА ЭНДОКРИНОЛОГИИ

ОЖИРЕНИЕ: ОПРЕДЕЛЕНИЕ, ПРОФИЛАКТИКА, ТЕРАПЕВТИЧЕСКИЕ ПОДХОДЫ

OBESITY: DEFINITIONS, PREVENTION, TREATMENT APPROACHES

Учебно-методическое пособие

Минск БГМУ 2025

УДК 616-056.257-084-085(075.8)
ББК 54.15я73
О-45

Рекомендовано Научно-методическим советом университета в качестве учебно-методического пособия 16.01.2025 г., протокол № 5

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Ожирение: определение, профилактика, терапевтические подхо-
О-45 ды = Obesity: definitions, prevention, treatment approaches : учебно-методическое пособие / Ю. В. Дыдышко, Т. В. Мохорт, А. П. Шепелькевич [и др.]. – Минск : БГМУ, 2025. – 47 с.

ISBN 978-985-21-1835-4.

Отражены современные аспекты диагностики и профилактики ожирения, освещены современные терапевтические подходы к коррекции заболевания.

Предназначено для студентов 5–6-го курсов медицинского факультета иностранных учащихся, обучающихся на английском языке.

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ISBN 978-985-21-1835-4

LIST OF ABBREVIATIONS

ACTH — adrenocorticotropic hormone
ADA — American Diabetes Association
ADHD — attention-deficit/hyperactivity disorder
AgRP — agouti-related protein
BAT — brown adipose tissue
BDNF — brain-derived neurotrophic factor
BMI — body mass index
CCK — cholecystokinin
CT — computed tomography
CVD — cardiovascular disease
DASH — Dietary Approaches to Stop Hypertension
DCCT — Diabetes Control and Complications Trial
DXA — dual-energy x-ray absorptiometry
DNP — dinitrophenol
GIP — glucose-dependent insulinotropic polypeptide
GLP1 — glucagon-like peptide 1
IL6 — interleukin 6
FDA — Food and Drug Administration
FTO — fat mass and obesity-associated
HCG — human chorionic gonadotropin
MCH — melanin-concentrating hormone
MRI — magnetic resonance imaging
NAFLD — nonalcoholic fatty liver disease
NPY — neuropeptide Y
POMC — pro-opiomelanocortin
TNFα — tumor necrosis factor α
WHO — World Health Organization
αMSH — α-melanocyte-stimulating hormone

MOTIVATIONAL CHARACTERISTIC OF THE TOPIC

Lesson topic: Diabetes mellitus and Obesity.
Total class time: 7 h.

Obesity is a chronic disease characterized by increased energy storage as adipose tissue. The resulting adiposopathy becomes a clinically important risk factor for multiple serious medical problems and early mortality. Obesity is also associated with impaired quality of life and considerable economic and social burden due to increased health care costs, loss of productivity, and life-years lost.

The purpose is intended to provide clinicians, researchers and other interested individuals with the components of obesity, general treatment goals, and tools to evaluate the quality of care.

Objectives:

1. To acquire a general idea of the pathogenetic features of obesity, be able to differentiate various types of the disease.
2. To study the classification of obesity.
3. To study diagnostic tests for obesity.
4. To study the main directions of obesity prevention, taking into account lifestyle modification and pharmacological options.
5. Consider the main therapeutic approaches to normalize body weight.

Requirements to the initial level of knowledge. To learn the topic completely student should know:

– main mechanisms regulating body weight;
– body fat distribution patterns.

Test questions from related disciplines:

1. Anatomy and topography of fat distribution patterns.
2. Physiological role of adipocyte.

Test questions:

1. Definition of the concept of obesity, main clinical manifestations, mechanisms of development.
2. Classification of obesity and differential diagnosis of types.
3. Obesity, diagnosis, risk factors for development.
4. The main approaches to the prevention obesity — modification of the image of fat, behavioral programs, nutrition, physical activity.
5. Possibilities of pharmacological treatment of obesity.

DEFINITION OF CONCEPT OBESITY

Obesity is not a new phenomenon. Figurines from the Paleolithic period depict female bodies with obesity dating back 38,000 years ago. Research suggests these figurines symbolize the advantageous metabolic adaptations to the extreme cold climate present during that period. Obesity was also described by Hippocrates, who made observations on the importance of diet in individuals with excess weight, also noting that the Scythians had obesity because they were sedentary.

In the second century of the common era, Galen described obesity as an illness for which he prescribed diet and exercise and used the term polysarkia to refer to extreme obesity. Even though obesity was documented to exist in earlier eras, the prevalence of obesity affecting a significant percentage of the population began its rising trajectory in the 1960s, corresponding to the advent of the industrialization

of processed foods contributing to the diet in the United States, touted as one of the main factors, if not the main factor, in the rise of obesity from 1960–2022. Until the past 2 decades, rates of obesity were higher in the United States than in other countries. Recently, other nations have caught up with industrialized lifestyles, particularly concerning dietary options consisting of highly processed and calorie-dense foods, to the point where currently more of the world's population is affected by deaths related to obesity than to being underweight.

Considering that the genetics of humans have not changed substantially during the time in which the dramatic rise in rates of obesity has occurred, the increase in obesity prevalence most likely has resulted from a complex interplay of genes and environment.

Mammals have evolved to acquire and store energy as fat to withstand times of food insecurity. Until the modern era, food scarcity had been a more substantial threat to existence than excess calories. A pound of fat containing 3500 calories may provide 2 to 4 days of survival for an individual without any food supply. In a calorie-restricted environment, 50 pounds of extra fat would make a substantial survival difference. Lean persons will die after only approximately 60 days of starvation when more than 35 % of body weight is lost. Persons with the disease of obesity can tolerate longer fasts, even for more than 1 year, without significant adverse effects.

Assuming genetic traits and inherent physiologic drives that favor eating and storing excess calories date back to antiquity, the modern obesity epidemic is more likely explained by changes in the food environment. As a consequence of modern agriculture and ease of transportation of food to the consumer, food is cheaper, more readily available, and more varied than ever before. Alternative explanations for obesity have also been proposed. For example, one posits that mammals can risk excess body weight when not subject to predation and that food uncertainty has not influenced the rise in obesity rates.

BRIEF HISTORY OF INEFFECTIVE OBESITY INTERVENTIONS

A diet limiting total caloric intake and increased exercise have been the cornerstones of obesity treatment since Hippocrates 2500 years ago. Various obesity treatments before the industrial revolution included cleansing with vinegar, cathartics, and laxatives, as well as purging. In more modern times, methods of increasing thermogenesis with thyroid hormone extracts were used beginning in the late 1800s. Some clinicians used dinitrophenol (DNP) to induce thermogenesis by uncoupling oxidative phosphorylation in the early 1900s. DNP was sold in capsules until the U.S. Food and Drug Administration (FDA) moved to ban it as dangerous in 1938. DNP had a brief comeback in the early 1980s and is still marketed through

the internet as an over-the-counter fat burner, mainly to the bodybuilding industry. Amphetamines as sympathomimetic agents were used for weight loss between 1932 and 1968 before it became a strictly regulated prescription drug for the management of attention-deficit/hyperactivity disorder (ADHD).

Human chorionic gonadotropin (HCG) was used from 1961 until recently to reduce food intake, but has been found to be ineffective compared with placebo. Fenfluramine/phentermine (fen/phen) was a popular combination agent in the 1990s, combining serotonin receptor activation of the 5-hydroxytryptamine-2c (5HT2c) receptor by fenfluramine with the epinephrine reuptake inhibitor phentermine, until it was found to be associated with cardiac valvulopathy and pulmonary hypertension from the fenfluramine component. Phentermine remains on the market today for short-term weight loss.

Phenylpropanolamine as a sympathomimetic agent was used in the late 1990s but was withdrawn from the market due to precipitation of stroke. Sibutramine was approved for obesity treatment by the FDA and withdrawn due to cardiovascular toxicity reported during a long-term cardiovascular outcomes trial.

Throughout the latter half of the 20th century until today, researchers have learned a great deal regarding appetite suppression and obesity treatment from the success of bariatric surgery for the treatment of extreme obesity. Initially assumed to work solely due to restriction of gastric contents and malabsorption of nutrients, it is now understood that bariatric surgery's mechanism of action (MOA) is driven by appetite suppression via alteration of the gut hormone milieu. Advances in bariatric surgery research have informed today's era of obesity treatment by illuminating the gut hormones that, among other functions, govern pathways to the arcuate nucleus leading to appetite and satiety.

Hence the antiobesity agents currently in use include agents that mimic GLP1, amylin, GIP, and, in the near future, glucagon, PYY, and oxyntomodulin, peptides that are dynamically involved in satiety after eating a meal.

DEFINITION OF OBESITY

Obesity is defined as an unhealthy excess in adiposity. Currently available strategies to quantify total body fat and determine its distribution, such as underwater weighing, dual-energy x-ray absorptiometry (DEXA) scanning, computed tomography (CT), and magnetic resonance imaging (MRI), are not practical methods for daily clinical use.

The current practical definition of obesity is determined by calculating body mass index (BMI) by dividing an individual's weight in kilograms by the square of height in meters

$$\text{BMI} = \text{weight (kg)} / \text{height (m}^2\text{)}.$$

Underweight, normal weight, overweight, and obesity are defined based on increased mortality risk and comorbidities predisposition. Table 1 summarize the classification of weight status by BMI proposed by the major national and international health organizations.

Table 1

Weight classification by BMI

Weight Classification	Obesity Class	BMI (kg/m²)		Risk of Obesity-related Diseases
		Europeans	Asians	
Underweight		< 18.5	< 17.5	Increased
Normal weight		18.5–24.9	17.5–22.9	Normal
Overweight		25.0–29.9	23.0–27.4	Increased
Obesity	I	30.0–34.9	27.5–32.4	High
	II	35.0–39.9	32.5–37.5	Very high
Extreme obesity	III	≥ 40.0	≥ 37.5	Extremely high

However, BMI is an imperfect index of adiposity. BMI calculations fail to factor in muscle mass. BMI calculations also do not differentiate body fat distribution, with increased metabolic disease risk imparted from intraabdominal, visceral fat than from subcutaneous fat. Therefore, two individuals with the same BMI may have entirely different body compositions if one has more muscle mass or subcutaneous fat than the other and, thus, lower metabolic risk.

Obesity is a heterogeneous disease regarding the onset and natural history. Some individuals develop the disease early on in life, whereas others gain weight later. Common clinical scenarios include weight gain during the peripubertal phase, during or after pregnancy, after illness, secondary to medications, stress, change of environment, and after menopause. Some individuals classified as having obesity may have significant metabolic disease irrespective of BMI, whereas others may be metabolically healthy even with high levels of adiposity.

The relationship between BMI and comorbidity is depicted in Fig. 1.

There is a U-shaped correlation between BMI and mortality demonstrated in several population-based cohort studies. Lower BMI is strongly associated with mortality from various causes, such as cancer; cardiovascular, respiratory, blood, endocrine, digestive, musculoskeletal, and urogenital conditions; and mental, behavioral, neurologic, and accidental causes of death. In fact, mental health conditions showed the strongest inverse associations with low BMI, which was also influenced by age and gender. In those with higher BMI, adiposopathy increases the risk for diabetes, cardiovascular disease, liver disease, cancer, sleep apnea, arthritis, and other diseases. The precise magnitude of excess weight associated with increased mortality risk remains somewhat unclear and likely depends on multiple factors.

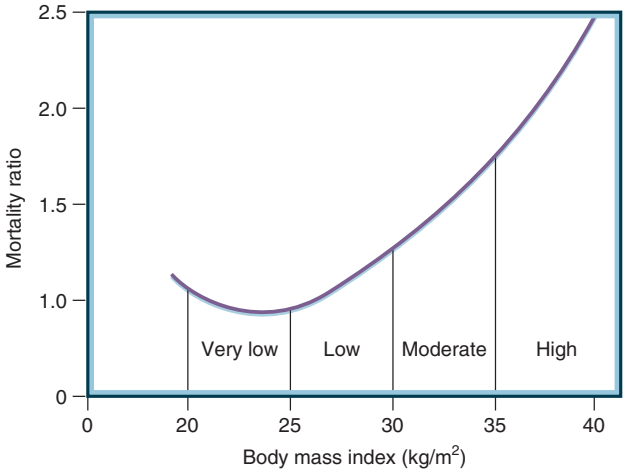


Fig. 1. Relative risk for morbidity and mortality in obese European populations

Body Fat Distribution. The relationship between BMI and health risk is not absolute but is influenced by body fat distribution, age, concomitant medical illness, weight gain, aerobic fitness, and ethnicity.

Excess body fat is not distributed equally in all people. Some people develop excess visceral obesity and are at higher risk of comorbidities than those with excess subcutaneous fat. Waist circumference correlates with abdominal fat mass and is a surrogate marker for visceral obesity and thus is a predictor of health outcomes in adult men and women regardless of age or ethnicity.

The relationship between waist circumference and comorbidities is strongest for the risk of type 2 diabetes, and waist circumference is an independent and better predictor of type 2 diabetes separate than the risk attributed to BMI. Waist circumference thresholds for increased cardiometabolic risk are 40 inches (102 cm) in White men and 35 inches (88 cm) in women; these cutoff values are derived from waist circumference values that correlate with a BMI of 30 kg/m² or greater, based on populations of European origin.

The BMI-associated health risk is influenced by ethnicity.

Asian/Pacific Islander populations have a greater risk for the development of type 2 diabetes and cardiovascular disease at lower BMI ranges than other populations. Accordingly, the World Health Organization proposed lower BMI cutoffs in these populations for public health action (see Table 1). Asian populations also tend to have more visceral obesity at lower BMI than other ethnic groups. Furthermore, at any given waist circumference, the relative mortality risk is higher for that individual.

World Health Organization guidelines define waist circumference thresholds in the Asian population as 35.4 inches (90 cm) for men and 31.5 inches (80 cm) for women. Different levels have been suggested in Japan and China, with cutoff values of 33.5 inches (85 cm) for men and 31.5 inches (80 cm) for women, and slightly lower values have been suggested in India. Black individuals also appear to have increased disease risk at lower BMI than individuals of European descent. For example, the equivalent risk BMI for diabetes is 30 kg/m² in Caucasian women and 26 kg/m² in Black women. There is also a significant sex difference in comorbid disease risk, with men having higher risk than women across the range of ethnicities.

The risk of developing obesity-associated diabetes or cardiovascular disease can be modified by aerobic capacity. The incidences of type 2 diabetes and cardiovascular fatality are lower in those who are physically fit, as defined by maximal ability to consume oxygen during exercise, compared with those who are unfit across a range of body adiposity. For example, in a population of middle-age men, low aerobic capacity was associated with increased mortality rates, independent of traditional risk factors, including smoking, blood pressure, and serum cholesterol, during more than 40 years of follow-up.

PHYSIOLOGY OF BODY ENERGY HOMEOSTASIS

Energy homeostasis, defined as the balance between energy intake and energy expenditure, is regulated by complex molecular and physiologic processes. Control of energy homeostasis requires physiologic integration of biologic signals from organs, such as the liver and brain, and from fat, muscle, and gut; nutrient-related signals; and postprandial neural and hormonal influences.

Regulation of energy intake is complicated because it includes both homeostatic and hedonic drivers of food intake. Homeostatic feeding is the component responding to signals aimed at maintaining weight, such as hunger occurring with long intermeal intervals, whereas hedonic feeding is defined as excess eating in the satiated state based on availability of highly palatable food orsocial cues that encourage eating. Eating can also be influenced by emotional moods including stress or depression, which lead to overconsumption of energy in some individuals, while decreasing food consumption in others.

Homeostatic Regulation of Energy Intake — Role of the Central Nervous System. The hypothalamus is essential for integrating complex signals that govern food ingestion. Pro-orexigenic neurons in the arcuate nucleus, which express neuropeptide Y (NPY) and agouti-related protein (AgRP), and appetite-inhibiting neurons, which express the pro-opiomelanocortin (POMC) gene and

process its product to α-melanocyte-stimulating hormone (αMSH), are two well-studied hypothalamic networks that inversely regulate appetite and thereby energy storage (Fig. 2).

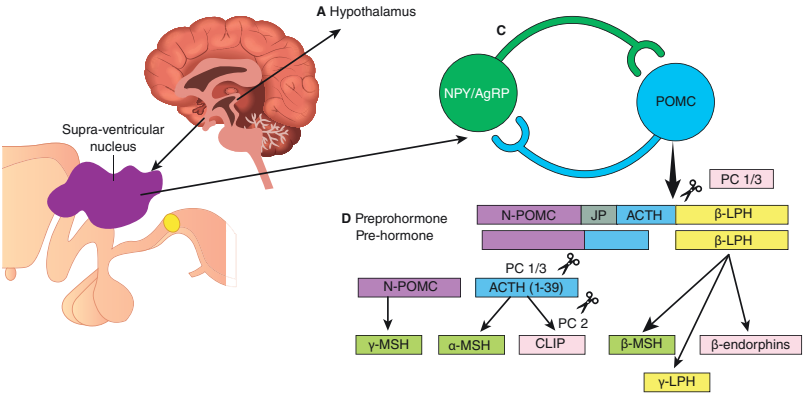


Fig. 2. Role of the central nervous system in homeostatic regulation of energy intake

Administration of both NPY and AgRP peptides into rodent brains markedly increased food intake, even in satiated rats. Direct stimulation of these neurons also induces feeding. However, eliminating expression of NPY, AgRP, or both peptides in transgenic mice is associated with at best minimal feeding phenotypes. Full ablation of the neuronal population is required to observe decreased feeding, suggesting that the neurotransmitter expressed by theses neurons, γ-aminobutyric acid, is more important than either peptide in regulating appetite. POMC neurons, a discreet population localized to the arcuate nucleus, play a role in inhibiting eating. The precursor protein POMC is processed to αMSH, which suppresses feeding. Elimination of POMC expression leads to obesity in both rodents and humans.

Furthermore, a downstream receptor for αMSH in the brain, the melanocortin 4 receptor (MC4R), is critical for maintaining energy balance. MC4R is regulated by both αMSH and agouti, and the output of *MC4R* neurons in the paraventricular nucleus and other locations represents a balance of AgRP and MSH signaling. The finding that *MC4R* deletion in mice and mutations of MC4R in humans are associated with obesity confirms the central role of these neurons in energy balance. Indeed, in humans, *MC4R* mutations are the most common cause of monogenic obesity. The prevalence of *MC4R* mutations has been estimated at 0.5 % and 1 % in adults with obesity, with higher prevalences among individuals with severe childhood-onset obesity and variability between ethnic groups.

Other areas in the hypothalamus contribute to feeding and weight. For example, the lateral hypothalamus contains populations of neurons expressing the neuropeptide melanin-concentrating hormone (MCH), and a distinct population expresses orexin. In rodents, MCH administration into the brain leads to an acute, robust increase in feeding, whereas genetic deletion of the neuropeptide leads to leanness

MCH antagonists inhibit feeding in several species; however, they are frequently associated with undesirable side effects such as insomnia, hypersexuality, aggression, and hypertension, complicating the development of effective therapeutic interventions targeting MCH.

MCH neurons receive inputs from the arcuate nucleus, and MCH appears to be important in the action of leptin. However, human biology is complicated by the presence of two receptors (MCH-R1 and MCH-R2) in higher mammals. Orexin is another lateral hypothalamic peptide implicated in stimulating feeding behavior. Still, its role in generalized arousal is more critical to its physiologic function, as rodents, dogs, and humans without orexin have narcolepsy. The endocannabinoid system is also involved in the regulation of food intake, particularly the cannabinoid 1 (CB1) receptors (encoded by *CNR1*) and their endogenous ligands, anandamide (*N*-arachidonoyl-ethanolamine) and 2-arachidonoylglycerol.

The absence of CB1 receptors in mice with a disrupted CB1 gene causes hypophagia and leanness. Administration of cannabinoids increases food intake and promotes body-weight gain, and treatment with selective CB1 receptor antagonists decreases food intake and body weight in obese mice. Although randomized controlled trials in obese individuals with a CB1 receptor antagonist found decreased body weight, administration of the antagonist was associated with depression and anhedonia, which complicated attempts to target the system for weight loss.

Homeostatic Regulation of Energy Intake — Role of the Peripheral Signals. Multiple peripheral signals regulate energy homeostasis. Leptin, the product of the ob gene, is critically important for weight maintenance. Leptin absence, resulting from gene mutations, is associated with absent appetite control resulting in morbid obesity in mice, rats, and humans. Although leptin is necessary for weight maintenance, it is not sufficient. As rodents develop obesity, adipose tissue synthesizes increased leptin, causing a rise in leptin levels in the circulation. However, these increased levels fail to decrease food intake. Likewise, most people with increased adiposity have high circulating leptin concentrations. Therefore, it is concluded that obesity is often associated with resistance to the action of leptin.

Most non-adipose tissue-related peripheral signals that influence energy balance are derived from the gut (Fig. 3).

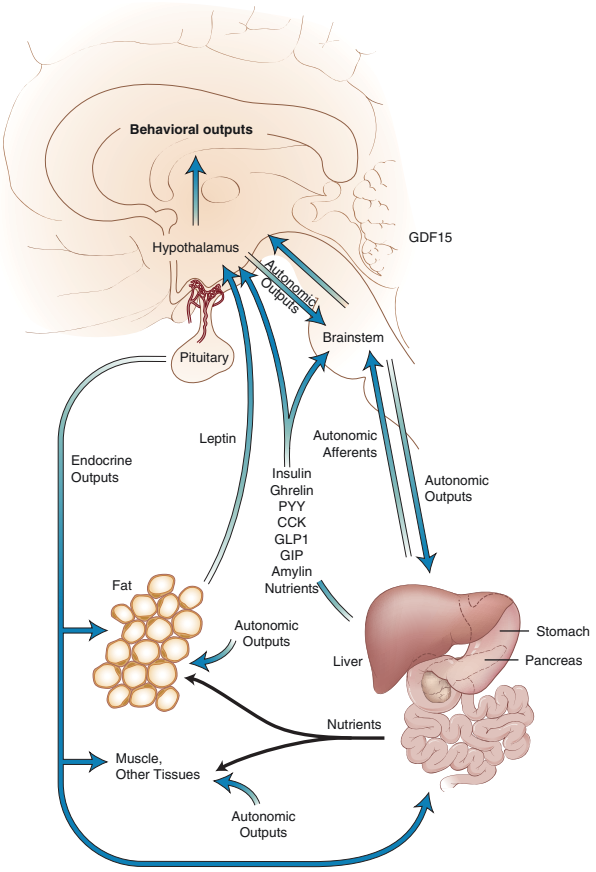


Fig. 3. Multiple peripheral signals and hormones regulate body weight

Ghrelin is a potent orexigenic hormone derived from the stomach that increases before meals and decreases after feeding. Acutely administered ghrelin causes animals and humans to consume larger than usual meals, and chronic ghrelin administration results in obesity in rodents. Several other gut peptides, or incretin hormones secreted by enteroendocrine cells, suppress appetite.

Of these, glucagon-like peptide 1 (GLP1), derived from preproglucagon, is secreted by the L cells of the intestine that also secrete peptide YY (PYY). GLP1 and PYY are co-secreted after a meal and induce satiety. GLP1, when infused directly into the rat ventricle, opposes the actions of orexigenic peptides including MCH and NPY. Glucose-dependent insulinotropic polypeptide (GIP), formerly

gastric inhibitory polypeptide, is secreted from K cells in the duodenum and proximal jejunum in response to food intake. The incretin effect of GIP is mainly to enhance glucose-dependent insulin release from pancreatic β-cells and thereby promote postprandial plasma glucose lowering. The role of GIP on central appetite regulation is not straightforward, and research has suggested that GIP receptor ligands poorly influence food intake on their own.

In contrast, when combined with GLP1-receptor agonists in a single peptide, appetite suppression and weight loss are enhanced, as seen with tirzepatide. The exact mechanism of appetite suppression resulting from dual GIP and GLP1-receptor agonism remains under debate, with studies pointing to the role of GIP in adipocyte metabolism and its effect on enhancing glucagon secretion.

Furthermore, some studies suggest that GIP receptor antagonism rather than agonism is responsible for central appetite suppression, adding to the controversy surrounding the physiologic role GIP plays in energy homeostasis.

Cholecystokinin (CCK), another gut peptide secreted from the L cells, stimulates bile release from the gallbladder after a meal, secretion of pancreatic enzymes, and a transitory sensation of satiety, which usually is compensated for by increased food frequency in rodents. The effects of CCK are mediated by stimulation of CCK-A receptors located on vagal afferents of the stomach and the liver, which stimulate satiety centers in the brainstem, eliciting a brief reduction in food intake.

Growth differentiation factor 15 (GDF15) is secreted by many tissues in response to stress such as infection, cancer, pregnancy, and cardiovascular events. It acts via the brainstem glial cell-derived neurotrophic factor (GDNF) family receptor alpha-like (GFRAL) receptor to modulate nutrient intake and has been associated with anorexia, cancer cachexia, and hyperemesis gravidarum. Transgenic mice with GDF15 that are overexpressed are leaner and protected from diet-induced obesity. Furthermore, the injection of GDF15 causes hypophagia and weight loss in rodents.

Genome-wide association studies link GDF15 and GFRAL variants to obesity traits, such as BMI and waist circumference. These findings have prompted drug development for GDF15 as a potential intervention for weight loss. Peptide YY (PYY), another hormone secreted from the L cells of the intestines, belongs to the pancreatic polypeptide family (including pancreatic polypeptide [PP] and NPY) and is also suggested to be a peripheral satiety signal.

There are two isoforms of circulating PYY, PYY1-36 and PYY3-36; the latter is the main isoform in the blood-brain barrier that binds to the Y2 isoform of the NPY receptor (NPY2R). NPY2R agonism results in anorexia and food aversion in rodents.

Amylin is a B-cell hormone co-secreted with insulin. It slows gastric emptying and thereby reduces meal size. Centrally, it stimulates hindbrain neurons to induce

anorexia and restores leptin sensitivity in the hypothalamus in rodents. A long-acting amylin analogue combined with the GLP1-receptor agonist semaglutide is currently in clinical trials for the treatment of obesity.

ENERGY EXPENDITURE

Energy expenditure is a critical component of weight homeostasis. Several factors contribute to total daily energy expenditure (Fig. 4).

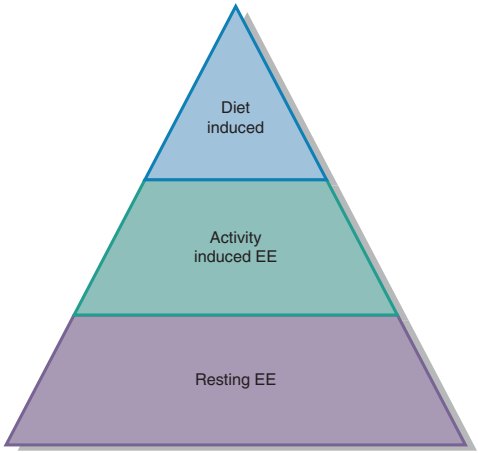


Fig. 4. The resting energy expenditure accounts for 70 % of total energy expenditure, also called the basal metabolic rate

The most significant component is basal or resting energy expenditure, defined as the energy required in the basal state for normal cellular and organ function; it has also been termed basal metabolic rate. Resting energy expenditure accounts for approximately 70 % of total energy expenditure. A second significant contributor is the energy expended by physical activity, representing a smaller contribution of about 20 % of the daily total. Voluntary activities such as exercise and involuntary activities important in maintaining posture and fidgeting contribute to this component of total energy expenditure. Digestion of ingested nutrients also contributes to energy expenditure. It is termed the thermic effect of food, accounting for about 10 % of the daily total and representing the energy expended in chewing, digestion, absorption, and sympathetic nervous system activation after a meal.

Resting energy expenditure is regulated by several mechanisms, mainly mediated by thyroid hormone. An excess of thyroid hormone, as seen in

thyrotoxicosis, leads to increased resting energy expenditure that in many individuals will lead to significant weight loss unless they experience compensatory hyperphagia. Indeed, weight loss can be a presenting symptom of hyperthyroidism.

In contrast to the apparent effects of thyroid hormone to regulate resting energy expenditure, the role of the sympathetic nervous system is less clear. Epinephrine and norepinephrine are critical regulators of metabolism across multiple organs, activating what is commonly referred to as the fight-or-flight response, but a precise role in regulating resting energy expenditure remains difficult to define. Sympathetic activity increases after meals and contributes to the thermic effect of food. In addition, patients with tumors secreting epinephrine and norepinephrine (pheochromocytoma) manifest downstream effects of increased sympathetic activity, such as tachycardia and hypertension, but rarely present with weight loss.

Although it is possible that individuals prone to obesity have lower sympathetic activity and therefore resting energy expenditure than those who maintain lower body weights, the role of sympathetic activity in energy homeostasis in humans is uncertain.

The effects of resting energy expenditure on weight gain also remain unclear. In a longitudinal study of 92 Pima Indians, the highest cumulative incidence of a 22-pound (10-kg) weight gain after 1 to 4 years was seen in those in the lowest tertile of resting energy expenditure at baseline. In contrast, no relationship between initial resting energy expenditure and weight change was found in the Baltimore Longitudinal Study on Aging, which followed 775 men for 10 years. However, currently available research technology is unable to detect small but chronic reductions in energy metabolism that may be clinically important over time. In addition, it is difficult to establish a causal relationship between energy expenditure and the development of obesity because energy metabolism measurements capture only a brief point in time and therefore may not reveal abnormalities that emerge during specific life stages. Genetic or environmental differences may also affect the relationship between resting energy expenditure and weight change.

The two other components of energy expenditure — voluntary activity (exercise) and nonexercise activities — contribute to obesity. Increased food consumption is required for energy homeostasis in the setting of increased voluntary activity, as seen in athletes, people with regular exercise, or physically demanding jobs. When these activities end, the resulting weight gain can be substantial.

Likewise, nonexercise activity thermogenesis, such as fidgeting, may contribute to weight maintenance, as individuals with higher nonexercise activity thermogenesis tend to have some resistance to weight gain.

Body Weight Set-Point. Many individuals will maintain a constant weight over years and even decades, supporting the theory that there is a set-point regulating food intake and energy expenditure so that weight stays constant. The set-point

theory is that a complex set of physiologic adaptations maintains body weight. According to the setpoint theory, body weight is predetermined such that weight loss promotes a decrease while weight gain promotes an increase in metabolic rate that acts to restore body weight to a preset level.

The effectiveness of the set-point has been called into question because many individuals will gain weight over time. Hypocaloric feeding reduces energy expenditure by an average of 8 kcal/kg of lean body mass in obese individuals but only 6 kcal/kg of lean body mass in normal-weight individuals, amounting to a 15 % to 20 % daily decrease.

This reduction cannot be completely accounted for by the accompanying decrease in body size, or lean or adipose body mass, and is considered a normal part of the physiologic adaptation to energy restriction. The decrease in energy metabolism with weight loss is largely appropriate for concomitant changes in body composition, and a persistent decrease might promote weight regain. However, the reduction in resting energy expenditure that occurs during negative energy balance is transient and does not persist during the maintenance of a lower body weight. Long-term maintenance of weight loss is not associated with an abnormal decrease in either resting or total energy expenditure when adjustments are made for changes in body composition, although this remains controversial.

When energy intake exceeds energy expenditure, weight gain occurs, but the amount of weight gained varies among individuals. Genetic factors can influence the amount of weight gained with overfeeding. Data from a study that fed monozygotic twins an extra 1000 kcal/day for 84 days found considerable variability in weight gained among different twin pairs but that members of each twin pair gained similar amounts of weight while overfed and then lost similar amounts during the postoverfeeding recovery period. The amount of weight gained may also reflect the extent of the increase in energy expenditure that is a consequence of overfeeding.

In another study, an increase in body fat after 8 weeks of overfeeding was inversely related to changes in nonvolitional energy expenditure (e.g., fidgeting), aspects of which may be regulated.

PATHOGENESIS OF OBESITY: GENES AND ENVIRONMENT

It is challenging to identify causal factors of obesity because there are few monogenetic forms of obesity, and many single nucleotide polymorphisms (SNPs) associated with excess weight are in noncoding regions of the genome. In addition, there are substantial social and environmental determinants of weight. Food environments are complex and include not just food availability but food cost, cultural perspectives of weight, and an individual's social network.

Environmental Effects in High-Risk Populations. A striking example of the effects of modern diet on obesity is seen in Pima Indians living in Arizona. A combination of diet and lifestyle changes starting in the 1950s resulted in an epidemic of both obesity and diabetes. The modern diet is much higher in fat (50 % of energy as fat) than the traditional Pima diet (15 % of energy as fat). In addition, Pima Indians who became urbanized were more sedentary, especially when compared with the Pima Indian population still living in the Sierra Madre Mountains of northern Mexico. These rural Pima Indians eat a traditional diet and are physically active as farmers and sawmill workers; they have a much lower incidence of obesity and diabetes than their Arizona kindred. Likewise, Aborigines of northern Australia are another high-risk population whose weight and health status has been compromised by exposure to a modern environment.

Urbanized Aborigines are heavier than and have a high prevalence of type 2 diabetes compared with rural kindred, who are usually very lean (BMI < 20 kg/m^2). The traditional Aboriginal diet included a low-fat, low-calorie diet of wild game, fish, and plants, as well as a high level of physical activity. Short-term (7 weeks) reexposure to the traditional lifestyle can result in weight loss and significant improvements or normalization of glucose tolerance and fasting glucose, insulin, and triglyceride concentrations in urbanized Aborigines with type 2 diabetes and hypertriglyceridemia.

Genetics and Obesity. *Monogenic Causes of Obesity.* Only a small percentage of people affected by obesity have an identified single gene mutation contributing to the disease. The most commonly identified mutation associated with obesity involves MC4R, expressed in the central nervous system in neurons downstream of those emanating in the arcuate nucleus. The effect of αMSH released from the arcuate nucleus on MC4R inhibits appetite, so a functional MC4R is essential to maintain normal body weight. Frameshift mutations in MC4R in individuals with childhood obesity, reported by multiple groups, may account for about 5 % of early-onset obesity. These are usually heterozygous, and a gene dosage effect is seen; individuals homozygous for the same mutation or double heterozygotes for different mutations will have more severe obesity. The range of mutations is very diverse. Individuals with MC4R mutations will respond to bariatric surgery, although the magnitude of response may vary depending on the specific mutation.

Other, much less common, mutations in the melanocortin signaling pathway involve those in the POMC gene, which leads to loss of all of the product peptides including adrenocorticotropic hormone (ACTH) and αMSH. The presentation of patients with POMC mutations is typically secondary to adrenal insufficiency from low levels of ACTH, usually observed in early life, and they tend to have red hair and pale skin from reduced melanocyte pigment production attributable to decreased αMSH production.

Although leptin is critical for the normal maintenance of energy balance, very few leptin-deficient humans have been identified, and leptin mutations are extremely rare. The first humans with a leptin mutation, which resulted in a protein that was not secreted, were identified in a pair of consanguineous cousins. Shortly thereafter, three members in a family with obesity were reported with leptin receptor mutations. There is remarkable consistency in the phenotype of mice and humans with an absolute deficiency in leptin signaling, whether as a result of absent leptin or a mutation in the leptin receptor. Both mice and humans demonstrate massive early-onset obesity, hyperphagia, exaggerated food-seeking behavior, and infertility. Normal pubertal development does not occur in the absence of leptin. The handful of individuals with leptin deficiency can be treated with exogenous leptin, which normalizes weight and food intake, permits puberty, and reestablishes insulin sensitivity. As would be expected, leptin is of no use in individuals with leptin receptor deficiency. Leptin is also not effective in most common forms of obesity, which, as previously noted, is a state of leptin resistance.

Prohormone Convertase 1 Gene Mutation. Prohormone convertase 1 (also known as proprotein convertase subtilisin/kexin type 1 [PCSK1]) cleaves POMC and is involved in the processing of peptides in enteroendocrine cells in the gut. A few individuals with mutations in PCSK1 and obesity have been identified. Although the initial report involved a mutation in PCSK1 in an adult obese woman with a history of severe childhood obesity, a significant number of individuals with this mutation present with diarrhea and failure to thrive. In some individuals, this then evolves into obesity, although the mechanisms promoting the transition remain poorly understood.

Mutation of the Neurotrophin Receptor TrkB. The neurotrophin brain-derived neurotrophic factor (BDNF) acts through a receptor kinase, TrkB, to potentiate synaptic transmission. Heterozygous deletion of BDNF in mice leads to a syndrome of hyperphagia obesity and aggression. In humans, mutations in this system are very rare but include a report of a chromosomal deletion encompassing the BDNF gene in a mother and child pair.

At least one case of a mutation in the TrkB signaling pathway associated with developmental delays and obesity has been reported in an 8-year-old boy. The mutation was associated with impaired receptor autophosphorylation.

Single-Minded Homolog 1 (SIM1) Gene Mutation. A de novo balanced translocation between chromosomes 1 and 6 was found in a severely obese girl who weighed 104 pounds (47 kg) at 5½ years of age. The mutation caused a disruption in SIM1, the human homolog of the Drosophila single-minded (sim) gene that regulates neurogenesis. SIM1 encodes a transcription factor involved in the formation of the paraventricular and supraoptic nuclei. It is likely that this mutation altered energy balance in this patient by stimulating food intake, because measured resting energy expenditure was normal. In addition, several

chromosomal deletions involving 6q14-q21, a region that includes SIM1, have been identified in obese patients presenting with developmental delay and a Prader Willi-like syndrome, although the specific role of SIM1 haploinsufficiency has not been definitively established.

Src Homology 2B 1 (SH2B1) Deficiency. Src homology 2B adapter protein (SH2B1) interacts with several receptors to modulate the signaling of ligands including leptin, insulin, and growth hormone. In mice, deletion of this gene results in obesity and insulin resistance when mice are exposed to a high-fat diet. In humans, this deletion is associated with a range of abnormalities including early-onset obesity and hyperphagia.

Consistent with a role in insulin signaling, problems with insulin sensitivity appear disproportionate to the severity of obesity. Behavioral abnormalities have also been reported. Interestingly, the result of deletions that include the SH2B1 gene at the chromosomal 16p11.2 site may be pleiotropic and not include obesity.

Obesity Syndromes. *Prader-Willi Syndrome.* Prader-Willi syndrome was initially described more than 60 years ago as an association of morbidobesity, short stature, hypogonadism, and cognitive deficiency. Prader-Willi results from a chromosomal abnormality in which the paternal segment of chromosome 15q11.2-q12 is either deleted or absent. Interestingly, maternal deletion of the same segment is associated with a distinct phenotype known as Angelman syndrome, which is an autistic spectrum disorder. Prader-Willi has a prevalence of 1 in 15,000 to 30,000 births. The molecular etiology has been linked to a deletion in the melanoma antigen gene (MAGE) family member L2 (MAGEL2), a regulator of ubiquitin kinase.

Bardet-Biedl Syndrome. Bardet-Biedl syndrome is rare, with a prevalence of less than 1 in 100,000, mostly seen in consanguineous populations. The disorder is clinically heterogeneous and includes obesity, hypogonadism, and abnormalities that include dysmorphic extremities, renal impairments, and retinopathies. Severe vision loss is not uncommon. Bardet-Biedl syndrome maps to multiple genes that lead to abnormal ciliary function; how these cause obesity remains unknown.

Polygenic Causes of Obesity. Obesity results from a complex interaction of genetic predisposition and a nutrient-rich environment. More than 100 polymorphisms have been identified as potentially contributing to the predisposition to obesity. However, most of these loci individually make only small weight contributions to obesity. Among hundreds of genes, the best association is with FTO (the fat mass and obesity-associated gene).

FTO was originally identified as a gene playing a role in programmed cell death. In 2007, three studies demonstrated an association between variations in FTO and body mass. Several polymorphisms have been identified. The 16 % of individuals homozygous for the risk allele SNP rs9939609 weigh about 3 kg more and have 1.67-fold increased odds of obesity when compared with those

not inheriting a risk allele. This association reflects a specific increase in fat mass and can be seen in those 7 years and older. A similar association with common FTO variants was reported in a population from Sardinia. These reports were followed by numerous reports of FTO and excess body weight in multiple human populations. However, the mechanistic link between FTO and obesity has been difficult to make. The phenotype of the SNPs is difficult to identify, with some reporting increased caloric intake and some reporting decreased physical activity. Mouse studies point to a role of FTO in regulating body composition.

FTO has also been implicated in reward systems and methylation of proteins involved in synaptic transmission and cell signaling, as FTO encodes a 2-oxoglutarate-dependent nucleic acid demethylase. However, the causal link between FTO and obesity remains elusive and raises significant questions as to how to best investigate the causality of human genetic variants in disease.

Most individuals, perhaps up to BMIs in the high 30 range, are likely physiologically normal and become obese as they respond to the temptations of modern environments rich in high-calorie food. Given the polygenic nature of obesity, where many variants in the same or different genes contribute only modestly to body weight but may act synergistically to quantitatively affect weight, it is likely that polygenic risk scores may better estimate the overall genetic risk of obesity from common variants rather than individual risk variants considered alone. Epigenetic factors may also contribute by regulating the expression of obesity-associated genes. A better understanding of factors contributing to the pathogenesis of obesity might be obtained if we use the BMI range to identify the relative risk of comorbidities rather than as a guide for discovering pathology. The search for genetic variants of disease might be more fruitful if the comparisons focused on extreme leanness and extreme obesity.

ADIPOSE TISSURE AS AN ENDOCRINE AND IMMUNE ORGAN

Until fairly recently, the traditional view of adipocytes was as a passive, efficient storage depot for triglycerides that would be released with fasting to provide fuel. This view changed as discoveries indicated adipocytes secrete multiple factors, termed adipokines, with both metabolic and immune functions (Table 2).

One of the first secreted factors was adipsin, a serine protease in the complement family, whose expression was impaired in both genetic and acquired obesity. Although more than 30 years have elapsed since this initial observation, the role of adipsin in adipocyte and systemic biology remains relatively obscure and serves as an example of some of the difficulties encountered in understanding adipocyte biology. Understanding immune responses in obesity is further complicated by findings of increased infiltration of immune cells in fat. Initially considered

pathologic, findings suggest that they may also play a positive role in adipose tissue metabolism by clearing lipids and senescent fat cells. Different types of infiltrating immune cells may play different roles within the adipose tissue. Multiple hormones and cytokines are synthesized in fat, a selection of which are considered here.

Table 2

Adipocyte-Secreted Factors

Category	Protein
Hormones	Leptin, resistin, angiotensinogen, adiponectin, estrogens, visfatin, glucocorticoids, angiopoietin 4, apelin
Cytokines	Interleukins 1, 6, 8, 10; monocyte chemoattractant protein 1; interferon-γ; tumor necrosis factor α
Extracellular matrix proteins	Various subtypes of collagen α1, various metalloproteinases, fibronectin, osteonectin, laminin, entactin, thrombospondin 1 and 2
Complement factors	Adipsin, complement C3, factor B
Enzymes	Cholesterol ester transfer protein, lipoprotein lipase
Acute phase response proteins	α1-acid glycoprotein, haptoglobin
Other	Fatty acids, plasminogen activator inhibitor 1, prostacyclin, vascular endothelial growth factor

Leptin. Potentially the most critical product of the adipocytes is the protein leptin, which is synthesized in the adipocyte and released into the circulation. Leptin is required for normal energy balance, as a genetic deletion in both rodents and humans is associated with morbid obesity, as noted earlier. Leptin synthesis is regulated, and levels fall dramatically with starvation, leading to many functional consequences including a decrease in fertility, which can be corrected by exogenous leptin in both mice and humans.

Leptin levels also rise with acute overfeeding. Although leptin deficiency leads to morbid obesity, most obese humans have high levels of leptin, and indeed adiposity correlates with circulating serum leptin levels in both rodents and humans, leading to the concept of leptin resistance, which is supported by attenuated induction of downstream mediators of leptin action in obese rodents. The existence of leptin resistance, which has recently been linked to the stability of the leptin receptor, also suggests that leptin does not serve as a biologic “adipostat” and that its primary function is to signal starvation.

Resistin. Resistin is another signaling polypeptide secreted by adipocytes. Resistin concentrations are increased in mice with diet-induced and genetic forms of obesity and insulin resistance. Administration of recombinant resistin to normal mice leads to impaired glucose tolerance and attenuated insulin action. Based on these findings, it has been proposed that resistin is a hormone that links obesity to diabetes by inducing insulin resistance.

Adiponectin. Adiponectin is a key signaling peptide produced by adipocytes; it is also the most abundant. Plasma adiponectin concentration are decreased in obesity and insulin resistance in both rodents and humans. Adiponectin acts to increase insulin sensitivity, and expression increases with improved insulin sensitivity, such as when animals or humans are treated with thiazolidinediones.

Weight loss independent of the type of diet is also associated with increases in circulating adiponectin. However, adiponectin structure is quite complex, being composed of protein dimers and tetramers. The ratio of high-molecular-weight isoforms to low-molecular-weight isoforms is more important than total adiponectin in determining insulin sensitivity and weight loss. Additionally, there are two receptors mediating its action. Administration of exogenous adiponectin lowers glucose in obese rodent models through suppression of hepatic gluconeogenesis, as well as promoting liver ceramide breakdown. Unfortunately, it has not been possible to develop adiponectin-based therapies due to the complex structure. Several SNPs of adiponectin in human populations have been reported and may be linked to cardiovascular disease; however, the possible mechanism(s) remain uncertain.

Estrogens. Adipose tissue contributes to total serum estrogen derived from androgens through the action of aromatase, which catalyzes the formation of estrone from androstenedione. The conversion rate of androstenedione into estrone increases with age and obesity. In women, after menopause, adipose tissue becomes a significant source of estrogen biosynthesis. Increased estrogen has been implicated in the risk of breast cancer in obese women. Adipose tissue also expresses estrogen receptors ERα and ERβ. Differential expression of estrogen receptors in different depots and gender differences in estrogen concentrations may explain, in part, differences in lipid accumulation in men and women. Postmenopausal women who lose weight have lower breast cancer risk than those with stable weight or weight gain. It is possible that this effect is modulated through adipose estrogens, although this remains speculative.

Selected Cytokines. Expansion of adipose tissue leads to a low-grade inflammatory state in fat. Increased expression of cytokines from adipose tissue results in the recruitment of macrophages, which may serve to aggravate inflammation and insulin resistance. The precise consequences of macrophage recruitment are unclear, because while promoting inflammation, they may also have beneficial effects related to buffering of released lipids (efferocytosis) and clearance of necrotic cells. Several dozen cytokines are synthesized in adipose tissue and have been reviewed extensively. Two key examples are discussed here.

Tumor Necrosis Factor α. Tumor necrosis factor α (TNFα) is an inflammatory cytokine that plays a role in many disease processes. It is synthesized by multiple cell types, including adipocytes, macrophages, monocytes, and neutrophils. TNFα regulates the expression of other cytokines, growth factors, and transcription factors. In adipocytes, TNFα expression increases with obesity and leads to localized inflammation that is associated with decreased insulin sensitivity.

Likewise, blocking TNFα action improves insulin sensitivity. A positive correlation exists between circulating TNFα concentrations and obesity; however, it seems likely that the major effects of TNFα are local. Notably, despite the widespread use of anti-TNFα treatments for rheumatologic diseases, improvements in insulin sensitivity and glycemia in patients with type 2 diabetes are not clinically evident.

Interleukin 6. Another proinflammatory cytokine increased in obesity is interleukin 6 (IL6), which may contribute to systemic inflammation and insulin resistance. Insulin sensitivity is inversely related to plasma IL6 concentrations, and IL6 directly impairs insulin signaling.

Administration of IL6 induces dose-dependent increases in fasting blood glucose in humans, probably by stimulating the release of glucagon and other counterregulatory hormones, by inducing peripheral resistance to insulin action, or both. IL6 and other proinflammatory cytokines may also play a direct role in regulating adipocyte metabolism and vascular health.

Brown Adipose Tissue. Brown adipose tissue (BAT) is a distinct fat depot that is structurally and functionally different from white adipose tissue; it contains multilocular fat vacuoles and large mitochondria and is intensively innervated by sympathetic nerves. BAT contributes to energy homeostasis in rodents, where it is part of the adaptation to cold exposure, but also plays a role in the adaptation to very-low-carbohydrate diets. Under these conditions, BAT is activated; as a result, there is an increase in the levels of the factor uncoupling protein 1 (UCP1), which generates a mitochondrial proton leak those results in less production of adenosine triphosphate and energy wastage through the generation of heat.

Recently, BAT depots have been identified in humans, which has increased interest in BAT biology. Human BAT can be activated by cold exposure and increased adrenergic activity. However, human BAT depots are relatively small, and it is unlikely that BAT plays a significant role in energy expenditure in otherwise healthy humans.

OBESITY-ASSOCIATED HEALTH COMPLICATIONS

Metabolic Syndrome. Metabolic syndrome refers to the common co-occurrence of multiple diseases with obesity, particularly obesity with a visceral distribution. Most of these obesity-related disorders are associated with increased cardiovascular disease risk. Metabolic syndrome has multiple definitions. National Cholesterol Education Program Adult Treatment Panel III includes any three of the following five clinical measures: increased waist circumference defined on the basis of ethnic specific criteria, elevated triglyceride levels, low high-density lipoprotein cholesterol levels, increased blood pressure, or high fasting glucose. World Health Organization criteria for metabolic syndrome include the presence

of insulin resistance along with the identification of at least two additional risk factors.

Metabolic syndrome leads to a 2-fold increased risk of cardiovascular disease and a 1.5-fold risk of increased mortality from all causes, based on a meta-analysis of studies that included more than 900,000 people. Obesity predisposes to cardiovascular disease through multiple mechanisms, as it increases the likelihood of type 2 diabetes, dyslipidemia, and hypertension, all of which are independent risk factors for cardiovascular morbidities. Factors secreted from the adipocyte can also promote a proinflammatory, prothrombotic state.

Type 2 Diabetes. Type 2 diabetes is a common consequence of excess adiposity. Indeed, more than 90 % of individuals with type 2 diabetes are obese. Rising prevalence rates of type 2 diabetes coincide with rising rates of obesity. Rates of diabetes across the continental United States range from a low of 7 % in Colorado to a high of 13.6 % in Mississippi, and rates in the U.S. territories of Guam and Puerto Rico are even higher, according to the National Diabetes Statistics Report (January 20, 2022; https://www.cdc.gov/diabetes/data/statistics-report/index.html).

Diabetes prevalence parallels the prevalence of obesity, which is lowest in Colorado, where rates range between 20 % and 25 %, and highest in the southeastern states, including Mississippi, with rates higher than 35 %. Risk of diabetes increases with earlier onset and more severe obesity. For example, the likelihood of developing diabetes is 70 % for women with a BMI greater than 35 at age 18 years, with an expected diagnosis of diabetes by the sixth decade.

An increased waist to hip ratio, reflective of increased visceral obesity, is also associated with increased diabetes risk.

Dyslipidemia. Primary dysfunction in the adipocyte is associated with abnormal lipid metabolism, increasing the risk of dyslipidemia. Abnormal lipid metabolism in association with genetic factors results in dyslipidemia, including hypertriglyceridemia; reduced high-density lipoprotein cholesterol levels; and an increased fraction of small low-density lipoprotein particles. This association is especially strong in persons with abdominal obesity.

Hypertension. There is a linear relationship between hypertension and BMI. Prevalence rates are more than twice as high in obese men and women compared with lean men and women, and the risk of hypertension increases with both age and weight gain. Approximately 70 % of hypertension in adults is attributable to excess adiposity, especially visceral adiposity. Obesity-related hypertension has distinct genetic determinants compared with hypertension in the absence of obesity. Physiologic mechanisms of obesity related hypertension include insulin resistance, sodium retention, increased sympathetic nervous system activity, activation of renin-angiotensin-aldosterone, and altered vascular function. Weight loss results in blood pressure reductions; however, the effects may not be durable.

Cardiovascular Disease. Obesity is associated with a significantly increased lifetime risk of cardiovascular disease, including coronary artery disease, heart failure, and cerebrovascular disease. Risks are higher for men and for those with visceral obesity. Absolute thresholds for weight-associated cardiovascular disease are hard to determine and can depend on the type of event being assessed, the subpopulation, and other confounding factors. In middle-age men, the risk of a cardiovascular event increases with increased BMI, and the risk of cardiovascular death is twofold for individuals with a BMI greater than 40 kg/m² compared with normal-range BMI. A similar increase in risk in cardiovascular events is seen in women, although the risk of cardiovascular death does not significantly correlate with BMI. Individuals living with a BMI in the overweight category mostly have similar longevity to those with a normal BMI except for the increased cardiovascular risk. Therefore, if left unaddressed even mild adiposity may lead to an increased exposure to cardiovascular morbidity.

In a recent analysis of data from both the Nurses' Health Study and the Health Professionals study, no increased cardiovascular risk was seen in the overweight category. When this was adjusted for lifetime weight history, a small increase was noted in the overweight BMI range, indicating that at lower excess weights, assessment of risk is complicated. Increasing BMI also increases the risk of ischemic cerebrovascular events in both men and women. The risk of fatal and nonfatal ischemic stroke is approximately twice as great in individuals with a BMI greater than 35 kg/m². In intermediate BMI ranges of greater than 25 kg/m² and up to 32 kg/m², it is difficult to assess the relative increased risk in otherwise healthy individuals. At least one study reports similar survival following an ischemic event in normal-weight and overweight subjects.

Obesity is also associated with an increased risk of thromboembolic disease, and the risk increases with higher waist circumference.

Liver Disease. As a result of the increasing prevalence of obesity, metabolic-associated liver disease, previously known as nonalcoholic fatty liver disease (NAFLD), is now the most common cause of chronic liver disease in both developed and developing countries. In the United States, NAFLD affects 30 % of the obese population and 53 % of obese children. Risk increases with additional excess weight such that prevalence increases to 90 % in morbidly obese populations. Hepatosteatosis is diagnosed when 5 % of all cells contain lipid droplets by histology or when MRI reveals more than 5 % fat in the liver. Diagnosis of NAFLD requires the exclusion of other causes of liver pathology, including alcohol abuse, viral infections, and biliary or autoimmune disease. Metabolic associated liver disease can progress unpredictably to steatosis, cirrhosis, and hepatocellular carcinoma. Progression to nonalcoholic steatohepatitis, characterized by hepatocyte apoptosis, inflammation, and fibrosis, is seen in 10 % to 20 % of NAFLD patients and poses a high risk for further progression to cirrhosis and hepatocellular carcinoma.

Unfortunately, it is not possible to identify individuals who will progress from NAFLD to nonalcoholic steatohepatitis and hepatocellular carcinoma at this time. Effective treatments include weight loss and GLP1-receptor agonists, vitamin E, and sodium-glucose cotransporter 2 inhibitors. Several molecular targets are currently in clinical trial for the treatment of metabolic-associated liver disease.

Obstructive Sleep Apnea. Overall effects of obesity on lung function are relatively benign. However, respiratory function can be significantly affected by obstructive sleep apnea that can be severe. Obstructive sleep apnea occurs when there is either complete or partial upper airway obstruction due to mechanical pressure in the neck. Daytime sleepiness is common. Sleep apnea is also an independent risk factor for hypertension and may predispose to type 2 diabetes. Weight loss is effective in improving indices of apnea.

Musculoskeletal Disease. Because overall body weight contributes to mechanical pressure at the hip and knee, obesity is a risk factor for osteoarthritis. Overweight increases the risk of knee osteoarthritis by almost twofold, whereas frank obesity is associated with additional risk. Overweight and obesity are more significant factors in new-onset knee pain than a previous knee injury. The increasing prevalence of overweight and obesity is also associated with increasing total knee and hip arthroplasty. Hyperuricemia and gout are also associated with obesity. The risk of gout also increases with body weight, and the relative risk in individuals with a BMI greater than 35 kg/m^2 is almost threefold higher compared with normal weight persons.

Cancer. Overweight and obesity increase the risk of certain cancers. Based on data from a prospective study in more than 900,000 adults in the United States, it was estimated that overweight and obesity could account for 14 % of all deaths from cancer in men and 20 % of such deaths in women. Obesity is associated with higher rates of death due to cancers of the gastrointestinal tract (liver, pancreas, stomach, esophagus, colon and rectum, and gallbladder) and kidney, multiple myeloma, and non-Hodgkin lymphoma, as well as prostate cancer in men and uterine, cervical, ovarian, and postmenopausal breast cancer in women. The risks of breast and endometrial cancer fatality increase with both obesity and weight gain after age 18 years. The risk of breast cancer increases with increasing BMI in postmenopausal women; in premenopausal women, increased BMI may actually protect against breast cancer.

Genetic, hormonal, and metabolic factors associating adiposity to cancers remain incompletely understood.

THERAPEUTIC APPROACH

Height and weight measurements are intrinsic to the physical examination; most electronic medical records automatically calculate BMI, which can also be calculated manually by dividing the weight in kilograms by the height in meters squared or by using the online calculator provided by the Centers for Disease Control and Prevention. Once the current BMI is known, an essential component of the medical history is determining an individual's weight trend over time, often by obtaining weight at age 18. For normal weight and modestly overweight individuals (i.e., BMI < 27 kg/m² without comorbidities for those with European heritage or 25 kg/m² for Asian heritage), counseling with no additional intervention other than monitoring weight over time is warranted.

Beyond weight, little additional evaluation is warranted for obesity per se. In those reporting early obesity, presenting during childhood or adolescence, who also have a family history, genetic testing for a mutation in MC4R might be considered. This is the only commercially available test, and it may be helpful in a small number of individuals who test positive. However, at present, there are no specific therapies that would be more effective if the mutation were present, so pursuing the test is dependent on clinical suspicion of physician and patient preference.

Management of overweight and obesity can be difficult. A conservative clinical approach is provided in Table 3.

Table 3

Suggested weight-loss treatment options based on BMI and risk factors

BMI (kg/m²)	Advice, Nutrition, Exercise	Pharmacotherapy[1]	Surgery[2]
25.0–26.9	Yes	No	No
27.0–29.9	Yes	Consider if there are risk factors and weight gain trajectory	No
30.0–34.9	Yes	Strongly consider with risk factors and weight gain trajectory	No
35.0–39.9	Yes	Yes	If drugs fail, with comorbidity
≥ 40	Yes	Yes	If drugs fail

[1] Pharmacotherapy should be considered in patients who are unable to achieve adequate weight loss with available conventional therapy and who do not have any absolute contraindications for drug therapy.

[2] Bariatric surgery should be considered in patients who are unable to lose weight with available conventional therapy and who do not have any absolute contraindications for surgery.

First, an individual must acknowledge a potential problem. At the time of annual physical examination, weight should be noted, BMI calculated, and a brief

overview of BMI and risk provided. In general, mildly overweight patients need to be advised of the advantages of modest weight loss and warned against additional weight gain. For individuals with a BMI greater than 27 kg/m² (25 kg/m² for Asians) or those with comorbidities, the risk of excess weight should be addressed and patients should be encouraged to be attentive to their weight, offered access to a nutritionist, provided with dietary advice, and given an approach to behavioral modification. Using a home scale for scheduled weighing time and recording the result alone may be ineffective for achieving weight loss, but it may help an individual be attentive to risk and may prevent or slow down further weight gain.

Individuals with a BMI greater than 35 kg/m² should be advised of risks, encouraged to obtain a consultation from a nutritionist, and be counseled in behavioral modifications, and a repeat visit should be scheduled within 3 to 4 months of the initial visit.

If the interval has passed without weight loss, pharmacotherapy should be considered. Although GLP1-receptor agonists (see later discussion) are highly effective, few individuals are willing to consider an injectable therapy at the outset; additionally, many insurance companies insist on a trial of available oral therapies to start.

This requirement may change when the GLP1-receptor agonists become generic, thereby increasing affordability and access. There is no reliable way of predicting a response to the various medications available; the initial choice needs to be individually tailored on the basis of the likelihood of compliance and risk of side effects.

Metabolic surgery options should be discussed. Once therapy is prescribed, it is critically important to evaluate weight loss within a short interval to determine effectiveness. An official weight, in a medical environment, should be recorded at 8 weeks. If no weight loss is observed, weight should be checked at 12 to 16 weeks. Weight gain should signal the cessation of therapy.

If weight loss is absent, or less than 5 % or 3.3 pounds (1.5 kg), therapeutic dose adjustments may be considered up to maximal approved levels or therapy should be discontinued between 12 and 16 weeks. If weight loss exceeds 3.3 pounds (1.5 kg), individuals should be recalled for weight checks every 8 weeks. If weight loss is ongoing, the decision to continue medical therapy over the long term needs to be evaluated on an individualized basis that balances the risk of medication with the benefit of reduced body weight.

Weight regains is common when pharmacotherapy is stopped.

Benefits of Intentional Weight Loss. Weight loss leads to several cardiometabolic benefits, which correlate with the percentage of body weight reduction. The mechanism by which reducing adiposity leads to these benefits is complex and not fully understood. One potential mechanism is the reduction in adipose tissue inflammation linked to insulin resistance.

Several studies demonstrated beneficial outcomes mainly related to carbohydrate metabolism and prevention of type 2 diabetes after achieving 5 % to 10 % weight loss. Furthermore, Klein et all demonstrated additional metabolic benefits from progressive weight loss. The favorable metabolic benefits included improvements in body composition, visceral adiposity, intrahepatic steatosis, markers for cardiovascular disease, and adipocyte gene expression involving inflammation, extracellular matrix, and cholesterol flux. Some improvements appeared early on and continued linearly proportionate to the percentage of weight loss, whereas others appeared at higher levels of weight loss of 11 % or more. Other studies of stepwise weight loss showed a progressive improvement in quality-of-life measures, mobility, ovarian function, and sleep apnea as endpoints. Higher percentages of weight loss typically achieved by metabolic surgery have been associated with favorable outcomes such as reduced major adverse cardiovascular outcomes and the incidence of obesity-related cancer.

Interventions used for obesity management include lifestyle modification such as diet and exercise, behavioral therapy, pharmacotherapy, and bariatric surgery. Due to the complex nature of obesity, combining two or more of these interventions is often desirable to achieve a meaningful and durable response.

DIETARY INTERVENTION

Caloric Restriction. Dietary intervention often involves reducing energy intake and promoting healthful food choices while maintaining a culturally appropriate and personally preferred eating pattern. Notably, a pound of fat contains 3500 calories; therefore, an individual aiming to lose 1 pound per week would require, in theory, a net daily calorie deficit of 500 calories. There is much debate in the literature as to whether increasing weight gain is solely the result of increased energy intake. Some defendants of the carbohydrate insulin model, for example, argue that foods of equal caloric value do not promote the same degree of adiposity. In other words, body weight is not simply the result of “calories in and calories out”, but rather a result of differences in energy partitioning whereby the body preferentially stores excess energy when highly processed and palatable foods are consumed. This enhanced nutrient partitioning is driven by hyperinsulinemia and other metabolic factors that promote fat storage. Others have argued that obesity is a disease of energy balance whereby the drive to consume a surplus of nutrients along with a reduction in active energy expenditure is the root cause. This model is referred to as the energy balance model. Proponents of this model and against the former one argue that genetic alterations in the homeostatic drive of energy balance, along with high levels of circulating nutrient substrates, show they are not, in fact, partitioned differently in people with obesity, and overfeeding

studies in humans and rodents show that an increase in adiposity is the result of increased energy intake.

Despite the numerous and often contradictory theories that aim to explain the rise in prevalence of obesity on a global scale, reducing the total energy intake remains the foundation of obesity management. There is not one ideal eating pattern that has proven to be more effective at promoting a durable long-lasting weight loss over another. Medical nutrition therapy aims to tailor dietary recommendations to each individual to produce the desired effect, whether it be weight loss, improved glycemic control, cardiovascular risk reduction, or a combination of multiple metabolic benefits.

Macronutrient Composition. Significant attention has been given to the macronutrient composition of diets in an attempt to determine what proportion of nutrients might lead to greater and more sustainable weight loss.

Evidence suggests that an ideal macronutrient composition with optimum percentages from carbohydrates, protein, and fats does not exist. Several studies have concluded that consistency is the most influential factor in predicting the outcome of a weight-loss diet. Therefore, the most effective macronutrient ratio is the one an individual prefers and to which they can adhere.

Some evidence exists to support increased satiety sensation with high-protein diets. Proteins also have a high thermogenic effect, which may promote weight loss in the short term. The optimum percentage of protein in the diet differs from one individual to another; however, in the absence of proteinuria and chronic kidney disease, the dietary reference intake is roughly 0.8 grams per kilogram or 15 % to 30 % of total energy intake.

Carbohydrates are a readily available source of energy and the primary nutrient that influences glycemia. The ideal carbohydrate intake required to maintain optimal health is not known. The body can maintain glucose levels in the absence of dietary carbohydrate intake through glycogenolysis and gluconeogenesis, or ketogenesis. There is no consensus on the definition of various carbohydrate compositions in diets. A reasonable interpretation would be to consider a low-carbohydrate eating pattern as one that contains 26 % to 45 % of total calories from carbohydrate, a very-low-carbohydrate diet as one that contains no more than 50 grams of nonfiber carbohydrates or < 26 % of total caloric intake, and a high-carbohydrate diet as one that consists of 45 % of total caloric intake as carbohydrates.

There is significant debate between those who favor low-fat diets over low-carbohydrate, high-fat Atkins-style diets. One study randomized 600 people with overweight or obesity to either a low-fat diet (20 grams of fat per day) or low-carbohydrate diet (20 grams of carbohydrate per day). Participants began to add fats or carbohydrates to their eating patterns. By the end of the study period, both

groups lost similar weight (the low-fat group lost 5.3 kg and the low-carbohydrate group lost 6 kg).

Dietary fiber is an essential component of a healthy eating pattern, and adequate fiber intake is often a struggle to maintain in low- or very-low-carbohydrate eating patterns. The daily recommended intake of dietary fiber is a minimum of 14 grams of fiber per 1000 kcal. The National Academy of Medicine recommends that dietary fats in the form of cis-monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids be included in the eating patterns of individuals as part of a heart-healthy diet. Furthermore, synthetic trans-fats should be avoided.

Eating Patterns. The definition of an eating pattern is the combination of foods and beverages that constitute one's personal daily nutrition intake. Most controlled studies show that weight loss is similar regardless of diet composition, although very-low-carbohydrate diets have a small early advantage.

A Mediterranean diet that emphasizes plant-based foods and monounsaturated fatty acids mainly from olive oil, fatty fish, eggs a few times a week, and minimal added sugars and honey have had mixed results with regard to weight loss, but nevertheless have shown benefits with regard to reduction in hemoglobin A1C, lipid profile, and cardiovascular events.

Vegetarian and vegan eating patterns have been associated with superior weight loss compared with nonvegetarian diets in a meta-analysis of 12 randomized controlled trials involving 1151 participants studied over a median duration of 18 weeks.

Durability of loss in the long term is not known but seems to remain significant even after 1 year compared with nonvegetarian diets. Vegan diets were associated with slightly more short-term weight loss (2.52 kg; 95 % confidence interval [CI], 3.02–1.98) compared with lacto-ovo-vegetarian diets (1.48 kg; 95 % CI, 3.43–0.47); however, it is unclear whether these differences among various eating patterns persist beyond 2 years.

Ketogenic diets are eating patterns characterized by very low carbohydrate intake (usually under 50 grams per day), modest amounts of protein, and high fat content designed to induce ketosis. Several variations of ketogenic diets exist. They range from "classic" ketogenic diets where 2 % to 4 % of energy is derived from carbohydrates and 90 % from fat, to a modified Atkins diet that includes 5 % to 10 % of energy from carbohydrates and 60 % to 65 % from fat. However, in general, most individuals who are not medically supervised and follow a ketogenic diet will consume < 50 grams of carbohydrates per day. Ketogenic eating patterns may be beneficial in the short term to promote weight loss (6–12 months). A meta-analysis of 38 studies including 6499 participants found that low-carbohydrate diets (under 40 % of energy from carbohydrates) led to a small but superior weight loss compared with those who consumed a low-fat diet (under 30 % of energy

from fat, where the mean difference was 1.30 kg; 95 % CI, −2.02 to −0.57), with considerable variability between individuals and between studies.

In controlled feeding studies, however, ketogenic diets have not been shown to be superior to other diets with similar caloric content such as low-fat vegetarian diets. The rapid weight loss seen in many individuals who are on ketogenic diets seems to be secondary to an initial loss of fat free mass such as total body water, glycogen, protein, and contents of the gastrointestinal tract.

There has been great public interest in intermittent fasting (over 60 % energy restriction on 2–3 days per week, or on alternate days) and time-restricted feeding (i.e., limiting the daily period of energy intake to ≤ 8–10 hours on most days of the week). Several studies and meta-analyses have concluded that with regard to weight loss, these specific patterns of restricting energy intake are no different than other calorie-restrictive diets.

Some evidence does exist to suggest that timing of food intake influences weight loss efforts, where individuals assigned to a morning eating window lost more weight than if they ate later in the day.

Physical Activity. In the past half century, sedentary behavior has increased with physical labor progressively mechanized, both commercially and domestically. Reduced activity-induced energy expenditure is estimated to represent a 140 kcal/day decline and in theory plays a role in the current rise of obesity prevalence. However, increasing physical activity through discretionary exercise is not particularly effective for weight loss. In a study of exercise alone, postmenopausal women were advised to exercise at moderate intensity for 45 minutes 5 days per week. Weight loss was minimal, averaging 2.8 pounds (1.3 kg) over the course of a year.

When coupled with diet, exercise has a modest effect to improve weight loss in men but only prevented weight gain in women. The failure of exercise to have a significant impact on weight loss may reflect compensatory overeating or insufficient exercise intensity or duration.

Behavior Modification. Behavior modification is an unspecific term that covers approaches to weight loss and/or limiting weight gain that include physical activity, avoiding sedentary behaviors, eating patterns and timing, food shopping habits, food pantry stocking, and sleep. Behavioral modification strategies and guidelines should be sensitively discussed with people living with obesity, especially those who present to their health care team for reasons unrelated to weight gain. Successful weight loss has been reported with combinations of exercise and intensive lifestyle modification that includes frequent monitoring and support. In the Look AHEAD study of individuals with type 2 diabetes and obesity, those randomized to the intensive lifestyle modification limb lost up to 17.6 pounds (8 kg) in the first year. Although, in general, individuals regained weight over time, weight loss of about 9 pounds (4 kg) persisted out to 4 years.

PHARMACOTHERAPY

There has been a tremendous advancement in pharmacotherapy for weight management, stemming from the expansion of scientific discoveries in the field of obesity (Additions 1 and 2).

To date, the most tolerated and effective class of medications for weight loss are GLP1-receptor agonists. Originally developed for the treatment of type 2 diabetes, they have transformed the landscape of pharmacotherapy and served as a launching platform for further drug discovery and development. The anorexic effects of GLP1-receptor agonists produced by continuous infusion were reported in the mid-1980s, and when the first commercially available GLP1-receptor agonist, exenatide, came to market for glucose control in type 2 diabetes, modest weight loss was noted. Subsequent studies found that weight loss effects could be extended to individuals with obesity who did not have diabetes.

The GLP1-receptor agonist liraglutide 3.0 mg was the first to receive an FDA approved indication for obesity management in the United States, Europe, and Japan. The Satiety and Clinical Adiposity-Liraglutide study (SCALE program) 1 through 4 are a series of clinical studies that demonstrated the effectiveness and safety of liraglutide. It is now approved for the management of obesity in adults and children 12 years and older. In the initial 52-week trial individuals lost 4.4 kg (95 % CI, 6.0–2.9 kg, $p < 0.0001$), and in a 2-year extension trial weight loss was 5.8 kg (95 % CI, 8.0–3.7 kg, $p \leq 0.001$).

Semaglutide 2.4 mg is the second GLP1-receptor agonist to receive FDA approval for long-term weight management in adults with obesity or overweight with at least one weight-related comorbidity. A series of clinical trials given the designation of Semaglutide Treatment Effect in People with Obesity (STEP) trials 1 through 8 have been conducted with a pool of over 4000 participants with and without diabetes. In the STEP 1 trial involving 1961 individuals without type 2 diabetes, those randomized to the semaglutide group had a mean reduction in body weight of 14.9 % or 15.3 kg versus the placebo group, which had an average weight loss of 2.4 % reduction in body weight after 68 weeks. This translated into an estimated treatment difference of −12.4 % (95 % CI, −13.4 to −11.5; $p < 0.001$). Furthermore, participants regained weight when the medication was blindly withdrawn, emphasizing the chronic nature of obesity and affirming the need for chronic management. The Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) trial results showed that in people with overweight/obesity and established cardiovascular disease without diabetes, semaglutide treatment was associated with a 20 % reduction in major adverse cardiac events during a mean exposure of 33 months. This is noteworthy, since previous trials of lifestyle and pharmacologic interventions have not demonstrated a strong effect in reducing the cardiovascular risk associated with overweight and

obesity. Currently, most GLP1-receptor agonists are administered by subcutaneous injection; only one, semaglutide, is available in an oral form and is indicated for the management of type 2 diabetes.

Oral GLP-1 receptor agonists (e.g., oral semaglutide and orfoglipron) are currently in phase 2 and 3 clinical trials for the management of obesity in individuals without type 2 diabetes. Results of the OASIS 1 trial showed that compared to placebo, individuals with obesity treated with oral semaglutide at a dose of 50 mg daily lost an average of 15.1 % of their baseline body weight after 68weeks. Orfoglipron, an oral small molecule GLP-1RA, was shown to produce an average categorical weight loss of 14.7 % in people with obesity participating in a phase 2 clinical trial after 36 weeks. Nausea, vomiting, diarrhea, and constipation represent the major side effects that limit use of GLP1-receptor agonists. In most individuals, symptoms are mild, tolerable, and subside with time. GLP1-receptor agonists have metabolic benefits beyond weight reduction such as improvements in glycemic control, sleep apnea, reduction in cardiovascular risk, and metabolic associated liver disease. Contraindications include history of recurrent pancreatitis and personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome.

Phentermine is a sympathomimetic that was approved for obesity treatment in 1959. It stimulates the release of norepinephrine, and to a lesser extent serotonin (5-hydroxytryptamine [5HT]) and dopamine. Weight loss with phentermine is approximately 5 % at 8 to 12 weeks, and typically it is administered at 15 to 37.5 mg. Phentermine dose is once daily in the morning with meals as a short-term adjunct (a few weeks) to behavioral weight loss approaches. A lower 8-mg dose for longer-term use is available.

The clinical effect of phentermine is to reduce appetite, and it appears to be most effective for individuals who start with greater hunger and less cognitive restraint on their eating behavior. Side effects of phentermine can include increased heart rate or blood pressure, insomnia, restlessness, dry mouth, diarrhea, constipation, and changes in sexual drive. Phentermine has been combined with topiramate into an extended-release (ER) formulation marketed as Qsymia, which is available in four doses ranging from combinations of 3.75/23 to 15/92 of phentermine to topiramate. Phentermine-topiramate ER has been evaluated in two large randomized clinical trials. Weight loss at 1 year demonstrated a dose-response relationship and was similar in both studies. In an intention-to-treat analysis after 1 year of therapy, the placebo-subtracted weight loss was approximately 9 % for the top dose and approximately 6.5 % for the recommended dose. Common adverse effects of phenterminetopiramate ER include dry mouth, dizziness, dysgeusia, constipation, insomnia, and paresthesia. Cognitive impairment (attention or memory deficits) is also reported and, when it occurs, leads to discontinuation of the drug.

Orlistat inhibits pancreatic lipase and thereby reduces enteric absorption of fatty acids. In turn, this leads to some degree of fat malabsorption. Excretion of about 30 % of ingested triglycerides, which is near the maximum plateau value, occurs at a dose of 360 mg/day (120 mg three times daily with meals). A meta-analysis of multiple weight loss studies indicated that about 50 % of individuals taking orlistat will lose weight, although weight loss at 1 year is small, with an average loss of 11 pounds (5 kg). Use of orlistat is limited by the common side effect of fatty diarrhea, which leads to reduced compliance. Systemic side effects directly related to the drug are uncommon because orlistat is not absorbed.

The naltrexone slow-release (SR)/bupropion SR combination, marketed as Contrave, is a μ-opioid receptor antagonist combined with a norepinephrine and dopamine receptor inhibitor. Bupropion has neuronal effects associated with reduced energy intake and increased energy expenditure, and naltrexone potentiates this effect such that the effects of the combination are greater than those with bupropion alone. The overall magnitude of weight loss is on the order of 5 %, but in trials, more patients lose 5 % of their body weight with treatment compared with placebo. There are improvements in lipid and glucose profiles and patient-reported outcomes, but small increases in heart rate and blood pressure.

Many new developments in pharmacotherapy are on the horizon. **The dual GIP/GLP1-receptor agonist tirzepatide** is a 39-aminoacid linear peptide conjugated to a C20 fatty acid moiety that binds to and activates two incretin receptors: GIP and GLP1.

Tirzepatide is currently FDA approved for the treatment of type 2 diabetes and obesity. In the SURPASS-1 trial investigating the effect of three doses of tirzepatide 5 mg, 10 mg, and 15 mg on hemoglobin A1C as the primary endpoint, the average weight loss was 20 % of total body weight in those who received the highest dose after 72 weeks of treatment.

The recently published SURMOUNT trial was conducted in participants without type 2 diabetes with the primary endpoint being weight loss. Here, 56.7 % of subjects randomized to tirzepatide 15 mg lost equal to or more than 20 % of their body weight, and 36.2 % lost equal to or more than 25 % of their baseline weight. Futhermore, tirzepatide 15 mg was shown to have persistent and durable weight loss effects in a recently published SURMOUNT-4 trial, where mean weight loss was 5.5 % of total body weight at 56 weeks after an initial 36-week lead-in period, where average weight loss was 20.2 %. At the end of the 88-week study period mean weight loss was 25.3 % for those who remained on the drug.

Several promising pharmacotherapy agents are in development

Mazdutide is a long-acting synthetic peptide related to oxyntomodulin that is a dual GLP1-receptor and glucagon-receptor agonist in phase 1b clinical trial. After 16 weeks, participants in the cohort who received 2.5/5.0/7.5/10.0 mg weekly doses lost 9.5 % of their total body weight at 16 weeks, and those who

received 3.0/6.0/9.0 mg weekly doses lost 11.9 % of their body weight at 12 weeks. The triple agonist retatrutide (LY3437943) stimulates glucagon, GIP, and GLP1 receptors. In a phase 2 clinical trial using weekly injections of this drug in participants with obesity, the least squares mean percentage in body weight was 17.5 % after 48 weeks in participants who received 12 mg.

Cagrilintide (NNC0174-0833) is a long-acting acylated amylin analogue. In a phase 1 clinical study using various doses of cagrilintide combined with semaglutide 2.4 mg weekly, the mean weight loss was 17.1 % at 20 weeks. This randomized double-blind study was unique in that 59 % of participants were men and 54 % were Black, thereby providing critically needed diversity in these clinical studies that historically include mostly women.

Bimagrumab (BYM338) is a novel treatment that may be the first pharmacotherapy agent to preserve skeletal muscle mass. It is a fully human monoclonal antibody that binds to the activin type II receptor (ActRII), thereby preventing the actions of natural ligands that negatively regulate skeletal muscle growth. In a phase 1 clinical trial, participants randomized to receive the drug had a reduction in their body fat mass of 20.5 % and a gain of 3.6 % in lean mass at 48 weeks.

Setmelanotide is an FDA-approved melanocortin-4 (MC4) receptor agonist indicated for the treatment of adults and children over the age of 6 with genetic obesity-caused POMC, proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency220 and Bardet-Biedl syndrome. It is administered daily by subcutaneous injection. Side effects include nausea, vomiting, and diarrhea, as well as skin pigmentation due to cross stimulation of the peripheral melanocyte receptors in the skin, and disturbances in sexual arousal (see Addition 2).

A nonsystemic oral hydrogel for weight loss has been approved by the FDA as an adjunct to a reduced-calorie diet and physical activity for weight management. In the Gelesis Loss Of Weight (GLOW) study, a 24-week, multicenter, randomized, doubleblind, placebo-controlled study in patients with BMI ≥ 27 and ≤ 40 kg/m² and fasting plasma glucose ≥ 90 and ≤ 145 mg/Dl (5.0 and 8.1 mmol/L, respectively), Gelesis100-treated patients had twice the odds of losing ≥ 5 % and ≥ 10 % weight loss versus placebo (adjusted OR: 2.0, $p = 0.0008$; OR: 2.1, $p = 0.0107$, respectively). Furthermore, 5 % of responders achieved an average weight loss of 10.2 %.

A summary of medications approved for weight loss, along with maximal placebo-adjusted weight loss, is provided in Addition 1

BARIATRIC SURGERY

Attempts to treat obesity through surgical procedures were first attempted more than 60 years ago, with almost all initial procedures involving shunts between the jejunum and the colon (Addition 3).

Jejunoileal bypass surgery was effective for weight loss but was associated with significant complications, including liver disease, liver failure resulting in death, and protein malnutrition. Thus, this surgical approach was largely abandoned. A decade later, a report on the success of Roux-en-Y gastrojejunostomy in more than 600 morbidly obese patients revealed that this surgical approach was effective with very little morbidity and mortality.

Although many consider bariatric surgery as a draconian approach to obesity, weight loss is substantial and sustained, and it is associated with remission or improvement of type 2 diabetes, dyslipidemia, hypertension, and other weight-related comorbidities that may occur early following surgery and persist for years.

Not surprisingly, after the procedure, decreased levels of inflammatory markers have also been reported. Surgical weight loss may reduce mortality by as much as 30 % to 40 % in the severely obese, although these studies were not randomized. There is some controversy regarding whether the severity of obesity is the optimal characteristic to use when considering a patient for metabolic surgery; however, the accepted indications for surgery are a BMI greater than 40 kg/m² or a BMI between 35 and 40 kg/m² with an associated comorbidity.

Four surgical procedures are offered for obesity therapy: adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, and biliopancreatic diversion (see Addition 3). Although biliopancreatic diversion is effective, few procedures are currently performed because of the higher rates of complication. Adjustable gastric banding has also become less common, with Rouxen-Y and gastric sleeve surgery now also routinely performed laparoscopically, providing more rapid recovery. In addition, gastric banding has significantly lower expected weight loss.

Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic diversion, and adjustable gastric banding have been studied in relation to metabolic outcomes. Sleeve gastrectomy is the current leading procedure in the United States. Similar weight loss is achieved, of almost 11 pounds (5 kg) per month for the first 4 months, with weight nadir between 6 and 24 months and effects that can persist over years. Perioperative mortality with bariatric surgery is low and reported as 0.04 % to 0.3 %, similar to that of a cholecystectomy. Potentially fatal risks include pulmonary emboli, sepsis, and bleeding. Because of the underlying increase in cardiovascular disease, the likelihood of cardiovascular risk is higher in the perioperative period. Of concern would be a leak at the anastomosis site, which can lead to sepsis and needs to be diagnosed and treated aggressively. Overall, the incidence of adverse events in the initial 28-day period was less than 5 %.

Hypoglycemia can occur as a long-term complication of weight loss surgery, which may occur to some degree in up to 14 % of individuals without a prior history. Severe hypoglycemia is only reported in a small number of patients; it appears to be more common after the Roux-en-Y procedure and may be managed by continuous blood glucose monitoring and carbohydrate support, although, on occasion, somatostatin analogues or diazoxide are necessary to reduce insulin secretion following meals.

Patients having Roux-en-Y gastric bypass should be followed for development of anemia and deficiencies of fat-soluble vitamins, because the absorption of iron and fat-soluble vitamins can be impaired, leading to low levels even in the setting of standard replacement therapy with oral multivitamins. Iron infusion therapy may be needed in some patients. Bone health should be monitored. Bariatric surgery may also exacerbate depression and may increase the likelihood of this comorbidity after surgery. Rates of depression are high in individuals with morbid obesity, which is also associated with increased suicide risk. A psychological evaluation for depression and emotional postsurgical support is an essential part of the care of individuals undergoing surgery.

Endoscopic Interventions for Weight Management. Endoscopic obesity treatment has emerged to fill the treatment gap between lifestyle therapy, antiobesity medications, and bariatric surgery. Bariatric endoscopy can be classified as a primary treatment for obesity and type 2 diabetes, bridge to various surgeries (bariatric, orthopedic, or transplant), or revisional post-bariatric surgery for weight regain. Endoscopic treatment's MOA can be primarily anatomic (restrictive or space-occupying) or physiologic (hormonal) or a combination of both, just as most of the surgical procedures are a combination of these MOAs producing satiety and change in the body weight set-point.

Gastric Balloons. The gastric balloons are space-occupying devices that have undergone a metamorphosis and have been improved on since the "gastric bubble" was approved by the FDA in 1985. Gastric balloons recently on the market are listed here with total weight loss (TWL) and distinguishing characteristics:

1. Orbera Gastric balloon (single balloon, fluid-filled) requiring endoscopic placement and removal; TWL 11.3 % at 1 year; commercially available.

2. Obalon Balloon system (triple balloon, gas-filled) with swallowable placement and endoscopic removal; reported TWL 10 % at 6 months; not commercially available.

3. Spatz Adjustable Balloon system (single balloon, fluid-filled with connecting tube for volume adjustment) requiring endoscopic placement and removal; TWL 14.9 % at 8 months; under FDA review.

4. Elipse Balloon (Allurion) (single balloon, fluid-filled) swallowable with fluoroscopic guidance for placement and self-emptying mechanism for removal at 4 months; data pending and under FDA review.

Gastric Remodeling. Gastric remodeling is performed via endoscopic suturing or plication, and currently there are two devices approved by the FDA for tissue approximation: the Overstitch (Apollo Endosurgery) and the Incisionless Operating Platform (USGI Medical).

These devices are FDA approved and commercially available.

The procedures performed are listed here with distinguishing characteristics:

1. Endoscopic sleeve gastrectomy is the most common remodeling procedure. It involves placing several sutures in a running stitch along the greater curvature of the stomach, with sometimes a second layer placed medially for reinforcement. TWL reported as 16.5 % at 12 months. This is endoscopically reversible if necessary.

2. Primary obesity surgery endoluminal (POSE), or gastric plication, involves placing tissue plications primarily in the fundus of the stomach; because this is serosal apposition it is not reversible. A more distal pattern is known as distal POSE or POSE2 where placement of plications is in the gastric body. Traditional POSE TWL reported as 12.1 % and 13.2 % over 6 and 12 to 15 months, respectively.

Aspiration Therapy. Aspiration therapy uses a gastrostomy tube with an external port at the skin for aspiration of stomach food contents after eating with a portable device for aspiration. The tube is placed endoscopically via a pull-technique and the port is attached at 1 to 2 weeks. TWL is reported at 17.8 % at 1 year. This therapy was FDA approved but is not commercially available.

Transpyloric Shuttle, Endoluminal Barrier, and the Fractyl system are three other devices that are in trials or not commercially available as yet.

Summary. Obesity results from complex interactions of individuals' risk and environmental influences. The first-order advice regarding diet and exercise is rarely successful. In the past decade, there have been some significant improvements in medical therapy, as GLP1-receptor agonists have demonstrated effectiveness in at least 30 % of individuals. Bariatric surgery has become safer and more acceptable. However, the demand for therapies persists.

CLINICAL CASES

1. Patient S. is 48 years old. The body height is 167 cm, body weight is 103 kg. She visited the surgeon to complain about recurrent furunculosis. The fasting glucose test showed fasting glucose 6.4 mmol/L. What is the preferred management strategy?

2. Patient N. is 49 years old, a driver. A periodic health examination detected Fasting glucose 6.2 mmol/l. The body height is 170 cm, body weight is 90 kg, blood pressure is 140/85 mm hg. What management are you going to choose?

3. Patient R. is 55 years old, a teacher. A periodic health examination detected Fasting glucose 5.1 mmol/L. The body height is 157 cm, body weight is 59 kg, blood pressure is 150/90 mm hg. What is your diagnosis and treatment?

4. Patient A. is 35 years old, a programmer. A periodic health examination detected Fasting glucose 6.3 mmol/L. The body height is 163 cm, body weight is 88 kg, blood pressure is 130/80 mm hg. What is your further management?

LITERATURE

Basic

1. *Harrison`s* principles of internal medicine / ed. by D. L. Longo, D. L. Kasper, J. L. Jameson [et. al]. – 20th ed. – New York [etc.] : McGrawHill Medical, 2018. – Vol. 1. – 1796, [158] p. : ill. – Index: p. i1–i158.

Additional

2. *Endocrinology* : textbook for students of higher medical with the 4th level of accreditation with English as the language of instruction / P. M. Bodnar [et. al]. ; ed. by P. M. Bodnar. – 4th ed., updated. – Vinnytsia : Nova Knyha, 2017. – 327 p.

3. *Williams* textbook of endocrinology / S. Melmed [et al.]. – 14-th ed. – Philadelphia : Elsevier, 2024. – 1798 p. : fig., tabl. – Index: p. 1606–1625.

4. *American* Diabetes Association, Standards of Care in Diabetes-2023 / Diabetes Care. – 2023. – Vol. 46, iss. suppl. 1. – 298 p.

5. *American* Diabetes Association Standarts of Medical care in Diabetes / Diabetes Care. – 2025. – Vol. 48, suppl. 1,8. – P. 167–180.

6. *Harrison`s* principles of internal medicine / ed. by D. L. Longo, D. L. Kasper, J. L. Jameson [et. al]. – 20th ed. – New York [etc.] : McGrawHill Medical, 2018. – Vol. 2. – 3610, [158] p. : ill. + 1 электрон. опт. диск (DVD-ROM). – Index: p. i1–-i158.

7. *Internal* medicine: critical care : textbook / O. Ya. Babak [et. al]. ; ed. by. O.Ya. Babak, O. M. Bilovol. – Kyiv : AUS Medicine Publishing, 2018. – 368 p.

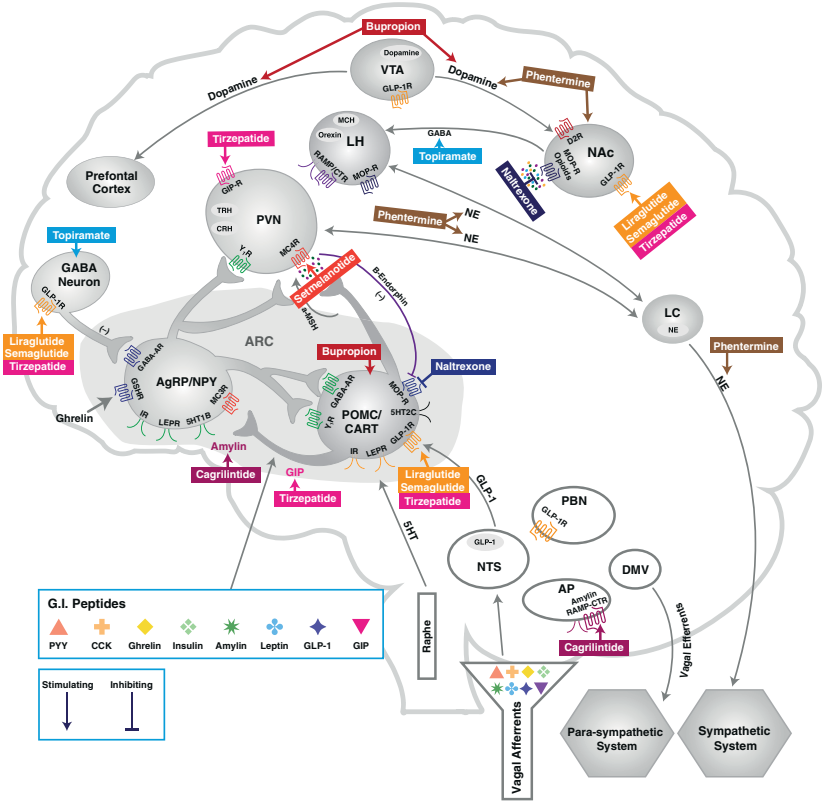
Addition 1

FDA-APPROVED MEDICATIONS USED FOR CHRONIC WEIGHT MANAGEMENT

Year Approved	Generic Name	Dose	Trade Name	Placebo-Corrected Anticipated Weight Loss (kg)
1959	Phentermine	8, 15, 30, 37.5 mg	Lonamin, Adipex-P, Fastin, Oby-Trim (approved only for short-term weight loss)	Approved for short-term use only
1999	Orlistat	60 mg OTC; 120 mg capsules, 3 times daily	Xenical, Ally (over the counter)	2.63
2012	Phentermine-topiramate extended release	3.75 mg / 23 mg 7.5 mg / 46 mg 11.25 mg / 69 mg 15 mg / 92 mg	Osymia	8.80
2014	Liraglutide	3 mg SC daily	Saxenda (approved for obesity)	5.24
2014	Naltrexone HCl/Bupropion HCl	8 mg / 90 mg per tablet; full dose, 4 tabs/day	Contrave	4.95
2021	Semaglutide 2.4	2.4 mg SC per week	Wegovy	15.3
2023	Tirzepatide	15 mg IV weekly	Zepbound	25 % at 88 weeks

Note: Intensity of lifestyle interventions and maximum weight loss differs in studies. Represented values mean weight loss in excess of placebo.

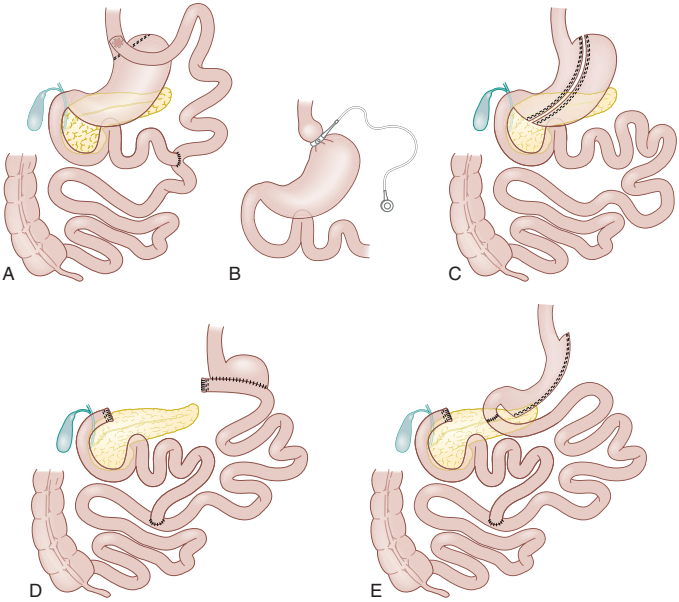
SUMMARY OF THE ANTIOBESITY MEDICATION (AOM) ACTION SITES



Bupropion acts on multiple sites of the brain (not all illustrated), weakly stimulates POMC neurons, and increases dopaminergic activity in the mesolimbic system. Naltrexone is an opioid antagonist that blocks the μ opioid receptor (MOP-R) thereby disrupting β-endorphin inhibitory feedback. Phentermine is a sympathomimetic norepinephrine-releasing agent that also increases serotonergic and dopaminergic activity. Its action sites are not fully elucidated (partly illustrated here). Topiramate is a GABA-receptor modulator, acting on GABAergic postsynaptic neurons and GABA-AR. Setmelanotide is the MC4R agonist, binding its receptor in paraventricular nucleus (PVN) and LH (not illustrated). Liraglutide and semaglutide are short-acting and long-acting GLP1 analogues, respectively.

They stimulate GLP1R in multiple sites in the brain (not fully illustrated). Tirzepatide is the GIP-based GIPR/GLP1R dual agonist. It stimulates both GIPR and GLP1R in multiple brain sites (not fully illustrated). Cagrilintide is a long-acting acylated nonselective amylin analogue that binds and activates both RAMP and CTR. Arrows represent stimulation and bars represent inhibition in the figure.

BARIATRIC SURGERY SCHEMES



Schematic diagrams of Roux-en-Y gastric bypass (A), laparoscopic adjustable gastric banding (B), sleeve gastrectomy (C), biliopancreatic diversion (D), and biliopancreatic diversion with duodenal switch (E). (Modified from Bradley D, Magkos F, Klein S. Effects of bariatric surgery on glucose homeostasis and type 2 diabetes.

CONTENTS

Учебное издание

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ОЖИРЕНИЕ: ОПРЕДЕЛЕНИЕ, ПРОФИЛАКТИКА, ТЕРАПЕВТИЧЕСКИЕ ПОДХОДЫ

OBESITY: DEFINITIONS, PREVENTION, TREATMENT APPROACHES

Учебно-методическое пособие

На английском языке

Ответственная за выпуск Т. В. Мохорт
Переводчик Ю. В. Дыдышко
Компьютерная вёрстка М. Г. Миранович

Подписано в печать 16.04.25. Формат 60×84/16. Бумага писчая «PROJECTA Special».
Ризография. Гарнитура «Times».
Усл. печ. л. 2,79. Уч.-изд. л. 2,81. Тираж 50 экз. Заказ 268.

Издатель и полиграфическое исполнение: учреждение образования
«Белорусский государственный медицинский университет».
Свидетельство о государственной регистрации издателя, изготовителя,
распространителя печатных изданий № 1/187 от 24.11.2023.
Ул. Ленинградская, 6, 220006, Минск.