REVIEW ARTICLE

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Mechanisms, Pathophysiology, and Management of Obesity

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Seven of the top 10 leading causes of death and disability in the United States today are chronic diseases (e.g., cancer and diabetes).[1] Prevention and treatment of most of these conditions must address the close link with obesity. People who are overweight or obese account for more than two thirds of the U.S. population[1] and are overrepresented in primary care practices.[2] Some professional organizations now classify obesity, defined as a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30 or higher, as a disease.[3] Management of overweight (BMI, ≥25) or obesity in the clinical setting, alone or in combination with a chronic disease, is the focus of this review.

MECHANISMS

ENVIRONMENT

Chronic diseases and obesity emerged as leading health concerns over the past century through shared environmental changes. Infectious diseases, which in 1900 were the main cause of death,[4] are now largely controlled, and the lifespan in the United States has increased almost three decades since 1900. Factors favoring a positive energy balance and weight gain over the past several decades include increasing per capita food supplies and consumption, particularly of high-calorie, palatable foods that are often served in large portions[5,6]; decreasing time spent in occupational physical activities and displacement of leisure-time physical activities with sedentary activities such as television watching and use of electronic devices[7,8]; growing use of medicines that have weight gain as a side effect (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org)[9]; and inadequate sleep.[10] These and many other factors, in combination with medical innovations that have reduced mortality from infectious diseases and prolonged the lifespan, set the foundation for the conjoint epidemics of chronic disease and obesity.[11]

GENETIC FACTORS

Not all people exposed to prevailing urban and rural environments become obese, which suggests the existence of underlying genetic mechanisms operating at the individual level. Although estimates vary, twin, family, and adoption studies show that the rate of heritability of BMI is high, ranging from 40 to 70%.[12] Eleven rare monogenic forms of obesity are now recognized (Table S2 in the Supplementary Appendix), including a deficiency of the leptin and melanocortin-4 receptors, which are expressed mainly in the hypothalamus and are involved in neural circuits regulating energy homeostasis.[13] Heterozygous mutations in the melanocortin-4 receptor gene are currently the most common cause of monogenic obesity, appearing in 2 to 5% of children with severe obesity.[13,14]

A widely used strategy to discover polygenic mechanisms conferring susceptibility to common obesity involves screening the entire genome in large samples with the goal of identifying single-nucleotide polymorphisms associated with BMI and other traits linked with obesity.[13] Over 300 loci have been identified in genomewide association studies, although collectively these loci account for less than 5% of individual variation in BMI and adiposity traits.[13] The most prominent signals using this approach are the *FTO* gene variants; persons carrying one or two copies of the risk allele have a 1.2-kg or 3-kg increase in weight, respectively, as compared with persons without copies of the allele.[13] Whole-exome and whole-genome sequencing offers the possibility of identifying new molecular targets and improved risk-prediction markers.

Changes in gene transcription and translation through environmental influences can occur without modifications in the DNA nucleotide sequence. Epigenome-wide association studies are elucidating prenatal and postnatal exposures that may influence metabolic health outcomes.[15] Epigenetic effects may thus account for additional between-individual differences in BMI and phenotypic obesity traits.[12]

Energy-Balance Dysregulation

Genes and environment interact in a complex system that regulates energy balance, linked physiological processes, and weight.[13,14] Two sets of neurons in the hypothalamic arcuate nucleus that are inhibited or excited by circulating neuropeptide hormones control energy balance by regulating food intake and energy expenditure. Short-term and long-term energy balance is controlled through a coordinated network of central mechanisms and peripheral signals that arise from the microbiome and cells within adipose tissue, stomach, pancreas, and other organs.[14] Brain regions outside the hypothalamus contribute to energy-balance regulation through sensory-signal input, cognitive processes, the hedonic effects of food consumption, memory, and attention.[14]

Reducing food intake or increasing physical activity leads to a negative energy balance and a cascade of central and peripheral compensatory adaptive mechanisms that preserve vital functions.[16] Viewed clinically, these effects may be associated with relative reductions in resting energy expenditure, food preoccupation, and many other metabolic and psychological processes that depend on the magnitude and duration of caloric restriction.[17,18] An increase in central orexigenic signals may account for a subtle and often unappreciated counterregulatory increase in appetite and food intake that limits the degree of predicted weight loss that is associated with interventions such as exercise programs.[19] These well-established metabolic and physiological effects that appear during weight loss may be maintained in the weight-reduced state.[16,17] Although the magnitude and underlying mechanisms of these effects in humans remain unclear, the implication is that persons who are no longer obese may not be physiologically and metabolically identical to their counterparts who were never obese.[16,17] High relapse rates are in accord with this view and are consistent with the concept of obesity as a chronic disease that requires long-term vigilance and weight management.

Pathophysiological Features

Anatomical Effects

Excess adiposity typically evolves slowly over time, with a long-term positive energy balance. Accretion of lipids, mainly triglycerides, in the adipose tissue occurs in conjunction with volume increases in skeletal muscle, liver, and other organs and tissues; the excess weight in persons who are overweight or obese includes variable proportions of these organs and tissues.[20] An obese person with stable weight, as compared with a person without overweight or obesity, thus has larger fat and lean mass, along with higher resting energy expenditure, cardiac output, and blood pressure and greater pancreatic β-cell mass.[20,21] Insulin secretion in the fasting state and after a glucose load increases linearly with the BMI.[22]

With weight gain over time, excess lipids are distributed to many body compartments. Subcutaneous adipose tissue holds most of the stored lipid at a variety of anatomical sites that differ in metabolic and physiological characteristics.[23] Most of the adipocytes in subcutaneous adipose tissue are white (see the Glossary for definitions of the types of fat cells), owing to stored triglycerides; relatively small and variable amounts of thermogenic brown and beige adipocytes are also present in adults.[24] Obesity is accompanied

Glossary

White adipocytes: White adipocytes are the main cell type found in human adipose tissue. Energy-yielding triglycerides and cholesterol ester are stored within the large intracellular lipid droplets. Leptin, adiponectin, and other adipokines are among the proteins secreted by white adipocytes.

Brown adipocytes: With the use of imaging methods, deposits of brown adipocytes are observed within supraclavicular, paravertebral, mediastinal, and other adipose-tissue depots in adults. Multiple lipid droplets and uncoupling protein 1–containing mitochondria are found within brown adipocytes, which can be activated to produce heat through sympathetic nervous system stimulation after cold exposure.

Beige adipocytes: Thermogenic beige or "brite" (brown-and-white) adipocytes are found scattered within white adipose tissue. They are characterized by multiple lipid droplets and uncoupling protein 1–containing mitochondria and have a progenitor cellular origin. "Browning" of white adipose tissue can be induced with cold exposure, exercise, and some endocrine hormones.

by increases in macrophages and other immune cells in adipose tissue, in part because of tissue remodeling in response to adipocyte apoptosis.[25] These immune cells secrete proinflammatory cytokines, which contribute to the insulin resistance that is often present in patients with obesity.

Visceral adipose tissue is a smaller storage compartment for lipids than is subcutaneous adipose tissue, with omental and mesenteric fat mechanistically linked to many of the metabolic disturbances and adverse outcomes associated with obesity.[23,24] Adipose tissue surrounds the kidney, and the blood-pressure increase with renal compression may contribute to the hypertension frequently observed in patients who are obese.[21] Obesity is often accompanied by an increase in pharyngeal soft tissues, which can block airways during sleep and lead to obstructive sleep apnea.[26] Excess adiposity also imposes a mechanical load on joints, making obesity a risk factor for the development of osteoarthritis.[27] An increase in intraabdominal pressure purportedly accounts for the elevated risks of gastroesophageal reflux disease, Barrett's esophagus, and esophageal adenocarcinoma among persons who are overweight or obese.[28]

METABOLIC AND PHYSIOLOGICAL EFFECTS

Adipocytes synthesize adipokines (cell-signaling proteins) and hormones, the secretion rates and effects of which are influenced by the distribution and amount of adipose tissue present.[24] Excessive secretion of proinflammatory adipokines by adipocytes and macrophages within adipose tissue leads to a low-grade systemic inflammatory state in some persons with obesity.[24]

Hydrolysis of triglycerides within adipocytes releases free fatty acids, which are then transported in plasma to sites where they can be useful metabolically. Plasma free fatty acid levels are often high in patients with obesity, reflecting several sources that include the enlarged adipose tissue mass.[24]

In addition to being found in adipose tissue, lipids are also found in liposomes, which are small cytoplasmic organelles in proximity to the mitochondria in many types of cells.[29] With excess adiposity, liposomes in hepatocytes can increase in size (steatosis), forming large vacuoles that are accompanied by a series of pathological states, including nonalcoholic fatty liver disease, steatohepatitis, and cirrhosis.[30] Accumulation of excess lipid intermediates (e.g., ceramides) in some nonadipose tissues can lead to lipotoxicity with cellular dysfunction and apoptosis.[24]

Elevated levels of free fatty acids, inflammatory cytokines, and lipid intermediates in nonadipose tissues contribute to impaired insulin signaling and the insulin-resistant state that is present in many patients who are overweight or obese.[24,31] Insulin resistance is also strongly linked with excess intraabdominal adipose tissue.[24,31] This constellation of metabolic and anatomical findings is one of several pathophysiological mechanisms underlying the dyslipidemia of obesity (elevated fasting plasma triglyceride and low-density lipoprotein cholesterol levels and low levels of high-density lipoprotein cholesterol), type 2 diabetes, obesity-related liver disease, and osteoarthritis. Elevated bioavailable levels of insulin-like growth factor 1 and other tumor-promoting molecules have been implicated in the development of some cancers.[32]

Chronic overactivity of the sympathetic nervous system is present in some patients with obesity and may account in part for multiple pathophysiological processes, including high blood pressure.[21] Heart diseases, stroke, and

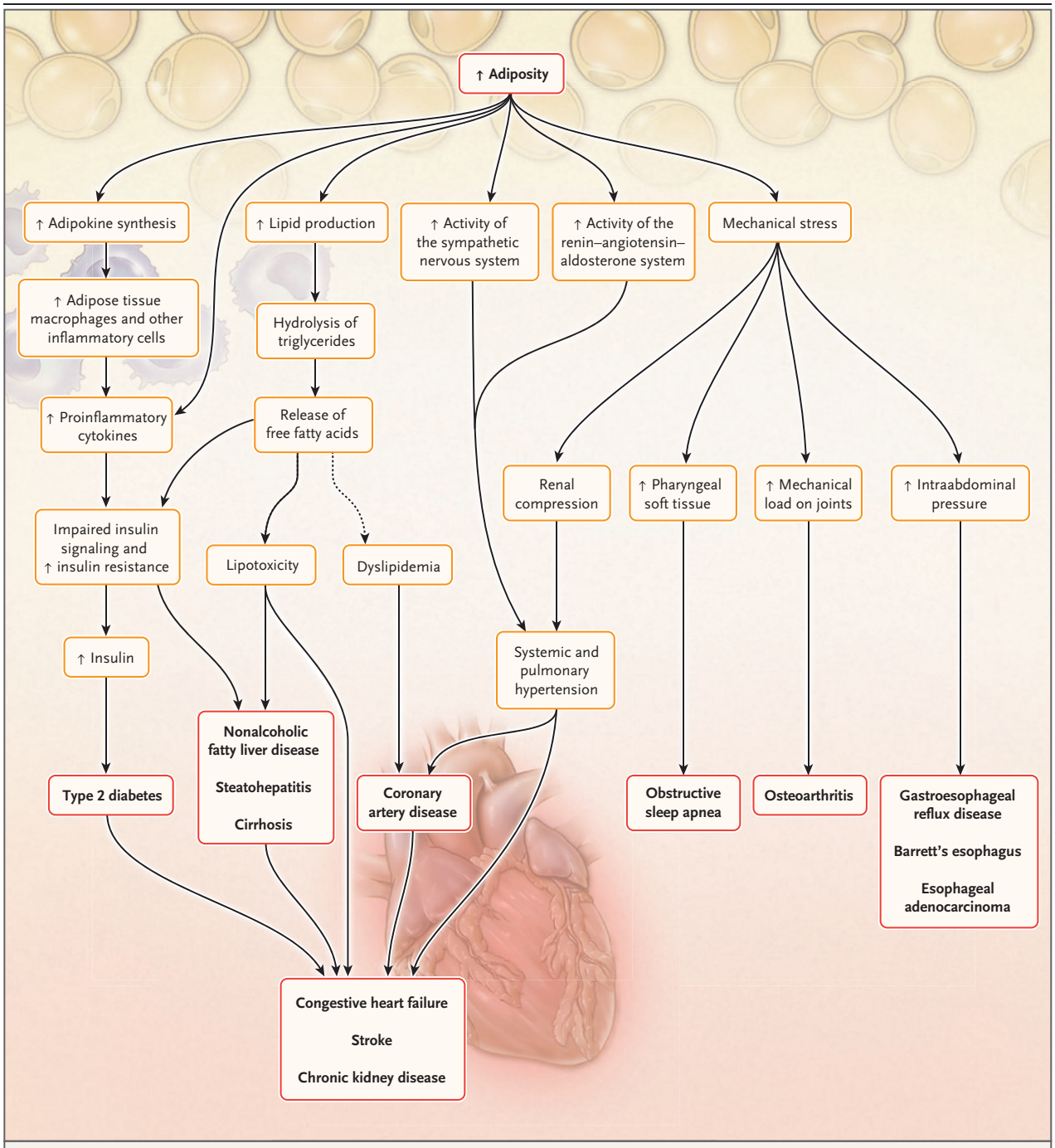

Figure 1. Some Pathways through Which Excess Adiposity Leads to Major Risk Factors and Common Chronic Diseases.
Common chronic diseases are shown in red boxes. The dashed arrow denotes an indirect association.

chronic kidney diseases all have as their main pathophysiological mechanisms high blood pressure and the cluster of findings associated with insulin resistance, obesity-associated dyslipidemia, and type 2 diabetes. Figure 1 shows some of the pathways by which the mechanical, metabolic, and physiological effects of excess adiposity lead to coexisting chronic diseases.

PSYCHOLOGICAL EFFECTS

Obesity is associated with an increased prevalence of mood, anxiety, and other psychiatric disorders, particularly among persons with severe obesity and those seeking bariatric surgery.[33,34] Causal pathways between obesity and psychiatric disorders may be bidirectional.[35] Moreover, medications used to treat bipolar disorder, major depression, and some psychotic disorders can be accompanied by substantial weight gain (Table S1 in the Supplementary Appendix).[9,33]

RESPONSE TO WEIGHT LOSS

When a negative energy balance is induced by reducing food intake, increasing activity levels, or both, thermodynamic prediction models accurately define the weight-loss trajectory in adherent patients.[36] Most patients reach a weight-loss nadir earlier than predicted by these models, after only several months, and gradually gain weight thereafter. The regained weight is related to decreased adherence to diet and activity prescriptions and to increasingly recognized endogenous compensatory mechanisms.[16,37]

Moderate weight loss, defined as a 5 to 10% reduction in baseline weight, is associated with clinically meaningful improvements in obesity-related metabolic risk factors and coexisting disorders.[9,38,39] A 5% weight loss improves pancreatic β-cell function and the sensitivity of liver and skeletal muscle to insulin; a larger relative weight loss leads to graded improvements in key adipose-tissue disturbances.[40] These salutary effects were observed clinically in overweight and obese patients with type 2 diabetes who were treated with an intensive lifestyle intervention in the Look AHEAD (Action for Health in Diabetes) study.[41] At 1 year, patients had a mean weight loss of 8.6% of baseline weight, which was accompanied by significant reductions in systolic and diastolic blood pressure (of 6.8 and 3.0 mm Hg, respectively) and levels of triglycerides (of 30.3 mg per deciliter [0.34 mmol per liter]) and glycosylated hemoglobin (of 0.64%). A graded response was observed for these weight-sensitive measures, with larger weight losses accompanied by greater improvements.[42]

Moderate weight loss can translate to disease prevention in high-risk persons. Patients with overweight or obesity and impaired glucose tolerance who received an intensive lifestyle intervention in the Diabetes Prevention Program had a mean weight loss of 5.6 kg at 2.8 years and a 58% relative reduction in the risk of type 2 diabetes.[43] The incidence of type 2 diabetes remained 34% below the incidence in the control group at 10 years of follow-up, even though the participants in the intervention group had, on average, returned to close to their baseline weight.[44]

Mean losses of 16 to 32% of baseline weight produced by bariatric surgery in patients with severe obesity may lead to disease remission, including remission of type 2 diabetes in patients who undergo bariatric surgery, particularly Roux-en-Y gastric bypass.[45-50] Significant reductions in all-cause mortality have also been shown in observational studies of surgically treated patients.[51,52]

Although weight loss is an effective, broad-acting therapeutic measure, not all risk factors and chronic disease states respond equally well.[38,39,42] Severe obstructive sleep apnea, for example, improves but rarely fully remits in response to weight-loss treatments, including bariatric surgery.[26] Moreover, the beneficial clinical effects of moderate weight loss achieved with intensive lifestyle intervention did not reduce morbidity and mortality associated with cardiovascular disease after 9.6 years in the Look AHEAD study.[53] Well-established medical therapies must be used with weight loss to achieve good control of obesity-related coexisting conditions. Similarly, symptoms of some psychiatric disorders may improve with weight loss,[33,54] but adjunctive psychiatric care is critical, particularly in persons with moderate or severe disorders. For example, adjunctive care has been shown to be of value for improving mental health and eating behaviors such as binge eating.[34]

CLINICAL CARE

ASSESSMENT

The obese phenotype is complex, and some patients do not have any evident cardiometabolic effects, a phenomenon that has been called the "metabolically healthy" obese state.[55] Clusters of findings related to insulin resistance with an enlarged intraabdominal and upper-body subcutaneous adipose-tissue mass are consistent with the diagnosis of a metabolic syndrome.[24,31]

Although the BMI is a good proxy for adipos-

Table 1. Recommended Components of a High-Intensity Comprehensive Lifestyle Intervention to Achieve and Maintain a 5-to-10% Reduction in Body Weight.*

Component	Weight Loss	Weight-Loss Maintenance
Counseling	≥14 in-person counseling sessions (individual or group) with a trained interventionist during a 6-mo period; recommendations for similarly structured, comprehensive Web-based interventions, as well as evidence-based commercial programs	Monthly or more frequent in-person or telephone sessions for ≥1 yr with a trained interventionist
Diet	Low-calorie diet (typically 1200–1500 kcal per day for women and 1500–1800 kcal per day for men), with macronutrient composition based on patient's preferences and health status	Reduced-calorie diet, consistent with reduced body weight, with macronutrient composition based on patient's preferences and health status
Physical activity	≥150 min per week of aerobic activity (e.g., brisk walking)	200–300 min per week of aerobic activity (e.g., brisk walking)
Behavioral therapy	Daily monitoring of food intake and physical activity, facilitated by paper diaries or smart-phone applications; weekly monitoring of weight; structured curriculum of behavioral change (e.g., DPP), including goal setting, problem solving, and stimulus control; regular feedback and support from a trained interventionist	Occasional or frequent monitoring of food intake and physical activity, as needed; weekly-to-daily monitoring of weight; curriculum of behavioral change, including problem solving, cognitive restructuring, and relapse prevention; regular feedback from a trained interventionist

* Data are from the Guidelines (2013) for the Management of Overweight and Obesity in Adults, reported by Jensen et al.[39] The guidelines concluded that a variety of dietary approaches that differ widely in macronutrient composition, including ad libitum approaches (in which a lower calorie intake is achieved by restriction or elimination of particular food groups or by the provision of prescribed foods), can lead to weight loss provided they induce an adequate energy deficit. The guidelines recommended that practitioners, in selecting a weight-loss diet, consider its potential contribution to the management of obesity-related coexisting disorders (e.g., type 2 diabetes and hypertension). The guidelines did not address the possible benefits of strength training, in addition to aerobic activity. DPP denotes Diabetes Prevention Program.

ity at the group level, each patient's risk can be stratified further on the basis of a personal and family medical history, a psychiatric history,[33] and blood studies, as well as a behavioral history that includes information about physical activity, nutrition, and eating behavior.[34] Waist circumference is also a useful measure of intraabdominal and upper-body subcutaneous adipose tissue, and some guidelines include it as a risk marker in addition to or in place of the BMI.[31,39]

TREATMENT

Treatments should be aligned with the severity of overweight, associated coexisting chronic diseases, and functional limitations. Useful guidelines are available for evaluating an individual patient's health risks and treatment options.[38,39,56] The main treatment options with sufficient evidence-based support are lifestyle intervention, pharmacotherapy, and bariatric surgery.[9,38,39,57]

Lifestyle Intervention

Lifestyle interventions designed to modify eating behaviors and physical activity are the first option for weight management, given their low cost and the minimal risk of complications.[39] The aim for patients who are overweight or obese is to improve health and quality of life by achieving and maintaining moderate weight loss. Extensive research led to current recommendations that patients receive high-intensity behavioral counseling, with 14 or more visits in 6 months[39] (Table 1). A comprehensive program, delivered by a trained interventionist, results in a mean weight loss of 5 to 8%,[39] and approximately 60 to 65% of patients lose 5% or more of initial weight (Fig. 2). Less-intensive lifestyle counseling is an option for preventing additional weight gain in patients who are at low risk for disease or who choose not to participate in a high-intensity program.

Behavioral therapy, the core of lifestyle intervention, provides patients with techniques for adopting dietary and activity recommendations.[39] Foremost among these recommendations is regular recording of food intake, physical activity, and weight. This task can be facilitated by smartphone applications, activity counters, and cellular-connected scales.[39,63] Patients review their progress approximately weekly with a trained interventionist who provides encouragement and goal-setting and problem-solving instructions.[39]

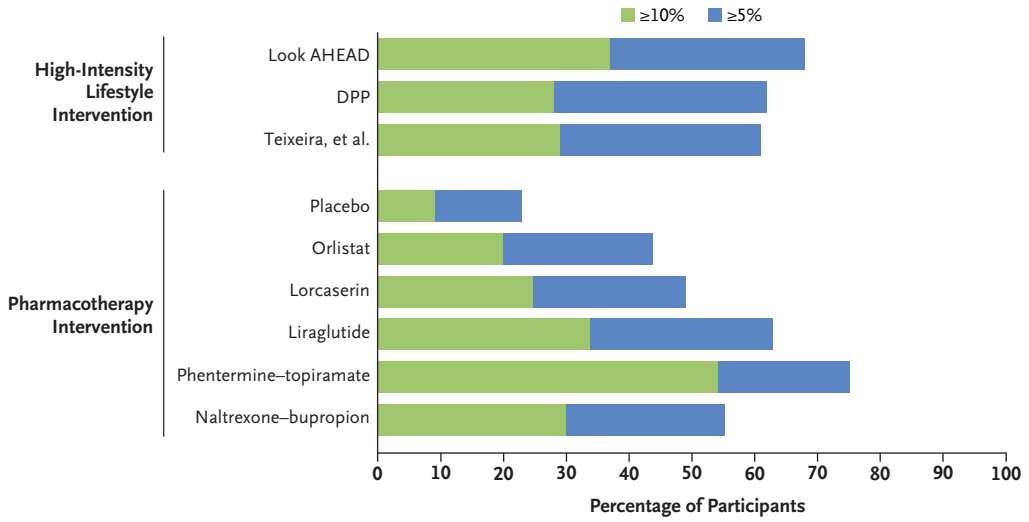

Figure 2. Weight Loss at 1 Year with High-Intensity Lifestyle Interventions or Pharmacotherapy Combined with Low-to-Moderate-Intensity Lifestyle Counseling.

Shown are the percentages of participants in randomized, controlled trials who had weight loss of at least 5% or at least 10% of their initial weight at 1 year after a high-intensity lifestyle intervention or pharmacotherapy that typically was combined with low-to-moderate-intensity lifestyle counseling (≤1 session per month). Percentages shown are cumulative; the percentage of participants who lost at least 5% of their initial weight includes the percentage who lost at least 10%. For example, 68% of participants in the Look AHEAD study lost at least 5% of their initial weight, and 37% of these participants lost at least 10%. The lifestyle intervention trials (Look AHEAD,[41] the Diabetes Prevention Program [DPP] trial,[43] and the trial reported by Teixeira et al.[58]) were selected because they were judged to be of fair or good quality by the Guidelines (2013) for the Management of Overweight and Obesity in Adults[39] and because the trial data are reported as categorical weight losses. Additional categorical weight-loss data from the DPP trial[43] were provided by the DPP Research Group. The median percentages of participants who had a weight loss of at least 5% or 10% with each of five medications approved for long-term weight management are from a meta-analysis by Khera et al.[59] Data on the percentage of participants with weight loss at 1 year of at least 15% of their initial weight were available for the Look AHEAD study[41,42] (16%), the DPP trial[43] (11%), liraglutide[60] (14%), phentermine–topiramate[61] (32%), and naltrexone–bupropion[62] (14%).

Primary care practitioners frequently provide recommendations for dietary and activity modification but are usually unable to offer high-intensity behavioral counseling.[64] Moreover, despite their role at the front line of obesity management, physicians receive minimal training in nutrition and activity counseling.[65] Recommendations alone, including encouragement to use a smart-phone application, result in minimal weight loss, which can frustrate both practitioners and patients. Referring patients to high-intensity community interventions is an important option. YMCAs increasingly offer a version of the Diabetes Prevention Program,[66] and commercial weight-loss programs can be prescribed if their safety and efficacy have been reported in peer-reviewed publications (e.g., Weight Watchers and Jenny Craig).[39] Telephone-delivered lifestyle interventions result in approximately the same weight loss as in-person counseling, thus encouraging the development of weight-management call centers.[67] Web-based interventions that include personalized interventionist feedback can be prescribed but typically result in only one half to two thirds of the weight loss achieved with in-person counseling.[39,68] Web-based interventions, however, potentially have greater reach and convenience and lower costs than in-person counseling.

Weight regain is common after a patient completes a lifestyle intervention program.[39] The most effective behavioral method for preventing weight regain is continued support on an every-other-

week or monthly basis, whether in person or by telephone.[39,69] Although long-term behavioral counseling is effective, it is not widely available. Moreover, when this approach fails to produce the additional weight loss that patients desire, it is challenging to persuade the patients to remain in counseling to maintain the smaller weight loss they have achieved.[39]

Pharmacotherapy

Pharmacotherapy is indicated as an adjunct to a reduced-calorie diet and increased activity for long-term weight management.[9,38,70] Medications may be considered in adults who have a BMI of 30 or higher or a BMI of 27 to 29 with at least one weight-related coexisting condition.[9] Pharmacotherapy and lifestyle intervention lead to additive weight loss and should be used together. Pharmacotherapy with lifestyle intervention may also be of benefit in facilitating the maintenance of reduced weight.[9,38,70]

Phentermine, the most widely prescribed weight-management medication in the United States, is a low-cost sympathomimetic amine that was approved by the Food and Drug Administration (FDA) in 1959 for short-term use (≤3 months).[9] The availability of five newer FDA-approved medications for weight management, along with complexities surrounding the prescribing of phentermine, has led some professional groups to discourage long-term use of phentermine.[9,38,70]

For approval of a new weight-loss drug, the FDA requires trials of at least 1 year's duration that show the safety of the drug and a mean difference of 5% or more in weight loss between the medication group and the placebo group. Alternatively, the proportion of drug-group participants who lose 5% or more of baseline weight must be at least 35% and approximately double the proportion in the placebo group.[70] The five medications approved for long-term weight management include three single drugs and two combination drugs. The main features of these drugs, which are typically combined with low-to-moderate-intensity lifestyle counseling (≤1 session per month), are summarized in Table 2.

In 1-year pivotal trials, total weight losses for the three monotherapies (orlistat, lorcaserin, and liraglutide), whose effects are mediated by different mechanisms, ranged from 5.8 to 8.8 kg (5.8 to 8.8% of initial body weight).[9,60,71,72] Placebo-subtracted weight losses, determined from a meta-analysis, ranged from 2.6 to 5.3 kg.[59]

The two combination medications (phentermine–topiramate and naltrexone–bupropion) include drugs that purportedly act additively or synergistically on neural weight-loss mechanisms.[61,62] In 1-year pivotal trials, total weight loss for these combination drugs ranged from 6.2 to 10.2 kg (6.4 to 9.8% of initial body weight); placebo-subtracted weight loss was 8.8 kg for phentermine–topiramate and 5.0 kg for naltrexone–bupropion.[59,61,62] Categorical 1-year weight losses for the five FDA-approved drugs are shown in Figure 2.

Weight loss achieved with pharmacotherapy is generally associated with improvements in risk factors and chronic diseases, as shown for glycosylated hemoglobin in patients with type 2 diabetes (Fig. S1 in the Supplementary Appendix). However, some drugs may increase the pulse rate[60] or attenuate expected blood-pressure reductions.[62] In addition, FDA-mandated postmarketing trials of cardiovascular disease outcomes in patients treated with these medications have yet to be completed, except in the case of liraglutide.[60]

Terminating medication after 12 to 16 weeks in patients who do not lose at least 5% of weight increases the likelihood of a clinically meaningful benefit in those who continue to receive treatment.[38,70] The benefit also may be increased by aligning the prescribed weight-loss medication with treatment of coexisting medical or psychiatric conditions.[9,38]

For a number of reasons, physicians do not use weight-loss medications to the extent that one might expect, given the scale of the obesity problem.[70] First, patients are often disappointed by moderate weight loss. Dissatisfaction with the results, coupled with requirements to pay a substantial portion of costs, may lead to short-term rather than long-term use. Also, some practitioners appear to have lingering concerns about medication safety and may be awaiting the outcome of FDA-mandated cardiovascular disease trials. Finally, weight regain is common after termination of drug treatment[70] and is discouraging to patients and practitioners. Long-term use of weight-loss medications, as approved by the FDA, may be necessary for long-term weight management, just as medications for hypertension, dyslipidemia,

Table 2. Medications Approved by the Food and Drug Administration for Long-Term Weight Management.*

Drug	Main Mechanisms of Action	Dose	Study Duration	Mean Weight Loss†	Common Side Effects	Contraindications
			wk	*kg (%)*		
Orlistat[71]	Pancreatic and gastric lipase inhibitor; resulting fat malabsorption reduces net energy intake	120 mg before meals (three times a day)	52	Drug, 8.8 (8.8); placebo, 5.8 (5.8); PSWL, 2.6	Oily spotting, flatus with discharge, fecal urgency, oily evacuation, increased defecation, fecal incontinence	Pregnancy, chronic malabsorption syndrome, cholestasis
Lorcaserin[72]	Selective $5HT_{2C}$ receptor agonist; promotes satiety to reduce food intake	10 mg twice a day	52	Drug, 5.8 (5.8); placebo, 2.2 (2.2); PSWL, 3.2	In patients without diabetes: headache, dizziness, fatigue, nausea, dry mouth, constipation; in patients with diabetes: hypoglycemia, headache, back pain, fatigue	Pregnancy
Liraglutide[60]	GLP-1 agonist; delays gastric emptying to reduce food intake	Starting dose, 0.6 mg given subcutaneously; dose increased weekly by 0.6 mg as tolerated to reach 3.0 mg	56	Drug, 8.4 (8.0); placebo, 2.8 (2.6); PSWL, 5.3	Nausea, vomiting, constipation, hypoglycemia, diarrhea, headache, fatigue, dizziness, abdominal pain, increased lipase levels	Pregnancy, personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2
Phentermine–topiramate[61]	Norepinephrine-releasing agent (phentermine), GABA receptor modulation (topiramate); decreases appetite to reduce food intake	Starting dose, 3.75 mg/23 mg for 2 wk; recommended dose, 7.5 mg/46 mg; maximum dose, 15 mg/92 mg	56	Drug, 8.1 (7.8) at recommended dose, 10.2 (9.8) at maximum dose; placebo, 1.4 (1.2); PSWL, 8.8	Insomnia, dry mouth, constipation, paresthesias, dizziness, dysgeusia	Pregnancy, hyperthyroidism, glaucoma, MAOIs, hypersensitivity to sympathomimetic amines
Naltrexone–bupropion[62]	Opioid antagonist (naltrexone), dopamine and norepinephrine reuptake inhibitor (bupropion); acts on CNS pathways to reduce food intake	1 tablet (8 mg of naltrexone and 90 mg of bupropion) daily for 1 wk; dose subsequently increased each wk by 1 tablet per day until maintenance dose of 2 tablets twice a day at wk 4	56	Drug, 6.2 (6.4); placebo, 1.3 (1.2); PSWL, 5.0	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea	Uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, drug or alcohol withdrawal, use of MAOIs, long-term opioid use, pregnancy

* For each medication, weight-loss data are from a pivotal phase 3 trial submitted to the FDA for drug approval.[60-62,71,72] CNS denotes central nervous system, GABA gamma-aminobutyric acid, GLP-1 glucagon-like peptide 1, $5HT_{2C}$ 5-hydroxytryptamine 2C, and MAOI monoamine oxidase inhibitors.
† Data on placebo-subtracted weight loss (PSWL) are from a meta-analysis of studies.[59]

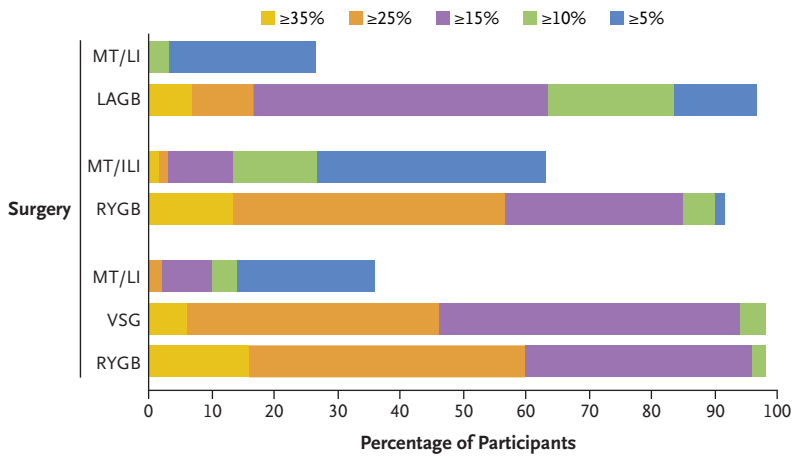

Figure 3. Weight Loss at 1 Year with Bariatric Surgery and Lifestyle Interventions as Compared with Lifestyle Interventions Alone.

Shown are categorical weight losses at 1 year in persons with overweight or obesity and type 2 diabetes who participated in randomized, controlled trials evaluating laparoscopic adjustable gastric banding (LAGB) combined with medical therapy and a lifestyle intervention (MT/LI) as compared with MT/LI alone,[46] Roux-en-Y gastric bypass (RYGB) combined with medical therapy and an intensive lifestyle intervention (MT/ILI) as compared with MT/ILI alone,[75] and vertical-sleeve gastrectomy (VSG) or RYGB combined with MT/LI as compared with MT/LI alone.[76] Percentages shown are cumulative; the percentage of participants who lost at least 5% of their initial weight includes the percentage who lost at least 10%, the percentage who lost at least 10% includes the percentage who lost at least 15%, and so on. For example, 97% of participants who underwent LAGB lost at least 5% of their initial weight, and 7% of these participants lost at least 35%.

and type 2 diabetes must be administered for the long term.

Bariatric Surgery

Between 2000 and 2010, the prevalence of class III obesity (BMI, ≥40) increased by 70%.[73] Since high morbidity and mortality rates are associated with class III obesity and with a BMI of 35 to 39 in the presence of a coexisting condition, the use of surgical weight-loss procedures has escalated. Although more effective than lifestyle and pharmacologic interventions, these procedures are associated with greater risks.[38,39,57,74]

In the United States, three main types of bariatric surgery are currently performed; a fourth procedure, biliopancreatic diversion, is performed in no more than 2% of cases.[57,74] Laparoscopic adjustable gastric banding, the least invasive and safest procedure, involves placing an inflatable silicone band around the gastric fundus to create a small (approximately 30-ml) pouch.[57] This restrictive procedure is reversible and does not cause anatomical gut changes. Roux-en-Y gastric bypass restricts food intake by creating in the upper gastric fundus a small (<50-ml) pouch anastomosed to a Roux limb of jejunum.[57] Food bypasses 95% of the stomach and duodenum and most of the jejunum. The recently introduced vertical-sleeve gastrectomy involves removal of approximately 70% of the stomach, with subsequent acceleration of gastric emptying.[57,74]

Gastric banding results in a mean weight reduction of 15 to 20% at 1 year. Larger reductions can be achieved with vertical-sleeve gastrectomy and Roux-en-Y procedures: approximately 25% and 30%, respectively.[52,57,74,75] More than half of patients who undergo Roux-en-Y gastric bypass have weight loss of 25% or more at 1 year (Fig. 3).[75]

Patients regain an average of 5 to 10% from their lowest weight at 10 years of follow-up,[45,52] with a higher frequency of full weight regain reported with gastric banding than with the other two operations. Concerns about efficacy and high reoperation rates have led to a decrease in the use of gastric banding in the United States, which accounted for only 6% of procedures in 2013, as compared with vertical-sleeve gastrectomy and Roux-en-Y gastric bypass, which accounted for 49% and 43% of procedures, respectively.

Pronounced clinical improvements are observed in most obesity-related health conditions, particularly type 2 diabetes, after Roux-en-Y gastric bypass, vertical-sleeve gastrectomy, and to a lesser extent, gastric banding. Six randomized studies with a duration of 2 or more years showed high rates of diabetes remission among patients treated with these surgical procedures (Table S3 in the Supplementary Appendix).[45-50] For example, in one 3-year study,[49] remission rates were 5% for intensive medical therapy alone, 24% for intensive medical therapy combined with vertical-sleeve gastrectomy, and 38% for intensive medical therapy combined with Roux-en-Y gastric bypass.

The large and sustained weight losses and metabolic improvements after Roux-en-Y gastric bypass and vertical-sleeve gastrectomy are due mainly to an increase in satiety and long-term hypophagia. The complex mechanisms that account for these effects are the subject of ongoing research; possible mechanisms include changes in taste, food preferences, gastric-pouch emptying rates, vagal signaling, gastrointestinal hormone activity, circulating bile acids, and the gut microbiome.[57]

Owing to the increasing use of laparoscopic procedures, the 30-day mortality rates for all bariatric surgeries have decreased over the past decade. Gastric banding now has the lowest perioperative mortality rate (approximately 0.002%), with rates of 0.2% and 0.3% for Roux-en-Y gastric bypass and vertical sleeve gastrectomy, respectively.[57,77] Serious perioperative adverse events parallel these findings, with rates of approximately 1% for gastric banding and approximately 5% for vertical-sleeve gastrectomy and Roux-en-Y gastric bypass.[57,77,78] About one fourth of patients treated with gastric banding or Roux-en-Y gastric bypass require surgical revisions at 10 or more years of follow-up; the data are limited for the more recently introduced vertical-sleeve gastrectomy.[57] More long-term studies with high follow-up rates are needed to confirm the available estimates.[57,73,79]

Limitations of current surgeries include high costs initially and at 1 year, risks of short- and long-term complications,[57,73,77,79] and weight regain in approximately 5 to 20% of patients.[45-50,55] However, Roux-en-Y gastric bypass and vertical-sleeve gastrectomy are by far the most effective long-term treatments for severe obesity, a condition associated with high morbidity, mortality, and health care costs.

BARRIERS TO TREATMENT

Only a small fraction of patients for whom these three classes of treatments are indicated actually receive them. Barriers to care include slow recognition among health care providers that obesity requires long-term management, inadequate physician training in nutrition and obesity, limited reimbursement for the full range of treatments, lack of effective and accessible lifestyle programs that can be administered locally or remotely at low cost to diverse populations, and limited referral of patients with severe obesity to experienced surgeons, even though bariatric surgery is a level A health-improving treatment option (i.e., with improvement based on data from multiple randomized trials or meta-analyses).[39] The hope is that a growing national, multidisciplinary network of medical professionals who have been trained and certified in the treatment of obesity will overcome some of these impediments to effective patient care.

CONCLUSIONS

Creating the conditions for healthy living in our modern environment, including prevention of obesity, is one of the great challenges for humankind. Practitioners alone, when caring for affected patients, cannot manage all the pathways leading to the genesis of excess adiposity but can proceed with the knowledge that the management interventions described here are likely to benefit the patients who receive them. Much more effort must be devoted to both the prevention and treatment of obesity as part of the global campaign to rein in the chronic disease epidemic.

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