THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Obesity

Pathophysiology and Management

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ABSTRACT

Obesity continues to be among the top health concerns across the globe. Despite our failure to contain the high prevalence of obesity, we now have a better understanding of its pathophysiology, and how excess adiposity leads to type 2 diabetes, hypertension, and cardiovascular disease. Lifestyle modification is recommended as the cornerstone of obesity management, but many patients do not achieve long-lasting benefits due to difficulty with adherence as well as physiological and neurohormonal adaptation of the body in response to weight loss. Fortunately, 5 drug therapies—orlistat, lorcaserin, liraglutide, phentermine/topiramate, and naltrexone/bupropion—are available for long-term weight management. Additionally, several medical devices are available for short-term and long-term use. Bariatric surgery yields substantial and sustained weight loss with resolution of type 2 diabetes, although due to the high cost and a small risk of serious complications, it is generally recommended for patients with severe obesity. Benefit-to-risk balance should guide treatment decisions. (J Am Coll Cardiol 2018;71:69–84) © 2018 by the American College of Cardiology Foundation.

Obesity, which is broadly defined as excess body weight for a given height, remains a continuing global health concern, as it is associated with increased risk of numerous chronic diseases including type 2 diabetes (T2D), hypertension, and cardiovascular disease (CVD). Body mass index (BMI) (weight in kg/height in m²), the most widely used formula to define overweight (BMI 25 to 29.9 kg/m²) and obesity (BMI ≥30 kg/m²), while not being a true measure of adiposity, is simple to use in health screenings and epidemiological surveys. A recent analysis of data from 195 countries revealed that the prevalence of obesity has doubled in more than 70 countries since 1980, and over 600 million adults were obese in 2015, with high BMI accounting for 4 million deaths globally (1). The pathogenesis of obesity is complex, with environmental, sociocultural, physiological, medical, behavioral, genetic, epigenetic, and numerous other factors contributing to causation as well as persistence (2).

PATHOPHYSIOLOGY

Controlling energy intake and energy expenditure are the main mechanisms by which energy balance is achieved. For this basic energetic equation, it is true that a calorie really is a calorie, and all calories are equal. However, we realize that not all calories are equal when we look beyond this purely energetic consideration and consider the pathogenesis of obesity-related comorbidities. Therefore, a proper explanation of the pathophysiology of obesity includes

2 parallel discussions: 1 from an energetic and 1 from a nutritional standpoint. Here, we focus mainly on the former, due in large part because there is considerable consensus for the mechanisms of energy balance regulation, whereas there is confusion and controversy regarding optimal nutrient composition (3,4). The distinction between the causes and consequences of obesity must be given due consideration, as also the importance of understanding obesity-independent and obesity-dependent pathophysiology of comorbidities including CVD.

On the basis of observations that individual adult body weight is remarkably stable and refractory to short-term experimental up or down perturbations under constant environmental conditions, most scientists agree that body weight or adiposity is actively regulated or defended (5). New insights suggest that the elevated body weight/adiposity in many obese subjects is defended just as it is in normal weight subjects (6), supporting the notion that obesity is a disease, thus shifting the blame from the person to the physiology.

Genome-wide association study-based data suggest a genetic predisposition for obesity with identification of more than 140 genetic chromosomal regions related to obesity (7). Gene expression related to BMI and general adiposity is highly enriched in the central nervous system (8). However, only a few genes with a large effect size on BMI have yet been identified. These are the genes encoding components of leptin and melanocortin signaling, as well as paternally expressed genes along a specific region of chromosome 15 responsible for Prader-Willi syndrome (9). In contrast to such monogenetic cases, common obesity is thought to be associated with a large number of genes with small effect sizes.

A widely held view is that obesity results from an interaction between environment/lifestyle and genetic susceptibility. Several hypotheses have been put forward to explain the existence of obesity susceptibility genes. The "thrifty" gene hypothesis posits that genes promoting energy intake and high fuel efficiency were selected over genes promoting energy-guzzling during human evolution (10). The "drifty" gene hypothesis argues that the evolutionary selection pressure for genes keeping body weight/adiposity to a minimum relaxed when humans invented weapons and fire about 2 million years ago, and thus were no longer threatened by predators,

with the consequence of a random drift of genes allowing increased adiposity (11).

The early origins of adult disease hypothesis suggests that obesity can develop in offspring from mothers exposed to metabolic hardship such as undernutrition, obesity, and diabetes (12). One of the molecular mechanisms responsible for early-life metabolic programming is epigenetic modification of genes through methylation, histone modifications, chromatin remodeling, and noncoding RNA alterations (13). Importantly, such epigenetically determined increased risk for adult obesity can be transmitted to future generations, further accelerating the obesity epidemic. Thus, finding the tools and therapies to break the vicious circle of epigenetic programming is an important target of obesity research.

Given the disproportionally high expression of obesity-associated genes and epigenetic modifications in the central nervous system, it is highly likely that obesity genes act, not only within the hypothalamic homeostatic regulator of energy balance, but also within neural circuits that are involved in interactions with an obesogenic environment, including circuits underlying reward-based decision making, learning and memory, delayed discounting, and spatial orientation.

CONTROLLING FOOD INTAKE IN AN ENVIRONMENT OF PLENTY

Although the brain primarily regulates food intake as a behavior, it relies on information from the rest of the body and from the environment to make the decision to eat or not to eat. Well over 50 years ago, seminal studies established the hypothalamus as a key hub for the detection of hunger and organization of eating behavior (14). Since then, the importance of the hypothalamus has been confirmed, with much detail added to its functional and chemical anatomy (15). In addition, the importance of crosstalk (**Figure 1**) between the hypothalamus and other brain regions, as well as with the periphery, has been recognized (16).

A key function of the basomedial hypothalamus is to detect shortages in nutrient supply, both short term and long term, and translate them into behavior. To this end, separate groups of chemically distinct neurons (agouti-related peptide/neuropeptide Y [AGRP/NPY] and proopiomelanocortin/cocaine and amphetamine regulated transcript [POMC/CART]) are sensitive to circulating metabolites and hormones signaling availability of energy, such as leptin, ghrelin, insulin, and glucose, in addition to neural signals reflecting the nutritional status of the gut conveyed

through the vagus nerve and brainstem (5). Even though every tissue and cell has its own evolutionarily conserved energy sensor, and much of energy needs can be covered by cell- and tissue-autonomous and peripheral reflexes without involving the brain, the hypothalamus should thus be considered a master energy sensor that integrates past, current, and future needs of the entire body with prevailing or expected environmental conditions (17). Thus, any interference with the normal functions of this hypothalamic circuitry leads to impairments in energy balance regulation, and much research effort is directed to this circuitry.

It is increasingly clear that the integrative capacity of the hypothalamus is also enriched by extensive crosstalk with other brain areas such as the cortex and limbic system, which are concerned with processing external sensory information, cognitive and emotional control, and reward-based decision making. Even before it is tasted and absorbed, food can have powerful effects on the brain through visual and olfactory stimuli. This is particularly important for humans in an environment with high food availability and constant reminders of appetizing food by conditioned stimuli and the media. Neuroimaging studies have identified several key brain nodes and networks that are differentially affected by visual food stimuli under conditions of fasting, weight loss (induced by both calorie restriction and bariatric surgery), refeeding, overfeeding, exercise, hormone infusion, leanness and obesity, as well as voluntary cognitive control (18). Besides areas obviously involved in processing of visual stimuli, a salience network, associated with the motivation, desire, and craving for food, particularly palatable and high-energy food (also referred to as "wanting"), consisting of areas in the frontal cortex, ventral and dorsal striatum, and amygdala was found to be more activated in obese versus lean subjects (19). An inhibitory network centered around the dorsolateral prefrontal cortex is activated in subjects instructed to resist craving (20), and this ability of cognitive self-control is greater in patients with the highest weight loss after gastric bypass surgery (21). Furthermore, connectivity between the salience and inhibitory network and other cortical areas (referred to as hedonic controls), as well as the hypothalamus (homeostatic controls) is different in lean versus obese subjects (22). Therefore, the classical dichotomy between homeostatic and hedonic controls has given way to a more unified and integrative or allostatic control system and an effective strategy to prevent or treat obesity based on targeting multiple pathways (17).

FIGURE 1 Neural Pathways and Systems Controlling Ingestive Behavior and Energy Balance

Schematic diagram shows the 3 heavily interconnected major brain areas constituting the core processor for the control of ingestive behavior and its relation to the gastrointestinal tract and other peripheral organs involved in energy storage and utilization. The hindbrain is mainly concerned with meal size control, because it possesses all the elements to detect sensory information mediated by vagal afferents and circulating factors, and generate motor output associated with the ingestion, digestion, and absorption of food. The corticolimbic system, consisting of large cortical areas, basal ganglia, hippocampus, and amygdala, is intimately connected to the hypothalamus and brainstem, and provides the emotional, cognitive, and executive support for ingestive behavior. The hypothalamus via its connections with the other areas is central for the drive to eat and can potently modulate peripheral organs by autonomic and endocrine outflow. Reproduced with permission from Berthoud et al. (17).

Regulation of intake of specific nutrients is still poorly understood, even though it has direct and powerful implications on metabolic and cardiovascular diseases. Whether the same neural system responsible for controlling total calories is also responsible for controlling intake of carbohydrates, fats, and proteins, and what conveys specificity remains to be demonstrated. The neural control of salt intake may serve as a blueprint for deciphering such specificity in the circuitry (23).

MAXIMIZING ENERGY EXPENDITURE IN THE MODERN WORLD

Besides energy intake, energy expenditure is the other important determinant of energy balance and body weight. Much of the control of energy expenditure is tightly coupled to the controls of food intake

and embedded in the powerful integrative hypothalamic energy sensor and regulator of body weight and adiposity. If we accept the notion that adult body weight is actively defended, any increase in energy expenditure will be compensated by increased energy intake. This outcome is supported by many, but not all, human studies using exercise to increase energy expenditure and reduce body weight (24). Thus, selective increase of energy expenditure as a strategy to reduce body weight/adiposity would only work if it can be at least partially uncoupled from this compensatory increase in food intake, and deciphering the molecular mechanisms involved in coupling energy expenditure to energy intake would go a long way in finding novel obesity therapies. Interestingly, complete uncoupling appears to occur in the activity-based rodent model of anorexia nervosa, where rodents paradoxically reduce food intake in the face of increased expenditure in a running wheel (25). Identification of this powerful uncoupling process could provide useful molecular targets for a new class of antiobesity drugs that would prevent the compensatory increase in food intake typically observed after a bout of physical activity (24). Alternatively, strategies to cognitively influence this uncoupling process would also be valuable. By not replacing, but enhancing, the effects of physical activity, such an approach would take advantage of the many other beneficial effects of exercise on cardiovascular (26) and mental health (27).

BMI, BODY SHAPE AND COMPOSITION, AND DISEASE RISK

The patient's size and shape can be used to estimate their risk of developing cardiovascular and other noncommunicable chronic diseases. The 2 most available measures of body size are height and weight. As first reported in 1842 by Adolphe Quetelet, weight varies across adults as height squared (28). Several carefully analyzed large samples of men and women of variable ethnicity have largely confirmed Quetelet's seminal observation (29). By dividing weight by height squared (kg/m^2), a shape index is created that is independent of height.

The emerging area of nutritional epidemiology 5 decades ago prompted Ancel Keys and his colleagues to seek a simple shape index highly correlated with weight, but independent of height (30). The investigators examined several shape indices relative to adiposity as assessed with underwater weighing and skinfold anthropometry methods. The highest correlation between the evaluated adiposity measures and a shape index was for weight/height^2, renamed from Quetelet's Index to BMI. Numerous studies that have since examined the relations between BMI and clinical outcomes have suggested that disease risk and mortality rates are higher in people with BMI at the low and high ends of population BMI distributions. Some debate continues on the "optimum" BMI for maintaining health and longevity (31), but there is near universal acceptance of ranges consistent with good health (32).

BMI ranges for Americans and Europeans for underweight, normal weight, overweight, and obese are <18.5, 18.5 to 24.9, 25 to 29.9, and ≥30 kg/m^2, respectively (32). Various health panels (32,33) have further stratified obesity by BMI cutpoints: 30 to 34.9 kg/m^2 (class I), 35 to 39.9 kg/m^2 (class II), ≥40 kg/m^2 (class III), ≥50 kg/m^2 (class IV), and ≥60 kg/m^2 (class V). Recommended cutpoints for overweight and obesity are lower in some Asian nations (34).

Adiposity, defined as percent fat, increases as a curvilinear function of BMI. Fat-free mass, including the mass of skeletal muscles and visceral organs, also increases in relation to BMI (29). Left ventricular (LV) mass, including LV wall thickness and internal dimensions, is larger with greater adiposity, particularly at BMI ≥30 kg/m^2 (35). The risks of LV hypertrophy, hypertension, CVD, atrial fibrillation, and heart failure (HF), all increase in relation to BMI (2,36–39). HF relative risk for every 5-unit increment in BMI was recently reported as 1.41 with a 95% confidence interval (CI) of 1.34 to 1.47 for HF incidence and 1.26 with a 95% CI of 0.85 to 1.87 for HF mortality (39). Ten- and 30-year risk scores in simplified Framingham models include BMI as a CVD predictor variable (40).

BMI as a measure of adiposity and health outcomes at the individual level is often challenged because percent fat and risk for any given BMI can be highly variable secondary to patient sex, age, race/ethnicity, cardiovascular fitness levels, and many other factors (41,42). BMI should be evaluated as part of the initial patient assessment but interpreted with the knowledge that additional history, physical examination, and laboratory studies are important at arriving at an accurate risk assessment and treatment plan (32). Although both cross-sectional and longitudinal observations link BMI with a range of cardiovascular effects and outcomes, some controversy surrounds the "obesity paradox" (43). A number of studies report associations with obesity as defined by BMI and "protective" effects in patients in whom HF has been diagnosed (43). Although the mechanisms underlying the obesity paradox are unknown, attention is now being directed at measures of body composition beyond BMI as an adiposity phenotype (43,44).

FIGURE 2 Interrelations Among Adiposity Biomarkers
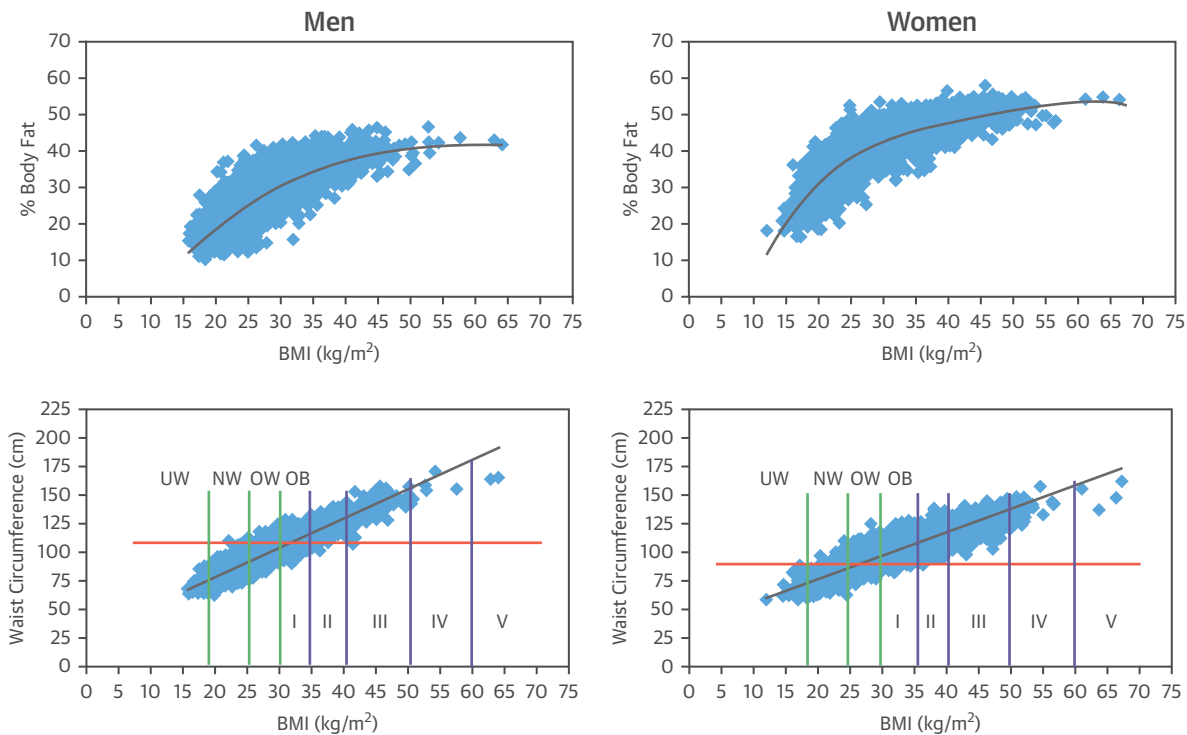
(Upper panels) Percent (%) body fat measured by dual-energy x-ray absorptiometry versus BMI in participants of the National Health and Nutrition Survey (1999 to 2006). The data were fit with polynomial regression lines (R[2] men, 0.61; women, 0.68; both p < 0.001). Note the curvilinear relation between body mass index (BMI) and % fat and the wide range of % body fat at any given level of BMI. (Lower panels) Waist circumference versus BMI in the same group of subjects as in the **upper panels** (R[2] men 0.84; women 0.80; both p < 0.001). **Horizontal lines** are shown at waist circumference cutpoints (>102 cm men, >88 cm women), above which health risks increase within the BMI range 24.9 to 34.9. No additional waist circumference predictive value is present with BMI levels ≥35. **Vertical lines** identify BMI ranges for underweight (UW), normal weight (NW), overweight (OW), and obesity (OB) classes I to V. Definitions of severe obesity are variable in the medical literature.

Not all adipose tissue depots are associated with the same magnitude of chronic disease risk, an observation that launched a search for body size and shape measures with predictive value beyond BMI. Waist circumference is a body size measure that encircles subcutaneous and visceral adipose tissues, some visceral organs, skeletal muscle, and bone. Although highly correlated with BMI (**Figure 2**), waist circumference measurements in some studies add to or exceed the disease risk predictive value of BMI alone (45). As an example, Yusuf et al. (46) found that the odds ratio for acute myocardial infarction in a case-control study was significant for waist circumference (1.77, 95% CI: 1.59 to 1.97) even after adjustment for BMI (p < 0.0001, top vs. bottom quintiles). By contrast, Aune et al. (39) found in a meta-analysis of 23 prospective studies that a 10-cm waist circumference increment (relative risk 1.41 [95% CI: 1.34 to 1.47]) and a 5-U BMI increment

(1.29 [95% CI: 1.21 to 1.37]) were both associated with increased risk of HF.

The mechanistic basis (**Central Illustration**) attributed to the associations between waist circumference and risk is the capture of patient variance in mesenteric and omental adiposity, hepatic steatosis, and other known anatomic changes linked with obesity-related pathophysiological derangements (2). At present, the mixed results of studies positioning BMI against waist circumference lead us to continue support of the current obesity guidelines suggesting that waist circumference be measured in people with a BMI between 25 and 34.9 kg/m^2 to refine risk prediction, with levels of >88 cm and >102 cm considered high in women and men, respectively (32). Waist circumference measurements at BMI ≥35 kg/m^2 add little predictive value beyond that of BMI alone because most patients already have waist circumference levels above the cutpoints (32).

CENTRAL ILLUSTRATION Adiposity-Associated Major Risk Factors for Developing HF and Other Weight-Related Comorbidities
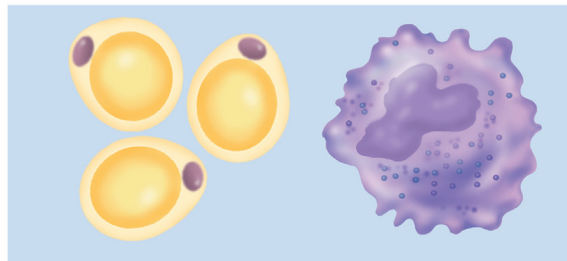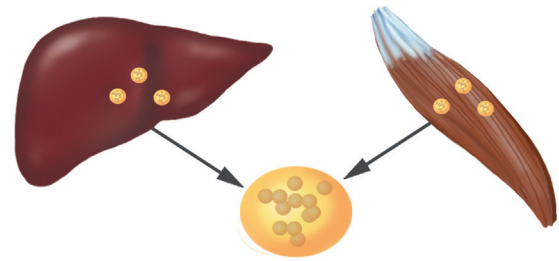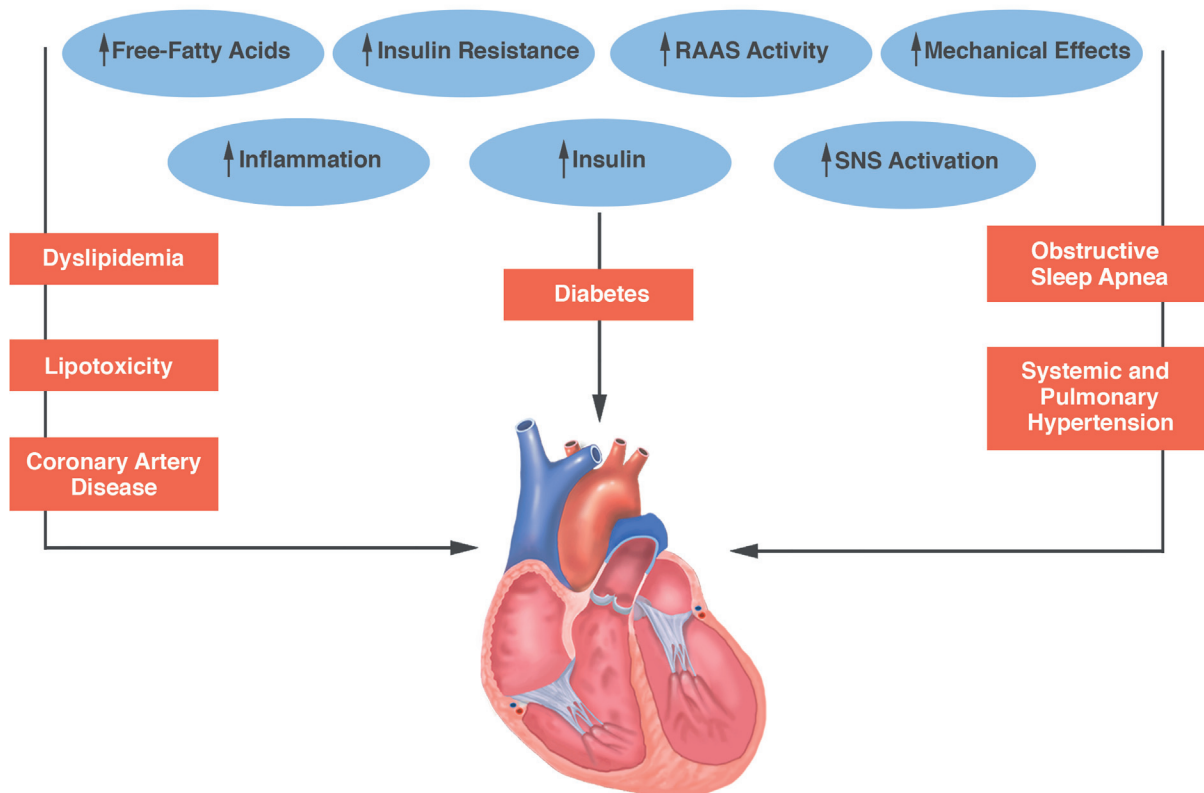
Gadde, K.M. et al. J Am Coll Cardiol. 2018;71(1):69–84.

Increased plasma levels of free-fatty acids and cytokines, intracellular non-adipose tissue lipids (e.g., liposomes), and ectopic adipose tissue depots (e.g., within the visceral compartment) can contribute to systemic inflammation, insulin resistance, and overactivity of the sympathetic nervous system. The metabolic and anatomic effects of excess adiposity can lead to the development of type 2 diabetes, nonalcoholic fatty liver disease, obesity-related dyslipidemias, high blood pressure, and osteoarthritis. The cascade of these pathophysiological mechanisms and associated diseases are the main contributors to obesity-related heart failure. HF = heart failure; RAAS = renin-angiotensin aldosterone system; SNS = sympathetic nervous system.

Several additional shape indices that include waist circumference measurements are available that purportedly show improved associations with percent body fat, visceral adiposity, health risks, and mortality rates than BMI or waist circumference alone. These include "a body shape index" [47] and the "body roundness index" [48]. Other measures such as waist-to-hip circumference ratio, waist-to-height ratio, and body adiposity index have also been reported to be associated with cardiovascular risk factors in some studies, but not in others [46,49,50].

Although body weight, height, and circumferences are the main somatic measures that can be applied in the clinical setting, more advanced technologies can probe other lipid depots associated with CVD risk. In addition to within the visceral compartment, adipose tissue is found embedded in discrete locations around the myocardium and kidney, within skeletal muscles, and in several other anatomic sites [2,51]. Associations between the size of these adipose tissue deposits and clinical outcomes have been reported with quantification by magnetic resonance imaging (MRI), computed tomography, and echocardiography [52]. Small lipid droplets, the size of which can be quantified using MRI, also reside within the cytoplasm of cardiomyocytes, skeletal muscle cells, hepatocytes, and pancreatic β-cells [52]. These ectopic lipid deposits have also been linked with pathological states that include cardiomyopathies, liver diseases, and adult-onset diabetes [53].

Relatively small thermogenic brown adipose tissue deposits and beige adipocytes are present to a varying extent in adults and can be quantified with imaging methods such as positron-emission tomography and MRI [51]. Thermogenic brown adipocytes are found within supraclavicular, mediastinal, and other deposits, and are characterized by mitochondria that have uncoupling protein-1 that can be stimulated through cold exposure and sympathetic nervous system mechanisms [2]. Beige adipocytes, found embedded within white adipose tissue, are also thermogenic and can be activated by exercise, cold exposure, and hormonal actions [2].

MEDICAL EVALUATION OF PATIENTS WITH OBESITY

Recent practice guidelines for the management of obesity [32] recommend assessment of BMI at least annually for all adult patients seen in clinical practices. Waist circumference measurement provides additional information to determine the risk of comorbidities, especially CVD risk. For patients with overweight and obesity, standard assessment includes medical history including medical conditions and medications that could be contributing to weight gain, sleep apnea, history of weight gain, family history of obesity, dietary and physical activity habits, environmental and cultural factors impacting weight, pattern of weight changes over the years, and history of weight loss attempts; and physical examination, blood pressure assessment, and fasting glucose and lipid measures. For patients receiving medications that are known to induce weight gain, alternative treatment choices should be considered, when possible.

MANAGEMENT OF PATIENTS WITH OBESITY

Weight loss should be recommended for all patients with obesity and also for overweight patients in the presence of comorbid conditions such as pre-diabetes, diabetes, hypertension, and dyslipidemia. For most patients who need to lose weight for medical reasons, the initial goal should be 5% to 10% weight loss over the first 6 months [32]. A common theme of various professional guidelines developed in the United States, Europe, and elsewhere for management of patients with obesity is the emphasis on a multimodal lifestyle intervention that includes dietary changes, increase in physical activity, and behavior modification. Pharmacotherapy, medical devices, and bariatric surgery are other treatment options for patients needing additional interventions. It is important to recognize that currently, the diagnosis of obesity is made with a formula that uses height and weight, not on the basis of a specific biomarker. Hence, the contributing causes of obesity and its pathophysiology might not be the same for all patients. Therefore, there is considerable heterogeneity of response [54] to approved and established treatments, whether these are lifestyle modifications, drug therapies, or surgical interventions. In numerous analyses of the moderators and mediators of response to therapeutic interventions for obesity, the most consistent factor that appears to predict long-term weight loss success is the rate of initial weight loss [55]. Hence, when employing nonsurgical interventions for obesity, it would be prudent to choose an alternative or augmentation approach when the current modality has yielded less than optimal results after 3 to 4 months.

LIFESTYLE INTERVENTIONS

To successfully achieve clinically meaningful weight loss of 5% to 10%, a comprehensive, intense lifestyle intervention is needed that includes at least 14

in-person sessions within 6 months (32). Effective weight loss interventions, which include dietary modification via the prescription of a calorie-reduced diet, increased exercise or physical activity, and behavioral strategies to foster adherence to dietary and physical activity recommendations, can be delivered via individual or group sessions, with both approaches being effective at promoting weight loss. Common behavioral strategies include self-monitoring of diet and physical activity, regular or daily weighing, behavioral contracts, goal setting, and stimulus control (e.g., limiting the locations where one eats). Comprehensive lifestyle interventions that incorporate portion-controlled foods and daily weighing are effective at promoting weight loss over the short and long term (56,57). Face-to-face counseling is considered most effective, with electronic treatments receiving moderate strength of evidence, and telephone-based treatments having low evidence (32).

After achieving initial weight loss, long-term weight loss maintenance remains challenging and continued participation in comprehensive weight loss treatment for 1 or more years is necessary (32). The focus of treatment during follow-up is maintaining adherence to dietary and physical activity recommendations. Weight loss maintenance is facilitated by continued and regular personal contact with professionals, rather than by more passive approaches, such as newsletters (56). Continued use of portion-controlled foods as part of a healthy meal plan also facilitates long-term weight loss maintenance (57). A higher level of physical activity is generally needed for weight maintenance (58), and it is important to recognize that exercise, independent of weight loss, confers significant health effects (59).

Internet-based weight loss treatments are available, though many are passive and low in treatment intensity, which likely limits their efficacy. For example, randomized participation in a weight loss program delivered via a commercial website resulted in weight loss of only 1% after 4 and 12 months (60). Maintaining utilization of Internet-based interventions has proven to be challenging (61). Nonetheless, Internet-based interventions that promote more intensive treatment have been found to be more efficacious (62,63).

Weight loss applications or "apps" for smartphones and other portable devices are a logical extension of Internet-based interventions. Weight loss apps are very popular, yet only a small percentage (∼15%) included 5 or more evidence-based practices for weight management (64). Despite their popularity, weight loss apps have limited evidence of efficacy (65), though smartphone-based approaches and apps that rely on evidence-based weight loss principles have been found to promote clinically meaningful weight loss that is commensurate with the amount of weight loss observed in face-to-face interventions (66).

EFFECTS OF WEIGHT LOSS ACHIEVED WITH LIFESTYLE INTERVENTIONS ON CVD

Weight loss of 5% to 10% results in improvements in cardiometabolic risk factors (32). The DPP (Diabetes Prevention Program) study is the largest and longest randomized controlled trial (RCT) to date that examined the effect of weight loss achieved with diet and exercise on the onset of diabetes among participants who were at risk (67). The study randomized 3,234 patients with pre-diabetes to an intensive lifestyle intervention (ILI) to promote weight loss, metformin, or placebo. Over a mean follow-up of 2.8 years, the ILI, metformin, and placebo groups lost 5.6, 2.1, and 0.1 kg, respectively. The ILI and metformin reduced the incidence of diabetes by 58% and 31%, respectively, relative to placebo. At the 10-year follow-up from randomization, the metformin group maintained their modest weight loss, whereas the ILI group regained much of their initial weight loss (68). Importantly, the ILI and metformin groups reduced diabetes incidence by 34% and 18%, respectively, compared with placebo, cumulatively over the 10-year period, although the incidence rates were similar among the 3 groups in the 5.7-year follow-up when the ILI group experienced weight regain. These results emphasized the importance of weight loss, as well as weight loss maintenance, on diabetes risk.

The Look AHEAD (Action for Health in Diabetes) trial examined the effect of weight loss with lifestyle intervention among patients with established T2D. A total of 5,145 overweight/obese adults, 45 to 74 years of age, with T2D were randomized to an ILI or a control group consisting of diabetes support and education. At 1 year, patients assigned to ILI had greater weight loss (8.6% vs. 0.7%), greater reduction in glycosylated hemoglobin (HgA$_{1c}$) (7.3% to 6.6% vs. 7.3% to 7.2%), improved fitness level, and greater improvements in a host of disease risk factors, such as blood pressure and lipid profile (69). After a median 10-year follow-up when the study was stopped on the basis of a futility analysis (70), the ILI group had greater weight loss (6.0% vs. 3.5%) and greater reductions in HgA$_{1c}$, but there was no difference between groups (1.83 vs. 1.92 events per 100

person-years; hazard ratio 0.95; 95% CI: 0.83 to 1.09; p = 0.51) in major adverse cardiovascular events (MACE) (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina). These results suggested that a modest weight loss (2.5% greater weight loss relative to control) via diet and exercise alone might not be sufficient to reduce adverse cardiovascular events at the group level, though the use of statins and improved medical management of CVD risk factors might have diminished the differences between the groups. A recent analysis found that baseline HgA$_{1c}$ and general health distinguished participants who did and did not benefit from the intervention (71). This analysis revealed that 85% of participants in the intervention group averted cardiac events, but 15% had increased rate of events, which might have negatively affected the main study results.

EFFECT OF DIETS ON CVD RISK FACTORS

Some studies find that diet type affects disease risk factors even in the context of similar weight loss. For example, a low-carbohydrate diet resulted in larger improvements in high-density lipoprotein and triglycerides after 1 year compared with a low-fat conventional diet, even though both diets yielded similar weight loss (72). A large subsequent study found similar results over 2 years (73). Specifically, both a low-carbohydrate and a low-fat diet promoted weight loss of ~7% over 2 years, but the low-carbohydrate diet was associated with greater increases in high-density lipoprotein levels and had more adverse effects. Nevertheless, a meta-analysis of low-carbohydrate high-protein diets found that long-term benefits of such diets are marginal (74), and some authors have argued to end the debate over the "best diet" and to focus on adherence to dietary and exercise recommendations, which is the most consistent predictor of weight loss (75). It is unlikely that any single diet works best for all people, and it is conceivable that diet type interacts with personal factors to affect responses to different diets, as indicated by interest in personalized or precision medicine. At least 1 study has demonstrated meaningful differences in weight loss in response to diets based on baseline levels of fasting plasma glucose; specifically, people with elevated fasting plasma glucose levels lose more weight and better maintain weight loss with low glycemic load diets that include more whole grains and fiber (76).

The DASH (Dietary Approaches to Stop Hypertension) study compared the effects of 3 diets for 8 weeks on blood pressure (77). The 3 diets were a control diet, a diet rich in fruits and vegetables, and a "combination diet" rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat. Relative to control diet, the combination diet (−5.5 and −3.0 mm Hg for systolic and diastolic, respectively) and the fruit and vegetable diet (−2.7 and −1.9 mm Hg) reduced blood pressure. Similar results were obtained after adjusting for weight change. For the combination diet, the effect was larger among subjects with hypertension at baseline (−11.4 and −5.5 mm Hg vs. control diet for systolic and diastolic blood pressure, respectively).

Mediterranean diets have been found to protect against cardiovascular disease in epidemiological studies. A large RCT tested the effect of 2 Mediterranean diets (one that was supplemented with extra-virgin olive oil, and another that was supplemented with mixed nuts) compared with a control diet on the primary prevention of cardiovascular events (78) among 7,447 subjects 55 to 80 years of age with a mean BMI of 30 and high CVD risk. After a median follow-up of 4.8 years, relative to the control diet, both Mediterranean diets reduced the incidence of MACE (hazard ratios 0.70 and 0.72).

In summary, weight loss achieved with diet and exercise improves cardiometabolic risk factors, reduces the incidence of diabetes, and improves glycemic control (67-69) in patients with pre-diabetes and diabetes, although failing to reduce MACE at the group level among patients with type 2 diabetes after 10 years in the Look AHEAD trial (70); a recent post hoc analysis, however, found that 15% of participants in the intervention group who were characterized by mild or well-treated diabetes and a negative perception of their health had increased rate of events, which might have contributed to the failure to find a mean group effect (71). Blood pressure can be improved, even without large weight loss, by eating a diet that is high in fruits, vegetables, and low-fat dairy, and low in saturated fat and total fat (77); however, the long-term effects of such a diet on morbidity and mortality have not been examined. For prevention of MACE in patients at high risk, the evidence to date supports Mediterranean diets supplemented with olive oil or nuts (78). Finally, the 2013 Guidelines for the Management of Overweight and Obesity in Adults specify that clinicians should consider the effects of weight loss diets on all risk factors and should work with nutrition professionals to prescribe a weight loss diet that addresses the needs of the individual patient (32).

PHARMACOTHERAPY

Pharmacotherapy should be a consideration for patients with a BMI of ≥30 kg/m² and BMI of ≥27 kg/m² with weight-related comorbidities such as T2D (32), and is the next logical therapeutic approach for patients who have historically failed to benefit from lifestyle modification approaches and for those with difficulty maintaining weight loss over the long term. Patients should be counseled about what to expect from medications, including the beneficial and adverse effects. With the exception of orlistat, all currently approved antiobesity medications help patients limit their caloric intake and achieve better compliance with their diet plan. Reduction in energy intake is achieved primarily via enhancement of satiety and reduction in hunger and food cravings (79). Because medications do not modify the choices patients make with regard to food selection, it is still important to counsel the patients about lifestyle changes, such as avoiding energy-dense foods. As is the case with all nonsurgical weight loss interventions, there is some weight regain when currently approved antiobesity medications are continued beyond a year, and more weight is regained when the medication is stopped (80). Because obesity is a chronic condition, when a patient is continuing to benefit from an antiobesity medication and tolerating it well, and if there are no safety issues that limit chronic use, consideration should be given to continuing the medication as long as benefit outweighs risk. Clinical trials data provide very little guidance to the clinician with regard to making the right selection for a specific patient. Weight loss in the first 3 to 4 months is the only consistent predictor of further success with all currently available antiobesity medications. In most cases, if 5% weight loss is not achieved after 3 to 4 months, discontinue drug therapy, barring a few cases when there is significant improvement in comorbidities despite marginal weight loss (80).

Four medications—phentermine, diethylpropion, phendimetrazine, and benzphetamine—all structurally related to amphetamine, and approved for short-term use only, have been available for well over 50 years in the United States. Phentermine is by far the most prescribed antiobesity medication in the United States, perhaps due to its low cost and ease of use. In two recent 12-week RCTs, both conducted in Korea, phentermine 30 mg/day was associated with >6% weight loss relative to placebo (81,82). In a 28-week RCT conducted in the United States, phentermine 15 mg/day led to 4.4% placebo-subtracted weight loss (83). Common adverse effects of phentermine and other drugs in this class are dry mouth, constipation, and insomnia. There is some abuse potential with these drugs, more so with phendimetrazine and benzphetamine.

Of the 5 medications (**Table 1**) currently approved in the United States for long-term weight management, orlistat is the only one with a purely peripheral mechanism of action. Available since 1999 in many countries, it is a gastric and pancreatic lipase inhibitor that reduces absorption of fat in the gut, thereby decreasing caloric intake. In RCTs of 1- to 2-years duration, orlistat treatment led to ∼3% weight loss relative to placebo (84,85). In a 4-year RCT, orlistat treatment yielded ∼2.4% placebo-subtracted weight loss and decreased incidence (6.2% vs. 9.0%) of diabetes among patients with obesity and pre-diabetes (86). Currently, orlistat is the only weight loss drug approved for use in adolescents. Despite its good safety profile, orlistat's use is limited by its gastrointestinal adverse effects, including oily stools/spotting, flatus, and fecal urgency. Patients should be advised to take a daily multivitamin supplement to make up for reduced absorption of fat-soluble vitamins.

Lorcaserin is a serotonergic drug with selective agonism for 5-HT$_{2C}$ receptors. In 3 RCTs, lorcaserin treatment achieved 3.0% to 3.6% placebo-subtracted weight loss at 1 year (87-89). When lorcaserin was continued for the second year, nearly one-half of the weight lost was regained (87). Prescribing information for lorcaserin recommends discontinuation of the drug if weight loss is <5% after 12 weeks. Yet, in a recently published trial, only 28% of patients on lorcaserin achieved 5% weight loss at 12 weeks (90). Overall, lorcaserin is tolerated well, but its efficacy is marginal. In light of the observations of valvular heart disease in patients treated with the withdrawn serotonergic drugs fenfluramine and dexfenfluramine, echocardiographic assessments were performed in RCTs of lorcaserin revealing a relative risk of 1.16 (95% CI: 0.81 to 1.67) for the drug. The Food and Drug Administration (FDA) required a cardiovascular outcomes trial (CVOT), which is underway.

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist, approved at 1.8 mg for T2D and at a higher dose of 3.0 mg for obesity. It is administered as daily subcutaneous injection. Liraglutide results in 4.0% to 5.4% placebo-subtracted weight loss at 1 year (91,92). In one of the trials in which double-blind treatment was extended for an additional 2 years, 2.0% of pre-diabetic patients on liraglutide developed diabetes compared with 6.2% on placebo (93). In a

TABLE 1 Drugs for Long-Term Weight Management

Drug	1-Year Weight Loss, Placebo-Subtracted	Adverse Events	Precautions	Contraindications and Limitations
Orlistat	~3%	Fecal urgency, fecal incontinence, flatus with discharge, oily spotting	Daily multivitamin to make up for malabsorption of fat-soluble vitamins	Chronic malabsorption syndrome; cholestasis
Lorcaserin	3.0% to 3.6%	Headache, dizziness, fatigue, nausea, dry mouth, constipation, cough, hypoglycemia in patients with diabetes	Monitor for symptoms of serotonin toxicity. Monitor for signs and symptoms of valvular heart disease.	Safety of use in patients taking antidepressants is unknown
Liraglutide	4.0% to 5.4%	Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain, headache, fatigue, hypoglycemia, increased lipase	Causes thyroid C-cell tumors in rats and mice. Discontinue if pancreatitis is suspected.	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Do not use with insulin or other GLP-1 agonists.
Phentermine/topiramate	8.6% to 9.3%	Paresthesia, dizziness, insomnia, dysguesia, constipation, dry mouth	Small increase in heart rate. Monitor electrolytes to detect metabolic acidosis and elevated creatinine. Monitor closely for depression, anxiety, and memory problems.	Glaucoma; hyperthyroidism; within 2 weeks of taking MAOIs. REMS requires negative pregnancy test before treatment and monthly thereafter to reduce the risk of teratogenicity
Naltrexone/bupropion	3.3% to 4.8%	Nausea, vomiting, headache, dizziness, insomnia, dry mouth, diarrhea	Monitor for suicidal ideation and behavior. Monitor for increases in heart rate and blood pressure. Rare cases of hepatotoxicity	Uncontrolled hypertension; seizure disorders; chronic opioid use; anorexia nervosa or bulimia; during withdrawal from alcohol, barbiturates, benzodiazepines, and antiepileptic drugs; within 2 weeks of taking MAOIs; coadministration with other bupropion-containing products

Pregnancy is a contraindication for all. Lorcaserin and phentermine/topiramate are Schedule IV controlled substances. For orlistat, weight loss is based on various meta-analyses. For all others, weight losses shown are from phase 3 trials. When multiple doses were tested, the weight loss shown is for the most effective dose.

MAOIs = monoamine oxidase inhibitors; REMS = risk evaluation and mitigation strategy.

weight maintenance trial, obese patients who lost an average 6.0% with a low-calorie diet, achieved an additional 6.2% weight loss with liraglutide (vs. 0.2% for placebo) over a year (94). A CVOT with a median follow-up of 3.8 years demonstrated lower MACE incidence with liraglutide 1.8 mg among patients with T2D (95). Nausea and diarrhea are very common with liraglutide, especially in the first month.

Phentermine/topiramate (PHEN/TPM) is the first combination therapy approved in the United States for the treatment of obesity in 2012. Of all the currently approved antiobesity drugs, PHEN/TPM has the most robust efficacy, with a placebo-subtracted 1-year weight loss of 8.6% to 9.3% at the 15/92 mg dose in 2 large RCTs (96,97). Topiramate, an antiepileptic drug, is reported to carry teratogenic risk of oral clefts; therefore, a negative pregnancy test is required for women of childbearing potential before starting PHEN/TPM and monthly thereafter. Paresthesia is the most common adverse effect of PHEN/TPM, especially at the start of therapy. Adverse effects related to mood and memory need close attention of the clinician. The complex dose titration of PHEN/TPM and its potential for inducing cognitive and mood-related adverse effects requires a skilled clinician.

Naltrexone/bupropion (NB) is the second combination therapy for obesity, approved in late 2014.

In 1-year RCTs, at the recommended dose of 32/360 mg/day, NB is associated with 3.3% to 4.8% placebo-subtracted weight loss (98-100). Weight loss with NB is not associated with improvement in blood pressure or lipids. Nausea is a very frequent and bothersome adverse effect of NB therapy, leading to high dropout rates in RCTs. NB is also associated with heart rate and blood pressure increases that concerned the FDA to require a CVOT, which unfortunately was stopped due to inappropriate disclosure of data by the sponsor while the trial was ongoing (101). NB requires complex dose titration.

In summary, 5 medications are currently approved in the United States for long-term management of obesity, with placebo-subtracted weight loss ranging from ~9% for PHEN/TPM to ~3% for lorcaserin and orlistat (102).

MEDICAL DEVICES

Six FDA-approved medical devices (Table 2), including a laparoscopic adjustable gastric band (LAGB), are available for obesity management. We will discuss the LAGB procedure in the bariatric surgery section.

Three intragastric balloons are approved for use up to 6 months to assist weight loss among patients

TABLE 2 Medical Devices for Weight Management

Device	Indications	Weight Loss vs. Control	Adverse Events	Contraindications
Intragastric balloons				
Orbera	BMI 30–40 kg/m² Up to 6 months	10.2% vs. 3.3%	Abdominal pain, bloating, nausea	Prior GI surgery, inflammatory GI disease, gastroduodenal ulcers, large hiatal hernia, esophageal structural abnormalities, esophageal motility disorders, gastric mass, severe coagulopathy, hepatic insufficiency or cirrhosis, serious mental disorders, alcoholism or drug addiction, unable to use proton pump inhibitors during device use, or receiving aspirin, NSAIDs, or blood thinners
ReShape Duo		6.8% vs. 3.3%	Rare cases of gastrointestinal obstruction or perforation	
Obalon		6.6% vs. 3.4% (at 6 months)		
Electrical stimulation systems				
Maestro	BMI 35–45 kg/m² Long-term use	9.2% vs. 6.0%* (at 1 yr)	Pain at neuroregulator disc site, heart burn, abdominal pain, nausea, belching	Cirrhosis, portal hypertension, esophageal varices, large hiatal hernia
Gastric emptying systems				
AspireAssist	Age >22 yrs BMI 35–55 kg/m² Long-term use	12.1% vs. 3.5% (at 1 yr)	Pain, abdominal discomfort, nausea, change in bowel habits, electrolyte abnormalities, irritation or infection at site	Prior GI surgery, esophageal stricture, severe gastroparesis, inflammatory GI disease, severe ulcers or bleeding conditions, or gastric masses, chronic abdominal pain, coagulation disorders, moderate-to-severe anemia, hepatic insufficiency or cirrhosis, serious pulmonary or cardiovascular disease, eating disorders, physical or mental disability that could affect compliance, poor general health

*Control was sham stimulation.
BMI = body mass index; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

with BMI of 30 to 40 kg/m². Orbera (Apollo Endosurgery, Austin, Texas) is a single balloon that is introduced in the stomach via an endoscopic procedure. Once in place, the balloon is filled with 400 to 700 ml of saline to expand. ReShape (ReShape Medical, San Clemente, California) is similar except it uses 2 balloons. Obalon (Obalon Therapeutics, Carlsbad, California) is a swallowable capsule that opens once inside the stomach and the balloon is filled with air via an inflation catheter. All 3 gastric balloons are for use up to 6 months only. Some weight is regained in the months following removal of the devices.

The Maestro Rechargeable System (EnteroMedics, St. Paul, Minnesota) is a form of vagal nerve blockade that is thought to work by suppressing neural communication between the stomach and the brain, leading to increased satiety and decreased caloric intake (103). Electrodes placed on the trunks of the vagus nerve at the gastroesophageal junction are connected to a rechargeable pulse generator called a neuroregulator, which is secured subcutaneously. Obviously, it is more invasive than the gastric balloons and requires surgeons skilled in laparoscopic procedures.

AspireAssist (Aspire Bariatrics, King of Prussia, Pennsylvania) is a device that consists of a gastrostomy tube that connects to a skin port outside of the abdomen. The patient attaches an external connector and tubing to the skin port, opens the port valve, and flushes out food 20 to 30 min after each meal. To prevent obstruction in the tube, food needs to be thoroughly chewed. Serum electrolytes should be monitored. Some patients may need potassium supplementation. For a detailed discussion of medical devices for weight management, refer to a recent comprehensive review by Lee and Dixon (104).

BARIATRIC SURGERY

Bariatric surgery has gained considerable popularity in the past decade, with about half a million procedures performed annually worldwide (105). Surgery is indicated for patients with BMI ≥40 kg/m² and ≥35 kg/m² in the presence of weight-related comorbidities such as T2D, with lower BMI cutoffs for LAGB. Common surgical procedures are sleeve gastrectomy (SG) (58%), Roux-en-Y gastric bypass (RYGB) (38%), LAGB (3%), and biliopancreatic diversion with duodenal switch (1%), for which minimal outcomes data exist (106). RYBG is associated with the most weight loss in long-term follow-up studies (Table 3). In one study of 2,410 patients, weight losses at 4-year follow-up for RYGB, SG, and LAGB were 27%, 18%, and 11%, respectively (107).

LAGB is the least invasive of the 4 procedures and involves laparoscopic placement of an adjustable silicone band around the gastric fundus. Advantages of

TABLE 3 Bariatric Surgery

Procedure	Weight Loss*		Pros and Cons†	
	1 Year	≥6 Years	Pros	Cons
LAGB	14% to 30%	13% to 14%	• Short outpatient procedure • Adjustable and reversible • Low rate of complications • Low risk of malabsorption of vitamins and minerals	• Less long-term weight loss than other bariatric procedures • High rates of reoperation for band slippage, obstruction, or erosion • Possible progressive dilation of esophagus due to band obstruction
RYGB	23% to 43%	25% to 28%	• Large and sustained long-term weight loss • High rates of T2D remission	• Complex procedure requiring skill • Requires hospital stay of 1 to 2 days • Higher rate of perioperative complications compared with LAGB and SG • Late complications that include marginal ulcer, internal hernia, and small bowel obstruction. • Needs long-term vitamin and mineral supplementation
Sleeve gastrectomy	20% to 28%	22%	• Significant weight loss • Less complex procedure compared with RYGB • Can be converted to RYGB at a later stage • Less risk of vitamin and mineral deficiencies	• Somewhat higher risk of weight regain compared with RYGB • Higher rate of complications compared with LAGB • Post-operative GERD • Late complications that include chronic obstructive symptoms

Biliopancreatic diversion with duodenal switch is not listed in the table because it accounts for ∼1% of bariatric surgeries. *Source of data: Piché et al. (108). †Adapted from Schauer et al. (113).

GERD = gastroesophageal reflux disease; LAGB = laparoscopic adjustable gastric banding; RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy; T2D = type 2 diabetes.

this procedure are that it can be done in an outpatient setting, has the least complications, and is reversible. Two band devices, Lap-Band (Apollo Endosurgery) and Realize (Ethicon, Somerville, New Jersey), were FDA approved. The Realize Band was discontinued in early 2017. LAGB results in 14% to 30% weight loss after a year (108). Although weight regain is more common with LAGB relative to other procedures, there is long-lasting benefit for some patients (104,108).

In the SG procedure, a staple line is placed along the greater curvature of the stomach followed by removal of approximately 80% of the lateral aspect of the stomach in a vertical fashion. SG has gained popularity in the past decade due to procedural ease and less frequency of serious complications (106).

In RYGB, a small stomach pouch is created in the upper stomach. The jejunum is then divided and the middle part of it, the Roux limb, is connected to the stomach pouch, thus allowing food to bypass most of the stomach. The procedure is more demanding than SG and has a slightly higher rate of complications, but is associated with the largest sustained weight loss with a very high rate of remission of T2D (109,110).

Bariatric surgery is now endorsed by leading diabetes organizations as an effective intervention for T2D, by inclusion in the treatment algorithm (111) with a recommendation for patients with class III obesity and for those with class II obesity whose hyperglycemia is inadequately controlled by lifestyle and medical therapy. Bariatric surgery also leads to a significant reduction in the prevalence of hypertension and dyslipidemia over 2-year follow-up, although data from RCTs of longer follow-up are inadequate (112). Serious complication rates for bariatric surgery rates have decreased over the years, with recent studies showing perioperative morbidity and mortality rates of 5% and 0.3%, respectively (113,114).

CONCLUSIONS

Obesity, besides impairing quality of life, is associated with numerous chronic diseases. Fortunately, weight reduction improves management of many of these diseases, especially T2D. Although global obesity prevalence has not decreased, more therapeutic options are available today, thus improving management of patients with obesity and related comorbidities.

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