According to recent estimates, approximately two thirds of adults in the United States are overweight or obese.\(^1\) Obesity is associated with alterations in glucose metabolism, dyslipidemia, and hypertension. These conditions, in turn, are associated with an increased incidence of type 2 diabetes mellitus and cardiovascular disease, which ultimately leads to increased morbidity and mortality. Abdominal obesity, in particular, has been identified as a key risk factor. Accordingly, therapeutic lifestyle change remains the cornerstone of treatment for patients with obesity. Therapeutic lifestyle change is effective; even moderate weight loss leads to clinical improvements. However, lifestyle change is often challenging to implement, and pharmacologic therapies may become necessary. Available pharmacologic and surgical treatment modalities for patients with obesity are fraught with challenges of their own, including poor patient adherence and presence of adverse events. The author outlines available modes of treatment and their consequences for patients with obesity.

The obesity epidemic is associated with numerous health-related sequelae, including alterations in glucose metabolism, dyslipidemia, and hypertension. These conditions, in turn, contribute to an increased risk of the development of type 2 diabetes mellitus and cardiovascular disease, which ultimately leads to increased morbidity and mortality. Abdominal obesity, in particular, has been identified as a key risk factor. Accordingly, therapeutic lifestyle change remains the cornerstone of treatment for patients with obesity. Therapeutic lifestyle change is effective; even moderate weight loss leads to clinical improvements. However, lifestyle change is often challenging to implement, and pharmacologic therapies may become necessary. Available pharmacologic and surgical treatment modalities for patients with obesity are fraught with challenges of their own, including poor patient adherence and presence of adverse events. The author outlines available modes of treatment and their consequences for patients with obesity.

Address correspondence to Thomas B. Repas, DO, Department of Medicine, University of Wisconsin Hospital and Clinics, 600 Highland Ave, Madison, WI 53792-3284.

Dr Repas has served on the speakers bureaus of GlaxoSmithKline Inc, Novo Nordisk Inc, sanofi-aventis US, and Takeda Pharmaceuticals North America Inc.

E-mail: tb.repas@hosp.wisc.edu
The American Diabetes Association has proposed a more robust characterization of cardiometabolic risk. Specifically, the likelihood of both T2DM and CVD developing is increased by a number of interrelated risk factors, including abdominal obesity, alterations in glucose metabolism, atherogenic dyslipidemia, inflammatory markers, and smoking. Several studies suggest that abdominal obesity may play the most pivotal role. The concept of cardiometabolic risk is depicted in Figure 2.

**Management Strategies for Cardiometabolic Risk**

There are two primary strategies for the management of cardiometabolic risk:

- ** Modification of underlying risk factors, and
- ** Separate treatment for each individual risk factor, as appropriate.

Treatment of patients for underlying risk factors includes weight loss in obese or overweight individuals, increased physical activity, and an antiatherogenic diet. The management of car-
Figure 2. Cardiometabolic risk (i.e., risk of development of type 2 diabetes and cardiovascular disease) is increased by a number of interrelated factors. These factors include a patient’s abnormal lipoid metabolism, age, genetics, hypertension, inflammation hypercoagulation, insulin resistance, overweight/obesity, sex, and smoking. ApoB indicates apolipoprotein B; BP, blood pressure; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

diometabolic risk factors can also include treatment with available pharmacologic agents, including antihyperlipidemic agents to affect dyslipidemia, antihypertensive agents to reduce blood pressure, and antihyperglycemic agents to reduce elevated fasting glucose levels. However, because many cardiometabolic risk factors co-occur, this approach could lead to polypharmacy, decreased patient adherence, and poor outcomes.23

Although some disagreement exists concerning the underlying pathophysiologic mechanisms of cardiometabolic risk, obesity—in particular, abdominal or visceral obesity—is thought to play a central role.19,20 Adipose tissue, which was formerly thought to be a relatively inert storage depot, is now known to be an active endocrine organ.20 Adipose tissue releases fatty acids and has been associated with higher levels of the inflammatory marker C-reactive protein and lower levels of the adipose-specific circulating protein adiponectin, which has been shown to improve insulin sensitivity.24 Reducing body weight has been shown to improve markers of inflammation, regardless of how the weight loss was accomplished. Specifically, lifestyle change (eg, caloric restriction, exercise training), pharmacologic therapy, and weight loss surgery have all been associated with improvements in inflammatory marker levels.25-28

As previously mentioned, abdominal obesity is a key component of cardiometabolic risk. An elevated waist circumference in patients with a body mass index (BMI) between 25.0 and 34.9 has been shown to be associated with a number of health risks, including increased risks of dyslipidemia, hypertension, T2DM, and CVD.25 Thus, even patients who do not meet the clinical definition of obesity (ie, BMI>30.0) may have elevated disease risk if they have an elevated waist circumference. Conversely, not every obese patient has an elevated cardiometabolic risk. Rather, for a given amount of body fat, people who have a high distribution of intra-abdominal visceral fat are more likely to have elevated cardiometabolic risk factors.21 Accordingly, management of obesity—in particular abdominal obesity—is central to the management of cardiometabolic risk.

Screening Patients for Obesity

Body mass index is an important indicator for defining obesity, and waist circumference is an important factor in strategies for determining obesity risk. Measurements of waist circumference should be taken by placing the measuring tape snugly around the body without compressing. The measurement should be taken at the top of the right iliac crest during normal respiration.5

A waist circumference greater than 89 cm (35 inches) for women and greater than 102 cm (40 inches) for men is considered to be a high-risk waist circumference. Waist circumference may be most useful for patients who have a normal weight or who are overweight, rather than obese. It is not necessary to measure waist circumference when a patient’s BMI is greater than 35.0, because it confers little additional predictive value in such patients.29

Measuring waist circumference is a simple and practical strategy for estimating a patient’s visceral fat, which is associated with an increased risk of atherogenic dyslipidemia, fasting hyperinsulinemia, and T2DM. It is also a simple and practical way to determine if the patient has elevated levels of apolipoprotein B, which are associated with a 20-fold increase in the risk of coronary heart disease developing in asymptomatic middle-aged men.30

In addition to measurements of BMI, a thorough medical history should be obtained and a complete physical examination should be conducted when identifying and evaluating an obese patient. It is important to identify patients who need to be treated for obesity, as well as to assess a patient’s smoking status and family history of CVD to determine risk for future CVD events. A patient’s weight history and lifestyle should also be determined to help elucidate factors contributing to the obesity. Medical history is a critical factor, because certain conditions may predispose patients to obesity or may influence health in other ways (eg, some medications, including glucocorticosteroids, atypical antipsychotics, tricyclic antidepressants, and specific anticoagulants such as valproic acid may cause obesity).5
Assessing Patients With Obesity

Assessment of an obese patient has three major goals and include making the following determinations:

- Is treatment indicated?
- Is treatment safe for the patient?
- Is the patient ready and motivated to lose weight?5

Current treatment guidelines for obesity suggest taking into account several risk factors, including age; dyslipidemia (ie, alterations in both HDL and LDL cholesterol levels); family history of coronary heart disease; hypertension; impaired fasting glucose levels; and smoking. Figure 3 presents the guidelines for assessing obese patients as recommended by the National Institutes of Health (NIH), the National Heart, Lung, and Blood Institute (NHLBI), and the North American Association for the Study of Obesity (NAASO).29

According to the NIH/NHLBI/NAASO guidelines,29 patients who are overweight (BMI 25.0-29.9) and have one comorbidity (eg, dyslipidemia or hypertension) should be advised to make therapeutic lifestyle changes to prevent additional weight gain. Overweight patients with two or more comorbidities should be advised to make lifestyle changes geared toward losing weight. A low-calorie diet, increased physical activity, and behavioral therapy are the recommended strategies for both weight maintenance and weight loss. For overweight patients with a BMI between 27.0 and 29.9, pharmacotherapy should be considered in the presence of comorbidities.29

For patients with any level of obesity (BMI ≥ 30.0), both lifestyle therapy and pharmacotherapy are indicated. Weight loss surgery is also a therapeutic option, though it is indicated only for severely obese patients with comorbidities in cases where other treatment options have failed. The NIH/NHLBI/NAASO treatment guidelines for obese patients are presented in Figure 4.

When assessing whether a patient is ready to lose weight, the following questions should be considered:

- What are the patient’s reasons for wanting to lose weight?
- What support does the patient expect to receive from family and friends?
- What does the patient perceive as the risks and benefits of weight loss?
- What are the patient’s attitudes toward physical activity?
- What have been the patient’s previous weight loss attempts?
- What potential barriers to weight loss exist for the patient?

**Treating Patients for Obesity**

Therapeutic lifestyle change is an important treatment strategy for obese patients, even when pharmacotherapy is indicated. Evidence from research into therapeutic lifestyle change has shown that increasing weight loss and physical activity can result in improvements in numerous other cardiometabolic risk factors. These factors include dyslipidemia, glucose tolerance, hypertension, waist circumference, and weight.

The Diabetes Prevention Program (DPP) was a randomized trial examining the effect of lifestyle change and metformin use on the prevention of T2DM among patients with impaired glucose tolerance (N=3234). At the beginning of the study, 2532 (78%) patients had elevated waist circumference, 1838 (57%) had low HDL levels, 1472 (46%) had elevated triglyceride concentrations, 1466 (45%) had elevated blood pressure, and 1060 (33%) had high fasting plasma glucose levels. Patients randomly assigned to receive treatment with lifestyle change (n=1079) showed improvements in blood pressure, fasting plasma glucose levels, triglyceride concentrations, and waist circumference after 3 years. By contrast, patients randomly assigned to receive treatment with metformin (n=1073) had improvements in only fasting plasma glucose levels and waist circumference after 3 years. Thus, the DPP study showed that lifestyle intervention resulted in improvements in cardiometabolic risk factors. The greatest improvements were in blood pressure and waist circumference. Among DPP lifestyle participants, weight loss was also the dominant predictor of reduced incidence of T2DM.

Based on the effectiveness of lifestyle change, the NIH/NHLBI/NAASO guidelines recommend that most overweight and obese people should make long-term dietary changes to reduce caloric intake. For most women, diets of 1000 kcal/d to 1200 kcal/d are effective. Diets of 1200 kcal/d to 1600 kcal/d are appropriate for most men and women who weigh more than 165 pounds or who exercise on a regular basis. Patients should be educated on food composition, labeling, preparation, and portion size. Dietary recommendations should take into account personal preference to increase the likelihood of success.

In addition to dietary changes, physical activity is also recommended, because it increases energy expenditure and plays an important role in weight maintenance. Physical activity also reduces the risk for CVD. Research on lifestyle physical activity has shown that exercise need not be continuous to be beneficial. Accordingly, the US Department of Health and Human Services (HHS) recommends that adults accumulate a minimum of 30 minutes or more of moderate-intensity activity on most days of the week to reduce the risk of chronic disease. However, success in reaching weight-loss goals is more likely the greater the total duration of physical activity is per day. Thus, the HHS recommends that adults engage in at least 60 to 90 minutes of moderate-intensity physical activity per day to sustain weight loss.

Because lifestyle changes can be difficult for patients to make, adding behavior therapy may be a useful adjunct. Behavior therapy strategies that may be effective are cognitive restruc-
turing, contingency management, problem solving, self-monitoring, social support, stimulus control, and stress management. The combination of dietary changes, increased physical activity, and behavior therapy can be effective for weight management.

The National Weight Control Registry (NWCR) has collected data since 1994 on patients who have been successful at long-term maintenance of weight loss. The NWCR reported in 1997 that success in losing weight was closely associated with both diet and exercise in patients (N = 784). Nearly all registry members indicated that weight loss led to improvements in their energy level, general mood, physical health, physical mobility, and self-confidence. Conversely, predictors of weight gain included—at entry into the registry—more recent weight losses (<2 years vs ≥2 years) and larger weight losses (>30% maximum weight vs <30% maximum weight), as well as higher levels of depression and binge eating. The results of the NWCR study suggest that weight regain may be attributed mostly to failure to maintain behavior changes.

Although therapeutic lifestyle change is an important strategy for improving cardiometabolic risk, research in this area has been plagued with challenges. Studies of therapeutic lifestyle change have numerous limitations, including substantial participant loss to follow-up, differing rates of attrition between treatment groups, lack of control groups, and inadequate study duration. Weight regain is common, with 35% of patients in the NWCR study regaining weight during 1 year of follow-up.

Implementing therapeutic lifestyle change in clinical practice has been notoriously difficult. In the DPP study, participants in the lifestyle-change group had extensive support in their efforts to achieve the modest goal of losing 7% of their body weight. Despite this support, only 49% of the lifestyle-change participants who were in the study after approximately 24 weeks (n = 1017) met this weight loss goal. Thus, therapeutic lifestyle change is an important strategy for treating patients at cardiometabolic risk, but it may not be sufficient.

In addition to lifestyle alterations, medical intervention is often necessary. Currently available pharmacotherapy for long-term use in the management of obesity is limited to two agents: orlistat and sibutramine hydrochloride monohydrate. Both agents are effective when prescribed in concert with therapeutic lifestyle change. However, each of these antiobesity agents also has adverse effects that limit their long-term use and patient adherence.

Orlistat, a pancreatic lipase inhibitor, targets intestinal lipases, thus preventing the hydrolysis of triglycerides and the ultimate absorption of fatty acids and monoacylglycerols in the form of micelles—by mucosal cells of the intestine.

Figure 5. Orlistat inhibits intestinal lipases, preventing the hydrolysis of triglycerides (TG) and the absorption of fatty acids (FA) and monoacylglycerols (MG)—in the form of micelles—by mucosal cells of the intestine.

Figure 6. Sibutramine hydrochloride monohydrate (blue xs) inhibits the reuptake of norepinephrine, serotonin, and dopamine (blue circles) by nerve cells in the brain. This results in the suppression of a patient’s appetite.
monoacylglycerols by the intestine (Figure 5). In a multicenter, 57-week study of 391 obese men, a subgroup analysis of patients with elevated fasting glucose levels indicated that treatment with orlistat was associated with salutary effects on a number of obesity and glycemic end points. These end points included a mean decrease in body weight of 6.2% versus 4.3% with placebo (P < .001) and a mean decrease in hemoglobin A1c of 0.28% versus 0.18% with placebo (P < .001). In the group receiving orlistat, fasting glucose levels decreased by 3.6 mg/dL, compared with the group receiving placebo, which had an increase of 9.72 mg/dL in fasting glucose levels (P < .001).

In a review of 11 weight-loss studies involving orlistat, treatment with orlistat was shown to achieve a 2.9% greater weight loss than placebo. Orlistat has also been shown to result in improvements in fasting glucose, hemoglobin A1c, LDL cholesterol, and total cholesterol levels and waist circumference in patients with T2DM. Marginal differences were observed in patients’ HDL cholesterol and triglyceride levels.

Orlistat has a reasonable safety profile, given its nonsystemic mechanism of action in the gastrointestinal tract. However, it is poorly tolerated because of its gastrointestinal adverse effects, with a 16% to 40% higher rate of these effects among orlistat-treated patients than among patients receiving placebo. Orlistat is known to reduce fat absorption, leading to decreased fat content in the stool. Orlistat also reduces absorption of certain fat-soluble vitamins, including vitamins A, D, E, and K.

Sibutramine, by contrast, works centrally as an inhibitor of norepinephrine reuptake, serotonin reuptake, and, to a lesser extent, dopamine reuptake (Figure 6). The result is the suppression of appetite. The US Food and Drug Administration approved sibutramine for long-term use in weight loss, noting that it should be used in conjunction with a hypocaloric diet.

In a randomized controlled clinical trial involving 605 obese patients, sibutramine therapy lasting for 2 years was associated with an overall decrease of 8.5 cm in waist circumference (P < .001 versus placebo) and an overall increase of 20.7% in serum HDL cholesterol (P < .001 versus placebo).

Fooled data from a review of five pharmacotherapy studies showed that on average, sibutramine was associated with 4.6% greater weight loss than placebo. This review also showed that sibutramine therapy resulted in a decrease in waist circumference of 4 to 5 cm. In addition, sibutramine use was associated with increases in HDL levels and decreases in triglyceride concentrations—but no changes were observed in LDL, total cholesterol, or blood glucose levels.

Sibutramine use has been linked to a number of adverse effects, including increases in both systolic and diastolic blood pressure, raising concerns regarding its use in patients with comorbidities. It should be used with caution in hypertension and should be avoided in patients with uncontrolled hypertension, history of coronary artery disease, congestive heart failure, arrhythmia, and/or stroke. Sibutramine therapy has also been shown to be effective in treating depression, dry mouth, and insomnia. These events were observed in patient groups at rates ranging from 7% to 20%.

When all other methods of treatment (eg, therapeutic lifestyle change, pharmacotherapy) have failed, obesity surgery may be an option for patients with clinically severe obesity (ie, BMI ≥ 40), or BMI ≥ 35 with comorbid conditions. Two types of surgery have been demonstrated to be effective: banded gastroplasty and Roux-en-Y gastric bypass

Because of the lifelong monitoring required after weight-loss surgery and the risk of perioperative complications, weight-loss surgery is recommended only after all other options have been exhausted.

Comment

The obesity epidemic has had numerous personal and societal consequences, including increased morbidity and mortality, as well as increased healthcare use. Abdominal obesity, in particular, has been linked to increased risk of dyslipidemia, hypertension, T2DM, and CVD. Although treatment modalities are available to manage obesity, they are fraught with challenges, including poor patient adherence and presence of adverse events. The increasing prevalence of abdominal obesity coupled with the limitations of currently available antiobesity medications has generated increased interest in novel modes of therapy.

References


