

Obesity-Related Cardiometabolic Complications

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Obese patients are at increased risk for developing numerous cardiometabolic complications, including hypertension, insulin resistance, diabetes mellitus, dyslipidemia, and cardiovascular disease (CVD). These complications are associated with an increase in mortality and appear to be related to the changes in adipocytes that occur with obesity. The enlarged adipocytes found in obese individuals release more glycerol, free fatty acids, and proinflammatory factors and less adiponectin. Some of these changes result in insulin resistance, which appears to be integral to the development of the obesity-associated cardiometabolic complications. Weight loss and increased physical activity are key to reducing the risk for obese individuals to develop cardiovascular complications. However, many patients also require drug therapy. Because many obese patients have multiple cardiometabolic complications, ideally, drug therapy that has positive effects on multiple CVD risk factors should be used. Therapies directed at obesity, such as sibutramine and endocannabinoid receptor blockers (eg, rimonabant), have shown improvements in weight, blood pressure, the lipid profile, and glucose levels. (*Clinical Cornerstone*. 2008;9[1]:11–22) © 2008 Elsevier. All rights reserved.

With the alarming increase in the prevalence of obesity over the past several decades, obesity is now considered a major public health concern in the United States and abroad. In the United States, approximately one third of adults are obese,^{1,2} and worldwide an estimated 312 million people are obese.³

Obese individuals have an increased rate of mortality. Data from the National Health and Nutrition Examination Survey (NHANES)⁴ estimated that there were 111,909 excess deaths in 2000 among individuals aged ≥ 25 years who were obese (body mass index [BMI] ≥ 30 kg/m²) compared with those who were of normal weight (BMI 18.5–25 kg/m²). In a study by Adams et al⁵ of US men and women aged 50 to 71 years, the risk of death was 2 to 3 times higher among obese subjects than among those of normal weight. The impact of obesity on mortality is particularly high among those who are severely obese (BMI ≥ 35 kg/m²).⁴ Severe obesity is associated with a decrease in life expectancy of 5 to 20 years.⁶ In fact, it has been suggested that within the first half of the 21st century, a leveling off or even a decrease in life expectancy may occur in the United States as a result of the increased prevalence of obesity.⁶

KEY POINT

The impact of obesity on mortality is particularly high among those who are severely obese (BMI ≥ 35 kg/m²). Severe obesity is associated with a decrease in life expectancy of 5 to 20 years.

The increased mortality rate observed in obese patients may be attributable, in large part, to the increased prevalence of cardiometabolic diseases in this population. Obese patients are at increased risk for morbidity from cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke; type 2 diabetes mellitus (DM); hypertension; dyslipidemia; gall bladder disease; osteoarthritis; sleep apnea; respiratory problems; gynecologic problems; and breast, prostate, colon, and endometrial cancer.^{1,7–9} In 2004, an estimated 112,150 excess

deaths due to CVD occurred in obese patients.⁹ Furthermore, a study of the age-adjusted death rate for CHD¹⁰ found that an increase in BMI from 25.6 kg/m² in 1980 to 28.2 kg/m² in 2000 accounted for an 8% increase in deaths over the same period.

The development of cardiometabolic complications in obese patients appears to be related to changes in adipocytes that occur with obesity. In the past, adipocytes were thought to be storage cells for fat; however, recent research has found that adipocytes act as an endocrine organ and are critical to the control of many metabolic processes.¹¹

Adipocytes release protein hormones, the best studied of which are adiponectin and leptin.¹¹ Adiponectin enhances insulin sensitivity, increases free fatty acid (FFA) oxidation, and decreases serum levels of FFAs, glucose, and triacylglycerol. It also inhibits tumor necrosis factor (TNF)- α -induced expression of adhesion molecules and the transformation of macrophages to foam cells. Leptin affects food intake through a direct effect on the hypothalamus. In obese subjects, levels of plasma adiponectin are reduced while serum levels of leptin are increased; however, the effects of leptin are blunted in these individuals.

The enlarged adipocytes of obese individuals release more glycerol, FFAs, and proinflammatory factors (eg, TNF- α , interleukin-6, inducible nitric oxide synthase) and procoagulant factors, than do those of individuals of normal weight.¹¹ Furthermore, there are increased numbers of macrophages in obese individuals compared with individuals of normal weight, and these macrophages also produce proinflammatory factors.¹¹ The increase in the levels of FFA and glycerol that occurs in obese persons is thought to contribute to the development of insulin resistance.¹¹ Research continues to explore the connections between obesity-related changes in adipocytes and the development of the cardiometabolic complications associated with obesity.

HYPERTENSION

In 2000, almost 1 billion people worldwide had hypertension, and by 2025, this number is expected to increase by ~60% to 1.56 billion.¹² In the United States, a comparison of NHANES data (1988–1994 vs 1999–2000) demonstrated an increase of ~30% in the number of adults with hypertension,¹³ and the increasing prevalence of obesity is believed to be an important contributor.³

The prevalence of hypertension in obese individuals is 3 times as high as that in individuals of normal weight,¹⁴ and the incidence is 5 times as high.³

KEY POINT

In 2000, almost 1 billion people worldwide had hypertension, and by 2025, this number is expected to increase by ~60% to 1.56 billion, in part, because of the worldwide increase in obesity.

Various mechanisms have been suggested to explain the increased prevalence of hypertension among obese subjects.¹⁵ In such persons, hypertension may result from overactivity of the sympathetic nervous system, overactivity of the renin-angiotensin-aldosterone system (RAAS), endothelial dysfunction, and renal function abnormalities. Numerous factors may contribute to the increased sympathetic activity observed in these subjects, including increased levels of leptin, activation of the RAAS, elevated aldosterone levels, increased FFAs, hyperinsulinemia, and low levels of adiponectin.

Since hypertension is a major risk factor for CVD morbidity, control of blood pressure levels is critical. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)¹⁶ recommends a treatment goal of <140/90 mm Hg, or <130/80 mm Hg in those who also have diabetes or renal disease. The JNC 7 guidelines also recommend lifestyle management for all hypertensive patients. Lifestyle management includes weight loss; regular aerobic activity (≥ 30 minutes per day most days of the week); adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan, which is rich in fruits, vegetables, and low-fat dairy products and low in saturated and total fat; reduced dietary sodium (≤ 100 mmol/d); and moderate alcohol consumption. **Table I** describes the approximate reduction in systolic blood pressure (SBP) that may be achieved with each of these lifestyle modifications.¹⁶

For the many patients whose hypertension cannot be managed with lifestyle management alone, the JNC 7

TABLE I. APPROXIMATE REDUCTIONS IN SYSTOLIC BLOOD PRESSURE AS A RESULT OF LIFESTYLE MODIFICATIONS.

Modification	Approximate Reduction in Systolic Blood Pressure, Range*
Weight reduction	5–20 mm Hg/10-kg weight loss
Adoption of DASH eating plan	8–14 mm Hg
Dietary sodium restriction	2–8 mm Hg
Physical activity	4–9 mm Hg
Moderate alcohol consumption	2–4 mm Hg

DASH = Dietary Approaches to Stop Hypertension.

*The effects of implementing these modifications are dose- and time-dependent and could be greater for some individuals.

Adapted with permission from *Hypertension*. 2003;42:1206–1252.

recommends adding pharmacotherapy to the treatment regimen.¹⁶ Appropriate agents include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, β -blockers, calcium channel blockers (CCBs), and diuretics. While the JNC 7 guidelines do not provide specific guidelines for the treatment of hypertension in obese persons, recent studies^{17,18} have examined the treatment of hypertension in this population. For example, Sharma et al¹⁷ demonstrated the efficacy of an angiotensin II receptor blocker/thiazide diuretic combination for reducing blood pressure in obese hypertensive patients with type 2 DM.

In a double-blind, placebo-controlled study of hypertensive overweight or obese patients, Scholze et al¹⁸ compared the weight-loss agent sibutramine (a norepinephrine, dopamine, and serotonin reuptake inhibitor) plus a multidrug antihypertensive regimen (felodipine/ramipril, verapamil/trandolapril, or metoprolol succinate/hydrochlorothiazide) with the multidrug antihypertensive regimen alone. Overall, the combination of sibutramine and antihypertensive therapy was associated with a greater decrease in body weight, BMI, and waist circumference than the antihypertensive therapy alone. While the addition of sibutramine to all 3 antihypertensive regimens enhanced weight loss and reduction of BMI, it was more effective in the felodipine/ramipril and verapamil/trandolapril groups than in the metoprolol/hydrochlorothiazide group. No significant changes in SBP or diastolic blood pressure (DBP) levels measured during office visits were noted between the sibutramine and placebo groups. While 24-hour

blood pressure analysis also demonstrated no difference in SBP between groups, DBP was increased in the sibutramine group. Compared with the group treated with the antihypertensive regimen only, the sibutramine-treated group showed greater improvements in glucose tolerance, fasting plasma glucose (FPG), and triglyceride levels. However, the improvements in glucose tolerance and triglyceride levels were attenuated in the metoprolol/hydrochlorothiazide group. The results of this study suggest that when treating hypertension in obese patients, use of an ACE inhibitor and a CCB may be preferred to the use of a β -blocker and a diuretic.

Hypertension is also an important predictor of CVD complications in patients with type 2 DM. The US Preventive Services Task Force recently updated its recommendations about screening for type 2 DM in adults.¹⁹ The task force suggests that individuals who are asymptomatic for type 2 DM but who have either treated or untreated sustained blood pressure levels $>135/80$ mm Hg be screened for type 2 DM. Blood pressure goals for individuals with type 2 DM should be lower than for those without it. Therefore, detection of type 2 DM at this early, asymptomatic stage will assist clinicians in determining how aggressive treatment for hypertension needs to be in these patients.

DIABETES AND INSULIN RESISTANCE

Along with obesity, the prevalence of diabetes and insulin resistance is also increasing. The worldwide prevalence of diabetes is expected to increase from 171 million in 2000 to 366 million in 2030, and the incidence of impaired glucose tolerance (IGT) is expected to increase to 420 million by 2025.³ These estimates are largely based on the increasing weight of the population. In fact, ~90% of cases of type 2 DM are thought to be attributable to excess weight.³ Obese patients who have diabetes are considered to be at very high absolute risk for mortality; therefore, it is recommended that they be advised to make lifestyle changes and that they receive early, intensive treatment to reduce risk for disease progression.¹

Studies continue to explore the connection between obesity and insulin resistance/type 2 DM. The adipose tissue of obese individuals has been shown to release substances—nonesterified fatty acids, glycerol, hormones, and proinflammatory cytokines—that are involved in the development of insulin resistance.²⁰ Decreased levels of

KEY POINT

Along with obesity, the prevalence of diabetes and insulin resistance is also increasing. In fact, ~90% of cases of type 2 DM are thought to be attributable to excess weight.

adiponectin also link obesity with insulin resistance, hyperinsulinemia, and type 2 DM.^{11,21} Insulin resistance promotes the development not only of type 2 DM but also of other obesity-related complications, including hypertension, dyslipidemia, and CVD.²² Generally, the American Diabetes Association (ADA)²³ recommends screening for diabetes with an FPG test and/or a 2-hour oral glucose tolerance test every 3 years in persons ≥ 45 years of age. However, because of the increased risk for diabetes and prediabetes with obesity, the ADA suggests that screening for diabetes be performed at a younger age and more frequently in people who are overweight and have additional risk factors for diabetes (**Table II**). Individuals are considered to have diabetes if they have symptoms of diabetes and a casual plasma glucose level ≥ 200 mg/dL, FPG level ≥ 126 mg/dL, or 2-hour plasma glucose level ≥ 200 mg/dL. Individuals with an FPG level of 100 to 125 mg/dL are considered to have impaired fasting glucose (IFG), and those with a 2-hour plasma glucose level of 140 to 199 mg/dL are considered to have IGT. The term *prediabetes* is used to refer to individuals with IFG or IGT.

For persons with prediabetes, as well as for those with overt type 2 DM, the ADA recommends implementation of a diet and exercise program, as modest weight loss reduces insulin resistance.²³ In those with IGT, weight loss of 5% to 10% of initial body weight and daily physical activity have been shown to prevent progression to overt type 2 DM. Over 3 years, intensive lifestyle modification reduces the risk of progression from prediabetes to overt diabetes by ~60%. In the recent Look AHEAD (Action for HEALth in Diabetes) multicenter study of overweight or obese subjects with type 2 DM,²⁴ obese diabetic patients who participated in an intensive lifestyle intervention program that promoted weight loss and weight maintenance through decreased caloric intake and

TABLE II. RISK FACTORS FOR DIABETES.

- Body mass index ≥ 25 kg/m²*
- Habitually physically inactive
- First-degree relative with diabetes
- Member of a high-risk ethnic population (eg, African American, Latino, Native American, Asian American, Pacific Islander)
- Delivered a baby weighing >9 lb or diagnosed with gestational diabetes
- Hypertension ($\geq 140/90$ mm Hg)
- HDL-C <35 mg/dL and/or triglycerides >250 mg/dL
- Polycystic ovary syndrome
- Impaired glucose tolerance or impaired fasting glucose on previous testing
- Clinical conditions associated with insulin resistance (eg, acanthosis nigricans)
- History of vascular disease

HDL-C = high-density lipoprotein cholesterol.

*Measure may vary in some ethnic populations.

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increased physical activity lost an average of 8.6% of their initial body weight. Mean glycosylated hemoglobin (HbA1c) levels were also reduced. Furthermore, they showed improvements in fitness, blood pressure, triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels. A limitation of lifestyle modification programs, however, is that many patients find it difficult to sustain participation.²³

KEY POINT

For persons with prediabetes, as well as for those with overt type 2 DM, the ADA recommends implementation of a diet and exercise program, as modest weight loss reduces insulin resistance.

Pharmacotherapy may be considered in patients with diabetes as well as in those with prediabetes. Drugs that have been approved for the management of type 2 DM include insulin, sulfonylureas, metformin, thiazolidine-

diones, α -glucosidase inhibitors, glucagon-like peptide-1 agonists, and amylinomimetics. Metformin, acarbose, orlistat, and rosiglitazone have all been shown to prevent the development of diabetes in patients with prediabetes.²³ Of the drugs that have been approved for the management of type 2 DM, metformin and exenatide have a beneficial effect on weight, while others, such as thiazolidinediones, sulfonylureas, and insulin, are associated with weight gain (Table III).²⁵ Ideally, in obese patients, blood glucose should be managed with treatment regimens that do not further increase weight gain.

DYSLIPIDEMIA

There is also an increased risk of dyslipidemia in obese patients. Obesity is associated with elevated serum levels of triglycerides and decreased serum levels of HDL-C.^{22,26} The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)²⁶ considers an optimal low-density lipoprotein cholesterol (LDL-C) level to be <100 mg/dL and a normal triglyceride level to be <150 mg/dL. A serum HDL-C level of <40 mg/dL is considered low.

Insulin resistance and obesity-related changes in adiponectin levels may contribute to the development of dyslipidemia. Decreased levels of adiponectin have been associated with increased levels of triglycerides and LDL-C, as well as decreased levels of HDL-C.²⁷ Insulin resistance that accompanies obesity has also been associated with increased levels of LDL-C and triglycerides and decreased levels of HDL-C.²²

KEY POINT

There is an increased risk of dyslipidemia in obese patients. Insulin resistance and obesity-related changes in adiponectin levels may contribute to the development of dyslipidemia.

The NCEP ATP III treatment goals (Table IV) for dyslipidemia are based on LDL-C levels.²⁶ Obesity is not considered to be a risk factor that requires modification of these goals. The NCEP ATP III guidelines state that the incremental risk associated with obesity independent

TABLE III. EFFECTS OF HYPOGLYCEMIC AGENTS ON WEIGHT.²⁵

Drug Class	Effect on Weight
Secretagogues	Gain
Biguanides (metformin)	Reduction
α -Glucosidase inhibitors	Neutral
Thiazolidinediones	Gain
Insulin	Gain
Insulin analogues	Neutral
Glucagon-like peptide-1	Reduction
Amylin analogue	Reduction
Dipeptidyl peptidase-4 inhibitors	Neutral

of other accompanying risk factors is uncertain; therefore, obesity should be considered a direct target for clinical intervention rather than an indicator for lipid-modifying pharmacotherapy.

The NCEP ATP III guidelines recommend the implementation of therapeutic lifestyle changes, such as reduced intake of saturated fats and cholesterol, weight reduction, and increased physical activity, in all patients with dyslipidemia.²⁶ No specific guidelines are provided for drug therapy in obese patients; however, a recent analysis²⁸ of data examining the use of atorvastatin or pravastatin for lipid lowering suggests that obese subjects may require more intensive lipid-lowering therapy than subjects with lower BMIs. Obese patients may also require ≥ 1 drug to control dyslipidemia; for example, a statin may be needed to reduce LDL-C levels, and niacin or a fibrate may be needed to reduce triglyceride levels and increase HDL-C levels.²²

In some obese patients, drugs with other indications may have a positive effect on the lipid profile, thus eliminating the need for lipid-lowering agents. For example, in obese patients who have diabetes and hypertriglyceridemia, the use of hypoglycemic agents such as insulin, sulfonylureas, metformin, and thiazolidinediones has been associated with reductions in triglyceride levels.²⁶ Consequently, in some of these patients, use of an oral hypoglycemic agent may be sufficient to control both glucose and lipid levels. The weight-loss agent sibutramine has also been shown to have positive effects on the lipid profiles of obese patients.¹⁸

TABLE IV. NCEP ATP III TREATMENT GOALS FOR LDL-C.

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy*
High: CHD or CHD risk equivalent [†] (10-year risk >20%)	<100 mg/dL (<70 mg/dL, optional [‡])	≥100 mg/dL [§]	≥100 mg/dL (<100 mg/dL, consider drug options*)
Moderately high: 2+ risk factors [¶] (10-year risk 10%–20% [#])	<130 mg/dL ^{**}	≥130 mg/dL [§]	≥130 mg/dL (100–129 mg/dL, consider drug options ^{††})
Moderate: 2+ risk factors [¶] (10-year risk <10% [#])	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower: 0–1 risk factor ^{‡‡}	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL, LDL-lowering drug is optional)

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; LDL-C = low-density lipoprotein cholesterol; TLC = therapeutic lifestyle changes; CHD = coronary heart disease; LDL = low-density lipoprotein.

* When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve a ≥30% to 40% reduction in LDL-C levels.

[†] CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia. CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with a 10-year risk for hard CHD >20%.

[‡] Very-high risk favors the optional LDL-C goal of <70 mg/dL, and in patients with high triglycerides, a non-high-density lipoprotein cholesterol (HDL-C) goal <100 mg/dL.

[§] Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride or low HDL-C levels, or metabolic syndrome) is a candidate for TLC to modify these risk factors, regardless of LDL-C level.

^{||} If baseline LDL-C is <100 mg/dL, initiation of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

[¶] Risk factors include cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication), low HDL-C (<40 mg/dL), family history of premature CHD (first-degree male relative <55 years of age; first-degree female relative <65 years of age), and age (men ≥45 years; women ≥55 years).

[#] Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.

^{**} Optional LDL-C goal <100 mg/dL.

^{††} For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.

^{‡‡} Almost all people with 0 to 1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0 to 1 risk factors is not necessary.

Source: Grundy SM, Cleeman JI, Bairey Merz N, et al, for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227–239.

CARDIOVASCULAR RISK

Many obese patients have multiple risk factors for CVD, including obesity itself, as well as hypertension, prediabetes, diabetes, and dyslipidemia.^{1,29} Furthermore, CVD is the major cause of the increased mortality observed in obese patients.^{9,30} Consequently, the National Institutes of Health (NIH) guidelines¹ on the treatment of obesity suggest that control of CVD risk factors should be given the same emphasis as weight-loss therapy since risk factors for CVD will be reduced whether or not weight-loss efforts are successful.

Like many of the cardiometabolic complications associated with obesity, the increased risk for CVD in obese patients may be attributable to insulin resistance as well as decreased levels of adiponectin. Insulin re-

sistance leads to impaired thrombolysis, inflammation, and endothelial dysfunction.²² It also contributes to the development of hypertension, diabetes, and dyslipidemia.²² Adiponectin inhibits key components of atherogenesis, including TNF- α -induced expression of adhesion molecules; therefore, reductions in adiponectin levels may be expected to promote the development of atherosclerosis.¹¹

Studies have demonstrated that by modifying CVD risk factors, the rate of CVD mortality can be reduced.^{10,16,26} Ideally, treatment efforts should be employed that affect multiple modifiable CVD risk factors. Weight loss, for example, has been associated with reduced blood pressure and blood glucose levels, increased insulin sensitivity, and improved lipid profiles.^{1,16,23,24,31}

KEY POINT

Control of CVD risk factors should be given the same emphasis as weight-loss therapy since risk factors for CVD will be reduced whether or not weight-loss efforts are successful.

While any amount of weight loss is beneficial, a 10% reduction in body weight is generally desirable for reducing disease risk factors.¹ Generally, diet modification is key to achieving this weight loss. The NIH recommends a weight-reduction diet of 1000 to 1200 kcal/d for women and 1200 to 1600 kcal/d for men.¹

Results of a 2-year study by Shai et al³² in 322 moderately obese subjects (BMI: mean, 31 kg/m²) suggest that a healthy diet has benefits beyond weight reduction. In this study, participants were randomized to 1 of 3 diets: a low-fat/restricted-calorie diet; a Mediterranean/restricted-calorie diet; or a low-carbohydrate/non-restricted-calorie diet. Mean (SD) overall weight losses at 24 months were 2.9 (4.2), 4.4 (6.0), and 4.7 (6.5) kg, respectively. Maximum weight loss occurred between study months 1 and 6. All groups lost weight, but reductions were greater in the Mediterranean and low-carbohydrate groups than in the low-fat group ($P < 0.001$). Among the 45 women in the study, those on the Mediterranean diet lost more weight than did those on either the low-fat or the low-carbohydrate diet. Of the 36 participants with type 2 DM, changes in FPG and insulin levels were more favorable among those assigned to the Mediterranean diet than among those assigned to the low-fat diet (FPG, $P < 0.001$). Improvements in biomarkers (eg, HDL-C, triglycerides, ratio of total cholesterol to HDL-C, C-reactive protein, adiponectin, leptin) continued even after the achievement of maximum weight loss at 6 months.

Many patients, however, have difficulty achieving and maintaining clinically significant weight loss with diet alone. The US Food and Drug Administration has approved 2 weight-loss drugs, sibutramine and orlistat, that may be used along with diet to enhance weight loss and maintenance.

Increased physical activity also has positive effects on multiple CVD risk factors, including hypertension, dys-

lipidemia, and diabetes.^{16,23,31} Furthermore, increased physical activity may help in preventing weight gain.¹ Obese patients should be encouraged to adhere to the current guidelines from the American College of Sports Medicine and the American Heart Association,^{33,34} which recommend moderate-intensity aerobic activity for a minimum of 30 minutes 5 days a week or vigorous-intensity activity for a minimum of 20 minutes 3 days a week. Patients who have been sedentary should initiate physical activity slowly and gradually increase the intensity over time.¹

Behavioral strategies such as self-monitoring, stress management, stimulus control, contingency management, cognitive restructuring, and social support may enhance compliance with dietary changes and increased physical activity and assist in losing weight and maintaining weight loss.¹

The implementation of lifestyle modifications can modify many CVD risk factors; however, in many obese patients, lifestyle modification alone is not sufficient. Results of the Look AHEAD study³⁵ showed that while intensive behavior modification to promote weight loss and physical fitness in overweight patients with diabetes resulted in decreases in HbA1c, blood pressure, and LDL-C levels, only 10% of enrolled patients achieved all 3 goals of HbA1c $<7\%$, blood pressure $<130/80$ mm Hg, and LDL-C <100 mg/dL. Furthermore, as the degree of obesity increases, the probability of achieving these goals is reduced.

Drugs that may be effective in modifying multiple CVD risk factors in obese patients should be considered when lifestyle modification alone is not sufficient. Exenatide, an incretin analogue, has been approved as monotherapy for the treatment of type 2 DM. An open-label study³⁶ of patients with type 2 DM who were treated with exenatide in addition to metformin and/or a sulfonylurea for ≥ 3 years demonstrated reductions in HbA1c, blood pressure, triglyceride, and total cholesterol levels, as well as body weight, and an increase in HDL-C levels. The most frequently observed adverse effect with exenatide was nausea.

Rimonabant, a CB₁ receptor blocker that is currently in development, increases adiponectin gene expression and production in adipose tissue.³⁷ Use of rimonabant has been associated with improvements in HbA1c, insulin, and lipid levels, as well as reductions in body weight and blood pressure.³⁸⁻⁴¹

CONCLUSIONS

Obese patients are at increased risk for several cardio-metabolic complications, including hypertension, diabetes, insulin resistance, dyslipidemia, and CVD. Decreased adiponectin levels appear to be an important link between obesity and these complications. Although it is necessary to address all obesity-associated complications, CVD is a major contributor to the increased mortality observed in obese patients. While weight loss and increased physical activity can have positive effects on many of the CVD risk factors that occur in obese patients, in many cases, pharmacotherapy is also required. Recent studies have demonstrated that several new drugs have positive effects on weight, blood glucose, lipid profiles, and blood pressure; however, long-term studies examining the effects of these agents on CVD mortality are needed.

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Dialogue Box

EDITORIAL BOARD

When a person becomes obese, is it primarily due to preexisting fat cells becoming “fatter” or to an increase in the number of fat cells?

CANNON

This is a fascinating area, which is evolving in our understanding. I had believed it was the former, that is, that people have a fixed number of fat cells. In obesity, fat cells not only accumulate more fat but also seem to “reset” their size. After becoming larger, it is almost as if they like their new size, and their appetite signal recalibrates to the larger size. This is why, in part, it may be so difficult for people to get back down to an ideal weight after becoming obese. However, in some patients, the number of fat cells increases. Interestingly, it seems worse metabolically to have larger fat cells. This is an area we all need to become aware of—the fact that different patients may have different profiles of how they get fat—some whose fat cells increase in size and others who develop greater numbers of fat cells.

EDITORIAL BOARD

Why doesn’t liposuction change the risk factors of obesity?

CANNON

Liposuction removes subcutaneous fat and not the visceral fat that is at the root of the risk factors of obesity. Visceral fat cells generate more leptin and inflammatory cytokines and, conversely, less of the protective cytokine, adiponectin. They also are much more heavily involved in the metabolic consequences of obesity. Subcutaneous fat cells generate much less of these harmful cytokines; thus, simply removing them has a lesser impact on the metabolic pathways associated with obesity.

EDITORIAL BOARD

Does the presence of obesity influence your management of hypertension?

CANNON

The greatest impact for me is in the patient who is initially found to have borderline hypertension. I am more inclined to push lifestyle interventions and more likely to delay initiating an antihypertensive agent in an obese patient with a blood pressure hovering around 140/90 mm Hg. In such a patient, I try to take advantage of the natural tendency for patients to want to avoid taking a medication. I try to hold that out for them—I tell them that I’ll be forced to start them on a medication they will need to take for the rest of their lives unless they start exercising, watching their diets, and losing weight. This can be a strong incentive, and I really use it as leverage in obese patients with high blood pressure (or elevated cholesterol). Although I still advocate lifestyle interventions in obese patients who are already on blood pressure medications, I tend to be even more persistent in patients at the time of their initial presentation.

EDITORIAL BOARD

In patients in whom you decide to start an antihypertensive medication, does the presence of obesity influence your choice of agent?

CANNON

No, not particularly.

EDITORIAL BOARD

Do you foresee a role for measuring serum adiponectin levels in clinical practice?

CANNON

Clearly, serum adiponectin has furthered our understanding of the pathophysiology of obesity, and it serves as a helpful reminder that there are real biologic consequences associated with obesity that go beyond cosmetic. We now know that obesity affects a number of metabolic pathways and that, in addition to affecting how someone looks or the size pants they wear, it also puts them on the road to developing diabetes, causes their blood pressure to rise, and causes inflammation in their blood vessels. However, to warrant the usefulness of a test in clinical

Dialogue Box

practice, it has to influence you to do something differently. In this regard, I think measuring serum adiponectin levels in clinical practice is still far off. On the other hand, I think that once the results of JUPITER (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) become known, a laboratory marker likely to take off in clinical practice will be C-reactive protein (CRP). JUPITER was a primary prevention trial that enrolled subjects with a relatively normal low-density lipoprotein cholesterol (LDL-C) level of <130 mg/dL but a CRP concentration >2 mg/L. This study was stopped 2 years early because of an overwhelming benefit seen in those treated with rosuvastatin 20 mg/d compared with placebo. This study showed that measuring CRP concentrations helped to identify a high-risk group of patients with an LDL-C level <130 mg/dL in whom intensive statin therapy was beneficial. This is an example of a medical treatment being driven by a blood test. At this time, the measurement of adiponectin levels would not qualify for clinical use.

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With regard to primary and secondary prevention, how aggressive are you with drug therapy to optimize high-density lipoprotein cholesterol (HDL-C) and triglyceride levels?

CANNON

At present, I go after the LDL-C level very aggressively as a primary and probably secondary goal. Trying to get LDL-C levels down into target range and urging patients to engage in lifestyle interventions are my first- and second-line therapies. I have not been using niacin very much to raise HDL-C levels, but a growing number of cardiologists are starting to “tune in” to niacin. It is a very difficult drug for patients to take because of the issue of flushing, but there certainly is growing interest. There are 2 ongoing studies looking at adding niacin to statin therapy. Although we have angiographic data that suggest a benefit, there really are no outcome data indicating that adding niacin to statin therapy provides further benefit. For hypertriglyceridemia, we treat trigly-

ceride levels >500 mg/dL, and I consider treatment even if the levels are only a few hundred. I usually start with omega-3 fatty acids, going up to doses as high as 4 g/d. For those who don't respond, I then move on to a fibrate.

EDITORIAL BOARD

What LDL-C levels do you target?

CANNON

For patients with known coronary or vascular disease, I aim for an LDL-C level <70 mg/dL. I also aim for that level in patients who have not had a clinical event but who have vascular imaging evidence of atherosclerosis (eg, a positive calcium score). For primary prevention, I have generally aimed for <100 mg/dL in patients with risk factors. This may change now in the aftermath of JUPITER. In this study, patients with a baseline LDL-C of ~110 mg/dL appeared to have derived benefit from 20 mg/d of rosuvastatin, which further reduced LDL-C levels by 50%, down to the 55-mg/dL range. The results of this trial suggest that we should consider abandoning the more complicated idea of having multiple LDL-C targets for different levels of coronary disease risk. It may be that we will soon simply treat aggressively whether patients have known disease or fall into the high-risk category. Thus, one day, we may target all patients to an LDL-C level <70 mg/dL.

EDITORIAL BOARD

What about patients without known disease or cardiovascular risk factors?

CANNON

In a patient with no coronary risk factors, I would favor aggressive lifestyle intervention and aim for a minimum target <130 mg/dL. However, the JUPITER results may have us all checking CRP levels to help determine if we should be more aggressive in the case of an elevated CRP.

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Did the results of the ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin vs

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Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) trial cause you to change the way you use ezetimibe?

CANNON

It actually didn't change my practice at all because I've always been a high-dose statin guy. Most of my patients with coronary disease are already on high-dose statin

therapy. However, if these patients do not achieve goal (<70 mg/dL) despite treatment with a high-dose statin, then I would add ezetimibe. In the primary-prevention outpatient setting, I might start with 40 mg/d of simvastatin, a drug that has a proven mortality reduction rate. If the LDL-C level remained above goal, I would try atorvastatin 80 mg/d or rosuvastatin 40 mg/d. If the LDL-C level remained above goal, then I would consider adding ezetimibe.