

METABOLIC SYNDROME

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Learning Objectives

1. Assess the role of abdominal obesity and insulin resistance in the development and pathophysiology of metabolic syndrome.
2. Assess the relationship between metabolic syndrome and the risk of cardiovascular disease and type 2 diabetes mellitus.
3. Diagnose metabolic syndrome using the most appropriate risk factor criteria.
4. Design an appropriate plan, including goals of therapy and integration of nondrug therapy, for treatment of the underlying and metabolic risk factors in metabolic syndrome.
5. Apply currently available consensus guidelines to the treatment of atherogenic dyslipidemia, hypertension, and glucose dysregulation in patients with metabolic syndrome.
6. Evaluate the potential role of pharmacotherapeutic agents that target the underlying pathophysiology of metabolic syndrome.

Overview

Although metabolic syndrome seems to have only recently engaged the attention of the medical community, the concept that an interrelated group of metabolic abnormalities is often present in people who develop cardiovascular disease and/or type 2 diabetes mellitus (DM) has been recognized for decades. The metabolic and underlying risk factors that are components of metabolic syndrome include abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance with or without glucose intolerance, low-grade inflammation, and a prothrombotic state. During the past 20 years, this clustering of metabolic health risks has been known by several names (e.g., insulin resistance syndrome, syndrome X, the deadly quartet, hypertriglyceridemic waist). However, the term most commonly used in clinical practice today is *metabolic syndrome*. Although the predictive and clinical utility of

metabolic syndrome has been debated in some circles, it generally is accepted that metabolic syndrome serves as a construct to identify individuals who have an increased long-term risk of atherosclerotic cardiovascular disease (ASCVD) with or without type 2 DM.

The primary factor driving the heightened awareness of metabolic syndrome is its high prevalence in the United States and worldwide. Cross-sectional analyses of U.S. adults 20 years and older show age-adjusted metabolic syndrome prevalence estimates of 29.2% (1988–1994) and 32.3% (1999–2002). Epidemiologic studies show that the prevalence of metabolic syndrome is higher in men than in women (31.4% vs. 27.0%) and differs by race and ethnicity (e.g., Mexican Americans, 31.9%; whites, 23.8%; and African Americans, 21.6%). Another alarming trend is the increased incidence of metabolic syndrome in young people. Estimates of metabolic syndrome prevalence are 30% to 50% in overweight children and adolescents.

Associated Health Risks

In general, the presence of metabolic syndrome confers a 1.5- to 3-fold increase in the relative risk of ASCVD. A meta-analysis showed that patients with metabolic syndrome had a 1.78 times higher relative risk of cardiovascular events and death compared with individuals without metabolic syndrome. After adjustment for traditional cardiovascular risk factors, metabolic syndrome was associated with a 1.54 times higher relative cardiovascular risk. Notably, women with metabolic syndrome had a 1.33 times higher relative risk of cardiovascular events and death compared with men.

The number of metabolic syndrome components also influences the degree of risk. In one study, the presence of four or more metabolic syndrome risk factors was associated with a 3.7 times higher risk of cardiovascular events. However, data suggest that the metabolic syndrome construct is less likely to predict cardiovascular or total mortality in individuals older than 65 years. Later in life, certain metabolic syndrome components (e.g., hypertension) are more closely tied with increased cardiovascular risk than

Abbreviations in This Chapter

ACE	Angiotensin-converting enzyme
AHA/NHLBI	American Heart Association National Heart, Lung and Blood Institute
apoB	Apolipoprotein B
ARB	Angiotensin receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
CHD	Coronary heart disease
DM	Diabetes mellitus
HDL-C	High-density lipoprotein cholesterol
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LDL-C	Low-density lipoprotein cholesterol
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
PPAR	Peroxisome proliferator-activated receptor

is metabolic syndrome itself. Thus, metabolic syndrome as a construct to identify individuals with an increased long-term risk of ASCVD is most applicable to middle-aged adults.

Although viewed as a multiplex risk factor for ASCVD, metabolic syndrome is also associated with a 3.5- to 5-fold increase in the risk of type 2 DM. This is a logical association given that insulin resistance underlies the clustering of metabolic risk factors and that insulin resistance precedes the development of type 2 DM. Like ASCVD, the risk of type 2 DM increases linearly with the number of metabolic risk factors present. One study showed that individuals with four or more metabolic syndrome risk factors had about a 25-fold increased risk of type 2 DM. Beyond ASCVD and type 2 DM, metabolic syndrome is associated with an increased risk of myriad diseases such as nonalcoholic fatty liver disease, cholesterol gallstones, obstructive sleep apnea, and gout.

Pathophysiology

Abdominal obesity and insulin resistance are viewed as the core defects underlying the pathophysiology of metabolic syndrome. These two risk factors are highly interrelated; therefore, it is difficult to ascertain which one plays the predominant role in metabolic syndrome pathogenesis and progression. In addition, metabolic syndrome pathophysiology is complicated by contributing factors such as dysregulation of adipose tissue-derived cytokines, inflammation, genetics, race/ethnicity, physical inactivity, diet, hormone imbalances, drugs, and age. As such, it is unrealistic to assume that metabolic syndrome is caused by a single underlying defect. Instead, it is the combination of numerous risk factors, primarily driven

by obesity and insulin resistance, which gives rise to the development of this clustering of metabolic health risks.

Obesity

Some experts view metabolic syndrome as the metabolic complications of obesity. Obesity is associated with numerous adverse health consequences such as cardiovascular disease, type 2 DM, hypertension, dyslipidemia, and insulin resistance. Recent changes in the understanding of adipose tissue biology have led to the view that adipose tissue is no longer a benign storage depot, but rather, a metabolically active endocrine organ. Adipocytes release a variety of substances into the circulation including, but not limited to, free fatty acids, interleukin-6, tumor necrosis factor alpha, plasminogen activator inhibitor-1, adiponectin, leptin, monocyte chemoattractant protein-1, lipoprotein lipase, and angiotensinogen. Adipose tissue-derived proteins cause alterations in glucose and lipid metabolism in muscle, liver, and fat. Furthermore, these substances promote local and systemic inflammatory and thrombotic states. To date, the most widely studied adipose tissue-derived substances are free fatty acids, interleukin-6, tumor necrosis factor alpha, adiponectin, and plasminogen activator inhibitor-1.

Release of nonesterified fatty acids from adipose tissue is increased in obese states. Elevated circulating concentrations of free fatty acids result in diminished hepatic and muscle insulin sensitivity, increased hepatic cholesterol production, and altered endothelial function. The inflammatory cytokines interleukin-6 and tumor necrosis factor alpha impair insulin signaling and lead to insulin resistance and adipose tissue lipolysis. Furthermore, adipose tissue-derived interleukin-6 stimulates C-reactive protein production in the liver. C-reactive protein, an acute-phase reactant, is a major biomarker of the chronic low-grade inflammation present in obesity and metabolic syndrome. Adiponectin, an insulin-sensitizing, anti-inflammatory, and potentially anti-atherogenic protein, is secreted exclusively by adipose tissue. Higher circulating adiponectin concentrations are associated with a decreased risk of ASCVD. For reasons not yet fully elucidated, adiponectin secretion is paradoxically decreased in states of obesity, insulin resistance, type 2 DM, and ASCVD. It is hypothesized that other cytokines (e.g., tumor necrosis factor alpha, interleukin-6) inhibit the secretion of adiponectin. Plasminogen activator inhibitor-1, an inhibitor of fibrinolysis, is increased in obesity and metabolic syndrome. Adipose tissue-derived cytokines and free acids also stimulate the production of fibrinogen in the liver, further contributing to a prothrombotic state.

Excess adipose tissue is recognized as a major contributor to metabolic syndrome; however, the location of this fat is also an important consideration. Visceral fat located deep within the abdominal cavity is more metabolically active than subcutaneous fat. Visceral fat delivers free fatty acids and cytokines directly to the liver through the portal circulation; consequently, intra-abdominal fat is more closely tied to metabolic risk factors than subcutaneous fat. Taken together, adipose tissue (particularly fat in the visceral compartment) is an active endocrine organ that secretes a variety of substances that mediate the unfavorable metabolic, inflammatory, and thrombotic environment of metabolic syndrome.

Insulin Resistance

Insulin resistance is a physiologic state in which the ability of target tissues (e.g., muscle, liver, fat) to respond to the normal actions of insulin is diminished. Consequently, the ability of insulin to promote glucose uptake, inhibit hepatic glucose production, and suppress lipolysis in target tissues is decreased. Compensatory hyperinsulinemia is often present in insulin-resistant states as the body works to maintain glucose homeostasis. However, with time, the pancreas is often unable to secrete sufficient amounts of insulin to maintain glucose homeostasis. As a result, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or type 2 DM may ensue. In some studies, insulin resistance and hyperinsulinemia have been associated with an increased risk of ASCVD.

Excess free fatty acids are thought to be responsible for the development of insulin resistance in obesity and metabolic syndrome. In turn, a vicious cycle ensues whereby insulin resistance further promotes adipose tissue lipolysis, resulting in even greater release of free fatty acids into the circulation. Hepatic insulin resistance results in increased triglyceride and apolipoprotein B (apoB) production and in decreased high-density lipoprotein cholesterol (HDL-C), all of which are characteristic lipid abnormalities observed in metabolic syndrome. Insulin resistance also causes diminished glucose uptake in muscle and fat and causes increased glucose production in the liver. With time, this contributes to overt glucose abnormalities such as prediabetes or type 2 DM. Insulin resistance and hyperinsulinemia are associated with overactivity of the sympathetic nervous system, increased sodium reabsorption in the kidney, and decreased vasodilation, all of which may contribute to the development of hypertension. In addition, through alterations in insulin signaling and the expression of cytokines, insulin resistance is thought to contribute to the inflammatory and thrombotic states observed in metabolic syndrome.

The broad physiologic effects of insulin resistance on metabolic risk factors have spurred some experts to view it as the underlying cause of metabolic syndrome. Indeed, insulin resistance is present in many, but not all, patients with metabolic syndrome. Insulin resistance is also closely intertwined with obesity. However, not all obese patients are insulin resistant, nor are all insulin-resistant patients obese. In addition, it is difficult to measure insulin resistance in clinical practice. The gold standard measurement of insulin resistance—the hyperinsulinemic euglycemic clamp test—is purely a research tool. Surrogate measures of insulin resistance exist, such as fasting plasma insulin concentrations or the homeostasis model assessment calculation (fasting insulin [in microunits per milliliter] times fasting glucose [in milligrams per deciliter] divided by 405). However, these surrogate measures are flawed because of the variability in insulin measurements between laboratories and the absence of cut points to indicate insulin resistance or hyperinsulinemia. For these reasons, it is challenging to pinpoint the exact role insulin resistance plays in the development of metabolic syndrome. It is more likely that insulin resistance contributes, at least partially, to the development of most metabolic syndrome risk factors.

Characterization and Diagnosis

Abdominal Obesity

Computed tomography and magnetic resonance imaging are the most accurate tools to assess intra-abdominal adiposity. However, these measurements are expensive and impractical to routinely use in the clinical setting. Measurement of an individual's waist circumference with a cloth tape measure is a simple yet practical way to assess intra-abdominal fat. To measure waist circumference, the patient should stand in the upright position. The top of the iliac crest (hip bone) and the bottom of the lower rib should be palpated, and the midway point between these two landmarks should be marked. Waist circumference should be measured at the midway point at the end of a gentle exhalation. The measuring tape should be flat to the body and snug but not tight.

The American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) metabolic syndrome diagnostic criteria define abdominal obesity as a waist circumference of 102 cm or greater in men or 88 cm or greater in women. People of Asian descent may have metabolic risk factors (e.g., insulin resistance) with only modest increases in waist circumference. Therefore, in this racial group, lower waist circumference cut points of 90 cm or greater in men or 80 cm or greater in women are appropriate. In addition, certain individuals of non-Asian descent (e.g., those with a family history of type 2 DM in first-degree relatives younger than 60 years, polycystic ovary syndrome, nonalcoholic steatohepatitis) may have metabolic risk factors or insulin resistance with only moderate increases in waist circumference (i.e., 94–101 cm in men, 80–87 cm in women).

Because metabolic risk factors are often present with only marginal increases in waist circumference, the International Diabetes Federation (IDF) metabolic syndrome diagnostic criteria use lower waist circumference cut points. Specifically, the IDF guideline defines abdominal obesity as 94 cm or greater in men or 80 cm or greater in women. Ethnic-specific waist circumference cut points are also provided for the following populations: Europid, South Asian, Chinese, Japanese, South and Central America, Sub-Saharan Africa, Eastern Mediterranean, and the Middle East.

There has been debate about why body mass index (BMI), an indicator of total body adiposity, is not present in most metabolic syndrome diagnostic criteria. Indeed, BMI and waist circumference are highly correlated measures, with studies reporting correlation coefficients of about 0.80. However, for a given BMI, studies show that the location of fat, rather than the total amount of body fat, is most predictive of metabolic and cardiovascular risks. In the clinical setting, BMI should be ascertained to classify individuals as underweight (less than 18.5 kg/m²), normal weight (18.5 kg/m² to 24.9 kg/m²), overweight (25 kg/m² to 29.9 kg/m²), obese (30 kg/m² to 39.9 kg/m²), or extremely obese (40 kg/m² or greater). After BMI determination, measurement of waist circumference should be performed. Unfortunately, waist circumference is not

routinely measured by many practitioners even though it is simple, inexpensive, and informative. Compared with BMI assessment alone, measurement of waist circumference is more likely to identify a subgroup of overweight or obese patients who are particularly insulin resistant or who are likely to carry additional metabolic abnormalities (e.g., hypertriglyceridemia). Thus, the routine measurement of waist circumference should be promoted in clinical practice.

Atherogenic Dyslipidemia

Dyslipidemia in metabolic syndrome is characterized by the presence of elevated triglycerides, low HDL-C, and normal to elevated low-density lipoprotein cholesterol (LDL-C). Elevated triglycerides and the presence of low HDL-C serve as individual components in the diagnosis of metabolic syndrome. Further evaluation of dyslipidemia in patients with metabolic syndrome, especially those with high triglycerides, often reveals high concentrations of small, dense LDL-C particles and elevated concentrations of apoB, a lipoprotein whose concentration represents the sum of all particles considered to have the highest atherogenic potential. When LDL-C particles are small and dense, their atherogenic potential is increased. Similarly, when apoB is elevated, atherogenesis is also elevated. Concentrations of apoB may provide a better representation of cardiovascular risk than LDL-C. However, measurement and monitoring of apoB are not yet universally performed.

Hypertension

An elevated systolic or diastolic blood pressure is another criterion for metabolic syndrome. For patients without comorbid medical conditions, blood pressure levels above 140/90 mm Hg are considered elevated. Patients at high risk of cardiovascular disease are considered hypertensive if their blood pressure is above 130/80 mm Hg. Patients in this category include those with DM, chronic kidney disease, known coronary artery disease, a coronary artery disease equivalent (e.g., carotid artery disease, peripheral artery disease, abdominal aortic aneurysm), or a 10-year Framingham risk score of 10% or more.

Elevated Fasting Glucose

Elevated fasting glucose is defined as fasting plasma glucose of 100 mg/dL or greater. This definition includes patients with IFG; fasting plasma glucose between 100 mg/dL and 126 mg/dL and type 2 DM (fasting plasma glucose of 126 mg/dL or greater). Thus, *elevated fasting glucose* represents a progressive continuum of abnormal glucose homeostasis. Although not explicitly listed under the elevated fasting glucose category, IGT is also recognized as a state of altered glucose homeostasis. Impaired glucose tolerance is defined as a 2-hour plasma glucose concentration between 140 mg/dL and 200 mg/dL on a 75-g oral glucose tolerance test, in the presence of fasting plasma glucose less than 126 mg/dL. The states of IFG and IGT are commonly referred to as *prediabetes*. The conversion of prediabetes to type 2 DM occurs at a rate of 5% to 10% per year. In addition, most studies have shown that IFG and IGT are independent, albeit weak, risk factors for cardiovascular disease.

A plasma glucose concentration after an overnight fast is the test of choice to identify IFG or type 2 DM. Individuals with normoglycemia or IFG may benefit from an oral

glucose tolerance test because it may uncover the presence of IGT or type 2 DM. An oral glucose tolerance test may be particularly useful in individuals who are at high risk of developing type 2 DM (e.g., those with a strong family history of type 2 DM, prior gestational diabetes, polycystic ovary syndrome). Furthermore, an oral glucose tolerance test is required to determine whether pharmacologic therapy should be instituted in patients with prediabetes.

Prothrombotic and Pro-inflammatory State

Fibrinogen, plasminogen activator inhibitor-1, cytokines, and C-reactive protein are often elevated in patients with metabolic syndrome, resulting in a prothrombotic and pro-inflammatory state. Besides C-reactive protein, these biomarkers of inflammation and thrombosis are not routinely evaluated in clinical practice. C-reactive protein is often measured in the laboratory as high-sensitivity C-reactive protein. High-sensitivity C-reactive protein concentrations greater than 3 mg/dL represent a state of inflammation and a higher risk of ASCVD.

Diagnostic Criteria

During the past 10 years, several groups have developed criteria for the identification and clinical diagnosis of metabolic syndrome. These criteria have emerged on the basis of the relative importance each group assigns to certain metabolic risk factors. Numerous criteria are available; however, the AHA/NHLBI and IDF criteria are the most commonly used because of their simplicity and practicality in the clinical setting. Although more complicated, World Health Organization (WHO) criteria are also used in some parts of the world. The AHA/NHLBI, IDF, and WHO metabolic syndrome diagnostic criteria are provided in Table 1-1.

Management of Metabolic Syndrome

Role of the Pharmacist

Pharmacists play an integral role in the independent and collaborative management of the individual components of metabolic syndrome. The benefit of the pharmacist to the care of these patients has been documented in a variety of clinical settings including community pharmacy, managed care, and independent clinical practice. In these and other settings, pharmacists provide care through screening and identification of high-risk individuals, through collaborative practice agreements with supervising physicians, and by means of multidisciplinary collaboration. Outcomes achieved by pharmacists that relate to metabolic syndrome include significant reductions in blood pressure, lipids, weight, and hemoglobin A1C. The advent and expansion of point-of-care technology, allowing pharmacists to independently assess patient risk factors at the time of a clinic visit, will further increase the pharmacist's role in this area.

Risk Assessment

Determining the best pharmacotherapeutic approach for patients with metabolic syndrome is dependent on the known or estimated risk of ASCVD, which may vary widely among patients who meet criteria for metabolic syndrome. For instance, a patient with metabolic syndrome may have existing coronary artery disease and/or existing type 2 DM. Such patients are at a much higher risk of ASCVD than patients with metabolic syndrome who do not have existing diseases. Similarly, goals of therapy vary widely given the presence or absence of disease. Treatment of patients who do not have diabetes or clinically evident atherosclerotic disease is focused on preventing the development of these diseases. For these patients, the Framingham risk assessment tool (<http://hp2010.nhlbi.nih.net/atpiii/calculator.asp?usertype=prof>) can be used to predict a patient's 10-year risk of coronary heart disease (CHD). The Framingham risk assessment tool quantifies this risk and provides guidance for the appropriate treatment goals for these patients. Table 1-2 provides metabolic syndrome treatment goals based on Framingham risk. For patients with existing elevated fasting glucose or diagnosed diabetes, interventions aimed at preventing microvascular and macrovascular complications are implemented. Treatment

of patients with existing atherosclerotic disease is focused on the prevention of secondary vascular events.

Underlying Risk Factors

The primary goal of metabolic syndrome management is to decrease the risk of ASCVD and type 2 DM. The principal way to accomplish this goal is to institute lifestyle interventions that target lifestyle risk factors such as obesity, physical inactivity, atherogenic diet, and smoking. Regardless of ASCVD risk, all patients with metabolic syndrome are candidates for lifestyle intervention. Metabolic risk factors such as atherogenic dyslipidemia, elevated blood pressure, or prediabetes can benefit from lifestyle interventions. If metabolic syndrome is present in patients with existing ASCVD or diabetes, lifestyle strategies and pharmacologic therapies should be instituted according to current consensus guidelines to decrease complications associated with these conditions.

Abdominal Obesity

In patients with abdominal obesity, the primary weight-loss goal is a 7% to 10% reduction in total body weight during a period of 6–12 months. The ultimate goal is to achieve a BMI less than 25 kg/m² and a waist circumference less than 102 cm in men and less than 88 cm in women. This

Table 1-1. AHA/NHLBI, IDF, and WHO Metabolic Syndrome Diagnostic Criteria

	AHA/NHLBI	IDF	WHO
Number of required criteria	Any 3 of 5 below	Abdominal obesity plus 2 others below	Type 2 diabetes mellitus, ^a IFG, ^b IGT, ^c or lowered insulin sensitivity ^d plus 2 others below
Abdominal obesity	Waist circumference \geq 102 cm in men or \geq 88 cm in women	Increased waist circumference (population-specific ^e [e.g., Europid \geq 94 cm in men or \geq 80 cm in women])	Waist-to-hip ratio of $>$ 0.90 in men or $>$ 0.85 in women and/or BMI $>$ 30 kg/m ²
Elevated triglycerides	\geq 150 mg/dL, or drug treatment for high triglycerides (i.e., fibrates or nicotinic acid)	\geq 150 mg/dL, or drug treatment for high triglycerides (i.e., fibrates or nicotinic acid)	\geq 150 mg/dL
Low HDL-C	$<$ 40 mg/dL in men or $<$ 50 mg/dL in women; or drug treatment for low HDL-C (i.e., fibrates or nicotinic acid)	$<$ 40 mg/dL in men or $<$ 50 mg/dL in women; or drug treatment for low HDL-C (i.e., fibrates or nicotinic acid)	$<$ 35 mg/dL in men or $<$ 39 mg/dL in women
Elevated blood pressure	Systolic \geq 130 mm Hg and/or diastolic \geq 85 mm Hg; or drug treatment for hypertension	Systolic \geq 130 mm Hg and/or diastolic \geq 85 mm Hg; or drug treatment for hypertension	\geq 140/90 mm/Hg
Elevated fasting plasma glucose	\geq 100 mg/dL; or drug treatment for elevated glucose	\geq 100 mg/dL; or drug treatment for elevated glucose	Required, see first row in this column
Other	—	—	Microalbuminuria \geq 20 mcg/minute or albumin-to-creatinine ratio \geq 20 mg/g

^aType 2 diabetes mellitus = fasting plasma glucose of 126 mg/dL or greater or 2-hour post load glucose of 200 mg/dL or greater.

^bImpaired fasting glucose = fasting plasma glucose between 110 mg/dL and 125 mg/dL and 2-hour post load glucose less than 140 mg/dL. The American Diabetes Association has since revised the definition of IFG to be fasting plasma glucose between 100 mg/dL and 125 mg/dL.

^cImpaired glucose tolerance = fasting plasma glucose less than 126 mg/dL and 2-hour post load glucose between 140 mg/dL and 199 mg/dL.

^dInsulin sensitivity glucose uptake below the lowest quartile for background population under investigation, as measured under hyperinsulinemic euglycemic clamp conditions.

^eEuropid \geq 94 cm men or \geq 80 cm women; South Asian and Chinese \geq 90 cm men or \geq 80 cm women; Japanese \geq 85 cm men or \geq 90 cm women; ethnic South and Central Americans \geq 90 cm men or \geq 80 cm women; Sub-Saharan Africans \geq 94 cm men or \geq 80 cm women; Eastern Mediterranean and Middle East (Arab) populations \geq 94 cm men or \geq 80 cm women.

AHA/NHLBI = American Heart Association/National Heart, Lung and Blood Institute; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; WHO = World Health Organization.

Information from the American Heart Association/National Heart, Lung, and Blood Institute metabolic syndrome diagnostic criteria; International Diabetes Federation metabolic syndrome definition, and World Health Organization metabolic syndrome definition.

Table 1-2. Treatment Goals Based on Framingham Risk for Patients Without Existing Disease

Framingham Risk (%)	Blood Pressure (mm Hg)	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	FPG (mg/dL)	Aspirin
< 10	< 140/90	< 160, ^a < 130 ^a	< 190, ^b < 160 ^b	< 100	Consider ^c
10–20	< 130/80	< 130, < 100 ^d	< 160, < 130 ^d	< 100	Yes
> 20	< 130/80	< 100, < 70 ^e	< 130, < 100 ^e	< 100	Yes

^aGoal less than 160 mg/dL for patients with 0 or 1 major risk factor (i.e., cigarette smoking, hypertension, low HDL-C, premature coronary heart disease, or age); goal less than 130 mg/dL for patients with two or more major risk factors.

^bGoal less than 190 mg/dL for patients with 0 or 1 major risk factor; goal less than 160 mg/dL for patients with two or more major risk factors.

^cSome patients with metabolic syndrome will meet criteria according to the U.S. Preventive Services Task Force statement concerning the use of aspirin for the prevention of cardiovascular disease.

^dMultiple major risk factors, severe and poorly controlled risk factors (especially continued cigarette smoking), or metabolic syndrome.

^eEstablished coronary heart disease plus any of the following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), metabolic syndrome, or recent acute coronary syndrome.

FPG = fasting plasma glucose; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol.

Information from Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735–52; Rosendorff C, Black HR, Cannon CP, Gersh BJ, Gore J, Izzo JL Jr, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation* 2007;115:2761–88; and National Institutes of Health. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Available at www.nhlbi.nih.gov/guidelines/cholesterol/index.htm. Accessed June 5, 2009.

degree of weight loss can be achieved by reducing caloric intake by 500–1000 calories per day and increasing physical activity. The physical activity component should focus on the accumulation of 30–60 minutes of moderate-intensity exercise coupled with increased daily lifestyle activities (e.g., pedometer step tracking, gardening, housework) for 5 days/week or more. Exercise stress testing should be performed before initiating an exercise program in individuals with existing cardiovascular disease, recent acute coronary syndrome, or recent revascularization.

Regarding weight loss, the most common question both patients and health care practitioners pose is: Which type of diet is most effective? Although no consensus exists about which diet is most effective for patients with metabolic syndrome, data suggest that a Mediterranean-style diet may be particularly beneficial in this population. Mediterranean-style diets incorporate foods rich in monounsaturated fats (e.g., olive oil) and omega-3 fatty acids (e.g., fish). In addition, these diets include daily amounts of fruit (250–300 g), vegetables (125–250 g), nuts (25–50 g), and low-fat whole grains (400 g). A study of patients with metabolic syndrome found that after 2 years of intervention, a Mediterranean-style diet was associated with a significantly greater amount of weight loss than a control diet (–4.0 kg vs. –1.2 kg). In this study, the Mediterranean-style diet also favorably modulated metabolic risk factors such as inflammatory cytokines and insulin sensitivity. At the end of the study, metabolic syndrome was still present in 44% of patients in the Mediterranean-style diet group compared with 87% of patients in the control group.

Recently, a clinical study compared Mediterranean-style, low-fat, and low-carbohydrate diets. Study participants were moderately obese and had many metabolic risk factors. After 2 years, weight loss was greater with the nonrestricted-calorie low-carbohydrate diet (–4.7 kg) and the restricted-calorie Mediterranean diet (–4.4 kg) compared with the restricted-calorie low-fat diet (–2.9 kg). Subgroup analysis showed that the low-carbohydrate diet had the most favorable effect on lipids, whereas the Mediterranean-style diet was associated with the largest decrease in

fasting plasma glucose and the greatest improvement in insulin sensitivity.

Another study compared the effectiveness of four popular diets: Atkins (carbohydrate restriction), Zone (macronutrient balance), Weight Watchers (calorie restriction), and Ornish (fat restriction). After 1 year of intervention, weight loss did not differ significantly between the diet groups. Notably, more patients prematurely discontinued the Atkins and Ornish diets (48% and 50%, respectively) compared with the Weight Watchers and Zone diets (35% discontinuation in both groups). Taken together, these studies suggest that selection of a diet based solely on the anticipated amount of weight loss is not enough. Instead, consideration must be given to patient food preferences and the likelihood of patient adherence. Diets such as the Weight Watchers program or a Mediterranean-style diet, which incorporate a variety of food choices that can be tailored to different lifestyles or medical conditions, may prove to be the best means for successful and long-term weight loss.

Patients often request pharmacologic therapy to assist in their weight-loss endeavors. However, weight-loss drugs have limited use in patients with metabolic syndrome because these agents cause only 3% to 5% greater weight loss compared with placebo. In addition, pharmacologic weight-loss drugs are associated with significant adverse effects. Agents such as orlistat, sibutramine, phentermine, or diethylpropion are usually reserved as adjuncts to diet and exercise in patients with a BMI greater than 30 kg/m² whose diet and exercise alone have not resulted in sufficient weight loss. Pharmacologic therapy may be considered for individuals with a BMI between 27 kg/m² and 30 kg/m² if obesity-related disease (e.g., type 2 DM, cardiovascular disease, hypertension, dyslipidemia, sleep apnea) is present and diet and exercise alone have not worked.

When selecting a pharmacologic weight-loss agent, careful consideration must be given to the adverse effect profile and any contraindications to therapy. Orlistat is an intestinal lipase inhibitor that decreases dietary fat absorption by 30%. Patient adherence to orlistat is typically poor because of significant gastrointestinal adverse

effects (e.g., flatulence, oily stools, fecal incontinence). Sibutramine, a centrally acting inhibitor of serotonin and norepinephrine reuptake, is associated with increased blood pressure, increased heart rate, arrhythmias, and central nervous system adverse effects. Therefore, sibutramine may not be appropriate for patients with hypertension or cardiovascular disease. Phentermine and diethylpropion are centrally acting adrenergic stimulants. Although they effectively suppress appetite, both agents are associated with increased blood pressure, increased heart rate, and central nervous system stimulation. Furthermore, there is a risk of dependence and abuse with these agents.

Bariatric surgery is a potential treatment option for obesity; however, it is usually reserved for individuals with a BMI of 40 kg/m² or greater (i.e., morbid obesity). Bariatric surgery may be considered for the patient with a BMI between 35 kg/m² and 40 kg/m² if obesity-related disease is present and the patient has been unable to lose weight with lifestyle interventions alone. In the appropriate patient, bariatric surgery results in substantial health benefits such as resolution of diabetes, hypertension, hyperlipidemia, and sleep apnea; however, the anticipated benefits must outweigh the potential risks associated with this surgery. Psychosocial

factors (e.g., psychiatric disorders, binge-eating disorder, substance abuse, low socioeconomic status) must be fully evaluated before surgery because these conditions may negatively influence the extent of weight loss after surgery. Although not recommended in clinical guidelines, a recent study showed that, compared with conventional diabetes therapy, bariatric surgery improved type 2 DM remission rates and glycemic control in patients with type 2 DM who had a BMI between 30 kg/m² and 40 kg/m².

Metabolic Risk Factors

For patients with metabolic syndrome but without existing diabetes or ASCVD, pharmacotherapy focuses on treating the individual components of metabolic syndrome. Therapeutic interventions target the treatment of atherogenic dyslipidemia, hypertension, elevated fasting plasma glucose, and prothrombotic state. Figure 1-1 is an algorithm summarizing the management of metabolic risk factors in the patient with metabolic syndrome.

Atherogenic Dyslipidemia

Treatments targeting the characteristic atherogenic dyslipidemia in patients with metabolic syndrome have

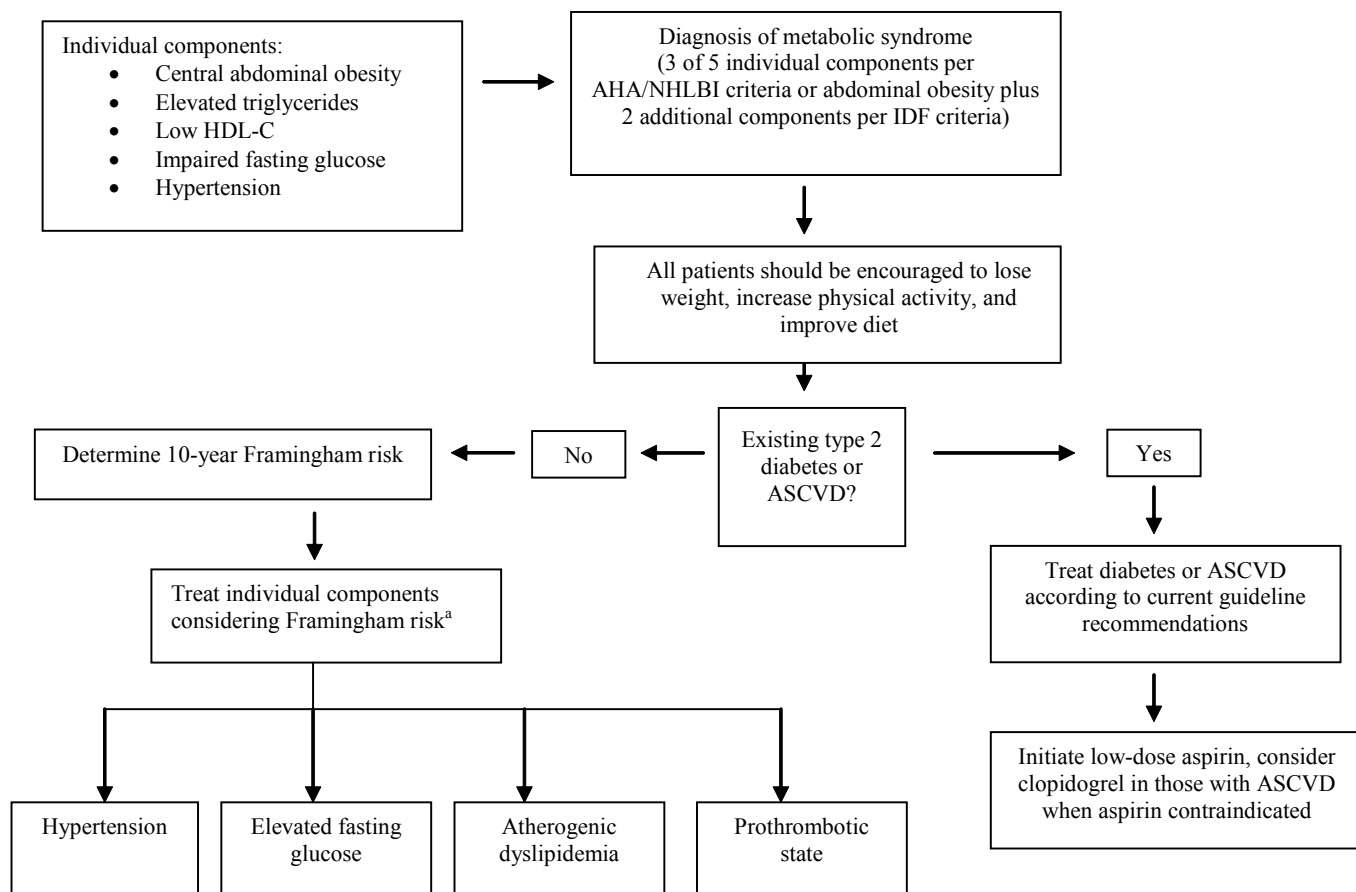


Figure 1-1. Algorithm for the management of metabolic syndrome.

^aRefer to Table 1-2.

AHA/NHLBI = American Heart Association/National Heart, Lung and Blood Institute; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation.

not been evaluated in controlled trials. However, the cardiovascular benefit of lowering LDL-C has been well studied and well documented. Because of this, the primary target remains LDL-C in patients with metabolic syndrome.

The LDL-C goal in this population is determined by the presence or absence of risk factors, as well as the presence or absence of CHD or CHD equivalence (i.e., diabetes, ischemic stroke, abdominal aortic aneurysm, peripheral vascular disease, or Framingham risk score of 20% or greater). Patients with CHD or CHD equivalence have a minimal LDL-C goal of less than 100 mg/dL. In patients without CHD or CHD equivalence, the LDL-C goal varies with risk factors according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines. To achieve the LDL-C goal in patients with metabolic syndrome, treatment with HMG CoA reductase inhibitors (statins) remains the preferred initial therapy. Statins are potent reducers of LDL-C with strong evidence supporting cardiovascular benefit, although the evidence is not specific for patients with metabolic syndrome. In addition to reducing LDL-C, statins reduce all other apoB-containing lipoproteins.

When statin therapy is not tolerated, or when maximal statin therapy does not achieve the desired LDL-C reduction, additional LDL-C lowering therapy with ezetimibe, bile acid sequestrants, or niacin is warranted. Monotherapy with bile acid sequestrants must be done cautiously in patients with metabolic syndrome because of their propensity to increase triglycerides. Bile acid sequestrants can also be difficult to tolerate. Ezetimibe can provide an 18% reduction in LDL-C when used as monotherapy or when added to existing statin therapy. Nicotinic acid reduces all apoB lipoproteins, reduces triglycerides, and raises HDL-C.

Patients who have existing cardiovascular disease and risk factors for metabolic syndrome, especially high triglycerides (200 mg/dL or greater) with a non-HDL-C of 130 mg/dL or greater and a low HDL-C (40 mg/dL or less), are deemed at very high risk and should be considered for treatment to achieve an LDL-C goal of less than 70 mg/dL. Aggressive treatment of LDL-C in patients with metabolic syndrome is supported by findings from a subgroup analysis of the Treating to New Targets Study. The study randomized 10,001 patients with baseline CHD to atorvastatin 10 mg or 80 mg. The 5584 study patients with metabolic syndrome were evaluated by subgroup analysis for the primary end point of first major cardiovascular event. Treatment with atorvastatin 80 mg, which attained a mean LDL-C of 72.6 mg/dL, reduced the primary end point significantly compared with treatment with atorvastatin 10 mg, which attained a mean LDL-C of 99.3 mg/dL. Because the study only enrolled subjects with clinically evident CHD, results of the analysis can only be applied to patients with both metabolic syndrome and CHD.

Once the LDL-C goal is achieved in patients with metabolic syndrome, secondary targets are identified. For patients with a triglyceride concentration of 200 mg/dL or greater, the non-HDL-C becomes the secondary target. Non-HDL-C, defined as total cholesterol minus HDL-C, represents all cholesterol in the body considered atherogenic. Goal target for non-HDL-C is less than 30 mg/dL above the LDL-C goal. Intensifying LDL-C lowering therapy will lower total cholesterol and reduce overall atherogenic

particle burden. If goal non-HDL-C cannot be achieved with intensified statin therapy, the initiation of fibrate therapy or nicotinic acid is warranted. Nicotinic acid may be preferred given better evidence of safety when used in combination with statin therapy. Fibrates, in turn, can lower triglycerides, convert small LDL-C particles into larger particles, and raise HDL-C. Caution must be exercised when combining fibrates or niacin with statins because of an increased risk of myopathy or rhabdomyolysis. This interaction appears to be less likely with fenofibrate compared with gemfibrozil.

Goal concentrations for apoB have not been well defined. Non-HDL-C correlates well with apoB to calculate the amount of atherogenic particles when evaluated on a population basis. However, the two are often not concordant on the individual patient level. Given this, attainment of the non-HDL-C goal does not guarantee attainment of the apoB goal. A recent expert consensus proposed an apoB goal of less than 80 mg/dL to be targeted in patients at highest risk and a goal of less than 90 mg/dL for those with lower risk after the attainment of LDL-C and non-HDL-C goals. The highest-risk group includes those with known cardiovascular disease or those with diabetes plus an additional major risk factor (i.e., smoking, hypertension, or family history of premature coronary artery disease). There are few data to support the benefits of attaining the apoB goal compared with attaining LDL-C or non-HDL-C goals. To attain the apoB goal, intensification of statin therapy or the addition of nicotinic acid or fibrate therapy may be necessary.

After targeting LDL-C and non-HDL-C, increasing HDL-C to the greatest extent possible becomes the next focus of therapy in the treatment of dyslipidemia in metabolic syndrome. High-density lipoprotein cholesterol is anti-atherogenic, thus providing protection against cardiovascular disease. Interventions aimed at increasing HDL-C include the addition of a fibrate or nicotinic acid to statin therapy, increased physical activity, dietary modifications, weight reduction, and smoking cessation.

In clinical practice, practitioners can expect to use high-dose, high-potency statin therapy to achieve the LDL-C goal in patients with metabolic syndrome. The addition of a second LDL-C lowering therapy may be necessary to achieve the LDL-C goal. Ezetimibe is commonly used despite a lack of definitive evidence because of its tolerability, lack of drug interactions, and ease of administration. Attainment of the secondary goal, the non-HDL-C, can also be difficult. Many patients will have required maximal LDL-C lowering therapy to attain the LDL-C goal. In this population, the addition of a fibrate or nicotinic acid may be necessary to provide additional LDL-C and triglyceride lowering. Again, caution must be exercised when combining fibrates or niacin with statins because of an increased risk of myopathy or rhabdomyolysis. The use of high-dose omega-3 fatty acids can be beneficial in lowering elevated triglycerides, but it does not appear that omega-3 fatty acids lower apoB to a clinically significant extent. The benefit of fish oil in lowering overall atherogenic particle burden is unclear at this time. A summary of the magnitude of effect of select cholesterol-lowering agents on atherogenic dyslipidemia is provided in Table 1-3.

Hypertension

The specific treatment of hypertension in patients with metabolic syndrome has not been directly addressed by clinical trials. Furthermore, no guideline statement focuses on the treatment of hypertension in this population. Current recommendations for treatment are extrapolated from hypertension and metabolic syndrome guideline consensus statements and available clinical data.

According to the Seventh Report of the Joint National Committee, compelling indications (e.g., prior ischemic stroke, diabetes, chronic kidney disease, heart failure, existing coronary artery disease) dictate the choice of initial and preferred antihypertensive therapy for patients who have metabolic syndrome and a compelling indication. For patients who require blood pressure reduction for general heart disease prevention, or for patients at high risk of the development of coronary artery disease, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, and thiazide-type diuretics are all appropriate as first-line therapy or in combination as necessary. Therapy with β -blockers can be added to these antihypertensive classes but is primarily used in patients with stable angina, myocardial infarction, or left ventricular systolic dysfunction. In patients with metabolic syndrome but without a compelling indication, it is not clear which antihypertensive class provides the most cardiovascular and metabolic benefit. Furthermore, it is unclear which class or agent is preferred for initial therapy. Because patients who have metabolic syndrome but not diabetes are at an increased risk of developing diabetes, the propensity of a given antihypertensive class to induce hyperglycemia must be considered.

It is well documented that thiazide diuretics can impair glucose tolerance. Hypokalemia induced by thiazide diuretics is thought to impair insulin secretion, resulting in hyperglycemia. Findings from the Antihypertensive and

Lipid-Lowering Treatment to Prevent Heart Attack Trial showed that the incidence of new-onset DM was significantly higher in the group initially receiving chlorthalidone, a thiazide diuretic, than in the group initially treated with amlodipine or the group treated with lisinopril at 4 years follow-up. Despite these differences in the progression to diabetes between lisinopril, chlorthalidone, and amlodipine, there was no difference in the primary end point between the drugs.

It has been argued that the trial duration may not have been sufficient to determine the long-term effects of new-onset diabetes. A subgroup analysis of the trial evaluated the incidence of newly diagnosed diabetes in participants without diabetes but with metabolic syndrome at baseline. Patients with metabolic syndrome who were initially assigned to treatment with lisinopril were less likely to develop diabetes than those assigned to initial treatment with chlorthalidone. There was no statistical difference in the development of diabetes for patients who received initial treatment with lisinopril compared with amlodipine. Despite a higher incidence of newly diagnosed diabetes, patients initially treated with diuretic therapy had a lower risk of heart failure and combined cardiovascular disease than those treated with an ACE inhibitor. Again, the lack of a long duration brings this finding into question.

In contrast to thiazide-type diuretics, treatment with ACE inhibitors or ARBs has been postulated to delay or prevent the onset of diabetes. Inhibiting the formation of angiotensin II or blocking its action may increase insulin sensitivity and provide protection to the pancreas by enhancing bloodflow. Retrospective analysis of the Heart Outcomes Prevention Evaluation trial found that 3.6% of patients randomized to ramipril developed diabetes (by self-report) after a mean of 4.5 years compared with 5.4% randomized to placebo. Similarly, a retrospective analysis of the Candesartan in Heart Failure-Assessment of Reduction

Table 1-3. Approximate Effect of Select Cholesterol-Lowering Agents on Atherogenic Dyslipidemia

Drug and Daily Dosage	LDL-C (% reduction)	HDL-C (% increase)	Triglycerides (% reduction)	apoB (% reduction)
Statin				
Rosuvastatin, 5–40 mg	45–63	8–14	10–35	38–54
Atorvastatin, 10–80 mg	39–60	5–9	19–37	32–50
Simvastatin, 10–80 mg	27–45	6–8	14–24	21–37
Lovastatin, 10–40 mg	20–30	3–5	11–15	17–25
Pravastatin, 10–40 mg	21–31	6–8	14–19	16–26
Absorption inhibitor				
Ezetimibe, 10 mg	18	1	8	16
Fibrate				
Fenofibrate, 145 mg	21	11	30–50	15–20
Gemfibrozil, 1200 mg	10	14	30–50	17
Niacin				
Extended-release niacin, 1000–2000 mg	5–14	18–22	21–28	6–16
Bile acid sequestrant				
Colesevelam, 3800–4500 mg	15–18	3	+9–10	12
Omega-3 fatty acids (prescription)	+0–2	3–5	30–50	1–2

apoB = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

in Mortality and Morbidity Program trial found that 6% of those randomized to candesartan developed diabetes compared with 7.4% of those randomized to placebo. Several meta-analyses with similar findings prompted the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication trial. The trial prospectively evaluated the effect of ramipril versus placebo on the primary outcome of diabetes development in patients with IFG or IGT at baseline. Therapy with ramipril did not result in a significant decrease in the incidence of diabetes, but it did improve fasting glucose. These conflicting results prevent any definitive conclusion. Treatment with calcium channel blockers appears to be metabolically neutral with little to no effect on glucose tolerance. Similar to thiazide diuretics, β -blockers have been associated with hyperglycemia.

Patients with metabolic syndrome who have compelling indications for treatment with specific antihypertensive classes should be treated according to the Seventh Report of the Joint National Committee guidelines. It is reasonable to initiate ACE inhibitors (or ARB if ACE inhibitor intolerant) as preferred initial therapy in patients with metabolic syndrome but without compelling indications. As in most patients with hypertension, it is likely that two or more antihypertensive agents will be required to attain the blood pressure goal in these patients. Preferred combination therapy includes selection from an ACE inhibitor (or ARB if ACE inhibitor intolerant), thiazide-type diuretic, or calcium channel blocker. Currently, there are no strong data supporting a reduction in mortality with the use of β -blocker monotherapy for the treatment of hypertension. Unless a patient has a compelling indication for a different medication choice, a β -blocker should be initiated after combination therapy with an ACE inhibitor (or ARB), a thiazide-type diuretic, and a calcium channel blocker has been implemented.

Elevated Fasting Glucose

The goals of managing elevated fasting glucose in patients with metabolic syndrome are (1) in patients with prediabetes, to lower fasting glucose to less than 100 mg/dL to delay or prevent the progression to overt diabetes; and (2) in patients with type 2 DM, to intensively manage hyperglycemia and other metabolic risk factors (e.g., elevated blood pressure, hyperlipidemia, obesity) to decrease the risk of both microvascular and macrovascular complications.

Prediabetes

A target fasting glucose concentration of less than 100 mg/dL should be achieved through intensive lifestyle interventions that include both weight reduction (i.e., 5% to 10% total body weight loss) and increased physical activity (about 30 minutes/day on most, if not all, days of the week). In individuals with prediabetes, two lifestyle-intervention studies have shown that intensive lifestyle modifications reduced the risk of diabetes by 58% compared with the respective control groups. Furthermore, intensive lifestyle modifications decreased the incidence of metabolic syndrome by about 40% in individuals with prediabetes without metabolic syndrome at baseline. The lifestyle modification programs used in these studies have been intensive and rigorously monitored. For example, the Diabetes Prevention Program lifestyle intervention was a goal weight loss

of 7% or more and an exercise component of at least 150 minutes/week of moderate-intensity physical activity. Thus, diabetes risk reduction outcomes observed in well-controlled clinical studies may not completely translate to real-life practice when patient adherence to diet and exercise modification is inconsistent. Nonetheless, aggressive lifestyle-intervention programs that incorporate both weight loss and exercise are the primary means of preventing diabetes in patients with prediabetes.

The use of metformin to delay or prevent the development of type 2 DM may be appropriate in a select group of patients with prediabetes. Metformin decreases hepatic glucose production, increases skeletal muscle glucose uptake, and promotes weight loss. Lifestyle modification and/or metformin 850 mg two times/day is recommended for patients with both IFG and IGT and any one of the following: age younger than 60 years, BMI of 35 kg/m² or greater, family history of first-degree relative with type 2 DM, elevated triglycerides, reduced HDL-C, hypertension, or hemoglobin A1C greater than 6%. In the Diabetes Prevention Program, metformin 850 mg two times/day reduced the incidence of type 2 DM by 31% compared with placebo. In addition, metformin was associated with a 17% decreased incidence of metabolic syndrome in patients without metabolic syndrome at baseline. Although metformin is an effective diabetes prevention agent, both IFG and IGT must be documented before instituting therapy. Performing an oral glucose tolerance test to document IGT before starting metformin therapy may be resource- and cost-prohibitive in some clinical practices.

The thiazolidinediones rosiglitazone and pioglitazone have garnered considerable attention as potential diabetes prevention agents. The thiazolidinediones are agonists for the peroxisome proliferator-activated receptor- γ (PPAR γ), a nuclear receptor found abundantly in adipose tissue. By binding to the peroxisome proliferator response elements in target genes, thiazolidinediones activate the transcription of numerous genes involved in glucose and lipid metabolism and adipocyte differentiation. In addition, thiazolidinediones repress the transcription of certain genes involved in inflammation. In the clinical setting, these agents reduce fasting glucose concentrations, improve insulin sensitivity, increase adiponectin concentrations, and decrease concentrations of circulating inflammatory and prothrombotic markers, all of which would be beneficial in the patient with prediabetes. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication trial showed that in patients with prediabetes, rosiglitazone 8 mg once daily was associated with a 60% reduction in the relative risk of diabetes or death compared with placebo. Furthermore, rosiglitazone was associated with a 70% increased likelihood of regression to normoglycemia. A study with troglitazone, an agent withdrawn from the market because of hepatotoxicity, showed a 50% reduction in the incidence of diabetes in women with a history of gestational diabetes.

Despite impressive diabetes prevention data, safety concerns regarding weight gain, edema, and congestive heart failure have plagued the thiazolidinedione class. Therefore, routine use of rosiglitazone or pioglitazone in patients with prediabetes cannot be recommended. In addition, meta-analyses data suggest that rosiglitazone is

associated with an increased risk of cardiovascular events. Thiazolidinedione-associated weight gain is likely because of subcutaneous adipocyte differentiation and fluid retention. Although a greater number of small adipocytes may be advantageous from an insulin sensitivity standpoint, weight gain in patients with prediabetes is of concern because many of these patients are already likely to be overweight. Fluid retention and edema contribute to the increased risk of congestive heart failure associated with these agents. As such, both rosiglitazone and pioglitazone carry black box warnings about congestive heart failure. Data from a meta-analysis of rosiglitazone clinical studies also suggest that rosiglitazone increased the odds of myocardial infarction and cardiovascular death compared with other diabetes drugs or placebo. Pioglitazone does not appear to increase the risk of cardiovascular events; however, no large-scale clinical studies examining the ability of pioglitazone to prevent type 2 DM in patients with prediabetes have been published.

Acarbose, an α -glucosidase inhibitor that decreases postprandial glucose concentrations, has also been investigated as a diabetes prevention agent. In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus, acarbose 100 mg three times/day was associated with a 25% reduction in the risk of diabetes compared with placebo in patients with IGT. In addition, acarbose reduced the relative risk of cardiovascular event and new cases of hypertension by 49% and 34%, respectively. Acarbose is associated with a high incidence of gastrointestinal adverse effects and has a cumbersome dosing schedule. Thus, although the data on the ability of acarbose to prevent diabetes and reduce cardiovascular risk are intriguing, lack of patient adherence may limit its routine use in clinical practice.

Type 2 DM

Many, but not all, patients with existing type 2 DM also have metabolic syndrome. These patients deserve special attention for intensive management of hyperglycemia and other metabolic syndrome risk factors to decrease the risks of both microvascular and macrovascular complications. In patients with coexisting type 2 DM and metabolic syndrome, the primary goal of antihyperglycemic therapy is to decrease hemoglobin A1C to less than 7%. This primary goal should be accomplished through lifestyle intervention (i.e., diet and exercise) with or without pharmacologic therapy, according to current consensus guidelines. When selecting pharmacologic therapy for patients with type 2 DM and metabolic syndrome, additional consideration must be given to the potential for certain drugs to exacerbate or ameliorate other metabolic risk factors (e.g., obesity, insulin resistance, lipids).

Metformin improves hepatic insulin sensitivity and, unlike most other antihyperglycemic agents, is weight neutral, or even induces modest weight loss. Oral insulin secretagogues (e.g., the sulfonylureas) are unlikely to improve insulin sensitivity or metabolic risk factors beyond what can be expected as a result of their glucose-lowering effects. Sulfonylurea-associated weight gain (about 2 kg) may prompt more aggressive lifestyle modification strategies in obese patients with metabolic syndrome. The insulin-sensitizing and anti-inflammatory effects of the thiazolidinediones target the underlying pathophysiology

of metabolic syndrome. However, the beneficial effects on insulin sensitivity and inflammatory markers are tempered by thiazolidinedione-induced weight gain (about 2–4 kg). Both agents modestly increase HDL-C. Rosiglitazone increases LDL-C by about 20%, whereas pioglitazone has a neutral effect on LDL-C. Pioglitazone reduces triglycerides by about 20%, whereas rosiglitazone either has no effect or modestly increases triglyceride concentrations. The dipeptidyl peptidase-4 inhibitor, sitagliptin, is the newest oral antidiabetic agent. Sitagliptin has modest antihyperglycemic efficacy, producing a mean reduction in hemoglobin A1C of 0.7%. This agent may be advantageous in obese patients with type 2 DM and metabolic syndrome because it has a neutral effect on body weight. In addition, sitagliptin does not appear to adversely affect blood pressure or lipid concentrations.

Prothrombotic and Pro-inflammatory State

Lifestyle changes leading to weight loss can result in a reduction in high-sensitivity C-reactive protein concentrations, suggesting that inflammation is reduced with weight reduction. Therapy with statins can also reduce high-sensitivity C-reactive protein concentrations. Treatment with rosuvastatin 20 mg/day reduced the incidence of major cardiovascular events compared with placebo for an average follow-up of 1.9 years in patients without hyperlipidemia but with high-sensitivity C-reactive protein concentrations greater than 2 mg/L. In this study, about 40% of patients had metabolic syndrome at baseline. Rosuvastatin reduced high-sensitivity C-reactive protein concentrations by 37% and LDL-C by 50%.

Therapy with low-dose aspirin is indicated in patients with existing cardiovascular disease to reduce the risk of secondary thrombosis. For primary prevention, a variety of recommendations and guidelines exist. The AHA currently recommends that aspirin 75–160 mg/day be considered for the primary prevention of cardiovascular disease and stroke in patients with a Framingham risk score of 10% or more. The U.S. Preventive Services Task Force updated its recommendations for aspirin use in March 2009. Aspirin use is now recommended in men aged 45–79 to reduce the risk of myocardial infarction and in women aged 55–79 to reduce the risk of ischemic stroke unless the risk of gastrointestinal hemorrhage outweighs the benefit. Aspirin therapy is also routinely recommended in patients with diabetes, although the evidence supporting this recommendation has been recently challenged by results from recent trials. The American Diabetes Association and the AHA jointly recommend aspirin 75–162 mg/day for primary prevention of cardiovascular diseases in patients with diabetes who also have increased cardiovascular risk and no contraindication to aspirin therapy. Risk factors include age older than 40 years, cigarette smoking, hypertension, albuminuria, obesity, hyperlipidemia, and a family history of CHD.

Other Agents That Target Metabolic Syndrome Pathophysiology **Rimonabant**

The endocannabinoid system has been implicated in the pathophysiology of metabolic syndrome, playing a role in both central and peripheral energy metabolism balance. The cannabinoid receptor CB₁ is located in the central nervous

system, gastrointestinal tract, adipose tissue, liver, and muscle. Centrally, activation of CB₁ by endocannabinoids results in appetite stimulation. Peripherally, CB₁ activation results in altered satiety signals, promotion of visceral fat accumulation, lipogenesis, and hepatic and muscle insulin resistance. Discovery of these receptors led to the development of endocannabinoid system antagonists, most specifically, rimonabant. Blockade of CB₁ by rimonabant decreases weight, reduces waist circumference, increases HDL-C, and reduces triglycerides in overweight or obese patients. Despite these findings, rimonabant was not shown to affect the percent atheroma volume measured by intravascular ultrasonography compared with placebo in a randomized trial of patients with metabolic syndrome. Rimonabant also did not receive U.S. Food and Drug Administration approval because of safety concerns. Psychiatric events have been more common with rimonabant than placebo, and two deaths from suicide in patients taking rimonabant have been reported.

Dual PPAR γ /PPAR α Agonists

The thiazolidinediones, which are PPAR γ agonists, improve insulin sensitivity. The fibric acid derivatives, which are PPAR α agonists, have beneficial effects on lipids. Thus, a pharmacologic agent that simultaneously stimulates both PPAR γ and PPAR α receptors may be theoretically advantageous for patients with metabolic syndrome. However, the development of dual PPAR γ /PPAR α agonists has been fraught with safety issues. Muraglitazar, a dual PPAR γ /PPAR α agonist, was associated with an increased risk of death, myocardial infarction, and stroke in patients with type 2 DM. Tesaglitazar, another dual PPAR γ /PPAR α agonist, was associated with decreased hemoglobin and absolute neutrophil counts and with increased serum creatinine. Based on these concerns, development programs for muraglitazar and tesaglitazar have been discontinued. PPAR γ /PPAR α agonists currently under development will likely undergo significant scrutiny regarding cardiovascular safety before approval. In addition, whether simultaneous therapy with a PPAR γ agonist (glitazone) and PPAR α agonist (fibric acid derivative) poses risks similar to the dual PPAR γ /PPAR α agonists is unknown.

Exenatide

Exenatide is a synthetic version of exendin-4 that mimics glucagon-like peptide-1, an incretin hormone; exenatide is approved for the treatment of type 2 DM. By mimicking glucagon-like peptide-1, exenatide promotes glucose-dependent insulin secretion and decreases glucagon secretion during states of hyperglycemia. Furthermore, exenatide delays gastric emptying, reduces food intake, and improves satiety. As a result, exenatide is associated with an average weight loss of 1.5 kg and with beneficial effects on lipids. The safety and efficacy of exenatide in patients with metabolic syndrome, but without type 2 DM, remains to be determined. Considering that exenatide is an expensive subcutaneous injection, substantial benefits will likely have to be demonstrated for this agent to be used in patients without diabetes.

Patient Education

Patient education is an important component in the treatment of patients with metabolic syndrome and can prevent the development of metabolic syndrome in those with risk factors. The long-term risks of metabolic syndrome, including the development of ASCVD and diabetes, must be thoroughly discussed with each patient. Knowing long-term risk can provide incentives for patients to implement change. Because the syndrome is often the result of physical inactivity and obesity, patient education must focus on self-change in lifestyle behaviors. The AHA Web site (www.americanheart.org/presenter.jhtml?identifier=1200009) has education tools and information to help patients eat healthy foods, increase their physical activity, and manage their weight. For the tools and information to be used fully, it is important for the pharmacist to introduce the patient to the Web site and review some of the material available. To be maximally effective, any educational material used must be a supplement to a structured dietary and physical activity regimen prescribed by a health care professional.

Conclusion

Metabolic syndrome is recognized as a multiplex risk factor for cardiovascular disease and type 2 DM. Although the predictive usefulness of metabolic syndrome will continue to be debated, it does have practical utility in the clinical setting. Patients are often unmotivated to embark on lifestyle initiatives to improve their health. If assigning a name to this clustering of health risks motivates patients to take action, then the term *metabolic syndrome* has served its purpose. Furthermore, the concept of metabolic syndrome may prompt clinicians to more aggressively assess metabolic risk factors and institute intensive lifestyle modification counseling. In this respect, it is difficult to debate the individual and global health benefits of increased patient and provider awareness of metabolic syndrome.

Annotated Bibliography

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The AHA/NHLBI Scientific Statement provides updated diagnostic criteria and clinical management guidelines for metabolic syndrome in adults. The key updates in the AHA/NHLBI Scientific Statement include IFG, defined as fasting plasma glucose of 100 mg/dL or greater; provision of race- and ethnicity-specific cut points for waist circumference; inclusion of fibrates or nicotinic acid treatment as both high triglyceride and low HDL-C components in metabolic syndrome diagnostic criteria; and clarification of elevated blood pressure criteria (i.e., systolic blood pressure of 130 mm Hg or greater and/or diastolic blood pressure of 85 mm Hg or greater and/or antihypertensive drug treatment in a patient with a history of hypertension). The primary goal of the clinical management guidelines provided is to reduce the risk of ASCVD by addressing underlying modifiable risk factors.

such as obesity, physical inactivity, and an atherogenic diet. It is recommended that this be accomplished by intensive lifestyle modification, with subsequent use of drug therapy if the absolute risk of ASCVD is high.

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This article presents the 2005 IDF definition of metabolic syndrome. Individuals of certain races and ethnicities often have insulin resistance and metabolic syndrome with only slight increases in waist circumference. Therefore, the IDF definition provides detailed race- and ethnicity-specific values for waist circumference for individuals all over the world. Compared with the AHA/NHLBI Scientific Statement, the IDF definition places even greater emphasis on the role of abdominal obesity in the pathogenesis of metabolic syndrome. As a result, the presence of abdominal obesity is required for a diagnosis of metabolic syndrome. The IDF cut points for all other components of the syndrome (e.g., reduced HDL-C, increased blood pressure, increased fasting glucose, increased triglycerides) remain the same as the AHA/NHLBI Scientific Statement.

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The purpose of this contemporary review is to highlight the clinical evaluation and nonsurgical treatment of obesity in adults. Furthermore, this review article concisely highlights key points in the NHLBI weight-loss treatment guidelines (www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm). Briefly, BMI, waist circumference, and obesity-related conditions (e.g., hypertension, glucose intolerance, dyslipidemia, nonalcoholic fatty liver disease, obstructive sleep apnea) should be routinely assessed in all obese adults. Weight loss, even as little as 5% to 10%, favorably modulates many metabolic risk factors. It is recommended that weight loss be accomplished by reducing calorie intake and increasing physical activity. Many diets exist for weight loss such as low-fat, low-carbohydrate, low-glycemic index, high-protein, and commercial diets (e.g., Weight Watchers). However, no consensus exists on the ideal macronutrient composition for optimal weight loss. The principal tenet for weight loss is that energy intake must be less than energy expenditure. Pharmacologic therapy is considered appropriate for some individuals as an adjunct to lifestyle intervention when lifestyle interventions alone have failed. When selecting a weight-loss drug such as phentermine, diethylpropion, sibutramine, or orlistat, the adverse effects and contraindications to therapy should be factored heavily into the decision-making process. Furthermore, it must be recognized that no pharmacologic magic bullet exists for weight loss. The efficacy of available pharmacologic obesity therapies is mediocre, at best.

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The purpose of this study was to assess the effect of a Mediterranean-style diet on endothelial function and vascular inflammation in patients with metabolic syndrome. Patients with an NCEP ATP III diagnosis of metabolic syndrome were randomized in this single-blind study to a Mediterranean-style diet (n=90) or a control diet (n=90). The macronutrient composition of the Mediterranean-style

diet was 50% to 60% carbohydrates, 15% to 20% protein, total fat less than 30%, saturated fat less than 10%, and cholesterol consumption less than 300 mg/day. Patients were also advised to consume, on a daily basis, at least 250–300 g of fruit, 125–150 g of vegetables, 25–50 g of walnuts, 400 g of whole grains, and liberal amounts of olive oil. After 2 years of therapy, the Mediterranean-style diet was associated with a greater weight loss compared with the control diet (–4.0 kg vs. –1.2 kg, respectively, $p<0.001$). In addition, decreases in waist circumference, blood pressure, glucose, insulin, total cholesterol, and triglycerides and increases in HDL-C were greater with the Mediterranean-style diet compared with the control diet. The Mediterranean-style diet was also associated with greater reductions in markers of systemic vascular inflammation such as high-sensitivity C-reactive protein, interleukin-6, interleukin-7, and interleukin-18. Endothelial function, as measured by the L-arginine test, improved with the Mediterranean-style diet but remained stable with the control diet. This study demonstrated that a Mediterranean-style diet has favorable effects on metabolic syndrome and cardiovascular risk factors. However, additional studies are required to determine the mechanism by which this diet favorably modulates low-grade inflammation in metabolic syndrome.

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The Dietary Intervention Randomized Controlled Trial compared the effectiveness and safety of three diets: (1) a low-fat diet, (2) a Mediterranean-style diet, and (3) a low-carbohydrate diet. The restricted-calorie, low-fat diet was based on AHA guidelines and included 30% of calories from fat and 10% of calories from saturated fat. The restricted-calorie, Mediterranean-style diet consisted of no more than 35% of calories from fat and was rich in vegetables and low in red meat. Calorie intake was restricted to 1500 kcal in women and 1800 kcal in men for both the low-fat and Mediterranean-style diets. The nonrestricted-calorie, low-carbohydrate diet provided 20 g/day of carbohydrates initially, with a gradual increase to a maximum of 120 g/day. The study population included 322 moderately obese, middle-aged individuals who were randomized to one of the three closely monitored dietary interventions. After 2 years, weight loss was significantly greater with the low-carbohydrate diet (–4.7 kg) and Mediterranean-style diet (–4.4 kg) compared with the low-fat diet (–2.9 kg). Of all the diets, the low-carbohydrate diet was associated with the largest increase in HDL-C (+8.4 mg/dL) and the largest decrease in triglycerides (–23.7 mg/dL). Low-density lipoprotein cholesterol decreased with all diets, but the results were not statistically different between groups. High-sensitivity C-reactive protein decreased to the greatest extent with the low-carbohydrate diet (–29%) and the Mediterranean-style diet (–21%). In patients with diabetes, fasting glucose concentrations were lowered to the greatest extent (–32.8 mg/dL) with the Mediterranean-style diet. This study included a low percentage of women, and the closely monitored, work-setting intervention might not be readily applicable to other populations. Despite these limitations, the low-carbohydrate diet and Mediterranean-style diet appear to have the most favorable effects on metabolic risk factors.

6. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from

the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care* 2008;31:811–22.

This review is a consensus statement evaluating the appropriate management of lipoproteins in patients with cardiometabolic risk. Factors that can increase global cardiometabolic risk include dyslipoproteinemia, obesity, insulin resistance, hyperglycemia, smoking, physical inactivity, and genetics including family history. Dyslipoproteinemia is characterized by elevated triglycerides, a low HDL-C, and an increased number of small, dense, LDL particles. There is significant overlap between cardiometabolic risk and metabolic syndrome, especially as it pertains to the treatment of dyslipoproteinemia. In the statement, the authors describe the important role of both non-HDL-C and apoB in describing the true number of atherogenic particles in patients with elevated cardiometabolic risk, as well as in predicting cardiovascular disease risk. The authors also provide suggested lipoprotein goals for patients with cardiometabolic risk and lipoprotein abnormalities. For patients at highest risk, those with known cardiovascular disease, or those with diabetes plus smoking, hypertension, or a family history of premature coronary artery disease, the authors recommend an LDL-C less than 70 mg/dL, a non-HDL-C less than 100 mg/dL, and an apoB less than 80 mg/dL. For patients at high risk, including those without diabetes or cardiovascular disease but with two or more major risk factors (e.g., smoking, hypertension, family history) or those with diabetes but no other risk factors, the authors recommend an LDL-C less than 100 mg/dL, a non-HDL-C less than 130 mg/dL, and an apoB less than 90 mg/dL. Although current clinical practice is not quite at the point of evaluating apoB, this consensus represents an important thought process when interpreting risk and cholesterol goals for patients with metabolic syndrome.

7. Deedwania P, Barter P, Carmena R, Fruchart JC, Grundy SM, Haffner S, et al. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. *Lancet* 2006;368:919–28.

This publication is a post hoc analysis of the Treating to New Targets study. In the original study, 10,001 patients with CHD and LDL-C less than 130 mg/dL were randomized to atorvastatin 80 mg/day or atorvastatin 10 mg/day. In this analysis, the authors identified subjects from the original study who met criteria for metabolic syndrome. More than 5500 subjects with CHD and metabolic syndrome were identified. Subjects with metabolic syndrome randomized to atorvastatin 80 mg achieved a mean LDL-C of 72.6 mg/dL, whereas those randomized to atorvastatin 10 mg achieved a mean LDL-C of 99.3 mg/dL. Subjects were evaluated for the primary end point of time to first major cardiovascular event (i.e., death from CHD, nonfatal nonprocedural-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke). After a median of 4.9 years, 367 subjects (13%) assigned to atorvastatin 10 mg had a primary event compared with 262 (9.5%) of those assigned to atorvastatin 80 mg (hazard ratio 0.71; 95% confidence interval [CI], 0.61–0.84). Furthermore, significantly more subjects with metabolic syndrome had a primary event than those without, irrespective of treatment. The primary limitation of this article is its retrospective design. However, it provides the best data to date for validating LDL-C treatment goals in patients with metabolic syndrome. Subjects in the trial had both CHD and metabolic syndrome. Benefits from targeting a lower LDL-C should only be applied to this population.

8. Black HR, Davis B, Barzilay J, Nwachuku C, Baimbridge C, Marginean H, et al. Metabolic and clinical outcomes in individuals without diabetes but with metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension. *Diabetes Care* 2008;31:353–60.

This is a subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. More than 8000 patients with metabolic syndrome but without diabetes were identified, together with 9502 patients without metabolic syndrome. At 4 years, 17.1% of patients with metabolic syndrome who were assigned to chlorthalidone had developed diabetes, compared with 16% who were assigned to amlodipine and 12.6% assigned to lisinopril. In those without metabolic syndrome, the incidence of diabetes was less in those assigned to amlodipine (4.2%) or lisinopril (4.7%) compared with those treated with chlorthalidone (7.7%). Despite the difference in the incidence of diabetes, no differences in the primary end point of CHD (nonfatal myocardial infarction or CHD death) were seen in patients with or without metabolic syndrome for either amlodipine versus chlorthalidone or lisinopril versus chlorthalidone. This subgroup analysis provides further evidence that thiazide-type diuretics are associated with a higher incidence of new-onset diabetes compared with calcium channel blockers or ACE inhibitors. Furthermore, the results suggest that despite the higher incidence of new-onset diabetes, there is no cardiovascular benefit with using ACE inhibitors over thiazide-type diuretics in patients with metabolic syndrome.

9. Elliot WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007;369:201–7.

This meta-analysis evaluated the association between antihypertensive use and diabetes onset. The authors used a network meta-analysis, which is a statistical technique that allows both direct and indirect comparisons of two drugs even when the drugs have not undergone direct head-to-head comparisons. After trial identification and screening, 22 randomized, controlled trials were included in the analysis. Initial treatment with an ARB, ACE inhibitor, calcium channel blocker, or placebo was associated with significantly fewer cases of new-onset diabetes than with initial diuretic treatment. The incidence of diabetes with initial β -blocker therapy was no different from that seen with a diuretic. Compared with placebo, the incidence of diabetes onset was statistically lower only with ARB therapy and statistically higher only with diuretic therapy. This analysis reinforces findings from earlier meta-analyses and provides further information allowing comparisons between individual drug classes. Although useful, this analysis does not yet provide a definitive answer to the role of antihypertensives in diabetes onset.

10. Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* 2007;30:753–9.

The American Diabetes Association convened a consensus development conference to discuss the prediabetic states of IFG and IGT. It was determined that IFG and IGT have a heterogeneous pathogenesis, with principal defects of diminished first-phase insulin release in isolated IFG and diminished late-phase insulin release in isolated IGT. A high percentage of patients with prediabetes eventually develop diabetes, and diabetes confers an increased risk of ASCVD. Thus, a major reason to recommend interventions

for individuals with IFG and/or IGT is to reduce the long-term increased risk of ASCVD associated with diabetes. The Panel recommended intensive lifestyle intervention (i.e., 5% to 10% weight loss and 30 minutes/day of physical activity) as the treatment of choice for delaying or preventing the onset of diabetes in patients with prediabetes. Metformin was identified as the most appropriate drug therapy option for patients with prediabetes. However, metformin use was restricted to patients with both IFG and IGT and at least one other risk factor (i.e., age younger than 60 years, BMI of 35 kg/m² or greater, family history of diabetes in first-degree relatives, elevated triglycerides, reduced HDL-C, hypertension, or hemoglobin A1C greater than 6%). Fasting plasma glucose and a 2-hour oral glucose tolerance test were indicated as the tests of choice to identify all states of hyperglycemia. Individuals with IFG and IGT who are treated with metformin should be monitored semiannually, whereas individuals treated with lifestyle intervention should be monitored annually.

11. Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, et al. The effect of metformin and intensive lifestyle intervention on metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 2005;142:611–9.

The Diabetes Prevention Program randomized more than 3000 participants with IGT and fasting plasma glucose between 95 mg/dL and 125 mg/dL to intensive lifestyle intervention, metformin 850 mg two times/day, or placebo. In this ancillary report, one of the main objectives was to determine whether lifestyle intervention or metformin reduced the incidence of new cases of metabolic syndrome, or resolved existing cases of metabolic syndrome, in program participants. The presence of metabolic syndrome was ascertained using NCEP ATP III criteria (three or more of the following criteria: waist circumference greater than 102 cm in men and greater than 88 cm in women; triglycerides of 150 mg/dL or greater; HDL-C less than 40 mg/dL in men and less than 50 mg/dL in women; blood pressure 130/85 mm Hg or greater; and fasting plasma glucose 110 mg/dL or greater). In participants without metabolic syndrome at baseline, the incidence of metabolic syndrome during a 3-year period was reduced by 41% in the lifestyle-intervention group ($p<0.001$) and by 17% in the metformin group ($p<0.03$) compared with placebo. In participants with metabolic syndrome at baseline, resolution of metabolic syndrome occurred in 38% of the lifestyle-intervention group, 23% of the metformin group, and 18% of the placebo group. In all study participants, from baseline to 3 years, the prevalence of metabolic syndrome decreased from 51% to 43% in the lifestyle-intervention group ($p=0.003$), stayed constant in the metformin group (54% to 55%, $p>0.2$), and increased from 55% to 61% in the placebo group ($p<0.001$). In the entire study population, the observed effects of lifestyle on the prevention and resolution of metabolic syndrome were primarily driven by decreases in waist circumference and blood pressure. The external validity of this report is limited given the high-risk, glucose-intolerant population studied. However, these data suggest that lifestyle intervention has a dramatic, beneficial effect on both the prevention and resolution of metabolic syndrome.

12. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457–71.

Clinical studies have demonstrated that rosiglitazone effectively lowers blood glucose in patients with type 2 DM and prevents diabetes in patients with prediabetes. However,

the effects of rosiglitazone on cardiovascular morbidity and mortality have not been assessed in large-scale, long-term clinical trials. The purpose of this meta-analysis was to determine the effect of rosiglitazone on cardiovascular morbidity and mortality. Source material consisted of data from the original U.S. Food and Drug Administration submission package, a series of post-approval trials funded by the sponsor, and two large postmarketing studies. Studies included in the meta-analysis lasted more than 24 weeks, had randomized placebo or active comparator control groups, and had available outcomes data for myocardial infarction or death from cardiovascular outcomes. Compared with the control group, rosiglitazone was associated with an increase in the risk of myocardial infarction (odds ratio [OR] 1.43; 95% CI, 1.03–1.98) and an increase in the risk of death from cardiovascular causes (OR 1.64; 95% CI, 0.98–2.74). The results of this meta-analysis were tempered by several limitations including lack of access to original patient-level source data, lack of time-to-event analysis, low number of events overall, nonadjudicated cardiovascular outcomes, and the inclusion of studies that were not intended to assess cardiovascular outcomes. Despite these limitations, a signal for increased cardiovascular risk was evident for rosiglitazone therapy. These results have diminished enthusiasm for rosiglitazone as a diabetes prevention agent.

SELF-ASSESSMENT QUESTIONS

1. T.K. is a 45-year-old African American man who presents to his primary care physician for a discussion of the cholesterol results obtained 1 week ago during his annual physical examination. His fasting lipid panel is as follows: total cholesterol 240 mg/dL; low-density lipoprotein cholesterol (LDL-C) 149 mg/dL; high-density lipoprotein cholesterol (HDL-C) 35 mg/dL; and triglycerides 280 mg/dL. His blood pressure is 128/82 mm Hg. Which one of the following is the best measurement to be performed at this visit to assess the presence of metabolic syndrome in T.K.?
 - A. Plasma high-sensitivity C-reactive protein concentration.
 - B. Waist circumference.
 - C. Fasting plasma insulin concentration.
 - D. Height and weight to calculate body mass index (BMI).
2. H.M., a 43-year-old Hispanic woman with a history of gestational diabetes (12 years ago), presents to her primary care physician's office with concerns that she has diabetes. Her concerns stem from her recent attendance at a local health fair, at which she was told that her blood glucose was high (random finger-stick blood glucose of 180 mg/dL). H.M. is upset about this information because her mother died from complications of type 2 diabetes mellitus (DM) at age 68. Fasting laboratory tests at the physician's office visit show the following: plasma glucose 118 mg/dL, total cholesterol 190 mg/dL, LDL-C 109 mg/dL, HDL-C 45 mg/dL, and triglycerides 180 mg/dL. H.M.'s BMI is calculated to be 38 kg/m², waist circumference is 98 cm, and blood pressure is 130/80 mm Hg. Which one of the following is the best initial diabetes prevention treatment for H.M.?
 - A. Rosiglitazone 4 mg/day titrated up to 8 mg/day.
 - B. Metformin 850 mg/day titrated up to 850 mg two times/day.
 - C. Lifestyle modification with diet and exercise.
 - D. Acarbose 50 mg/day titrated up to 100 mg three times/day.
3. To support the clinical utility of identifying metabolic syndrome, which one of the following best justifies a metabolic syndrome clinic?
 - A. Metabolic syndrome is highly predictive of cardiovascular mortality in people older than 65 years.
 - B. Metabolic syndrome is more predictive of cardiovascular risk in men than in women.
 - C. Metabolic syndrome is predictive of a high short-term cardiovascular risk.
 - D. Metabolic syndrome is more predictive of cardiovascular risk than each metabolic syndrome risk factor alone in people younger than 65 years.
4. In designing the diagnosis and treatment algorithm for the clinic, which one of the following is the best measurement to initially assess type 2 DM risk in every patient who presents to the clinic?
 - A. Fasting plasma glucose concentration.
 - B. Random plasma glucose concentration.
 - C. Hemoglobin A1C level.
 - D. Oral glucose tolerance test.
5. In designing the plan to evaluate the success of the clinic, the primary end point is chosen to be resolution of metabolic syndrome. Which one of the following secondary end points is the best and most practical measure of the ability of the clinic intervention to alter the underlying pathophysiology of metabolic syndrome?
 - A. Change in lipids as measured by LDL-C.
 - B. Change in insulin sensitivity as measured by the hyperinsulinemic euglycemic clamp test.
 - C. Change in abdominal obesity as measured by waist circumference.
 - D. Change in systolic blood pressure as measured by 24-hour ambulatory monitoring.

Questions 6 and 7 pertain to the following case.

A.K. is a 65-year-old woman with metabolic syndrome and prediabetes. Clinical measurements show that her waist circumference is 91 cm; height is 165 cm; weight is 87.3 kg; blood pressure is 128/78 mm Hg; total cholesterol is 210 mg/dL; HDL-C is 45 mg/dL; LDL-C is 134 mg/dL; and triglycerides are 224 mg/dL. After a social history and dietary interview, A.K. reveals that she is a grandmother who, together with her husband, is raising her three grandchildren, ages 8, 10, and 12. A.K. prepares all of the meals for her family. The main meals primarily consist of pasta, white rice, bread, frozen vegetables, poultry, red meat, and occasionally fish. She admits to making fried food two times/week, making cookies or cakes three times/week, and never limiting portion sizes. Although she knows she has to lose weight, she does not want to make special meals for herself and prefers to cook meals that can feed everyone in her family.

Questions 3–5 pertain to the following case.

You are a clinical pharmacist at a busy family medicine clinic conducting a retrospective chart review of the types of obesity drugs prescribed to patients in your clinic. Of 100 patient charts evaluated, 60 patients appear to have metabolic syndrome. However, neither the presence of metabolic syndrome nor the clinical management plan is documented by providers. You view this as an opportunity to develop a pharmacist-run metabolic syndrome management clinic and develop a proposal to present to the board of directors outlining the development and potential effect of a metabolic syndrome management clinic in your clinic setting.

6. Which one of the following is the best initial weight-loss goal for A.K. during the next 6 months?
 - A. Decrease total body weight by 6 kg.
 - B. Decrease BMI to less than 25 kg/m².
 - C. Decrease waist circumference to less than 76 cm.
 - D. Decrease body fat to less than 20%.
 7. Given A.K.'s clinical and social history, which one of the following is the best diet plan to recommend?
 - A. Nonrestricted-calorie, low-fat diet.
 - B. Restricted-calorie, Mediterranean-style diet.
 - C. Nonrestricted-calorie, low-carbohydrate diet.
 - D. Restricted-calorie, liquid shake diet.
 8. D.B. is a 58-year-old obese man with a medical history significant for metabolic syndrome, uncontrolled hypertension, prediabetes, depression, and anxiety. Through diet and exercise alone, for the past 7 months, D.B. has lost 6.4 kg. Currently, his BMI is 32 kg/m², weight is 103.6 kg, and waist circumference is 112 cm. Despite his efforts, D.B. has not achieved his weight-loss goals with diet and exercise alone. D.B. is frustrated that his weight loss has reached a plateau, and he asks if there are any drugs that would help him lose more weight. Which one of the following is the best pharmacologic intervention to augment D.B.'s diet and exercise program?
 - A. Phentermine.
 - B. Orlistat.
 - C. Sibutramine.
 - D. Metformin.
 9. J.N. is a 47-year-old man with type 2 DM who recently completed participation in a Phase III clinical trial of a novel, dual peroxisome proliferator-activated receptor (PPAR) γ /PPAR α agonist. He took an active study drug for 24 weeks with no major adverse events. From baseline to week 24, which one of the following would be the most likely observed metabolic effect of the dual PPAR γ /PPAR α agonist?
 - A. Decrease in triglycerides from 220 mg/dL to 160 mg/dL.
 - B. Decrease in blood pressure from 140/90 mm Hg to 128/74 mm Hg.
 - C. Decrease in total body weight from 118 kg to 105 kg.
 - D. Decrease in serum creatinine from 1.5 mg/dL to 0.9 mg/dL.
 10. S.T. is a 65-year-old man with type 2 DM, metabolic syndrome, and congestive heart failure (New York Heart Association class III). His diabetes is uncontrolled, and his hemoglobin A1C is 7.8%. S.T. currently takes glyburide 10 mg two times/day. His BMI is 36 kg/m², waist circumference is 109 cm, blood pressure is 142/86 mm Hg, and serum creatinine is 1.7 mg/dL. His lipid panel shows the following: HDL-C 44 mg/dL, LDL-C 98 mg/dL, triglycerides 140 mg/dL, and total cholesterol 170 mg/dL. Which one of the following is the best agent to add to his current diabetes regimen to lower his hemoglobin A1C and improve metabolic syndrome risk factors?
 - A. Pioglitazone.
 - B. Metformin.
 - C. Acarbose.
 - D. Exenatide.
 11. Which one of the following patients with metabolic syndrome is the best candidate for bariatric surgery, assuming lifestyle interventions have failed to achieve the desired weight loss?
 - A. A patient with fasting plasma glucose of 90 mg/dL, BMI of 35 kg/m², and binge-eating disorder.
 - B. A patient with fasting plasma glucose of 118 mg/dL, BMI of 37 kg/m², and unstable angina.
 - C. A patient with fasting plasma glucose of 184 mg/dL, BMI of 39 kg/m², and sleep apnea.
 - D. A patient with fasting plasma glucose of 229 mg/dL, BMI of 41 kg/m², and bipolar manic depression.
 12. C.M. is a 66-year-old white man with a BMI of 23 kg/m², waist circumference of 81 cm, HDL-C 47 mg/dL, triglycerides 138 mg/dL, fasting plasma glucose 112 mg/dL, and blood pressure of 128/76 mm Hg. His current drugs are fenofibrate 120 mg once daily, tamsulosin 0.4 mg once daily, and ibuprofen as needed for back pain. Using metabolic syndrome diagnostic criteria, which one of the following statements is most accurate regarding C.M.?
 - A. He has metabolic syndrome according to American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) criteria.
 - B. He has metabolic syndrome according to International Diabetes Federation (IDF) criteria.
 - C. He has metabolic syndrome according to World Health Organization (WHO) criteria.
 - D. He does not have metabolic syndrome.
- Questions 13 and 14 pertain to the following case.**
- T.K. is a 55-year-old obese man with metabolic syndrome, osteoarthritis, type 2 DM, and a history of myocardial infarction. His stress test is normal. Through dietary changes alone, his weight decreased from 132 kg to 114 kg, and his waist circumference decreased from 132 cm to 112 cm during a period of 8 months.
13. Which one of the following is the best next step regarding T.K.'s lifestyle-intervention plan?
 - A. No change is recommended because the patient has already met appropriate weight-loss goals.
 - B. Initiate jogging (5 miles/hour) for 10 minutes three times/week.
 - C. Initiate swimming for 30 minutes three times/week.
 - D. Participate in gardening for 60 minutes three times/week.
 14. Which one of the following is the best assessment of thiazolidinedione use in T.K.?

- A. He should not use pioglitazone because it is reserved for individuals with documented insulin resistance, as measured by homeostasis model assessment.
- B. He should be given rosiglitazone because it is less likely to cause edema than pioglitazone.
- C. He should not use rosiglitazone because it is reserved for individuals who are at low risk of cardiovascular events.
- D. He should be given rosiglitazone because it is less likely to cause weight gain than pioglitazone.

Questions 15 and 16 pertain to the following case.

R.J. is a 65-year-old man with a history of myocardial infarction, hypertension, and depression. He currently takes metoprolol succinate 100 mg/day, lisinopril 40 mg/day, citalopram 20 mg/day, and aspirin 81 mg/day. Clinical measurements show that his waist circumference is 107 cm; height 178 cm, weight 100 kg, blood pressure 136/78 mm Hg, total cholesterol 237 mg/dL, HDL-C 42 mg/dL, LDL-C 140 mg/dL, triglycerides 245 mg/dL, and fasting plasma glucose 105 mg/dL. R.J. denies previous treatment for cholesterol, stating that he controls it with his diet and exercise.

15. Which one of the following is the best lipid goal for R.J. at this time?
 - A. Triglycerides less than 200 mg/dL.
 - B. LDL-C less than 70 mg/dL.
 - C. Non-HDL-C less than 130 mg/dL.
 - D. Apolipoprotein B (apoB) less than 80 mg/dL.
16. Which one of the following is the best treatment plan to initiate today for R.J.?
 - A. Colesevelam 3800 mg/day and rosiglitazone 2 mg/day.
 - B. Extended-release niacin 500 mg/day.
 - C. Gemfibrozil 600 mg two times/day and metformin 500 mg/day.
 - D. Rosuvastatin 10 mg/day.
17. S.P. is a 45-year-old man with diabetes, hypertension, continued cigarette smoking, and abdominal obesity. He is currently being treated with atorvastatin 10 mg/day, fenofibrate 48 mg/day, hydrochlorothiazide 12.5 mg/day, irbesartan 150 mg/day, aspirin 81 mg/day, metformin 1000 mg two times/day, and glipizide 10 mg two times/day. His full lipid panel is as follows: total cholesterol 144 mg/dL, LDL 67 mg/dL, HDL 46 mg/dL, and triglycerides 205 mg/dL. S.P.'s apoB was measured and found to be 110 mg/dL. Which one of the following is the best recommendation at this time?
 - A. Initiate extended-release niacin 500 mg/day.
 - B. Add fish oil 2 g two times/day.
 - C. Initiate ezetimibe 10 mg/day.
 - D. Increase atorvastatin to 80 mg/day.

Questions 18–20 pertain to the following case

D.N. is a 59-year-old man with no significant medical history. His most recent laboratory data show total cholesterol 152 mg/dL, LDL-C 95 mg/dL, HDL-C 38 mg/dL, triglycerides 275 mg/dL, and fasting plasma glucose 115 mg/dL. D.N.'s

2-hour plasma glucose concentration was 132 mg/dL after a 75-g oral glucose tolerance test. His blood pressure is 148/94 mm Hg, and his pulse rate is 92 beats/minute. D.N. weighs 93.2 kg and is 177.8 cm tall. The patient has smoked 1 pack of cigarettes daily for 32 years.

18. Which one of the following is the best blood pressure goal for D.N. at this time?
 - A. Less than 140/90 mm Hg.
 - B. Less than 130/85 mm Hg.
 - C. Less than 130/80 mm Hg.
 - D. Less than 120/80 mm Hg.
19. Which one of the following is the best initial hypertension treatment for D.N. at this time?
 - A. Lisinopril 5 mg/day.
 - B. Atenolol 25 mg/day.
 - C. Amlodipine 2.5 mg/day.
 - D. Hydrochlorothiazide 12.5 mg/day.
20. Which one of the following is the best treatment to initiate for D.N. at this time?
 - A. Rosiglitazone 2 mg/day.
 - B. Pravastatin 40 mg/day.
 - C. Aspirin 81 mg/day.
 - D. Metformin 500 mg/day.

