
The metabolic syndrome

Modify root causes, treat risk factors

You've heard about it. You've read about it. But do you actually know what it is? Can you identify patients at risk? This article reviews the criteria for the metabolic syndrome and explains what you can do for patients who have it.

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The condition known as the metabolic syndrome is a constellation of risk factors for the development of type 2 diabetes mellitus (DM) and coronary heart disease (CHD). Many of these risk factors—including abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states—play an important role in the development of this syndrome. These risk factors are commonly seen in a particular subset of patients who, when the metabolic syndrome is diagnosed, are at an even greater risk for developing CHD when compared to people who have only some or none of the risk factors. Because the metabolic syndrome consists of a number of different conditions, a precise etiology for the syndrome remains elusive.¹

A multitude of treatment options exist for the individual components of the metabolic syndrome, and many patients who have the syndrome will require multiple treatment modalities. With CHD being a leading cause of death in the United States,² the importance and public health implications of the metabolic syndrome are unquestionable. Continued research is needed to determine which medications are most effective and to help in limiting the rate of polypharmacy in our aging population. This article reviews the latest research on the metabolic syndrome and provides suggested interventions for affected patients based on the currently available data.

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The concept of the metabolic syndrome

In research studies, the term *metabolic syndrome* has been synonymous with the terms *syndrome X*, *insulin resistance syndrome*, and *dysmetabolic syndrome*. The common findings of obesity, hypertension, hyperlipidemia, and DM were first described in the 1960s, and the term *metabolic syndrome* was used first in the 1970s.¹ Researchers have found atherosclerosis and insulin resistance to be major underlying factors and possible etiologies for the metabolic syndrome.^{1,3,4}

Until the release, in 2001, of the Third Report of the Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP),⁵ the definition and guidelines for the metabolic syndrome generally fol-

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Learning objectives

- Review the risk factors associated with the development of the metabolic syndrome
- Describe the relationship between the metabolic syndrome and increased visceral adipose tissue and insulin resistance
- Discuss the lifestyle changes that are the cornerstone of treatment of the metabolic syndrome
- Describe the pharmacologic interventions to help control the risk factors

lowed a 1998 World Health Organization (WHO) report (see “Diagnostic criteria for the metabolic syndrome,” page 32). The WHO released this report in response to the lack of current data supporting insulin resistance as the cause of all components of the syndrome.^{5,6}

In a study comparing the definitions set forth by ATP III and the WHO report, the metabolic syndrome was diagnosed in 23.9% of the participants using the ATP III definition, compared to 25.1% when the WHO definition was used.⁷ This difference has been attributed to the direct inclusion of people with insulin resistance or as a result of the different criteria listed in the WHO definition for diagnosing central obesity.

The purpose of the NCEP ATP III report was to create a more simplistic approach for a diagnosis in clinical practice, with characteristics such as measuring only waist circumference to determine abdominal adiposity. Measures of BP, cholesterol, and fasting glucose are already standard in an office setting. All of these factors permit the practitioner to evaluate, diagnose, and treat metabolic syndrome more expeditiously.

Given the various comorbidities associated with the metabolic syndrome, ATP III provides a guide by stating that positive criteria for diagnosing the metabolic syndrome include a previous diagnosis of hypertension or DM, irrespective of current BP, glucose levels, or medications the patient may be taking. Also, prothrombotic and proinflammatory states, while not part of the inclusion criteria for diagnosis, are risk factors for CHD and DM. These factors, when assessed, contribute to a patient’s global risk for cardiovascular disease (CVD).

The Framingham risk assessment tool—which is available online at <http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof>—was created to help evaluate the global 10-year risk for MI and coronary death. The categories in this scoring system include age, total cholesterol, HDL cholesterol, systolic BP, treatment for hypertension, and cigarette smoking. The clinician evaluates the patient’s status for each of the categories and assigns a point value. Then the sum of the values for each category is determined, and the patient is given a moderate, moderate-high, or high-risk status for coronary heart disease. This helps clinicians define a patient’s current status and the level of treatment needed.

It is a common misconception that the diagnosis of metabolic syndrome carries an automatic high-risk for CVD.⁸ Only patients with a history of DM before the diagnosis of metabolic syndrome are automatically placed in the high-risk category. These persons are at an increased risk for developing CHD within 10 years, but it is important to evaluate other patients using the

KEY POINTS in this article

- ▶ The metabolic syndrome is a conglomeration of individual risk factors for the development of type 2 diabetes mellitus and coronary heart disease.
- ▶ These risks include high BP, dyslipidemia, increased fasting glucose levels and an increase in certain adipose tissue known as visceral adiposity. These risks usually occur together in a subset of patients.
- ▶ The primary underlying components for the development of this syndrome are increased visceral adipose tissue and insulin resistance
- ▶ The cornerstone of treatment is weight management and increased physical activity.

Framingham risk assessment to determine the level of treatment needed.

Other characteristics that have helped define the risk for developing CHD have included body mass index (BMI), cigarette smoking, socioeconomic status, and income. All of these factors are linked to an increased prevalence of the metabolic syndrome but are not considered criteria in the diagnosis.⁹

Understanding etiology

There is no clear consensus regarding the etiology or pathophysiology of the metabolic syndrome. Research has shown strong correlations between the syndrome and both obesity and insulin resistance as the major underlying components. Minor associations include hypertension and inflammatory responses. Insulin resistance causes abnormalities in cellular and metabolic pathways that affect several organ systems. The incidences of obesity, glucose intolerance, atherogenic dyslipidemia, hypertension, and a prothrombotic state are higher in persons with the metabolic syndrome than in the general population, but the etiology for this syndrome remains unknown.¹⁰⁻¹²

Increased adipose tissue and physical inactivity have long been known to decrease HDL cholesterol levels and increase LDL cholesterol and triglyceride levels, increasing the risk for atherosclerosis and CHD.¹³ Studies now show that intra-abdominal (visceral) adipose tissue, evaluated by CT scan, may play a more important role than subcutaneous fat in the etiology of insulin resistance and the metabolic syndrome.¹⁴⁻¹⁷ These results are important when applied to a patient with dyslipidemia and relatively no peripheral or subcutaneous fat. In other words, patients who are not obese can still have the metabolic syndrome.

The association between visceral adipose tissue and insulin resistance originated in a study that used the hyperinsulinemic-euglycemic clamp to show that in-

Diagnostic criteria for the metabolic syndrome

According to the National Cholesterol Education Program's Adult Treatment Panel III, persons who meet three or more of the following five criteria have the metabolic syndrome:¹

- Abdominal obesity with a waist circumference greater than 40 inches (102 cm) in men and 35 inches (88 cm) in women
- Triglyceride levels of 150 mg/dL or higher
- HDL cholesterol levels of less than 40 mg/dL in men and less than 50 mg/dL in women
- BP of 130/85 mm Hg or higher
- Fasting blood glucose of 110 mg/dL or higher*

The World Health Organization defines the metabolic syndrome as diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, plus two or more of the following:²

- BP of 160/90 mm Hg or higher
- Hyperlipidemia: triglyceride levels of 150 mg/dL or higher and/or HDL cholesterol levels of less than 35 mg/dL in men or less than 39 mg/dL in women
- Central obesity: waist-to-hip ratio greater than 0.90 in men or greater than 0.85 in women, or a body mass index greater than 30 kg/m²
- Microalbuminuria: urinary albumin excretion rate greater than 20 µg/min or an albumin-to-creatinine ratio greater than 20 mg/g.

*The American Diabetes Association has lowered the threshold for fasting blood glucose levels to 100 mg/dL.

1. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel in Detection, Evaluation, And Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf>. Accessed February 2, 2005.
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ulin resistance increases the amount of insulin secreted. The glucose clamp is a technique that utilizes arterial and venous catheters to maintain a constant blood glucose level by perfusion or infusion of glucose or insulin. Subsequent studies have shown that insulin resistance will diminish and plasma insulin levels will decrease when calorie restriction and physical activity are used to reduce intra-abdominal fat.^{16,17} Thus, where genetic predisposition was once thought to be the cause of insulin resistance, visceral fat and physical inactivity are now thought to play a key role as well.

Visceral adipocytes are generally larger than peripheral adipocytes and have been shown to release fatty acids more readily.¹⁶ With an increase in adipose tissue, nonesterified fatty acid levels in the bloodstream will also rise. These fatty acids inundate the liver, causing an increase in hepatic lipase activity. This creates an atherogenic dyslipidemia characterized by a decrease in HDL cholesterol and an increase in LDL cholesterol

and triglyceride levels.^{14,17-19} These fatty acids are also transported into the portal vein and will be deposited in muscle tissue. The lipotoxicity that develops at this level will decrease glucose oxidation, inhibit glucose-induced insulin secretion, and worsen insulin resistance.^{16,20}

In essence, when patients have excess adipose tissue, particularly in the visceral fat distribution, they will have elevated plasma fatty acid levels. As a result of this excess, there will be a disruption in normal cellular and vascular processes in a variety of different tissues in the body. This effect predisposes patients to insulin resistance and the metabolic syndrome, which increases the risk of CHD.¹⁴

To counter the theory that body mass is the underlying factor for the comorbidities associated with the metabolic syndrome, a relationship has been shown to exist between hyperinsulinemia and essential hypertension, irrespective of body mass.²¹ One explanation is that higher levels of insulin affect blood vessels by causing direct vasodilation. To compensate, the sympathetic nervous system is activated, resulting in vasoconstriction, sodium absorption, and increased cardiac output; the net effect is elevated BP.^{10,20} Untreated patients with primary hypertension exhibit higher levels of plasma insulin compared to normotensive patients. A genetic predisposition is often necessary for this characteristic to occur, because offspring of these patients can have altered glucose metabolism and be normotensive. Also, this effect of increased insulin and BP is not seen in secondary hypertension.

Another link between the cofactors of the metabolic syndrome was discovered after factor analysis of the Cardiovascular Health Study. A subclinical inflammation shows a possible connection to the insulin resistance syndrome through associations with body mass.²² Adipose tissue has been linked to an increase in levels of tumor necrosis factor, protein kinase C, and interleukin 6. These cytokines, principally found in the liver, endothelium, and fat deposits, can derail the insulin-signaling pathway.^{16,23} Combined with an increased level of insulin, these cytokines can also increase the production of plasminogen activator inhibitor-1 (PAI-1), which is produced in the vascular endothelium. When combined with plasminogen activator, PAI-1 will increase clotting by decreasing fibrinolytic activity. With increased clotting, endothelial function is disrupted, thus increasing the propensity for atherogenic plaque formation and ultimately increasing morbidity and mortality.

Stress has been said to induce the release of these cytokines, creating the inflammatory response and resulting in insulin resistance, type 2 DM, and the metabolic syndrome.²³ Treatment for this inflammation and

clotting disorder is aspirin, 81 to 325 mg daily, in patients with no contraindications.²⁰ However insulin resistance occurs, it will accelerate glucose intolerance because of the constant stimulatory effects on the β -cells of the pancreas. This will result in exhaustion and a decrease in insulin production.

Epidemiology: Prevalence is growing

Data compiled by the third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional study of 40,000 men and women from 1988 to 1994, produced the most recent database characterizing individuals based on their metabolic status. Researchers have used this database to show that approximately 20% of Americans have the metabolic syndrome as defined by ATP III. At the time of NHANES III, most people in the United States with the metabolic syndrome were older, obese, Mexican-American, or black. Other characteristics that are common among people with the metabolic syndrome are smoking, low income, high-carbohydrate diet, and physical inactivity. The incidence of the metabolic syndrome among men and women is roughly equal at 22.8% and 22.6%, respectively.^{6,9}

According to ATP III, when drug therapy is necessary for dyslipidemia, LDL cholesterol is the primary target.

Among Americans, the prevalence of metabolic syndrome increases with age. Roughly 6.7% of people aged 20 to 29 years and 44% of people aged 50 years and older have the metabolic syndrome.¹ When these percentages are applied to the 2000 US census numbers, approximately 47 million people have the syndrome.²⁰ The epidemic of obesity and DM among the US population suggests that the prevalence of metabolic syndrome is higher now than it was when the NHANES III data were compiled.

The NHANES data also indicate that people aged 50 years and older with the metabolic syndrome and DM have the highest risk for CHD. Diabetes without the metabolic syndrome is uncommon in persons older than 50. Participants in NHANES III without the metabolic syndrome or DM had the lowest CHD prevalence at 8.7%, and those with DM and the syndrome had the highest prevalence at 19.2%. People who had diabetes without the metabolic syndrome did not have an incre-

mental increase in CHD when compared with persons who had neither disorder.¹⁰

The NCEP, the American Diabetes Association, and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) continue to reevaluate and revise cut-off points for diagnosing dyslipidemias, hypertension, and DM. As a result, the prevalence of the metabolic syndrome will most likely rise.

Diagnosing the metabolic syndrome

Measuring for abdominal obesity is one of the most effective ways to detect the metabolic syndrome, where even borderline measurements ranging from 35 to 40 inches can carry an increase in concomitant atherogenic factors. Studies have shown that BMI and waist circumference (or waist-to-hip) measurements yield similar results when obesity is a factor. Both measurements correlate with an increased risk of heart disease.²⁴

Because insulin resistance is an important predictor of the metabolic syndrome, McAuley and colleagues have compared different methods for assessing insulin resistance, including fasting insulin levels, the homeostasis model assessment, and the Galvin method.²⁵ That study demonstrated that fasting insulin and triglyceride levels in a normoglycemic person can accurately predict insulin resistance.²⁵ Although measuring fasting glucose in an outpatient setting has been the standard for evaluating glucose tolerance and DM, determining plasma insulin levels has been shown to be more accurate, although more costly and less available in common medical settings and laboratories. If measuring fasting insulin levels becomes more common, this would allow the practitioner to begin treatment before DM develops.

Those blood tests could be one way to screen for the metabolic syndrome in a patient who has some risk factors but does not have high fasting glucose levels. This is critical because, by the time hyperglycemia develops into diagnosable type 2 DM, over half of these patients will have some form of microvascular and macrovascular disease—although many people with insulin resistance may be euglycemic and never develop type 2 DM.²⁰ Microalbuminuria, a marker for renal damage, has been seen in nondiabetic patients with some degree of insulin resistance.²¹

Another means of evaluating glucose intolerance and insulin resistance is the 2-hour glucose tolerance test. Generally speaking, the patient is considered to have insulin resistance when the fasting insulin concentration is above 15 μ U/mL in normoglycemic persons.

Therapeutic lifestyle change

Since the end results of the metabolic syndrome are DM and CHD, intervention is needed to improve lipid levels,

BP, and glucose levels in affected persons (see Table 1). The cornerstone of treatment of the metabolic syndrome is therapeutic lifestyle change (TLC), which consists of healthful eating, weight loss, and increased physical activity (see “The components of therapeutic lifestyle change,” page 35). The Finnish Diabetes Prevention Study and the Diabetes Prevention Program showed that TLC was successful in preventing type 2 DM and the metabolic syndrome. Interventions consisted of detailed advice about how to decrease saturated fat intake and increase fiber intake, weight reduction of 5% to 7% or more, increased physical activity, and sessions with a nutritionist or case manager.²⁶⁻²⁸

Dyslipidemia

According to ATP III, when drug therapy is necessary for dyslipidemia, LDL cholesterol is the primary target. Statins, nicotinic acid, or bile acid sequestrants should be used to achieve the optimal levels of LDL cholesterol based upon a risk assessment. Once the goal for LDL cholesterol has been reached (less than 100 mg/dL for patients with CVD), attention should move to other lipid abnormalities. ATP III suggests using nicotinic acid or fibrates to lower triglyceride levels and raise HDL cholesterol levels as necessary.

Statins The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial has shown that

statins lower LDL cholesterol levels and reduce the incidence of mortality associated with CHD in patients with known CVD.²⁹ Using a statin alone has been shown to decrease LDL cholesterol levels by 35% and to decrease very low-density lipoprotein (VLDL) levels by 39%.¹⁴ Statins also lower the incidence of MI or stroke by more than 33% in patients with coronary artery disease (CAD). The greatest impact was shown in persons older than 75 years.

The NCEP recommends an LDL level of less than 100 mg/dL in patients with CAD. Continuing a statin after patients have achieved that goal has reduced cardiovascular events by 25%.²⁰ The Heart Protection Study reported a reduction in cardiovascular morbidity and mortality regardless of baseline LDL cholesterol. Therefore, patients with an elevated risk for CVD should be using a statin regardless of their LDL cholesterol level.³⁰

Nicotinic acid Results of the Coronary Drug Project showed that niacin was the most effective agent in reducing cholesterol levels and the incidence of nonfatal MIs.³¹ In fact, niacin has been shown to be one of the most successful pharmacologic agents in raising HDL cholesterol levels and improving all lipid abnormalities, including lowering LDL cholesterol and triglyceride levels. Niacin lowers LDL levels more effectively than a statin, although not quite as well as a bile acid sequestrant. Hyperglycemia occurs in a modest number of niacin users, and approximately 10% to 30% of patients with diabetes will require adjustments in their hypoglycemic medications.³²

Fibrates The Veterans Administration HDL Intervention Trial (VA-HIT) found that gemfibrozil increased HDL cholesterol levels and decreased triglyceride levels by approximately 30%. This study also demonstrated that gemfibrozil can reduce death from CHD or nonfatal MI in patients who do not have high-risk LDL cholesterol levels.³³ The Diabetic Atherosclerosis Intervention Study (DAIS) looked at the effects of fenofibrate on persons with type 2 DM and also reported increased HDL cholesterol and decreased triglyceride levels. The progression of CAD was also reduced in this cohort.³⁴

Insulin resistance

The Diabetes Prevention Program showed success with the use of metformin, which can counteract insulin resistance by increasing insulin sensitivity and decreasing hepatic glucose production. Metformin can also delay or even prevent the development of type 2 DM. These results were seen in men and women and in all races.²⁸

Thiazolidinediones will improve glucose uptake by adipose tissue and skeletal muscle, leading to a de-

TABLE 1

Screening and treatment for the metabolic syndrome

Screening

- Weight
- BP measurement
- Waist circumference measurements for abdominal girth
- Blood testing for fasting glucose levels and a lipid profile

Treatment

- Therapeutic lifestyle changes
- Pharmacologic
 - Dyslipidemia: LDL cholesterol levels should be corrected first; use statins as first-line agents; nicotinic acid and fibrates can also be used
 - Insulin resistance: Use metformin or thiazolidinediones to improve insulin sensitivity
 - Hypertension: Use an ACE inhibitor or angiotensin receptor blocker to reduce BP and aid in the prevention of diabetes

Note: Vital signs and abdominal girth should be measured at every visit. The National Cholesterol Education Program recommends a fasting lipid profile at age 20 and every 5 years thereafter. Patients with lipid abnormalities may require more frequent measurements. As youth obesity rates increase, screening measurements for glucose and lipid abnormalities should be initiated early.

The components of therapeutic lifestyle change

The National Heart, Lung, and Blood Institute's Obesity Education Initiative (available at www.nhlbi.nih.gov/about/oei/) has reported that weight loss can decrease BP and LDL cholesterol and triglyceride levels, while increasing HDL cholesterol levels. Weight loss can also reduce blood glucose levels in persons with type 2 diabetes mellitus. The components of therapeutic lifestyle change are as follows:

- Reduce weight by 7% to 10% (1-2 lb lost per week) over 6 to 12 months
- Reduce calorie intake by 500 to 1,000 kcal per day
 - Less than 7% total calories should be saturated fats
 - Ingest no more than 200 mg cholesterol daily
- Increase physical activity
 - Initially, 30 to 45 minutes of moderate aerobic activity 3 to 5 times per week
 - Goal is more than 30 minutes of activity on most, if not all, days of the week.

crease in insulin secretion. The Troglitazone in the Prevention of Diabetes (TRIPOD) study showed an arrest in the decline of β -cell function in women with prior gestational DM.³⁵ The Diabetes Prevention Program discontinued the arm of its study that included troglitazone in the prevention of type 2 DM due to the drug's hepatotoxicity.

The thiazolidinediones that are available in the United States, pioglitazone and rosiglitazone, have a place in the prevention and treatment of insulin resistance seen in the early stages of the metabolic syndrome.³⁶ They may also help with the dyslipidemia associated with metabolic syndrome.

Hypertension

The ACE inhibitor ramipril has been shown to improve BP and aid in the prevention of DM. The Heart Outcome Prevention Evaluation (HOPE) study of 5,720 nondiabetic patients with vascular disease compared ramipril to a placebo. Diabetes developed in approximately 3.6% of the ramipril group, compared to 5.4% of the placebo group. The incidence of primary prevention of DM was reduced by 34% with the use of ramipril in the HOPE study.^{20,37} ACE inhibitors work by decreasing the loss of potassium and improving blood flow to the pancreas through vasodilation, which improves β -cell perfusion and functioning.³⁸ They also increase insulin-mediated glucose uptake by muscle.

ACE inhibitors and angiotensin receptor blockers (ARBs) are also renal protective. The RENAAL study reported a 28% reduction in albuminuria in diabetic patients using losartan, compared to 4% reduction in those using a placebo. Within the first 6 months, end-

stage renal disease was reduced by 45% each time urine albumin levels dropped by 50%.³⁹ Patients with albuminuria in excess of 1 g/24h should use whatever antihypertensive medication is necessary to reduce BP to 130/85 mm Hg or lower.

The United Kingdom Prospective Diabetes Study (UKPDS) was one of the first to include diabetic patients in BP research. The results of this study showed that BP control in persons with diabetes is just as important as control of their glucose levels. Tight control, with a BP of less than 150/85 mm Hg, produced a better outcome than did controlling BP to less than 200/105 mm Hg. Overall, this study reported that there was no level of control with which a patient finds a maximum benefit. The lower the glycohemoglobin (A1C) and the tighter the control of BP, the lower the risk of end-organ complications.⁴⁰

JNC 7 also recommends the use of an ACE inhibitor or ARB for BP control in patients with diabetes to help reduce the incidence of microalbuminuria and diabetic nephropathy.³⁷ Diuretics and β -blockers have been associated with a deterioration in glycemic control and the development of type 2 DM, although many clinical trials have shown both medications to be effective in long-term treatment.

Conclusion

The metabolic syndrome is a constellation of common risk factors for CHD, and patients with this syndrome face a 2- to 3-fold increased risk of coronary disease.⁴¹ Taken individually, each component of the metabolic syndrome has long been known to increase the risk of atherosclerosis. Addressing the metabolic syndrome successfully requires clinicians, first, to screen for the presence of its various components; second, to help patients adopt strategies that address the root causes of overweight and obesity, physical inactivity, and the closely associated insulin resistance; and finally to treat directly, usually with pharmacotherapy, as many of the underlying metabolic risk factors as possible. □

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