ABSTRACT

This paper discusses the prevalence and clinical significance of the metabolic syndrome and considers the importance of lipid and lipoprotein abnormalities in the metabolic syndrome in conferring cardiovascular and metabolic risk. The metabolic syndrome is a multiplex risk factor for cardiovascular and metabolic disease. Cardinal components of the metabolic syndrome include obesity (particularly abdominal obesity), dyslipidemia, hypertension, and insulin resistance with or without glucose intolerance. The metabolic syndrome affects approximately 47 million adults and 2 million adolescents in the United States, and its prevalence is increasing. Early detection and management of the components of the metabolic syndrome are critical for preventing or delaying the development of type 2 diabetes mellitus, heart disease, and other metabolic and cardiovascular complications. Early changes in the quality and quantity of specific blood lipids and lipoproteins constitute one of the earliest manifestations of the metabolic syndrome. These early changes in lipoproteins are important because they can contribute to the development of cardiovascular and metabolic disease and constitute a marker for the metabolic syndrome, thus affected individuals can be identified for early intervention.


THE METABOLIC SYNDROME AS A RISK FACTOR FOR TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE

Roger S. Blumenthal, MD*  

A substantial minority of adults and adolescents in the United States are affected by the metabolic syndrome, a constellation of physiologic abnormalities that are risk factors for type 2 diabetes mellitus and heart disease. Early detection and management of the components of the metabolic syndrome are critical for preventing or delaying the development of type 2 diabetes mellitus, heart disease, and other metabolic and cardiovascular complications. This paper discusses the prevalence and clinical significance of the metabolic syndrome and considers the importance of lipid and lipoprotein abnormalities in the metabolic syndrome in conferring cardiovascular and metabolic risk.

THE METABOLIC SYNDROME

MANIFESTATIONS

In his seminal 1988 Banting lecture, Dr Gerald Reaven identified a cluster of physiologic disturbances that he designated as syndrome X—a cluster of abnormalities, including dyslipidemia, hypertension, and fasting hyperinsulinemia, that occurred in the context of insulin resistance. Syndrome X, more commonly known today as the metabolic syndrome or the insulin resistance syndrome, is now established as a multiplex risk factor for cardiovascular and metabolic disease. Cardinal components of the metabolic syndrome include obesity (particularly abdominal obesity), dyslipidemia, hypertension, and insulin resistance with or without glucose intolerance (Table 1).

PREVALENCE

The metabolic syndrome is highly prevalent in the United States, affecting approximately 47 million adults. More than 1 in 5 adults (ie, 22%)—in a sample of 8814 individuals in the United States drawn from the 1988 to 1994 National Health and Nutrition Examination Survey III (NHANES III)—were deter-
mined to have the metabolic syndrome as defined by the criteria established by the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. In both men and women, the prevalence of the metabolic syndrome increased with age (Figure 1). Nearly 50% of those individuals 60 years and older were determined to have the metabolic syndrome.

A recently published follow-up study conducted by the Centers for Disease Control and Prevention (CDC) shows that the prevalence of the metabolic syndrome is increasing among American adults, particularly women. From 1994 to 2000, the age-adjusted prevalence of the metabolic syndrome increased by 23.2% in adult women and by 2.2% in adult men in the United States.

The metabolic syndrome affects more than 2 million adolescents in the United States. In a US population-based study, the overall prevalence of the metabolic syndrome among adolescents increased from 4.2% in 1994 to 6.4% in 2000. According to the study, adolescent boys were more likely to develop the metabolic syndrome than were adolescent girls. Regardless of gender, those individuals who were overweight were more likely than normal-weight adolescents to develop the metabolic syndrome. Approximately 33% of overweight adolescents had the metabolic syndrome.

The rise in prevalence of the metabolic syndrome coincides with an increase in the incidence of obesity in all age groups in the United States. Obesity is a component of the metabolic syndrome and a pathophysiologic contributor to and risk factor for other metabolic syndrome components.

**Clinical Significance**

Research has established that the presence of one component of the metabolic syndrome heightens the risk of having one or more of the other components. Furthermore, the degree of health risk associated with the metabolic syndrome is directly related to the number of components present. The metabolic syndrome is a substantial determinant of the risk of cardiovascular disease and a harbinger of type 2 diabetes mellitus, complications of which include coronary heart disease, neuropathy, peripheral vascular disease, and retinopathy.

The degree to which the metabolic syndrome predicts cardiovascular risk in women was assessed in the Women’s Ischemia Syndrome Evaluation study, which was designed to determine the relative contributions of obesity and the metabolic syndrome to coronary artery disease. Women (n = 780) referred for a coronary angiography to investigate suspected myocardial ischemia were assessed for angiographic coronary artery disease (defined as ≥50% stenosis) and a 3-year risk of major cardiac events (death, nonfatal myocardial infarction, stroke, or congestive heart failure). The results show that, although the metabolic syndrome and body mass index were significantly related, only the metabolic syndrome and not the presence of obesity per se predicted significant coronary artery disease or major adverse cardiovascular events. The researchers

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**Table 1. Manifestations of the Metabolic Syndrome**

- Obesity (particularly abdominal obesity)
- Atherogenic dyslipidemia
- Hypertension
- Insulin resistance with or without glucose intolerance
- Hyperglycemia

Data from JAMA. 2001;285:2486-2497.

**Figure 1. Age-Specific Prevalence of the Metabolic Syndrome**

Age-specific prevalence of the metabolic syndrome in a US population-based study.

concluded that the metabolic syndrome, but not body mass index, predicts cardiovascular risk in women. The goal of patient management, they suggested, is the control of modifiable risk factors to prevent transition to the metabolic syndrome.

Diabetes is considered a cardiovascular, in addition to a metabolic, disease because it increases the risk of adverse cardiac events. Patients with type 2 diabetes mellitus are at a significantly increased risk of cardiovascular morbidity and mortality as compared to those patients without diabetes:

- Patients with diabetes, as compared to individuals without diabetes, are 3 to 5 times more likely to develop cardiovascular disease.
- Cardiovascular disease, the most common cause of death in diabetic adults, is responsible for 8 of every 10 deaths among those patients with diabetes.
- Patients with type 2 diabetes mellitus significantly are more likely to experience fatal or nonfatal cardiovascular events than those patients without diabetes. In fact, patients with diabetes and no history of cardiovascular disease are as likely to experience fatal or nonfatal cardiac events as those patients without diabetes and a history of myocardial infarction. For example, in a study conducted in Finland (the East-West Study), the incidence of fatal or nonfatal myocardial infarction over a 7-year follow-up period was 19% among nondiabetic subjects with a prior myocardial infarction and 20% among diabetic subjects with no prior myocardial infarction (Figure 2). Patients with diabetes with a prior myocardial infarction were at extremely high risk of a myocardial infarction: 45% experienced a fatal or nonfatal myocardial infarction during the 7-year follow-up period (Figure 2).

Because diabetes confers a risk of cardiovascular death equivalent to that of established cardiovascular disease, the NCEP designates diabetes as a coronary heart disease risk-equivalent. Coronary heart disease risk-equivalents carry a risk of major coronary events equivalent to that of established coronary heart disease. Similarly, the American Heart Association emphasizes the link between diabetes and cardiovascular disease: “Because of the aging of the population and an increasing prevalence of obesity and sedentary life habits in the United States, the prevalence of diabetes is increasing. Thus, diabetes must take its place alongside the other major risk factors as important causes of cardiovascular disease. In fact, from the point of view of cardiovascular medicine, it may be appropriate to say, diabetes is a cardiovascular disease.”

Some evidence points to components of the metabolic syndrome, particularly insulin resistance, as pathophysiologic common denominators linking diabetes with cardiovascular disease. For example, a cross-sectional analysis of the NHANES III data found that the metabolic syndrome is significantly associated with self-reported history of myocardial infarction or stroke. Insulin resistance, hypertension, and hypertriglyceridemia were independently associated with increased risk of myocardial infarction or stroke. In a prospective study of more than 6000 participants from the NHANES II survey who were observed for an average of 13 years, an increased risk of coronary heart disease and cardiovascular mortality was demonstrated in individuals with the metabolic syndrome. Individuals with the metabolic syndrome and diabetes had an even greater risk for coronary heart disease, cardiovascular mortality, and total mortality (Figure 3).
The independent contribution of the metabolic syndrome to cardiovascular risk has also been demonstrated in populations outside the United States. The Kuopio Ischaemic Heart Disease Risk Factor Study, a population-based, prospective evaluation of more than 1200 Finnish men who at baseline did not have cardiovascular disease or diabetes, showed that men with the metabolic syndrome, as compared with those men without the metabolic syndrome, were 3 times more likely to die of coronary heart disease over a 9- to 14-year follow-up period.18 In the Botnia Study, which was conducted in Finland and Sweden, the relationship between the presence of the metabolic syndrome and cardiovascular sequelae was assessed in 3606 subjects over a median follow-up period of 6.9 years.19

The data show that those patients with the metabolic syndrome (regardless of whether they had a diagnosis of type 2 diabetes mellitus) were significantly more likely than those patients without the syndrome to experience cardiovascular morbidity and mortality. Individuals with the metabolic syndrome were 2.96 times more likely to have coronary heart disease, 2.63 times more likely to have had a myocardial infarction prior to the study, 2.27 times more likely to have had a stroke during the study, and 1.81 times more likely to die of cardiovascular causes. Of the patients with the metabolic syndrome, 12% died of cardiovascular causes as compared to 2.2% of those patients without the metabolic syndrome (Figure 4).19

Recent studies have demonstrated an association between the metabolic syndrome and subclinical atherosclerosis. Coronary artery calcification (CAC) is one measure of subclinical atherosclerosis and has the potential ability to reflect the impact of all risk factors on the arterial wall. In most studies, the metabolic syndrome predicted the severity of CAC independent of the Framingham risk score (FRS). Wong et al measured the prevalence and quantity of CAC among 1823 patients with diabetes, with metabolic syndrome and no diabetes, or with neither condition.20 The women with diabetes had a prevalence of CAC of 53%; those with metabolic syndrome and no diabetes, 51%; and those women with neither condition, 38% ($P < .001$). The men with diabetes showed a 75% prevalence of CAC; those with metabolic syndrome and no diabetes, 59%; and those with neither condition, 54% ($P < .001$).

A community-based study of 1120 asymptomatic white adults in Rochester, Minnesota,21 found that the metabolic syndrome was associated with a 17% increase in CAC prevalence and, among those patients who had detectable CAC, a 207% change in CAC quantity (age and gender-adjusted, $P < .001$). The metabolic syndrome remained positively and significantly associated with CAC after adjusting for the 10-year FRS ($P < .001$). The importance of the metabolic syndrome in identifying subclinical atherosclerosis has also been demonstrated.22 In a cohort of 455 white

![Figure 3. CHD, CVD, and Total Mortality Rates](image)

CHD, CVD, and total mortality rates in individuals with and without the metabolic syndrome and diabetes.
CHD = coronary heart disease; CVD = cardiovascular disease.

![Figure 4. Cardiovascular Deaths in Patients with or without the Metabolic Syndrome](image)

Data from Isomaa et al. Diabetes Care. 2001;24:683-689.19
asymptomatic Brazilian men, the metabolic syndrome increased the risk of any CAC (odds ratio [OR] 1.6; 95% confidence interval [CI], 1.0–2.6) and CAC higher than the 75th percentile (OR 1.8; 95% CI, 1.1–3.0). The metabolic syndrome was significantly associated with age-adjusted prevalence of CAC only in the low-risk group (FRS <10%; P = .01). These studies indicate that the metabolic syndrome substantially influences atherosclerotic disease burden and may be useful in risk assessment, especially for individuals classified at low or intermediate risk by FRS.

LIPOPROTEINS AND THE METABOLIC SYNDROME

Changes in the quality and quantity of specific blood lipids and lipoproteins constitute one of the earliest manifestations of the metabolic syndrome and can contribute to the development of cardiovascular and metabolic disease. In addition, these early changes in lipoproteins constitute a marker for the metabolic syndrome, thus affected patients can be identified for early intervention.

LIPOPROTEINS

Lipoproteins are large molecules composed of lipids (in the form of cholesterol, triglycerides, and phospholipids) and proteins (also known as apoproteins). Lipoproteins typically are spherical and comprise a core of water-insoluble components, including cholesterols and triglycerides, and a shell of more water-soluble components, including apoproteins and phospholipids. The lipid constituents of lipoproteins are energy sources, a key component of all cellular membranes, and also serve as the substrate for various hormones including androgens, estrogens, and corticosteroids. The protein constituents of lipoproteins provide structural stability to the lipoprotein molecule, serve as anchor points for interactions between lipoproteins and their targets, and contribute to the regulation of lipoprotein metabolism.

The main classes of lipoproteins include:

- **Chylomicrons.** Chylomicrons are synthesized predominantly in the intestine and are responsible for transporting dietary triglycerides and cholesterol from the intestines to the liver and other tissues.
- **Very low-density lipoprotein (VLDL).** VLDLs are synthesized primarily in the liver. Their main lipid constituent is liver triglycerides. VLDLs are synthesized from triglycerides by the action of an enzyme known as lipoprotein lipase.
- **Intermediate-density lipoprotein (IDL).** IDLs are synthesized from VLDL by the action of lipoprotein lipase in various tissues and organs, including the blood. The main lipid constituents of IDL are cholesterol and triglycerides.
- **Low-density lipoprotein (LDL).** LDLs are synthesized from IDL which come from VLDL in various organs and tissues, including the blood. Cholesterols are their primary lipid constituent.
- **High-density lipoprotein (HDL).** HDLs are synthesized in the intestine, liver, and plasma via complex biochemical pathways. The primary lipid constituents of HDL are cholesterols.

Lipoproteins vary in size and density. HDL particles are the smallest, most dense lipoproteins; VLDLs and chylomicrons are the largest, least dense lipoproteins. The size and density of lipoprotein particles is determined by the amount of cholesterol and triglyceride contained within their lipid cores. For example, the core composition of LDLs, which are ultimately synthesized from triglyceride-rich VLDL, is determined largely by plasma triglyceride levels. Elevation of plasma triglyceride levels favors a biochemical reaction, whereby VLDLs exchange their triglyceride molecules for cholesterol molecules contained in the core of the LDL. This reaction results in a cholesterol-depleted, triglyceride-rich LDL. In this form, the LDL is especially vulnerable to the activity of hepatic lipase, which transforms the large, cholesterol-depleted LDL to a smaller, denser LDL particle. This reaction is important in the pathogenesis of cardiovascular disease: small, dense LDL particles are more conducive to atherosclerosis than are larger, less dense LDL particles.

The metabolic syndrome is associated with a characteristic triad of lipoprotein abnormalities:

- Low HDL levels,
- High triglyceride/VLDL levels, and
- Elevations in small, dense LDL particles.

These lipoprotein abnormalities are brought about largely by an excess of blood levels of free fatty acids from which lipoproteins are synthesized. These elevations in free fatty acid levels are attributed partly to the inability of insulin to stimulate uptake and the use of free fatty acids in insulin-resistant tissues. For example, skeletal muscle, which normally uses free fatty acids for energy, cannot in an insulin-resistant state use free fatty acids circulating in the bloodstream.
levels of free fatty acids increase in the liver, which increases VLDL production in response.28

The lipoprotein profile characteristic of the metabolic syndrome was defined in part on the basis of data from the Insulin Resistance Atherosclerosis Study, a large multicenter study of insulin resistance and cardiovascular disease in African Americans, Hispanics, and non-Hispanic whites.29,30 Among 479 patients with type 2 diabetes mellitus, the patients who were insulin-resistant (n = 442), as compared with the patients who were insulin-sensitive (n = 37), had significantly lower levels of HDL cholesterol, which is vasculoprotective, and significantly higher levels of VLDL cholesterol and triglycerides (Table 2).29 Furthermore, mean LDL particle size was significantly smaller among patients who were insulin-resistant as compared to patients who were insulin-sensitive (256.9 angstroms vs 260.5 angstroms). Neither total cholesterol levels nor LDL cholesterol levels differed between the 2 groups of patients.

In an analysis of data from a larger sample of participants (n = 1549) in the Insulin Resistance Atherosclerosis Study, LDL particle size was correlated strongly and positively with the degree of insulin sensitivity (r = 0.21; P < .0001).30 Thus, the smaller the LDL particle size, the less the insulin sensitivity (and the greater the insulin resistance). LDL particle size was related inversely to fasting insulin levels—the smaller the LDL particle size, the greater the fasting insulin level. Unlike the smaller sample described earlier in this section, this sample of patients included diabetic and nondiabetic subjects to assess the relationships between cardiovascular risk factors and insulin resistance across a range of insulin sensitivities.

The lipoprotein profile characteristic of the metabolic syndrome also occurs in diabetes, but abnormalities in lipoproteins predate the development of diabetes by years. In an early analysis of data from the San Antonio Heart Study, the cardiovascular status of 614 Mexican-American men who were nondiabetic at baseline was compared to those men who developed type 2 diabetes mellitus and those who remained nondiabetic over an 8-year follow-up period.31 The results show that those men who developed type 2 diabetes mellitus had higher baseline levels of total cholesterol, LDL cholesterol, and triglycerides and lower HDL cholesterol levels than those men who did not develop diabetes. The lipid abnormalities were observed even in prediabetic patients who did not show signs of impaired glucose tolerance, an early sign of type 2 diabetes mellitus. Those men who developed type 2 diabetes mellitus also showed baseline abnormalities in body weight, blood pressure levels, blood glucose values, and blood insulin values.

These data show that the onset of lipoprotein abnormalities in insulin resistance and type 2 diabetes mellitus occurs substantially earlier than other manifestations of these conditions. Lipoprotein abnormalities in insulin resistance predate the onset of type 2 diabetes mellitus, in addition to diabetic macrovascular and microvascular complications. These early changes in lipoproteins undoubtedly contribute to the development of cardiovascular disease in patients with the metabolic syndrome. The early changes in lipoproteins also constitute a marker for adverse cardiovascular and metabolic outcomes, thus affected individuals can be identified for early intervention.

Strategies for recognizing and managing dyslipidemia and other components of the metabolic syndrome in clinical practice are explored later in this monograph in the article by Dr Michael H. Davidson.

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**Table 2. Cardiovascular Risk Factors as a Function of Insulin Sensitivity in Patients with Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Cardiovascular Risk Factor</th>
<th>Insulin-Resistant Patients (n = 442)</th>
<th>Insulin-Sensitive Patients (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>215.2</td>
<td>220.2</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>140.4</td>
<td>145.7</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>39.5</td>
<td>45.3</td>
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<tr>
<td>VLDL cholesterol, mg/dL</td>
<td>26.5</td>
<td>20.5</td>
</tr>
<tr>
<td>Total triglyceride, mg/dL</td>
<td>166</td>
<td>133</td>
</tr>
<tr>
<td>VLDL triglyceride, mg/dL</td>
<td>122.4</td>
<td>87.2</td>
</tr>
<tr>
<td>LDL size, angstroms</td>
<td>256.9</td>
<td>260.5</td>
</tr>
</tbody>
</table>

Shaded variables designate statistically significant differences (P < .05) between insulin-resistant patients and insulin-sensitive patients. HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.

REFERENCES


