The term **metabolic syndrome** describes the association of insulin resistance with a clustering of cardiovascular risk factors that includes central obesity, hypertension, dyslipidemia, and abnormal glucose tolerance. Individuals with these metabolic abnormalities are at increased risk of developing both cardiovascular complications and diabetes. This article discusses the pathogenesis of the metabolic syndrome and its relationship with central obesity and long-term complications. Early identification of patients with this condition will allow providers to intervene to prevent the development of both diabetes and heart disease.

**DEFINITION**

Several expert groups have developed criteria to define the metabolic syndrome. The most widely cited definitions are those from the World Health Organization (Table 1) and the National Cholesterol Education Program’s (NCEP’s) Adult Treatment Panel (ATP) III report. The most recent definition of the metabolic syndrome is the International Diabetes Federation (IDF) definition adopted in 2005 (Table 1). Metabolic syndrome can be diagnosed according to the IDF definition if central obesity is present along with 2 of 4 other factors: increased triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), increased blood pressure, and increased fasting plasma glucose (FPG). In the IDF definition, central obesity is both a requisite component for diagnosis and the underlying cause of the syndrome. The IDF has made a first attempt at providing ethnic group-specific cut-off points for waist circumference to define central obesity (Table 2). At the present time, the cut-off points are pragmatic estimates taken from various data sources. As more complete data sets become available, risk factors may be added and the cut-off points may be modified.

**PREVALENCE**

Regardless of the definition used, large numbers of adults in the United States meet the criteria for the metabolic syndrome. A survey examined the prevalence of the metabolic syndrome using data from the National Health and Nutrition Examination Survey (NHANES) 1999–2002, which is the most scientifically rigorous sample of the US population. In 3601 persons at least 20 years of age from the NHANES 1999–2002, the prevalence of metabolic syndrome was 33.7% in men and 35.4% in women using the NCEP ATP III definition. In comparison, the prevalence using the IDF definition was 39.9% of men and 38.1% of women. The percent agreement between the 2 definitions was 89.8% among men and 96% among women.

**TAKE HOME POINTS**

- The metabolic syndrome identifies individuals at increased risk of developing both diabetes and cardiovascular disease.
- Visceral fat cells are active endocrine organs that release free fatty acids and cytokines, which play a role in insulin resistance. Central obesity is associated with the metabolic syndrome.
- Fasting hyperglycemia is due to overproduction of glucose by the liver, while postprandial hyperglycemia is due to insulin resistance at the muscle.
- In the Diabetes Prevention Program, diet and exercise were twice as effective as drug therapy with metformin in preventing diabetes.
- The combination of a statin plus niacin provides the greatest impact in lowering low-density lipoprotein cholesterol and raising high-density lipoprotein cholesterol in a patient with the atherogenic dyslipidemia seen in the metabolic syndrome.
Table 1. Definitions of Metabolic Syndrome

<table>
<thead>
<tr>
<th>Components</th>
<th>World Health Organization</th>
<th>Adult Treatment Panel III</th>
<th>International Diabetes Federation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central obesity</td>
<td>Patient must have 1 glucose intolerance, impaired glucose tolerance of diabetes, and/or (2) insulin resistance, and 2 or more of the following:</td>
<td>Patient must have 3 or more of the following risk factors:</td>
<td>Patient must have central obesity plus any 2 of 4 factors:</td>
</tr>
<tr>
<td>Body mass index ≥ 30 kg/m² and/or waist-to-hip ratio &gt; 0.9 in men and &gt; 0.8 in women</td>
<td>Waist circumference &gt; 102 cm (&gt; 40 in) in men and &gt; 88 cm (&gt; 35 in) in women</td>
<td>Waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, with ethnicity-specific values for other groups (See Table 2)</td>
<td></td>
</tr>
<tr>
<td>Low high-density lipoprotein cholesterol</td>
<td>&lt; 35 mg/dL in men and &lt; 39 mg/dL in women</td>
<td>&lt; 40 mg/dL (1.03 mmol/L) in men and &lt; 50 mg/dL (1.29 mmol/L) in women</td>
<td>&lt; 40 mg/dL (1.03 mmol/L) in men and &lt; 50 mg/dL (1.29 mmol/L) in women, or specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td>Hypertension</td>
<td>SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or documented use of antihypertensives</td>
<td>&gt; 130/&gt; 85 mm Hg</td>
<td>SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>≥ 150 mg/dL</td>
<td>&gt; 150 mg/dL (1.7 mmol/L)</td>
<td>&gt; 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Albumin excretion rate ≥ 20 µg/min or albumin-to-creatinine ratio ≥ 30 mg/g</td>
<td>Not a component</td>
<td>Not a component</td>
</tr>
<tr>
<td>Increased fasting glucose</td>
<td>Not a component</td>
<td>&gt; 110 mg/dL (6.1 mmol/L)</td>
<td>&gt; 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes</td>
</tr>
</tbody>
</table>

DBP = diastolic blood pressure; SBP = systolic blood pressure.


PATHOGENESIS

Normal Insulin Action

To better understand the association between insulin resistance and the metabolic syndrome, we should first review insulin action under normal conditions. In the fasting state, the liver is responsible for maintaining adequate levels of plasma glucose.5–7 Over half of hepatic glucose production is needed to meet the needs of the brain and other neural tissues, which do not require insulin to metabolize glucose and are thus unaffected by insulin resistance. Most of the remaining glucose is metabolized by muscle, which requires insulin.5–7 In the fed state, carbohydrate ingestion leads to an increase in plasma glucose concentration, which stimulates insulin release from the pancreatic beta cells. The resultant elevation in plasma insulin suppresses hepatic glucose production and stimulates glucose uptake by peripheral tissues.5–7 The majority (~ 80%–85%) of glucose that is taken up by peripheral tissues is disposed of in muscle,5–7 with only 4% to 5% metabolized by adipocytes.8,9

Although fat tissue is responsible for only a small amount of total body glucose disposal, it plays a very important role in the maintenance of total body glucose homeostasis through its production of free fatty acids (FFAs). Small increments in the level of plasma insulin exert a potent antilipolytic effect, leading to a marked reduction in the plasma FFA level.9 The decline in plasma FFA concentration results in increased glucose uptake in muscle10 and reduces hepatic glucose production.11–13

Insulin Action in Resistant Individuals

Liver and muscle. Insulin resistance involving both muscle and liver leads to abnormal glucose metabolism. Hepatic insulin resistance results in failure to suppress glucose production in the liver following carbohydrate ingestion. Postprandial hyperglycemia then results from 2 inputs of glucose following a meal, one from the accelerated hepatic gluconeogenesis and the other from the diet. Nondiabetic individuals respond to a physiologic increase in plasma insulin by increasing...
muscle glucose uptake to a peak level of 10 mg/kg of leg weight per minute. In contrast, in lean type 2 diabetic individuals, the onset of insulin action is delayed for approximately 40 minutes and the ability of insulin to stimulate leg glucose uptake is reduced by 50%. In the basal state, the liver represents a major site of insulin resistance, which is reflected by overproduction of glucose. This accelerated rate of hepatic glucose output is the primary determinant of the elevated FPG concentration in type 2 diabetic individuals. In the fed state, the defects in insulin-mediated glucose uptake by muscle and the lack of suppression of hepatic glucose production by insulin contribute approximately equally to the disturbance in whole-body glucose homeostasis in type 2 diabetes.

Adipocyte. Obesity is the most common acquired cause of insulin resistance. Interestingly, a similar degree of insulin resistance is seen in obese nondiabetic and lean type 2 diabetic individuals (Figure 1). Obese nondiabetic individuals are able to maintain a normal blood glucose concentration in the face of increased resistance to insulin by increasing secretion. When obesity and diabetes coexist in the same individual, the severity of insulin resistance is only slightly greater than that in either the normal-weight diabetic or obese nondiabetic groups (Figure 1).

The central obesity associated with insulin resistance is associated with increased levels of plasma FFAs. Obese individuals have an expanded fat cell mass characterized by visceral adiposity. Visceral fat cells have a high lipolytic rate and are especially refractory to the antilipolytic effects of insulin. Released FFAs impair insulin secretion by the pancreas and circulate in plasma where they may be taken up in muscle and liver. Increased fat content correlates closely with the presence of insulin resistance in these tissues. FFAs released into the portal circulation are taken up by the liver and serve as substrate for the production of triglycerides carried in very-low-density lipoprotein (VLDL) particles. Visceral adipose tissue also produces cytokines, including leptin, tumor necrosis factor-α, and interleukin-6. These factors reduce insulin sensitivity in peripheral tissues. Visceral adipose tissue is also the site of production of adiponectin, a hormone associated with increased insulin sensitivity. Obesity is associated with decreased levels of adiponectin. Adiponectin has a number of antiatherosclerotic properties, including suppressing endothelial inflammatory response, decreasing vascular smooth muscle proliferation, decreasing vascular cell adhesion molecule-1 expression, and suppressing conversion of macrophages to foam cells. In humans, higher levels of adiponectin are associated with a lower risk of myocardial infarction (MI).

**TREATMENT**

The presence of the metabolic syndrome identifies patients at increased risk of developing both diabetes

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**Table 2.** Ethnicity-Specific Values for Waist Circumference

<table>
<thead>
<tr>
<th>Country/Ethnic Group</th>
<th>Waist Circumference (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europids</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥ 94</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 80</td>
</tr>
<tr>
<td>South Asians, Chinese</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥ 90</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 80</td>
</tr>
<tr>
<td>Japanese</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥ 85</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 90</td>
</tr>
</tbody>
</table>

Note: In the United States, the Adult Treatment Panel III values (102 cm male, 88 cm female) are still being used. European cut-off points are recommended for sub-Saharan Africans and Eastern Mediterranean and Middle East (Arab) populations. South Asian values are recommended for South and Central Americans.


**Figure 1.** Glucose disposal, a measure of muscle sensitivity to insulin, is equally reduced in lean type 2 diabetic (T2DM) individuals and obese nondiabetic individuals. The combination of type 2 diabetes and obesity only slightly increases insulin resistance. (Reprinted with permission from DeFronzo RA. Lilly lecture 1987. The triumvirate: beta cell, muscle, liver: A collusion responsible for NIDDM. Diabetes 1988;37:667–87. Copyright © 1988 American Diabetes Association.)
and cardiovascular disease. Because central obesity is necessary for the diagnosis and plays a major role in the pathogenesis of the syndrome, diet and exercise should be employed in all patients. In addition, insulin sensitizers have been shown in clinical trials to delay the onset of diabetes, and pharmacologic therapy of hypertension and dyslipidemia has been shown to reduce the risk of cardiovascular events.

**Diet and Exercise**

The Diabetes Prevention Program confirmed that modest weight loss in association with exercise can have a dramatic impact on insulin sensitivity and the progression to diabetes. In this study, approximately 3200 individuals with impaired glucose tolerance were randomized to lifestyle changes versus metformin or placebo. The study was originally planned to be ongoing for 5 years but was stopped after 2.8 years because the results at that point were conclusive. The placebo group developed diabetes at the rate of 11 cases per 100 person-years, while those in the lifestyle arm developed diabetes at a rate of 4.8% cases per 100 person-years—a 58% reduction in the risk of developing diabetes with diet and exercise. Surprisingly, a modest amount of diet and exercise yielded impressive results. The exercise program in the lifestyle group was walking 30 minutes 5 days each week. The mean weight loss over the 2.8-year study period was only 8 lb. Similar results were seen in the Finnish Diabetes Prevention Study.

**Diabetes Prevention**

The biguanides and the thiazolidinediones improve insulin sensitivity in target tissues. The biguanides primarily target hepatic tissue, while the thiazolidinediones are more potent insulin sensitizers and interact with peroxisome proliferator-activated receptor-γ (PPAR-γ) found in fat and muscle tissue. In the Diabetes Prevention Program study, approximately 1000 patients were randomized to metformin therapy. The metformin-treated patients showed a 4-lb weight loss on average and a 31% reduction in the risk of developing diabetes compared to placebo. Interestingly, young and overweight individuals had a greater reduction in the risk of developing diabetes than normal weight and older study patients.

The TRIPOD (Troglitazone in Prevention of Diabetes) study evaluated the ability of troglitazone to prevent the development of diabetes in women with a history of gestational diabetes. The rate of development of diabetes in the placebo arm of the study was approximately 12% per year compared to approximately 5% in the troglitazone group. Surprisingly, this study demonstrated total preservation of beta cell function over a 5-year period in women who had near normal beta cell function at baseline and initially responded to the drug. At the present time, no pharmacologic intervention is approved by the US Food and Drug Administration for prevention of diabetes.

**Hypertension**

Reduction in cardiovascular disease and in some cases, a reduction in the development of diabetes, has been demonstrated with angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers. Cardioprotection with ACE inhibitors has been demonstrated in a number of trials, including the Heart Outcomes Prevention Evaluation (HOPE), the Captopril Prevention Project (CAPPP), Fosinopril versus Amlodipine Cardiovascular Events randomized Trial (FACET), and the Swedish Trial in Old Patients with Hypertension-2 (STOP-2). In the HOPE study, the largest of these trials, 3577 normotensive diabetic patients were randomized to treatment with ramipril 10 mg daily versus placebo. At the end of the 4-year study period, patients in the ramipril treatment group showed a 37% reduction in risk of cardiovascular mortality and a 24% reduction in risk of overall mortality. Interestingly, a post hoc analysis of the nondiabetic individuals in the study showed a 30% reduction in the risk of developing diabetes in patients treated with ramipril versus placebo. In the LIFE study, losartan reduced cardiovascular events more than atenolol in diabetic patients. In addition, nondiabetic individuals who were randomized to losartan were 25% less likely to develop diabetes. These findings strongly suggest that drugs that block the angiotensin system should be considered first-line therapy for hypertension in insulin resistant individuals because of their proven ability to reduce both cardiovascular complications and the progression to diabetes.

**Dyslipidemia**

Insulin resistance is associated with a dyslipidemia characterized by high triglyceride levels, low HDL-C levels, and high levels of small, dense low-density lipoprotein cholesterol (LDL-C) (Figure 2). Patients with atherogenic dyslipidemia will usually require specific lipid-lowering therapy. The classes of drugs used in the treatment of adult dyslipidemia provide a range of lipid alterations, and clinical trials have established the value of these agents as monotherapy and in combination.

**Statin monotherapy.** Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), the most powerful LDL-C-lowering class, are the initial treatment step in individuals with elevated LDL-C levels. Post hoc
subgroup analyses of the major primary and secondary prevention trials included a sufficient number of type 2 diabetes patients to show that the various statins had benefits in diabetes patients at least equivalent to those in nondiabetes patients. A total of 2006 diabetic patients participated in 4 trials (LIPID, AFCAPS/TEX CAPS, CARE, 4S)\(^{34-39}\) out of a total of 24,222 patients randomized. Because each trial had its own entry criteria, the baseline levels of LDL-C varied from 136 mg/dL to 186 mg/dL, or 36% to 86% above the current recommended target level for patients with diabetes. Significant lowering of LDL-C levels occurred in all 4 trials, ranging from 25% to 36%. Over the course of the 5- to 6-year average follow-up period, major coronary events were found to be reduced as much in diabetic patients (19% to 45%) as in nondiabetic patients (23% to 37%).

The Heart Protection Study is the largest placebo-controlled coronary heart disease (CHD) prevention trial of statin therapy. It randomized more than 20,000 patients at clinical risk of experiencing a new CHD event by virtue of prior CHD, other atherosclerotic disease, diabetes, or hypertension to simvastatin 40 mg daily or placebo.\(^{40}\) This high-risk population included 5963 men and women with diabetes, 3982 of whom had no prior evidence of CHD. After an average follow-up of 5 years, there was a 24% relative risk reduction in major vascular events (CHD death, MI, stroke, or revascularization) with simvastatin treatment (P < 0.0001) in the total population. Notably, patients with a LDL-C level below 116 mg/dL at baseline had similar reductions in events compared to patients with a LDL-C level above 136 mg/dL. In patients with diabetes, there was a similar 25% risk reduction with treatment (P < 0.0001). The consistent reduction in CHD risk demonstrated in these randomized clinical trials involving more than 8000 patients with diabetes suggests that statins should be used in all patients at high risk for developing cardiovascular disease independent of LDL-C level.

**Fibrates**

A second major class of lipid-modifying drugs used for the reduction of CHD risk is the fibric acid derivatives (including gemfibrozil, fenofibrate, and bezafibrate). Several clinical trials in diabetic patients have demonstrated that lipid-altering effects and CHD risk reduction are associated with this class of agents.\(^{41-44}\) The Veterans Affairs HDL Intervention Trial (VA-HIT) enrolled 2531 men with known CHD, low HDL-C, and normal LDL-C levels; approximately 25% of the subjects who fit these entry criteria had diabetes, while 50% had either type 2 diabetes or hyperinsulinemia.\(^{45}\) In the total population, major coronary events were reduced 22% more with gemfibrozil treatment compared with placebo over a 7-year period.\(^{44}\) Virtually all the benefit of gemfibrozil was observed in the subgroups of patients with diabetes, hyperinsulinemia, or both (relative risk reductions, 30.5%, 27.3%, and 25.2%, respectively; P ≤ 0.02), while little benefit was seen in patients without these conditions.\(^{43,44}\)

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was designed to assess the effect of fenofibrate on cardiovascular disease in patients with diabetes. A total of 9795 patients were randomized to therapy with fenofibrate 200 mg daily versus placebo, making this by far the largest study ever completed in a diabetic population.\(^{45}\) The baseline lipid levels on no lipid-altering medication included a mean LDL-C level of 118 mg/dL, an HDL-C level of 42.6 mg/dL, and a triglyceride level of 153.3 mg/dL in both groups. The primary endpoint was the first occurrence of either a nonfatal MI or death from CHD. At the end of the FIELD trial, a nonsignificant 11% reduction (P = 0.16) in the primary outcome of first MI or coronary heart death was seen in the treatment group. This corresponded to a 24% reduction in nonfatal MI.
in fenofibrate-treated patients ($P = 0.01$) and a 19% increase in coronary heart disease mortality ($P = 0.22$). In the FIELD study, 5 fewer patients in the fenofibrate group than in the placebo group were placed on dialysis during the study and 75 fewer patients received laser therapy for retinopathy. There were 33 more deaths in the fenofibrate group than in the placebo group during the 5-year study. The most likely explanation for the disappointing effect of fenofibrate on cardiovascular events in the FIELD trial was the lack of treatment effect on HDL-C levels. By the end of the study, the difference in HDL-C levels between the fenofibrate and placebo groups was only 1%. Thus, the FIELD study does not support the use of fenofibrate in patients with average levels of triglycerides and HDL-C. The clinical utility of fenofibrate in patients with more severe hypertriglyceridemia or in combination with statin therapy remains to be demonstrated in a well-designed clinical trial.

**Niacin.** Niacin is the most effective pharmacologic agent currently available for increasing HDL-C levels. Niacin’s ability to decrease cardiovascular events was shown in the Coronary Drug Project, where CHD patients with hypercholesterolemia experienced a 27% relative reduction in nonfatal MI rates and an 11% reduction in long-term mortality. Recently, these results were analyzed by baseline FPG and 1-hour glucose challenge blood glucose values. In the post-hoc analysis, niacin reduced nonfatal MI and total mortality to a similar extent across all baseline glucose levels, even in patients with FPG of 126 mg/dL or greater.

**Statins plus fibrates.** Use of this drug combination has been limited following reports in the literature that it is associated with rhabdomyolysis and renal failure. However, in controlled clinical trials where study design minimized other drug interactions, only 1% of nearly 600 patients treated with this combination were withdrawn because of myalgias. Athyros and colleagues compared atorvastatin plus fenofibrate to either drug alone for 24 weeks in 120 patients with type 2 diabetes. The combination reduced LDL-C levels by 46% and triglyceride values by 50%, while HDL-C levels increased by 22%. This study shows that a statin-fibrate combination is attractive for diabetic patients with elevated LDL-C and triglyceride levels and for those who continue to have elevated triglycerides after reaching their LDL-C goal with statin monotherapy. Careful monitoring for symptoms of myopathy is recommended.

**Statins plus niacin.** The combination of a statin and niacin was associated with substantial clinical benefits in the HDL-Atherosclerosis Treatment Study (HATS), which enrolled 160 patients with CHD, including 34 patients with diabetes or impaired FPG levels. All patients had low-HDL-C, high triglyceride, and mildly elevated LDL-C levels and were randomized to treatment with antioxidants, simvastatin plus niacin, simvastatin plus niacin plus antioxidants, or placebo. After 3 years, patients treated with simvastatin-niacin regimens experienced a 60% to 90% reduction in the composite primary endpoint (CHD death, MI, stroke, or revascularization) compared with those treated with placebo or antioxidants alone ($P = 0.03$). Substantial improvements were also seen in the subgroup of patients with diabetes or impaired fasting glucose; simvastatin-niacin treatment was associated with a 31% decrease in LDL-C, a 40% decrease in triglycerides, and a 30% increase in HDL-C, while placebo or antioxidant treatments alone had little effect.

The purpose of the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 study was to assess the independent and additive effect of once-daily extended-release niacin 1000 mg versus placebo when added to optimal statin therapy. The study included men and women older than 30 years with known CHD, LDL-C levels below 130 mg/dL on statin therapy, and low HDL-C levels (< 45 mg/dL). The primary endpoint was change in carotid intimal medial thickness (CIMT), a measure of atherosclerosis in the carotid artery. The change in CIMT from baseline to 12 months was 0.044 mm in the placebo group ($P < 0.001$) and 0.014 mm in the extended-release niacin group ($P = 0.023$). Thus, the increase in CIMT was 3 times greater in the placebo group than in the extended-release niacin group.

**Summary.** In summary, the lipoprotein abnormalities associated with the metabolic syndrome are integrally related to the development and progression of atherosclerosis, and there is abundant evidence from clinical trials that type 2 diabetic patients receive benefit from aggressive lipid management. Statins, fibrates, and niacin each improve different aspects of the lipid profile and should be used selectively, based on individual patient characteristics. Combination therapies may provide the best therapeutic option for treating the atherogenic dyslipidemia of type 2 diabetes.

**CONCLUSION**

The metabolic syndrome describes a clustering of metabolic abnormalities due to the insulin resistance of obesity that increase the risk of developing diabetes and heart disease. The individual components and cut-off points of the syndrome will likely be modified as more data become available from studies in various populations. Early identification of the syndrome is necessary to allow effective interventions to prevent the development of complications.

HP
REFERENCES


