The Metabolic Syndrome:

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ABSTRACT: The metabolic syndrome, which presents as a cluster of atherogenic traits, confers an increased risk of coronary heart disease (CHD) that may be greater than the sum of the risks associated with the individual components. The principal components of the syndrome are abdominal obesity, elevated triglyceride level, low high-density lipoprotein cholesterol level, elevated blood pressure, and elevated fasting glucose. The presence of 3 of the 5 characteristics establishes the diagnosis. First-line therapy for the metabolic syndrome consists of lifestyle modification measures, such as weight reduction and physical activity; however, pharmacologic treatment may be necessary. Statin therapy decreases the elevated levels of low-density lipoprotein cholesterol and triglycerides characteristic of the metabolic syndrome. Control of nonlipid CHD risk factors, such as hypertension and diabetes, is also critical.

Two interrelated disorders are becoming increasingly prevalent in the United States. The first is obesity. According to National Health and Nutrition Examination Survey (NHANES) data, about 30.5% of the nation's adults are obese (body mass index [BMI], 30 kg/m\(^2\) or greater).\(^1\) An additional 34% are considered overweight (BMI, 25 to 29 kg/m\(^2\)).\(^1\) The second disorder is the metabolic syndrome—a cluster of lipid, metabolic, and coagulation abnormalities closely associated with obesity. This syndrome was first described in 1988 by Reaven,\(^2\) who proposed that insulin resistance was causally linked to hypertension and was associated with atherogenic dyslipidemia (elevated triglycerides, decreased high-density lipoprotein [HDL] cholesterol, and small low-density lipoprotein [LDL] particles), elevated blood pressure, impaired glucose tolerance, and abdominal obesity.

These conditions are all diagnostic criteria for the clinical definition of the metabolic syndrome issued by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program.\(^3\) Also referred to as syndrome X, the deadly quartet, and the insulin resistance syndrome, the metabolic syndrome is a potent risk factor for cardiovascular disease. The increasing prevalence of obesity is expected to herald a similarly marked increase in prevalence of both the metabolic syndrome and type 2 diabetes mellitus.\(^1,4\)

The public health implications of the increases in the prevalence of obesity and the metabolic syndrome are formidable. Almost 10% of the US health care budget is spent on the direct costs of obesity and physical inactivity.\(^5\) The increasing prevalence of the metabolic syndrome threatens to halt or reverse the 3-decade decrease in coronary heart disease (CHD) risk that has accompanied declining LDL cholesterol levels. The contribution of the metabolic syndrome to CHD risk equals that of cigarette smoking or an additional 10 years of age.\(^6\)

The good news is that patients with the metabolic syndrome appear to benefit from aggressive treatment at least as much as others at high risk for CHD. Here I discuss the diagnostic criteria for this syndrome and describe management strategies that can reduce the risk of CHD.

EPIDEMIOLOGY

Based on a representative sample of more than 8000 adults from the NHANES III database, the age-adjusted prevalence of the metabolic syndrome among adults aged 20 years or older in the United States is 23.7%; rates for men and women are similar.\(^7\) About 47 million persons have the metabolic syndrome. The prevalence increases with age, reaching more than 40% for men and women aged 60 years and older. Mexican Americans have a higher prevalence than blacks and non-Hispanic whites, which supports the premise that Mexican Americans have a predisposition to insulin resistance.\(^4\)

About 50% to 60% of obese persons have the metabolic syndrome, compared with fewer than 6% of persons with normal body weight (BMI, less than 25 kg/m\(^2\)).\(^4\)

ETIOLOGY

Environmental and genetic factors probably contribute to the development of insulin resistance and the metabolic syndrome, which arise, at least in part, from physical inactivity and excess body fat, particularly abdominal fat.\(^3\) Insulin resistance is thought to underlie the metabolic syndrome, but the
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Increased risk of CHD and diabetes was also demonstrated in the primary prevention West of intervention is warranted. The metabolic syndrome might identify a substantial number of patients in whom aggressive risk-factor treatment is likely to be beneficial. This finding suggests that screening for sub-clinical CHD in persons with the metabolic syndrome might yield cost-effective therapy. Approximately 50% of Framingham participants with the metabolic syndrome had a risk score that indicated a 10-year CHD risk greater than 20%. This finding suggests that screening for sub-clinical CHD in persons with the metabolic syndrome might identify a substantial number of patients in whom aggressive risk-factor intervention is warranted.

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A cluster of risk factors. The fact that the metabolic syndrome presents as a constellation of atherogenic traits is consistent with evidence that risk factors for CHD tend to cluster; persons in whom CHD develops rarely have only 1 risk factor. The Framingham Heart Study database was analyzed to compare the degree of risk-factor clustering expected by chance with the degree actually observed. Using extreme quintile values of 6 atherogenic risk factors (increased BMI; elevated levels of total cholesterol, triglycerides, and serum glucose; elevated systolic blood pressure; and decreased HDL cholesterol levels), the investigators found that clusters of 3 or more risk factors occurred at a rate well beyond that which would be expected by chance, and that the tendency for risk factors to cluster increased with weight gain and decreased with weight loss. The relative risk of CHD increased to 2.39 in men and 5.90 in women with 3 or more components of the cluster.

The metabolic syndrome is associated with an increased risk of CHD and type 2 diabetes that is equal to, and possibly greater than, the sum of its individual components. One cause of elevated levels of the inflammatory marker CRP appears to be obesity, presumably because excess adipose tissue releases inflammatory cytokines that elicit higher CRP levels. CRP has been implicated in CHD risk and atherosclerosis and is currently the focus of intense research interest. As part of the ongoing Women's Health Study—a trial of aspirin and vitamin E in primary prevention—the relationship of CRP and the metabolic syndrome and their effects on subsequent cardiovascular events were studied in 14,719 apparently healthy women aged 45 years and older who were followed for 8 years. At entry, 24% of the cohort had the metabolic syndrome. As the number of individual components of the syndrome increased from 0 to 5, the CRP level rose linearly (Figure). Women with the metabolic syndrome at baseline and the highest CRP levels (3 mg/L or higher) had a significantly higher probability of a cardiovascular event than those without the syndrome or with lower CRP levels. Moreover, the predictive power of the metabolic syndrome for CHD or type 2 diabetes was increased in patients with elevated CRP. The investigators concluded that measuring CRP adds important prognostic information regarding future vascular risk at all levels of severity of the metabolic syndrome. This conclusion applies to men as well as to women.

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Evidence from the trials. Among approximately 4500 participants in a family study of type 2 diabetes, the metabolic syndrome increased the risk of CHD and stroke 3-fold and the risk of cardiovascular death 5-fold. The CHD risk associated with the cluster of risk factors exceeded that associated with the individual components.

Similar findings were observed in a population-based sample of 888 men and women who participated in a study of carotid atherosclerosis and CHD. Approximately 50% of participants had the metabolic syndrome. The risk of development or progression of carotid atherosclerosis (greater than 40% stenosis) was significantly increased during the 5-year follow-up in participants with the syndrome. The risk was increased even in participants with mild abnormalities (eg, blood pressure less than 160/95 mm Hg). None of the individual components of the metabolic syndrome predicted these outcomes independently.

These results demonstrated that by focusing on single abnormalities, clinicians may overlook many per- sons at significant risk for cardiovascular disease. Approximately 20% of Framingham participants with the metabolic syndrome had a risk score that indicated a 10-year CHD risk of greater than 20%. This finding suggests that screening for sub-clinical CHD in persons with the metabolic syndrome might identify a substantial number of patients in whom aggressive risk-factor intervention is warranted.

Increased risk of CHD and diabetes was also demonstrated in the primary prevention West of intervention is warranted. The metabolic syndrome might identify a substantial number of patients in whom aggressive risk-factor treatment is likely to be beneficial. This finding suggests that screening for sub-clinical CHD in persons with the metabolic syndrome might yield cost-effective therapy. Approximately 50% of Framingham participants with the metabolic syndrome had a risk score that indicated a 10-year CHD risk greater than 20%. This finding suggests that screening for sub-clinical CHD in persons with the metabolic syndrome might identify a substantial number of patients in whom aggressive risk-factor intervention is warranted.
Scotland Coronary Prevention Study, in which 26% of participants had the metabolic syndrome at baseline. More than 95% of men with the syndrome were hypertensive and more than 85% also had elevated triglyceride and low HDL cholesterol levels. Men with 4 or 5 characteristics of the metabolic syndrome had a 3.7-fold increase in CHD risk and a 24.5-fold increase in new-onset diabetes compared with men without the syndrome.

In a recent subanalysis of data from NHANES III, approximately 44% of participants aged 50 years or older met the ATP III criteria for the metabolic syndrome. The highest age-adjusted prevalence of CHD (19.2%) was found in those persons with both the metabolic syndrome and diabetes, followed by those with the syndrome but without diabetes (13.9%). Persons without the metabolic syndrome, regardless of whether or not they had diabetes, had the lowest CHD prevalence (8.7% without diabetes; 7.5% with diabetes).

**MAKING THE DIAGNOSIS**

The diagnostic criteria for the metabolic syndrome are listed in Table 1. The principal components of the syndrome are abdominal obesity, elevated triglyceride level, low HDL cholesterol level, elevated blood pressure, and elevated fasting glucose. When 3 of the 5 characteristics are present, a diagnosis of metabolic syndrome can be made.

Although both overweight and obesity are associated with the metabolic syndrome, abdominal obesity is more highly correlated with metabolic risk factors than an elevated BMI. Thus, measurement of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

**TREATMENT**

The National Cholesterol Education Program now considers the metabolic syndrome a secondary target of therapy, after LDL cholesterol. Treatment can be approached in 2 ways (Table 2). First-line therapy addresses the root causes—that is, the life habits that result in overweight and obesity. Improvements in lifestyle factors reduce the risk of type 2 diabetes by 58%. However, this presents a daunting clinical challenge. Data collected in 2000 from a nationally representative sample indicate that 27% of adults engage in no physical activity whatsoever, and another 28.2% do engage in physical activity but not regularly. The same survey found that only 42.8% of obese persons who saw a health care provider for a routine checkup in the past year had been advised to lose weight. Nevertheless, nonpharmacologic measures should always form the core of the intervention program to reduce insulin resistance and modify associated metabolic risk factors.

**Nonpharmacologic approaches.** Encourage patients to avoid crash or fad diets and to adopt eating plans that involve a modest 500- to 1000-calorie-per-day reduction. A realistic goal is to reduce body weight by about 7% to 10% over a 6- to 12-month period. This can be accomplished through a diet that features a low intake of saturated fats, trans fats, and cholesterol; reduced consumption of simple sugars; and increased intake of fruits, vegetables, and whole grains. The addition of grapeseed oil to the diet will help raise HDL cholesterol levels; omega-3 fatty acids in fish oils reduce triglycerides. Emphasize behavioral changes, such as improved eating habits. Encourage patients to set dietary goals, plan meals, read labels, eat at regular times, reduce portion sizes, and avoid binges. Reinforce the benefits of social support, stress management, and a regular exercise regimen.

Regular exercise improves metabolic risk factors and reduces the likelihood of chronic disease. A daily minimum of 30 minutes of moderate-intensity exercise, such as brisk walking, helps weight reduction. Advise patients to avoid common sedentary activities, such as television watching and computer use.

**Pharmacologic therapy.** This strategy, which treats metabolic and other risk factors directly, has met with the most success to date. Decreasing LDL cholesterol levels is the core therapeutic measure for lowering CHD risk in patients with the metabolic syndrome. Statin therapy lowers LDL cholesterol levels and reduces risk substantially in these patients. Although the metabolic syndrome is defined by elevated triglyceride and low HDL cholesterol levels, about 60% of persons with the syndrome also have LDL cholesterol values above 130 mg/dL.

The effects of statin therapy on components of the metabolic syndrome were examined in the Scandinavian Simvastatin Survival Study (4S). Simvastatin treatment decreased the risk of major coronary events by 42% in patients with diabetes. In those with impaired fasting glucose, simvastatin reduced major coronary events by 38%, total mortality by 43%, and coronary mortality by 55%.

Another analysis of 4S data showed that major coronary event rates were highest in the group with...
elevated LDL cholesterol levels and the highest triglyceride and lowest HDL cholesterol levels. Other studies have shown that the most effective agent for lowering LDL cholesterol is also the most effective for lowering non-HDL cholesterol. In patients with elevated triglyceride levels (200 mg/dL or higher), ATP III has designated non-HDL cholesterol as a secondary target of therapy (after LDL cholesterol) and has set the goal for non-HDL cholesterol as 30 mg/dL higher than the goal for LDL cholesterol. A recent study of statin therapy in nearly 4000 patients with hypercholesterolemia showed that reductions in LDL cholesterol at 6 weeks ranged from 20% (with pravastatin) to 36% (with atorvastatin), and in non-HDL cholesterol from 17% (with fluvastatin) to 33% (with atorvastatin).

This result was confirmed in studies of rosuvastatin, the newest statin to be marketed in the United States; it reduces levels of LDL cholesterol more than the other statins. In randomized, double-blind comparisons of the usual starting doses of rosuvastatin and other statins, rosuvastatin produced significantly greater reductions in non-HDL cholesterol (43%) than atorvastatin, 10 mg (34%), simvastatin, 20 mg (33%), and pravastatin, 20 mg (25%). The incidence of adverse events with rosuvastatin was comparable to that observed with the other statins.

The importance of aggressive LDL lowering in the metabolic syndrome is under investigation in the prospective Comparative study with rosuvastatin in subjects with METabolic Syndrome (COMETS) study, which will compare rosuvastatin with atorvastatin and placebo in persons with the metabolic syndrome and elevated LDL cholesterol.

If additional therapy is needed to increase HDL cholesterol or lower triglycerides after the LDL cholesterol goal has been achieved, the ATP III guidelines recommend increasing the statin dose or adding nicotinic acid or a fibrate to the regimen. Low doses of statins are recommended if a fibrate is used, to reduce the risk of myopathy. Statin monotherapy can increase HDL cholesterol by up to 12% (simvastatin) or 14% (rosuvastatin); the addition of a fibrate or nicotinic acid will produce further increases, because each of these agents alone can raise HDL (10% to 15% and 15% to 30%, respectively).

Control of other risk factors. The other major CHD risk factors must be adequately controlled in persons with the metabolic syndrome. These include cigarette smoking, hypertension, elevated LDL cholesterol, and diabetes. For patients at intermediate and high CHD risk, low-dose aspirin is recommended to modify the prothrombotic-proinflammatory state. Management of insulin resistance with insulin-sensitizing agents in patients who do not have diabetes has not been shown to reduce CHD risk. These agents are therefore not recommended for this purpose.

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