Implications of the Metabolic Syndrome: the New Epidemic

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On the basis of traditional risk factors, a large number of individuals in the United States can be classified as at intermediate risk for the development of ischemic heart disease. The diagnosis of the metabolic syndrome can help determine whether patients at intermediate risk should be considered for more aggressive risk-factor reduction. The measurement of novel risk factors, such as inflammatory markers, can identify a group of patients at high intermediate risk. The Adult Treatment Panel of the National Cholesterol Education Program suggests considering a more aggressive low-density lipoprotein cholesterol treatment goal in this group of individuals. In addition, the presence of the metabolic syndrome is highly predictive of the development of diabetes mellitus. A treatment strategy focusing on aerobic exercise and weight loss can help delay or prevent the development of diabetes and can help reduce cardiovascular risk. For significant risk reduction to be achieved, treatment strategies must focus on therapy for all risk factors, including dyslipidemia, hypertension, and insulin resistance. **(Am J Cardiol 2005;96[suppl]:3E–7E)**

Coronary artery disease (CAD) remains the leading cause of death for men and women in this country. The identification of cardiovascular risk factors can determine the risk of developing heart disease and lead to beneficial preventive measures. A large number of individuals in the United States, however, can be classified as at intermediate risk for the development of CAD; more precise ways are needed to measure risk in this group. The designation of the metabolic syndrome as well as the use of novel risk markers can help to identify a cohort at higher risk within the intermediate risk category who may benefit from more aggressive risk-reduction therapies.

Determination of Risk

The standard method for calculating a patient's risk is the counting of traditional independent CAD risk factors (Table 1) and use of an algorithm based on a large data set, such as that of the Framingham study. The Adult Treatment Panel (ATP) of the National Cholesterol Education Program (NCEP) suggests categorizing individuals into 3 risk groups: high risk, defined as a >20% 10-year risk for patients with documented CAD or CAD risk equivalent disease; intermediate risk, defined as a 10% to 20% 10-year risk for patients with multiple risk factors; and low risk, defined as a <10% risk for individuals with ≤1 risk factor.[1] The 10-year risk assessment is carried out using a simplified version of the Framingham scoring system. Certain individuals are considered to be at high risk regardless of Framingham score. These individuals are classified as having CAD risk equivalent disease (Table 1). This category includes patients with diabetes mellitus and/or atherosclerotic disease in other vascular beds, such as peripheral arterial disease, abdominal aortic aneurysm, or symptomatic carotid artery disease. These patients have a >2% 1-year or >20% 10-year risk of having a coronary event.

There are a number of shortcomings to the Framingham scoring system for determination of cardiac risk. The scoring system does not include family history of premature CAD even though family history has been designated a major risk factor. The scoring system does not include risk factors that were not independent predictors of risk in this data set, such as obesity, sedentary lifestyle, and elevated triglyceride values. The metabolic syndrome is likewise not included as a component of the current scoring system. The Framingham scoring system does not discriminate risk very well in women aged <60 years and in the elderly. With this data set, women need to be 10 to 20 years older than men to achieve the same level of risk. In addition, the Framingham scoring system may not be applicable to all populations. Among Japanese American and Hispanic men, Native American women,[2] and a large Chinese cohort,[3] the Framingham functions overestimated CAD risk. The risk associated with hypertension, especially in black women, may be underestimated by the largely white Framingham population.[2]

The Framingham scoring system can be used as an initial estimate of risk, however. Evaluation of emerging risk factors can then be done to modify the initial prediction. This will be most important for the large group of individuals who are included in the intermediate risk category. After their basal risk is assessed by means of traditional risk factor

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Table 1
Major risk factors* for coronary artery disease (CAD) and CAD risk equivalent diseases

CAD risk factors
Cigarette smoking
Hypertension (≥stage 1, or using antihypertensive medication)
Low plasma levels of HDL cholesterol (<1.03 mmol/L [<40 mg/dL])
Family history of premature CAD (CAD in male first-degree relative <55 yr, CAD in female first-degree relative <65 yr)
Age (men aged ≥45 yr, women aged ≥55 yr)
CAD risk equivalent diseases
Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease)
Diabetes mellitus
Multiple risk factors, conferring a 10-yr risk for CAD >20%

*Exclusive of low-density lipoprotein cholesterol.
HDL = high-density lipoprotein.
Adapted with permission from *JAMA*.[1]

Table 2
Clinical identification of the metabolic syndrome*

Risk factors	Defining level
Abdominal obesity (waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥1.69 mmol/L (≥150 mg/dL)
HDL cholesterol	
Men	<1.03 mmol/L (<40 mg/dL)
Women	<1.29 mmol/L (<50 mg/dL)
Blood pressure	≥130/≥85 mm Hg
Fasting plasma glucose	≥6.11 mmol/L (≥110 mg/dL)

*Diagnosis requires the presence of ≥3 risk factors.
Adapted with permission from *JAMA*.[1]

analysis, individuals can be evaluated for criteria of the metabolic syndrome, novel risk factors such as inflammatory markers can be measured, and assessment for the presence of subclinical atherosclerotic disease can be performed. The presence of these additional factors may change an individual's risk calculation from low-intermediate to high-intermediate risk or even high risk. These patients can then be treated with more aggressive risk-reduction modalities to modify their future CAD risk. This type of analysis can help to identify the patient who is likely to be vulnerable to plaque rupture and acute coronary events.

The Metabolic Syndrome

The metabolic syndrome as defined by the NCEP[1] is described in Table 2. The metabolic syndrome is a constellation of risk factors that develop in individuals who have abdominal (visceral) obesity, an increased prevalence of insulin resistance, and an increased risk of diabetes. The presence of abdominal obesity is more highly correlated with the development of insulin resistance than is body weight or body mass index (BMI), so measurement of waist circumference is recommended for diagnosis of the metabolic syndrome. The development of insulin resistance leads to many of the metabolic abnormalities associated with this syndrome. Patients with insulin resistance tend to have an increased prevalence of small, dense, more atherogenic low-density lipoprotein (LDL) particles; below average plasma levels of high-density lipoprotein (HDL) cholesterol; elevated plasma levels of triglyceride-containing particles; endothelial dysfunction that can lead to hypertension; and impaired fasting plasma glucose levels.

Measuring the presence of novel risk factors can further modify the estimate of risk. This may be useful in determining the risk associated with the metabolic syndrome. The presence of inflammatory markers correlates with an increased risk of acute coronary events and thus may be a predictor of the existence of vulnerable plaques. C-reactive protein (CRP), one of the best-studied inflammatory markers, is associated with a number of medical conditions (Table 3).[4] Serum CRP levels correlate with the Framingham risk score[5] and, in a cohort of men aged 45 to 74 years, gave a significant contribution to coronary event prediction

Table 3
Conditions associated with increased C-reactive protein levels

Hypertension
Increased body mass index (obesity)
Cigarette smoking
Metabolic syndrome, insulin resistance, and diabetes mellitus
Low plasma levels of high-density lipoprotein-cholesterol and high plasma levels of triglycerides
Hormone replacement therapy
Chronic infection (eg, periodontal disease)
Chronic inflammation (eg, rheumatoid arthritis)

Adapted with permission from *J Geriatr Cardiol.*[4]

Table 4
Modalities to measure the presence of subclinical atherosclerotic disease

Exercise stress testing
Ankle-brachial blood pressure index (ratio)
Carotid intimal-medial thickness measurement
Electron-beam computed tomography calcium scoring
Magnetic resonance imaging
Measurement of endothelial dysfunction (brachial artery sensitivity)

that was independent of the Framingham score.[6] CRP levels can further modify risk associated with the metabolic syndrome. In women, the presence of ≥3 features of the metabolic syndrome is associated with high levels of CRP, and CRP measurement added prognostic value to the risk predicted by the metabolic syndrome alone.[7] A risk gradient has been shown between CRP values and all levels of the Framingham risk score, suggesting that a CRP-modified CAD risk score can be calculated to improve prediction of cardiac events.[8]

Finally, the single most useful piece of information in patients at intermediate risk is knowledge of whether subclinical atherosclerotic disease is present. Table 4 lists the available modalities that may measure subclinical disease. Exercise stress testing has been the standard screening test; however, it will reveal only occlusive lesions and cannot identify nonocclusive but vulnerable plaques. The ankle-brachial index (the ratio of systolic blood pressure in the posterior tibialis artery and the brachial artery) is easily determined in the office setting. A ratio of <0.9 indicates the likely presence of peripheral arterial disease and correlates with an increased risk of cardiovascular events. Calcium scoring by electron-beam computed tomography (EBCT) can quantify the burden of atherosclerotic disease. The higher the score, the more likely vulnerable plaques are present. EBCT and magnetic resonance imaging, however, are not universally available. Carotid intimal-medial thickness correlates with the incidence of coronary events, but the technology for determining this measurement is not readily available and accurate values may be difficult to reproduce outside of a research setting. Therefore, the optimal test to measure subclinical atherosclerotic disease has not yet been determined.

The metabolic syndrome has become common, with >22% of Americans fulfilling the criteria for this syndrome.[9] Not all of these individuals are at high cardiovascular risk. Risk-factor assessment—beginning with traditional risk-factor analysis and including determination of the risk elements of the metabolic syndrome, measurement of inflammatory markers or novel lipid parameters, and an assessment of subclinical atherosclerotic disease—has the potential of dividing this large group of individuals into low-intermediate and high-intermediate risk cohorts. Risk-reduction therapy can then be tailored to the risk group.

An underlying cause of the metabolic syndrome and diabetes, obesity has markedly increased in prevalence in this country.[10] A number of studies have correlated increasing weight with cardiovascular risk. For example, the Nurses' Health Study showed a correlation between body weight and mortality among middle-aged women. Women in the highest weight category (BMI ≥32.0) had a >4-fold risk of death due to cardiovascular disease compared with lean women.[11]

The metabolic syndrome is a precursor to the development of diabetes. Identifying individuals with the metabolic syndrome is a way to find a large number of patients who are destined to develop diabetes if no intervention is begun at an earlier stage in their disease. Patients who are euglycemic but insulin resistant with hyperinsulinemia may already have developed endothelial dysfunction and many of the metabolic abnormalities (eg, dyslipidemia, inflammation, prothrombotic state, oxidative stress) that may lead to the development of vascular disease. Intervention at this earlier stage may help prevent the development of diabetes and the vascular sequelae associated with this disease.

Treatment of the Metabolic Syndrome

Treatment of the metabolic syndrome should focus on the underlying causes. Since the obesity epidemic is a major cause of the metabolic syndrome, weight loss and exercise is the cornerstone of any treatment plan. Regular physical exercise may reduce plasma LDL and very-low-density lipoprotein cholesterol levels, raise plasma levels of HDL cholesterol, lower blood pressure, and improve insulin sensitivity.[1] Studies have proved a cardiovascular benefit to exercise. For example, 1 recent survey showed a strong protective effect of cardiovascular fitness against all-cause and cardiovascular mortality in men with the metabolic syndrome.[12]

Weight loss may also improve plasma lipid levels, lower blood pressure, improve insulin sensitivity, and reduce levels of inflammatory markers. Weight loss combined with an exercise program can delay and possibly prevent the development of diabetes in insulin-resistant individuals. The Diabetes Prevention Program examined a large cohort of individuals with insulin resistance.[13] A subset of participants began a lifestyle modification program with a goal of ≥7% weight loss and 150 minutes of physical activity per week. After an average follow-up of 2.8 years, the lifestyle intervention group achieved a nearly 60% reduction in the incidence of diabetes compared with the placebo group.

In addition to a therapeutic lifestyle program, it is necessary to address both the lipid and nonlipid factors in the metabolic syndrome to reduce cardiac risk. Lipid-lowering therapy across the spectrum of cardiovascular risk has been shown to be effective in preventing major cardiovascular events. LDL cholesterol should be the primary target of therapy. The Heart Protection Study showed that lipid-lowering therapy with simvastatin 40 mg/day in patients at high risk, including individuals who are in the CAD risk equivalent disease category, reduced the risk of major vascular events regardless of initial plasma cholesterol concentrations.[14] The Collaborative Atorvastatin Diabetes Study (CARDS) verified that lipid-lowering therapy with atorvastatin 10 mg/day for the primary prevention of cardiovascular disease is effective in a diabetic population even when plasma LDL cholesterol levels are not high.[15] The Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) demonstrated that lipid-lowering treatment with atorvastatin 10 mg/day in a cohort of patients with hypertension substantially reduced the incidence of major cardiac events, with benefit emerging within the first year of therapy.[16]

Since patients with the metabolic syndrome typically have a mixed hyperlipidemia, there has been interest in lipid-lowering modalities that may reduce plasma levels of triglycerides and raise plasma levels of HDL cholesterol as well as lower plasma levels of LDL cholesterol or change LDL cholesterol particles to a less atherogenic subfraction. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) used gemfibrozil 1,200 mg/day in a group of patients with CAD and low values for plasma HDL cholesterol.[17] Treatment reduced plasma levels of triglycerides by about 31% and increased plasma levels of HDL cholesterol by about 6% with no significant change in LDL cholesterol levels. The treatment group achieved a 24% reduction in cardiovascular events, a risk reduction similar to that achieved in the Heart Protection Study. Results of primary prevention trials with fibrates, such as the Helsinki Heart Study,[18] suggest that the subset of patients with high plasma levels of triglycerides and low levels of HDL cholesterol may achieve the greatest risk reduction with this class of agents. This describes the patient with the metabolic syndrome.

Additional studies on the optimal treatment of insulin resistance and hypertension in the metabolic syndrome are needed. There is interest in using agents such as the thiazolidinediones, currently prescribed for diabetes, for patients with the metabolic syndrome, in part because of possible favorable effects on cardiovascular risk factors.[19] Optimal goals for hypertensive therapy are needed for patients with the metabolic syndrome. There is emerging evidence suggesting that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may reduce the incidence of new-onset diabetes, as seen recently in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial.[20] These findings will require further study so that guidelines for the treatment of risk factors in patients with the metabolic syndrome can be formulated.

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