The Metabolic Syndrome

A Practical Guide to Origins and Treatment: Part II

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In this second part of discussing the components of the metabolic syndrome, we will discuss lipids and blood pressure criteria.

Low HDL Cholesterol and Elevated Triglycerides

Background

It is appropriate to consider jointly the effects of low HDL cholesterol (HDL-C) and high triglyceride levels as components of the metabolic syndrome (Mets). In observational studies, each of these factors is related to greater risk of coronary heart disease,1,2 and clinical trials have been undertaken to prevent outcomes.3 Persons with high triglycerides often have low HDL-C levels and small, dense LDL particles. Estrogen therapy and excessive alcohol intake may disrupt this pattern, as each may cause simultaneous increases in HDL and triglyceride levels.

A variety of environmental and genetic factors have been related to HDL-C and triglyceride levels in certain populations. For instance, lower HDL-C levels are found in cigarette smokers, obese persons, inactive individuals, and those who use androgens or 17 nor-derivatives of progesterone.4,5 Genetic variants of lipoprotein lipase, hepatic lipase, cholesterol ester transfer protein, and peroxisome proliferator-activated receptors (PPAR)-α have been shown to have effects on HDL-C and triglyceride levels in populations,6–10 contributing to the development of the Mets.

How Do You Make the Diagnosis?

Lipid levels are best obtained in a person’s usual, healthy state.11,12 Blood concentrations after a recent illness such as influenza, diarrhea, or a systemic disease accompanied by weight loss may reduce lipoprotein cholesterol levels, and physicians should be aware that it may be advisable to defer lipoprotein testing until acute illnesses have passed and the patient has recovered. A low HDL-C level (<40 mg/dL in men and <50 mg/dL in women) is one of the diagnostic criteria for the Mets. LDL-C levels are altered very little by fasting status, but triglyceride levels may increase greatly after eating, and diagnostic criteria for the MetS have been based on measurements done in persons who have typically fasted for 12 hours or more.

A variety of metabolic conditions can contribute to low levels of HDL-C and elevated triglycerides. For instance, primary hypothyroidism, use of protease inhibitors in persons treated for HIV, excess endogenous or exogenous glucocorticoids, acanthosis nigricans, and polycystic ovary syndrome are examples of disease processes that may be accompanied by lipid abnormalities that are characteristic of the MetS.13,14 Diagnosis of other diseases is important before instituting therapy for dyslipidemia, and screening with a thyroid-stimulating hormone level is appropriate to ensure that subclinical hypothyroidism is not missed. Glucose screening, discussed elsewhere in this article, is also appropriate in this setting.

What Are the Treatment Options for HDL-C and Triglycerides in the MetS?

The National Cholesterol Education Program has set forth guidelines for lipid management related to low HDL-C and elevated triglycerides.15 Where only lipid levels are abnormal, lifestyle intervention should be under-
taken first and the patient encouraged to follow a diet low in saturated fat and cholesterol, with caloric restriction. Exercise should be encouraged; the guidelines recommend 30 minutes of exercise 5 days a week. All of the exercise need not be taken at the same time on a given day, and the exercise need not be aerobic.

Many clinical trials demonstrate the efficacy of reducing LDL-cholesterol levels with statin therapy. The benefit of statin therapy also extends to patients with the MetS and type 2 diabetes mellitus (T2DM). However, there is growing evidence that modifying triglyceride and HDL-C levels with drug therapy will reduce risk for coronary heart disease independently of statin therapy or LDL lowering. For example, treatment with niacin acid and the Coronary Drug Project was related to lower risk of coronary death over long-term follow-up. More recently, therapy with gemfibrozil in the Veterans Administration HDL Intervention Trial (VA-HIT) led to triglyceride lowering of 31%, HDL-C raising of 6%, and no change in LDL-C. Participants in this trial of US military veterans with known coronary artery disease at the outset experienced a 24% reduction in coronary events (nonfatal myocardial infarction or coronary death) during follow-up. Corroborating evidence has been obtained in smaller clinical trials such as the HDL Atherosclerosis Trial (HATS) that used combination therapies such as niacin and colesterol and niacin and simvastatin to reduce the risk of progression of atherosclerosis and diminish the number of clinical events.

According to guidelines from the Adult Treatment Program III (ATP III) of the National Cholesterol Education Program, LDL cholesterol is the primary target of lipid-lowering therapy. LDL goals should be set according to the absolute risk of patients. Many patients with the MetS will be classified as being at high risk, ie, they will have established atherosclerotic cardiovascular disease or T2DM, or they will have a 10-year coronary heart disease risk >20% by Framingham scoring. Such patients will have an LDL goal <100 mg/dL. Most of the remaining patients with MetS will be at high enough risk to have an LDL goal of <130 mg/dL. If drug therapy is required to achieve the goals of therapy, the statins will represent first-line therapy.

However, in many patients with MetS, statin therapy alone will not correct abnormalities in triglycerides and low HDL. Especially when the MetS occurs in high-risk patients, consideration can be given to adding a second lipid-lowering drug, eg, nicotinic acid or fibric acid. Unfortunately, the combination of statin+phosphate carrier increased risk for severe myopathy. With this combination, it is prudent to avoid high doses of statins. Furthermore, clinicians should be selective in the use of combined therapy in patients at high risk. A clinical advisory reviewed selection of patients and reasonable precautions when statin therapy is used.

**Blood Pressure ≥130/85 mm Hg**

**Background**

Obesity and weight gain in middle age are positively correlated with blood pressure levels and highly related to the prevalence and incidence of hypertension in the population setting. This fact, coupled with the demonstration that reduction of blood pressure to levels ≤130/85 mm Hg in patients with diabetes and other persons at high risk of cardiovascular disease is efficacious, has led to including high blood pressure as part of the MetS. Trials and summary reports emphasized these opinions, and data from the Hypertension Optimal Treatment (HOT) study and the recommendations of the Joint National Committee on Hypertension reflect this intensive approach.

**How Do You Make the Diagnosis?**

Diagnosis is made by standard assessment of sitting blood pressure levels in subjects at rest. Persons on treatment with blood pressure medications should be considered to have satisfied the blood pressure ≥130/85 criterion even if measured blood pressure is <130/85 mm Hg.

**Treatment of Blood Pressure in the MetS**

Most of the affected persons in this setting are overweight or obese, and specific attention should be directed first toward weight loss and sodium reduction. Modest weight loss has been related to improvement in blood pressure, and general attention to co-morbid conditions is important for pharmacotherapy in this setting. Patient responses to individual pharmacological agents should be monitored, and factors other than the blood pressure response should be considered. For instance, use of diuretics has been associated with deterioration in glycemic control and the development of T2DM. Beta blockers have also been shown to be related to weight gain and T2DM in some population studies, but the long-term safety and efficacy of beta blockers and diuretics has been effectively demonstrated in many clinical trials, including the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) that included >40 000 patients.

**Impaired Fasting Glucose**

**Background**

Age, excess adiposity, genetic predisposition, inadequate physical activity, and other factors promote insulin resistance, and the reference method to assess the severity of the abnormality is an insulin clamp study. Other tests can be made without indwelling catheters, including options such as the frequently sampled intravenous glucose tolerance test, fasting insulin, and postprandial insulin levels after an oral glucose load. Each approach has advantages, but determination of insulin levels and insulin resistance is characteristic of research protocols and is not integral to regular clinical care. Higher levels of insulin in the fasting and postchallenge state in nondiabetic in-
individuals have been related to an increased risk of cardiovascular disease and later T2DM in several studies.26–30

How Do You Make the Diagnosis?
Measures of fasting glucose are important, and in the usual outpatient setting, a fasting level 110 to 126 mg/dL on 2 occasions is considered to be impaired fasting glucose according to the criteria of the American Diabetes Association, thus fulfilling one of the diagnostic criteria for the MetS. European experts included elevated fasting insulin levels in considering diagnosis of the MetS, but only fasting glucose data have been used for American criteria. The added utility of fasting insulin, postchallenge glucose and insulin levels, and glycosylated hemoglobin levels are all active areas of research but are not considered diagnostic criteria for the MetS at the present.

How Do You Treat Glucose Levels in the MetS?
Most individuals with the MetS have hyperglycemia. They may not have definite impaired fasting glucose and may happen to have elevated glucose levels after eating. An improvement in lifestyle habits and certain medications may lessen the risk of progression from impaired fasting glucose to frank T2DM, and the results of 2 clinical trials completed in the past 2 years are especially important. In the first of these trials, European investigators had patients with impaired fasting glucose follow their usual lifestyle or alter their habits to reduce fat, increase fiber, and exercise regularly. After 1 year, the subjects in the lifestyle intervention group experienced a 4.2-kg weight loss (versus 1 kg in controls), a 5-mm Hg systolic blood pressure decrement (versus 3 mm Hg controls), a 2 mg/dL increase in HDL-C (versus a 1 mg/dL increase among controls), an 18 mg/dL decrease in triglycerides (versus a 1 mg/dL decrease in controls), and an 11% rate of new T2DM over 4 years (versus 23% in controls).30 The overall 58% (23% versus 11% absolute rates) decreased risk of new T2DM was particularly striking in this investigation. The second trial was conducted in the United States and enrolled subjects with elevated fasting and postload plasma glucose levels. The study included 3 arms of therapy: lifestyle changes, metformin, and troglitazone. The troglitazone intervention was stopped early because of liver toxicity. In comparisons with placebo users, the persons who followed the lifestyle prescription experienced a 58% lower progression rate to T2DM and the metformin users had a 31% lower development of T2DM.31

Summary
The MetS as currently defined by the ATP III panel includes 5 components. The background for their inclusion in the syndrome, measurement of the factors, and the appropriate interventions are described in this review. The factors are highly interrelated, and the utility of this diagnostic entity is under critical evaluation as new and existing data are evaluated concerning the role of the syndrome in the development of cardiovascular and metabolic outcomes.

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References