ABSTRACT

A growing proportion of coronary artery disease morbidity and mortality is attributable to individuals who have diabetes or the metabolic syndrome, both of which are characterized by insulin resistance and multiple coronary risk factors. The most recent update of the National Cholesterol Education Program Adult Treatment Panel (ATP III) guidelines provides guidance in the management of coronary risk in patients who have diabetes or metabolic syndrome. The guidelines also recognize diabetes as a coronary risk equivalent, meaning that diabetic patients without coronary disease should be managed according to the same guidelines that apply to nondiabetic patients who have coronary disease. Patients with diabetes or metabolic syndrome have dyslipidemia characterized by low levels of high-density lipoprotein cholesterol and elevated triglyceride levels. Treatment of the dyslipidemia associated with diabetes and metabolic syndrome requires lifestyle changes and pharmacologic therapy, usually involving more than 1 drug.


Elevated total cholesterol and low-density lipoprotein (LDL) cholesterol are well-recognized risk factors for coronary atherosclerosis and myocardial infarction (MI). However, substantial numbers of MI patients do not have elevated cholesterol levels, but rather dyslipidemia characterized primarily by increased levels of triglycerides and low levels of high-density lipoprotein (HDL) cholesterol.

For the past several years, numerous research programs have devoted considerable attention toward identification of high-risk patients who have hypertriglyceridemia and decreased HDL levels. Clearly, diabetic patients represent 1 large group of patients with that type of dyslipoproteinemia. More recently, the same type of abnormal lipid profile has been associated with patients who have metabolic syndrome, a condition characterized by a clustering of coronary risk factors, including dyslipidemia, hypertension, and visceral obesity.

The most recent update of the National Cholesterol Education Program Adult Treatment Panel recommendations (ATP III) identified diabetes as a coronary heart disease risk equivalent. This designation means that diabetic patients without coronary disease should be managed with the same degree of clinical aggressiveness as nondiabetic individuals with documented coronary disease. The ATP III recommendations also recognize patients with the metabolic syndrome as being at high risk for coronary disease. The recommendations provide practicing physicians with criteria for identifying these high-risk patients and offer guidance for appropriate clinical management.
ATP III, Diabetes, and the Metabolic Syndrome

Diabetic patients have an increased risk for morbidity and mortality due to cardiovascular disease compared with nondiabetic patients. Diabetic patients also have multiple coronary risk factors. One particularly influential investigation of coronary disease due to diabetes showed that diabetic patients without coronary disease have a risk of MI comparable to that of nondiabetic patients who have documented coronary disease.3

Equally challenging are patients with the metabolic syndrome, many of whom eventually will develop diabetes. Over the years, the syndrome has proved difficult to define, but recent investigations have established that the condition is associated with a clustering of coronary risk factors.

Patients with the metabolic syndrome have dyslipoproteinemia characterized by 3 major traits: hypertriglyceridemia, and more specifically, increased accumulation of cholesterol-rich lipoprotein remnants; small, dense LDL; and low levels of HDL. Additionally, the metabolic syndrome is associated with insulin resistance, glucose intolerance, hypertension, and visceral obesity marked by abdominal fat accumulation. Any patient who has at least 3 of the characteristics meets the ATP III criteria for the metabolic syndrome. Though not cited by ATP III, a procoagulant state also exists in many patients with the syndrome.

Obesity appears to play a major role in the development of the metabolic syndrome. Treatment of obesity may represent the cornerstone of therapy for the metabolic syndrome, particularly given the growing prevalence of obesity in the United States and other Western nations.

In citing the metabolic syndrome as a high-risk condition, ATP III also attempted to provide physicians with easily recognized and measurable criteria to define the condition. The ATP III recommendations define abdominal obesity as a waist circumference exceeding 102 cm (40 in) in men and exceeding 88 cm (35 in) in women. Other characteristics of the metabolic syndrome include triglyceride elevations exceeding 150 mg/dL, HDL of less than 40 mg/dL in men and less than 50 mg/dL in women, blood pressure greater than 130/85 mm Hg, and glucose greater than 110 mg/dL.

Approximately 47 million Americans meet the ATP III criteria for the metabolic syndrome, according to data from the third National Health and Nutrition Examination Survey (NHANES III). The prevalence increases with age and it is found in 42% to 44% of individuals aged 60 to 69 years. As might be expected, the syndrome dramatically increases the risk of MI and cardiovascular disease in general.4

Lipoprotein Metabolism and the Metabolic Syndrome

Knowledge of the mechanisms of lipoprotein metabolism has improved substantially in recent years with recognition of the involvement of specific receptors, apoproteins, and transfer proteins. In particular, identification of 2 major transporter systems (ABC-A1 and ABC-G5/8) has provided important insight into the mechanisms by which HDL removes cholesterol from the cell, which has yet to be fully understood.

The ABC-A1 transporter facilitates movement of cholesterol from the cell into HDL. ABC-A1 moves cholesterol to the cell membrane, where it is picked up by apolipoprotein (apo)-A1 to initiate formation of nascent HDL, which is transformed into mature HDL by lecithin cholesterol acyl transferase (LCAT). Increased intracellular accumulation of cholesterol activates ABC-A1, which increases movement of cholesterol to the cell membrane and formation of nascent HDL. Lecithin cholesterol acyl transferase esterifies the cholesterol, resulting in higher levels of mature HDL. ABC-A1 represents an important target for strategies to turn on the mechanisms of cholesterol removal from peripheral cells.

The ABC-G5 and G8 transporters have key roles in metabolism of cholesterol in the gastrointestinal tract. Studies of patients with sitosterolemia, arising from defects in the G5 and G8 transporters, show that the patients have increased absorption of cholesterol and sitosterol. Normally, G5 and G8 decrease absorption of cholesterol, plant sterols, and shellfish sterols, shunt them toward the gut, and increase biliary secretion of cholesterol and plant and shellfish sterols. The ABC-G5/8 transporters
mediate selective removal of plant sterols and a portion of the cholesterol.

Advances also have occurred in the understanding of apoproteins, particularly apo-C3. Over the next few years, more information will emerge regarding the activity of C3, which is a key modulator of plasma lipoprotein metabolism. Apolipoprotein-C3 plays an especially important role in patients who have hypertriglyceridemia and low levels of HDL, which typify diabetes and the metabolic syndrome.

Apolipoprotein-C3 blocks lipoprotein lipase activity to prevent hydrolyzation of triglyceride and receptor-mediated clearance of lipoprotein particles, resulting in hypertriglyceridemia. Patients with diabetes and the metabolic syndrome have increased generation of cholesterol-rich remnants. Such patients also have higher concentrations of C3, which inhibits removal of the remnants by LDL receptor uptake mediated by lipoprotein lipase. The delayed clearance of cholesterol-rich remnants is accompanied by increased LDL oxidation. The delayed clearance of lipoprotein particles causes cholesterol-ester transfer protein to induce transfer of cholesterol from HDL into B lipoproteins, which become increasingly cholesterol rich. The rate of HDL degradation increases, leading to a fall in HDL levels.

Diabetes and the metabolic syndrome also are associated with the generation of dense LDL, which has increased susceptibility to oxidation and decreased affinity for LDL receptor. Dense LDL is more easily incorporated into the vessel wall. Other traits of dense LDL include increased concentration of C3 apoproteins, decreased apoB-mediated uptake, and an increased propensity for glycation. Dense LDL also is associated with endothelial dysfunction.

In summary, patients with diabetes or the metabolic syndrome have 3 major lipoprotein-related risks: increased concentrations of cholesterol-rich remnants; dense LDL, which is more atherogenic; and decreased levels of HDL.

**Implications for Clinical Management**

Again, ATP III not only faced a 2-fold challenge in developing recommendations to manage dyslipidemia in patients with diabetes or the metabolic syndrome, but the panel also needed to provide guidance for reducing LDL and atherogenic remnant particles. Part of the solution was to devise a better method to quantify B-containing apoproteins because LDL alone was insufficient. The challenge gave rise to the concept of non-HDL cholesterol.

Non-HDL cholesterol comprises LDL, dense LDL, and atherogenic remnant particles. Measuring LDL alone does not provide nearly as much information about the atherogenic potential of a patient's lipid profile. The ATP III recommendations introduced non-HDL cholesterol as a means of acquiring a target lipoprotein value that provides more useful information to guide the management of patients in the clinical setting.

Remnant assays are becoming commercially available, and some laboratories are beginning to offer quantitation of C3 protein as a means of providing a better assessment of atherogenic potential. Quantitation of apoB also has been proposed as a means of measuring non-HDL cholesterol, and other measurements likely will be proposed and evaluated in the near future.

The ATP III recommendations established non-HDL target values that are 30 mg/dL higher than those set for LDL. As a result, high-risk patients have a non-HDL cholesterol goal of 130 mg/dL, as compared with 100 mg/dL for LDL. For patients with intermediate and low risk, the corresponding non-HDL values are 160 mg/dL and 190 mg/dL.

The new emphasis on diabetes and the metabolic syndrome has increased the focus on strategies to raise HDL levels. Physicians currently have several options at their disposal. Statins raise HDL by 5% to 15%, fibrates by about 20%, and extended-release niacin by 15% to 35%.

The Veterans Affairs HDL Cholesterol Intervention Trial (VA-HIT) provided unequivocal evidence that treatment targeted primarily at HDL can reduce the incidence of cardiovascular endpoints in a high-risk population including many patients with diabetes and the metabolic syndrome. In that trial, treatment with a fibrate had no net effect on LDL levels, increased HDL levels by an average of 6%, and decreased triglycerides by 31%. The study established the principle that cardiovascular risk can be reduced by means other than lowering LDL.

**Summary**

A growing proportion of coronary disease morbidity and mortality can be attributed to a rise in the prevalence of diabetes and the metabolic syndrome.
Both conditions are characterized by the presence of multiple cardiovascular risk factors, and both are associated with substantially increased cardiovascular risk. The recent update of the National Cholesterol Education Program (NCEP) treatment guidelines recognize that diabetes confers a coronary risk equivalent to that of nondiabetic individuals with established coronary disease. The guidelines also identify the metabolic syndrome as a high-risk condition. The dyslipidemia of diabetes and the metabolic syndrome typically involves hypertriglyceridemia, low levels of HDL, and dense LDL particles. The NCEP guidelines recommend measurement of non-HDL cholesterol for more accurate quantitation of the lipid profile and assessment of cardiovascular risk in individuals with diabetes or the metabolic syndrome. Statins, fibrates, and extended-release niacin also have a role in the management of dyslipidemia in these high-risk patients.

REFERENCES