absorption by almost 60%, resulting in a reduction in delivery of dietary sterols in the liver and an increase in hepatic LDL receptor expression. The mean reduction in plasma LDL-C on ezetimibe (10 mg) is 18%, and the effect is additive when used in combination with a statin. Effects on TG and HDL-C levels are negligible. When used in combination with a statin, monitoring of liver transaminases is recommended. The only roles for ezetimibe in monotherapy are in patients who do not tolerate statins and in sitosterolemia.

BILE ACID SEQUESTRANTS (RESINS) Bile acid sequestrants bind bile acids in the intestine and promote their excretion rather than reabsorption in the ileum. To maintain the bile acid pool size, the liver diverts cholesterol to bile acid synthesis. The decreased hepatic intracellular cholesterol content results in upregulation of the LDL receptor and enhanced LDL clearance from the plasma. Bile acid sequestrants, including cholestyramine, colestipol, and colesevelam (Table 421-5), primarily reduce plasma LDL-C levels but can cause an increase in plasma TGs. Therefore, patients with hypertriglyceridemia generally should not be treated with bile acid–binding resins. Cholestyramine and colestipol are insoluble resins that must be suspended in liquids. Colesevelam is available as tablets but generally requires up to six to seven tablets per day for effective LDL-C lowering. Most side effects of resins are limited to the gastrointestinal tract and include bloating and constipation. Because bile acid sequestrants are not systemically absorbed, they are very safe and the cholesterol-lowering drug of choice in children and in women of childbearing age who are lactating, pregnant, or could become pregnant. They are effective in combination with statins and in combination with ezetimibe and are particularly useful with one or both of these drugs for patients with severe hypercholesterolemia or those with statin intolerance.

SPECIALIZED DRUGS FOR HOMOZYGOUS FH Two "orphan" drugs are approved specifically for the management of homozygous FH. They include a small-molecule inhibitor of MTP, called lomitapide, and an antisense oligonucleotide against apoB, called mipomersen. These drugs reduce VLDL production and LDL-C levels in homozygous FH patients. Due to their mechanism of action, each drug causes an increase in hepatic fat, the long-term consequences of which are unknown. In addition, lomitapide is associated with gastrointestinal-related side effects, and mipomersen is associated with skin reactions and flu-like symptoms.

LDL APHERESIS Patients who remain severely hypercholesterolemic despite optimally tolerated drug therapy are candidates for LDL apheresis. In this process, the patient's plasma is passed over a column that selectively removes the LDL, and the LDL-depleted plasma is returned to the patient. Patients on maximally tolerated combination drug therapy who have CHD and a plasma LDL-C level >200 mg/dL or no CHD and a plasma LDL-C level >300 mg/dL are candidates for every-other-week LDL apheresis and should be referred to a specialized lipid center.

422 The Metabolic Syndrome

Robert H. Eckel

The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus. Evolution of the criteria for the metabolic syndrome since the original definition by the World Health Organization in 1998 reflects growing clinical evidence and analysis by a variety of consensus conferences and professional organizations. The major features of the metabolic syndrome include central obesity, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, hyperglycemia, and hypertension (Table 422-1).

EPIDEMIOLOGY

The most challenging feature of the metabolic syndrome to define is waist circumference. Intraabdominal circumference (visceral adipose tissue) is considered most strongly related to insulin resistance and risk of diabetes and CVD, and for any given waist circumference the distribution of adipose tissue between SC and visceral depots varies substantially. Thus, within and between populations, there is a lesser vs. greater risk at the same waist circumference. These differences in populations are reflected in the range of waist circumferences considered to confer risk in different geographic locations (Table 422-1).

The prevalence of the metabolic syndrome varies around the world, in part reflecting the age and ethnicity of the populations studied and the diagnostic criteria applied. In general, the prevalence of the metabolic syndrome increases with age. The highest recorded prevalence worldwide is among Native Americans, with nearly 60% of women ages 45–49 and 45% of men ages 45–49 meeting the criteria of the National Cholesterol Education Program and Adult Treatment Panel III (NCEP:ATPIII). In the United States, the metabolic syndrome is less common among African-American men and more common among Mexican-American women. Based on data from the National Health and Nutrition Examination Survey (NHANES) 2003–2006, the age-adjusted prevalence of the metabolic syndrome in U.S. adults without diabetes is 28% for men and 30% for women. In France, studies of a cohort of 30- to 60-year-olds have shown a <10% prevalence for each sex, although 17.5% of people 60–64 years of age are affected. Greater global industrialization is associated with rising rates of obesity, which are expected to increase the prevalence of the metabolic syndrome dramatically, especially as the population ages. Moreover, the rising prevalence and severity of obesity among children is reflected in features of the metabolic syndrome in a younger population.

The frequency distribution of the five components of the syndrome for the U.S. population (NHANES III) is summarized in Fig. 422-1. Increases in waist circumference predominate among women, whereas increases in fasting plasma triglyceride levels (i.e., to >150 mg/dL), reductions in HDL cholesterol levels, and hyperglycemia are more likely in men.

RISK FACTORS

Overweight/Obesity Although the metabolic syndrome was first described in the early twentieth century, the worldwide overweight/obesity epidemic has recently been the force driving its increasing recognition. Central adiposity is a key feature of the syndrome, and the syndrome's prevalence reflects the strong relationship between waist circumference and increasing adiposity. However, despite the importance of obesity, patients who are of normal weight may also be insulin resistant and may have the metabolic syndrome.

Sedentary Lifestyle Physical inactivity is a predictor of CVD events and the related risk of death. Many components of the metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central), reduced HDL cholesterol, and increased triglycerides, blood pressure, and glucose in genetically susceptible persons. Compared with individuals who watch television or videos or use the computer <1 h daily, those who do so for >4 h daily have a twofold increased risk of the metabolic syndrome.

Aging The metabolic syndrome affects nearly 50% of the U.S. population older than age 50, and at >60 years of age women are more often affected than men. The age dependency of the syndrome's prevalence is seen in most populations around the world.

Diabetes Mellitus Diabetes mellitus is included in both the NCEP and the harmonizing definitions of the metabolic syndrome. It is estimated that the great majority (~75%) of patients with type 2 diabetes or impaired glucose tolerance have the metabolic syndrome. The presence of the metabolic syndrome in these populations relates to a