resistance in muscle. Insulin resistance also contributes to increased triglyceride accumulation in the liver (nonalcoholic fatty liver disease). Cytokines and FFAs also increase hepatic production of fibrinogen and adipocyte production of plasminogen activator inhibitor 1 (PAI-1), resulting in a pro-thrombotic state. Higher levels of circulating cytokines stimulate hepatic production of C-reactive protein (CRP). Reduced production of the anti-inflammatory and insulin-sensitizing cytokine adiponectin is also associated with the metabolic syndrome. *(Reproduced with permission from RH Eckel et al: The metabolic syndrome. Lancet 365:1415, 2005.)*

Leptin resistance also may be a pathophysiologic mechanism to explain the metabolic syndrome. Physiologically, leptin reduces appetite, promotes energy expenditure, and enhances insulin sensitivity when insulin resistance is associated with leptin deficiency. In addition, leptin may regulate cardiac and vascular function through a nitric oxide–dependent mechanism. However, when obesity develops, hyperleptinemia ensues, with evidence of leptin resistance in the brain and other tissues resulting in inflammation, insulin resistance, hyperlipidemia, and a plethora of cardiovascular disorders, such as hypertension, atherosclerosis, CHD, and heart failure.

The oxidative stress hypothesis provides a unifying theory for aging and the predisposition to the metabolic syndrome. In studies of insulin-resistant individuals with obesity or type 2 diabetes, the offspring of patients with type 2 diabetes, and the elderly, a defect in mitochondrial oxidative phosphorylation leads to the accumulation of triglycerides and related lipid molecules in muscle, liver, and perhaps other tissues, i.e., β-cells.

Recently, the gut microbiome has emerged as an important contributor to the development of obesity and related metabolic disorders, including inflammation and components of the metabolic syndrome. Although the mechanisms remain uncertain, interaction among genetic predisposition, diet, bile acid metabolism, and the intestinal flora is important.

Increased Waist Circumference Waist circumference is an important component of the most recent and frequently applied diagnostic criteria for the metabolic syndrome. However, measuring waist circumference does not reliably distinguish increases in SC