resistance contributes only partially to the increased prevalence of hypertension in the metabolic syndrome.

Another possible mechanism underlying hypertension in the metabolic syndrome is the vasoactive role of perivascular adipose tissue. Reactive oxygen species released by NADPH oxidase impair endothelial function and result in local vasoconstriction. Other paracrine effects could be mediated by leptin or other proinflammatory cytokines released from adipose tissue, such as tumor necrosis factor α.

Hyperuricemia is another consequence of insulin resistance and is commonly observed in the metabolic syndrome. There is growing evidence not only that uric acid is associated with hypertension but also that reduction of uric acid normalizes blood pressure in hyperuricemic adolescents with hypertension. The mechanism appears to be related to an adverse effect of uric acid on nitric acid synthase in the macula densa of the kidney and stimulation of the renin-angiotensin aldosterone system.

Proinflammatory Cytokines The increases in proinflammatory cytokines—including interleukins 1, 6, and 18; resistin; tumor necrosis factor α; and the systemic biomarker C-reactive protein—reflect overproduction by the expanded adipose tissue mass (Fig. 422-2). Adipose tissue–derived macrophages may be the primary source of proinflammatory cytokines locally and in the systemic circulation. It remains unclear, however, how much of the insulin resistance is caused by the paracrine effects of these cytokines and how much by the endocrine effects.

Adiponectin Adiponectin is an anti-inflammatory cytokine produced exclusively by adipocytes. Adiponectin enhances insulin sensitivity and inhibits many steps in the inflammatory process. In the liver, adiponectin inhibits the expression of gluconeogenic enzymes and the rate of glucose production. In muscle, adiponectin increases glucose transport and enhances fatty acid oxidation, partially through the activation of AMP kinase. Adiponectin levels are reduced in the metabolic syndrome. The relative contributions of adiponectin deficiency and overabundance of the proinflammatory cytokines are unclear.

CLINICAL FEATURES

Symptoms and Signs The metabolic syndrome typically is not associated with symptoms. On physical examination, waist circumference may be expanded and blood pressure elevated. The presence of either or both of these signs should prompt the clinician to search for other biochemical abnormalities that may be associated with the metabolic syndrome. Less frequently, lipoatrophy or acanthosis nigricans is found on examination. Because these physical findings characteristically are associated with severe insulin resistance, other components of the metabolic syndrome should be expected.

Associated Diseases • ***CARDIOVASCULAR DISEASE*** The relative risk for new-onset CVD in patients with the metabolic syndrome who do not have diabetes averages 1.5–3 fold. However, an 8-year follow-up of middle-aged participants in the Framingham Offspring Study documented that the population-attributable CVD risk in the metabolic syndrome was 34% among men and only 16% among women. In the same study, both the metabolic syndrome and diabetes predicted ischemic stroke, with greater risk among patients with the metabolic syndrome than among those with diabetes alone (19% vs. 7%) and a particularly large difference among women (27% vs. 5%). Patients with the metabolic syndrome are also at increased risk for peripheral vascular disease.

TYPE 2 DIABETES Overall, the risk for type 2 diabetes among patients with the metabolic syndrome is increased three- to fivefold. In the Framingham Offspring Study's 8-year follow-up of middle-aged participants, the population-attributable risk for developing type 2 diabetes was 62% among men and 47% among women.

Other Associated Conditions In addition to the features specifically associated with the metabolic syndrome, other metabolic alterations accompany insulin resistance. Those alterations include increases in ApoB and ApoCIII, uric acid, prothrombotic factors (fibrinogen, plasminogen activator inhibitor 1), serum viscosity, asymmetric dimethylarginine, homocysteine, white blood cell count, proinflammatory cytokines, C-reactive protein, microalbuminuria, nonalcoholic fatty liver disease and/or nonalcoholic steatohepatitis, polycystic ovary syndrome, and obstructive sleep apnea.

NONALCOHOLIC FATTY LIVER DISEASE *(SEE ALSO CHAP. 367e)* Fatty liver is a relatively common condition, affecting 25–45% of the U.S. population. However, in nonalcoholic steatohepatitis, triglyceride accumulation and inflammation coexist. Nonalcoholic steatohepatitis is now present in 3–12% of the population of the United States and other Western countries. Of patients with the metabolic syndrome, ~25–60% have nonalcoholic fatty liver disease and up to 35% have nonalcoholic steatohepatitis. As the prevalence of overweight/obesity and the metabolic syndrome increases, nonalcoholic steatohepatitis may become one of the more common causes of end-stage liver disease and hepatocellular carcinoma.

HYPERURICEMIA *(SEE ALSO CHAP. 431e)* Hyperuricemia reflects defects in insulin action on the renal tubular reabsorption of uric acid and may contribute to hypertension through its effect on the endothelium. An increase in asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, also relates to endothelial dysfunction. In addition, microalbuminuria may be caused by altered endothelial pathophysiology in the insulin-resistant state.

POLYCYSTIC OVARY SYNDROME *(SEE ALSO CHAP. 412)* Polycystic ovary syndrome is highly associated with insulin resistance (50–80%) and the metabolic syndrome, with a prevalence of the syndrome between 40% and 50%. Women with polycystic ovary syndrome are two to four times more likely to have the metabolic syndrome than are women without polycystic ovary syndrome.

OBSTRUCTIVE SLEEP APNEA *(SEE ALSO CHAP. 38)* Obstructive sleep apnea is commonly associated with obesity, hypertension, increased circulating cytokines, impaired glucose tolerance, and insulin resistance. With these associations, it is not surprising that individuals with obstructive sleep apnea frequently have the metabolic syndrome. Moreover, when biomarkers of insulin resistance are compared between patients with obstructive sleep apnea and weight-matched controls, insulin resistance is found to be more severe in those with apnea. Continuous positive airway pressure treatment improves insulin sensitivity in patients with obstructive sleep apnea.

DIAGNOSIS

The diagnosis of the metabolic syndrome relies on fulfillment of the criteria listed in Table 422-1, as assessed using tools at the bedside and in the laboratory. The medical history should include evaluation of symptoms for obstructive sleep apnea in all patients and polycystic ovary syndrome in premenopausal women. Family history will help determine risk for CVD and diabetes mellitus. Blood pressure and waist circumference measurements provide information necessary for the diagnosis.

Laboratory Tests Measurement of fasting lipids and glucose is needed in determining whether the metabolic syndrome is present. The measurement of additional biomarkers associated with insulin resistance can be individualized. Such tests might include those for ApoB, high-sensitivity C-reactive protein, fibrinogen, uric acid, urinary microalbumin, and liver function. A sleep study should be performed if symptoms of obstructive sleep apnea are present. If polycystic ovary syndrome is suspected on the basis of clinical features and anovulation, testosterone, luteinizing hormone, and follicle-stimulating hormone should be measured.

TREATMENT THE METABOLIC SYNDROME

LIFESTYLE *(SEE ALSO CHAP. 416)*

Obesity is the driving force behind the metabolic syndrome. Thus, weight reduction is the primary approach to the disorder. With weight reduction, improvement in insulin sensitivity is often accompanied by favorable modifications in many components of the