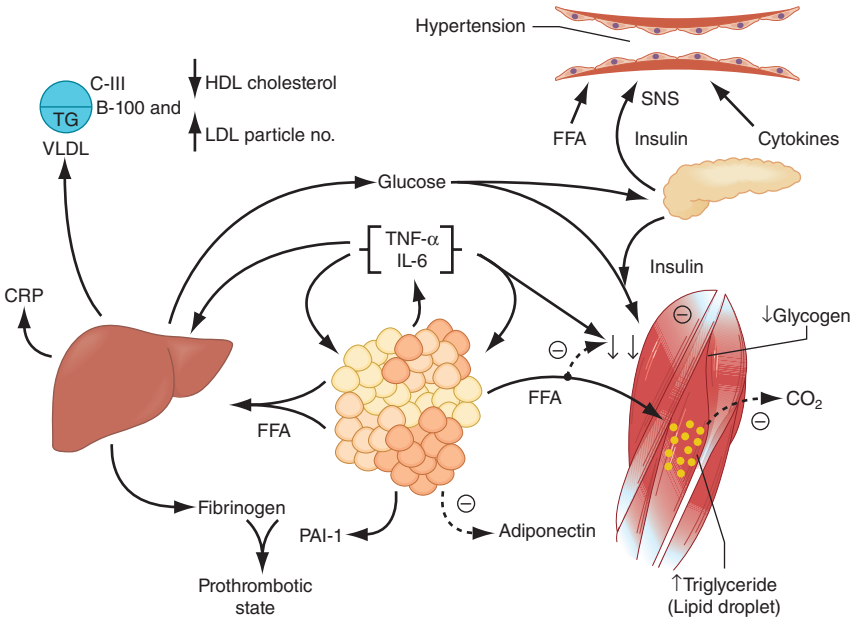

FIGURE 422-2 Pathophysiology of the metabolic syndrome. Free fatty acids (FFAs) are released in abundance from an expanded adipose tissue mass. In the liver, FFAs result in increased production of glucose and triglycerides and secretion of very low density lipoproteins (VLDLs). Associated lipid/lipoprotein abnormalities include reductions in high-density lipoprotein (HDL) cholesterol and an increased low-density lipoprotein (LDL) particle number (no.). FFAs also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation in triglyceride (TG). The increase in circulating glucose, and to some extent FFAs, increases pancreatic insulin secretion, resulting in hyperinsulinemia. Hyperinsulinemia may result in enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity and contribute to hypertension, as might higher levels of circulating FFAs. The proinflammatory state is superimposed and contributory to the insulin resistance produced by excessive FFAs. The enhanced secretion of interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) produced by adipocytes and monocyte-derived macrophages results in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating FFAs. IL-6 and other cytokines also enhance hepatic glucose production, VLDL production by the liver, hypertension and insulin resistance in muscle. Cytokines and FFAs also increase hepatic production of fibrinogen and adipocyte production of plasminogen activator inhibitor 1 (PAI-1), resulting in a prothrombotic 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. *(Modified from RH Eckel et al: Lancet 365:1415, 2005.)*

uncertain, interaction among genetic predisposition, diet, 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 adipose tissue from those in visceral fat; this distinction requires CT or MRI. With increases in visceral adipose tissue, adipose tissue–derived free fatty acids are directed to the liver. In contrast, increases in abdominal SC fat release lipolysis products into the systemic circulation and avert more direct effects on hepatic metabolism. Relative increases in visceral versus SC adipose tissue with increasing waist circumference in Asians and Asian Indians may explain the greater prevalence of the syndrome in those populations than in African-American men, in whom SC fat predominates. It is also possible that visceral fat is a marker for—but not the source of—excess postprandial free fatty acids in obesity.

Dyslipidemia (See also Chap. 421) In general, free fatty acid flux to the liver is associated with increased production of ApoB-containing, triglyceride-rich, very low-density lipoproteins (VLDLs). The effect of insulin on this process is complex, but *hypertriglyceridemia* is an excellent marker of the insulin-resistant condition. Not only is hypertriglyceridemia a feature of the metabolic syndrome, but patients with the metabolic syndrome have elevated levels of ApoCIII carried on VLDLs and other lipoproteins. This increase in ApoCIII is inhibitory to lipoprotein lipase, further contributing to hypertriglyceridemia and also associated with more atherosclerotic cardiovascular disease.

The other major lipoprotein disturbance in the metabolic syndrome is a *reduction in HDL cholesterol*. This reduction is a consequence of changes in HDL composition and metabolism. In the presence of hypertriglyceridemia, a decrease in the cholesterol content of HDL is a consequence of reduced cholesteryl ester content of the lipoprotein core in combination with cholesteryl ester transfer protein–mediated alterations in triglyceride that make the particle small and dense. This change in lipoprotein composition also results in increased clearance of HDL from the circulation. These changes in HDL have a relationship to insulin resistance that is probably indirect, occurring in concert with the changes in triglyceride-rich lipoprotein metabolism.

In addition to HDLs, low-density lipoproteins (LDLs) are modified in composition in the metabolic syndrome. With fasting serum triglycerides at >2.0 mM (~180 mg/dL), there is almost always a predominance of small, dense LDLs, which are thought to be more atherogenic although their association with hypertriglyceridemia and low HDLs make their independent contribution to CVD events difficult to assess. Individuals with hypertriglyceridemia often have increases in cholesterol content of both VLDL1 and VLDL2 subfractions and in LDL particle number. Both of these lipoprotein changes may contribute to atherogenic risk in patients with the metabolic syndrome.

Glucose Intolerance (See also Chap. 417) Defects in insulin action in the metabolic syndrome lead to impaired suppression of glucose production by the liver and kidney and reduced glucose uptake and metabolism in insulin-sensitive tissues—i.e., muscle and adipose tissue. The relationship between impaired fasting glucose or impaired glucose tolerance and insulin resistance is well supported by studies of humans, nonhuman primates, and rodents. To compensate for defects in insulin action, insulin secretion and/or clearance must be modified so that euglycemia is sustained. Ultimately, this compensatory mechanism fails, usually because of defects in insulin secretion, resulting in progression from impaired fasting glucose and/or impaired glucose tolerance to diabetes mellitus.

Hypertension The relationship between insulin resistance and hypertension is well established. Paradoxically, under normal physiologic conditions, insulin is a vasodilator with secondary effects on sodium reabsorption in the kidney. However, in the setting of insulin resistance, the vasodilatory effect of insulin is lost but the renal effect on sodium reabsorption is preserved. Sodium reabsorption is increased in whites with the metabolic syndrome but not in Africans or Asians. Insulin also increases the activity of the sympathetic nervous system, an effect that may be preserved in the setting of insulin resistance. Insulin resistance is characterized by pathway-specific impairment in phosphatidylinositol-3-kinase signaling. In the endothelium, this impairment may cause an imbalance between the production of nitric oxide and the secretion of endothelin 1, with a consequent decrease in blood flow. Although these mechanisms are provocative, evaluation of insulin action by measurement of fasting insulin levels or by homeostasis model assessment shows that insulin