surface (Fig. 24-30). In fact, one of the mechanisms by which exercise can improve insulin sensitivity is through increased translocation of GLUT-4 to the surface of skeletal muscle cells.

Obesity and Insulin Resistance. Multiple factors contribute to insulin resistance, of which obesity is probably the most important. The risk for diabetes increases as the body mass index (a measure of body fat content) increases. It is not only the absolute amount but also the distribution of body fat that has an effect on insulin sensitivity: central obesity (abdominal fat) is more likely to be linked with insulin resistance than are peripheral (gluteal/subcutaneous) fat depots.

Obesity can adversely impact insulin sensitivity in numerous ways (Fig. 24-32):

- *Free fatty acids (FFAs).* Cross-sectional studies have demonstrated an inverse correlation between fasting plasma FFAs and insulin sensitivity. Central adipose tissue is more "lipolytic" than peripheral sites, which might explain the particularly deleterious consequences of this pattern of fat distribution. Excess FFAs overwhelm the intracellular fatty acid oxidation pathways, leading to accumulation of cytoplasmic intermediates like diacylglycerol (DAG). These "toxic" intermediates can attenuate signaling through the insulin receptor pathway. In liver cells, insulin normally inhibits gluconeogenesis by blocking the activity of phosphoenolpyruvate carboxykinase, the first enzymatic step in this process. Attenuated insulin signaling allows phosphoenolpyruvate carboxykinase to "ramp up" gluconeogenesis. Excess FFAs also compete with glucose for substrate oxidation, leading to feedback inhibition of glycolytic enzymes, thereby further exacerbating the existing glucose imbalance.
- *Adipokines.* You will recall that adipose tissue is not merely a passive storage depot for fat but is a functional endocrine organ that releases hormones in response to changes in metabolic status (Chapter 9). A variety of proteins secreted into the systemic circulation by adipose tissue have been identified, and these are collectively termed *adipokines* (or adipose cytokines). Some of these promote hyperglycemia, and other adipokines (such as leptin and adiponectin) decrease blood glucose, in part by increasing insulin sensitivity in peripheral tissues. Adiponectin levels are reduced in obesity, thus contributing to insulin resistance.
- *Inflammation:* Over the past several years, inflammation has emerged as an important factor in the pathogenesis of type 2 diabetes. It is now known that an inflammatory milieu—mediated not by an autoimmune process such as type 1 diabetes but rather by proinflammatory cytokines that are secreted in response to excess nutrients such as free fatty acid (FFAs) and glucose—results in both insulin resistance and β-cell dysfunction. Excess FFAs within macrophages and β cells can activate the inflammasome, a multiprotein cytoplasmic complex that leads to secretion of the cytokine interleukin IL-1β (Chapter 3). IL-1β, in turn, mediates the secretion of additional pro-inflammatory cytokines from macrophages, islet cells, and other cells. IL-1 and other cytokines are released into the circulation and act on the major sites of insulin action to promote insulin resistance. Thus, excess FFAs can impede insulin signaling directly within peripheral tissues, as well as indirectly through the release of pro-inflammatory cytokines.

β-Cell Dysfunction

While insulin resistance by itself can lead to impaired glucose tolerance, **β-cell dysfunction is virtually a requirement for the development of overt diabetes**. In contrast to the severe genetic defects in β-cell function that occur in monogenic forms of diabetes (see later), β-cell function actually increases early in the disease process in most patients with "sporadic" type 2 diabetes, mainly as a compensatory measure to counter insulin resistance and maintain euglycemia. Eventually, however, β cells seemingly exhaust their capacity to adapt to the long-term demands of peripheral insulin resistance, and the hyperinsulinemic state gives way to a state of relative insulin deficiency.

Several mechanisms have been implicated in promoting β-cell dysfunction in type 2 diabetes, including:

- Excess free fatty acids that compromise β cell function and attenuate insulin release ("*lipotoxicity*")
- The impact of chronic hyperglycemia ("*glucotoxicity*")
- An abnormal "*incretin effect,*" leading to reduced secretion of GIP and GLP-1, hormones that promote insulin release (see earlier)
- Amyloid deposition within islets. This is a characteristic finding in individuals with long-standing type 2 diabetes, being present in more than 90% of diabetic islets examined, but it is unclear whether it is a cause or an effect of β-cell "burnout."
- Finally, the impact of genetics cannot be discounted, as many of the polymorphisms associated with an increased lifetime risk for type 2 diabetes occur in genes that control insulin secretion (see earlier).

Monogenic Forms of Diabetes

Although genetically defined causes of diabetes are uncommon, they have been intensively studied in the hope of gaining insights into the disease. As Table 24-6 illustrates, monogenic forms of diabetes are classified separately from types 1 and 2. These forms of diabetes result from either a primary defect in β-cell function or a defect in insulin receptor signaling (described later).

Genetic Defects in β-Cell Function. Approximately 1% to 2% of patients with diabetes harbor a primary defect in β-cell function that occurs without β-cell loss, affecting either β-cell mass and/or insulin production. This form of monogenic diabetes is caused by a heterogeneous group of genetic defects. The largest subgroup of patients in this category was traditionally designated as having "maturity-onset diabetes of the young" (MODY) because of its superficial resemblance to type 2 diabetes and its occurrence in younger patients. MODY can result from germline loss-of-function mutations in one of six genes (Table 24-6), of which mutations of *glucokinase* (*GCK*) are the most common. Glucokinase is a rate limiting step in oxidative glucose metabolism, which in turn, is coupled to insulin secretion within islet β cells (Fig. 24-28). Other rare genetic causes for primary defects in β cell function include mutations of