A role for antibodies in type 1 diabetes is suspected because of the observation that autoantibodies against islet antigens are found in the vast majority of patients with type 1 diabetes, as well as in asymptomatic family members at risk for progression to overt disease; in fact, the presence of islet cell antibodies is used as a predictive marker for the disease. However, it is not clear if the autoantibodies cause injury or are merely produced as a consequence of islet injury.

Pathogenesis of Type 2 Diabetes Mellitus

Type 2 diabetes is a complex disease that involves an interplay of genetic and environmental factors and a pro-inflammatory state. Unlike type 1 diabetes, there is no evidence of an autoimmune basis.

Genetic Factors

Genetic susceptibility contributes to the pathogenesis, as evidenced by the disease concordance rate of greater than 90% in monozygotic twins. Furthermore, first-degree relatives have 5- to 10-fold higher risk of developing type 2 diabetes than those without a family history, when matched for age and weight. Genome-wide association studies (GWAS) performed over the last decade have identified at least 30 loci that individually confer a minimal to modest increase in the lifetime risk for type 2 diabetes. The detailed description of these susceptibility loci is beyond the scope of this chapter, although many of the polymorphisms identified are in genes associated with *insulin secretion*. Elucidating the biochemical mechanisms through which these and other linked genes contribute to diabetes pathogenesis is a work in progress.

Environmental Factors

The most important environmental risk factor for type 2 diabetes is obesity, particularly central or visceral obesity. Greater than 80% of individuals with type 2 diabetes are obese, and the incidence of diabetes worldwide has risen in proportion to obesity. Obesity contributes to the cardinal metabolic abnormalities of diabetes (see later) and to insulin resistance early in disease. In fact, even modest weight loss through dietary modifications can reduce insulin resistance and improve glucose tolerance. A sedentary lifestyle (typified by lack of exercise) is another risk factor for diabetes, independent of obesity. Weight loss and exercise usually have additive effects on improving insulin sensitivity and are often the first non-pharmacological measures attempted in patients with milder type 2 diabetes.

Metabolic Defects in Diabetes

The two cardinal metabolic defects that characterize type 2 diabetes are:

- Decreased response of peripheral tissues, especially skeletal muscle, adipose tissue, and liver, to insulin (**insulin resistance**)
- Inadequate insulin secretion in the face of insulin resistance and hyperglycemia (**β-cell dysfunction**)

Insulin resistance predates the development of hyperglycemia and is usually accompanied by compensatory β-cell hyperfunction and hyperinsulinemia in the early stages of the evolution of diabetes (Fig. 24-32). Over time, the inability of β cells to adapt to increasing secretory needs for maintaining a euglycemic state results in chronic hyperglycemia and the resulting long-standing complications of diabetes.

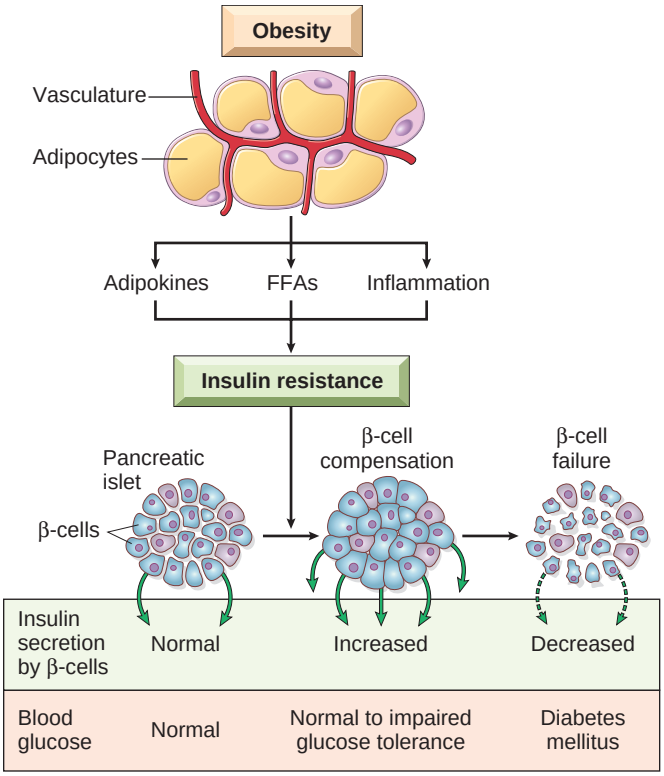

Figure 24-32 Development of type 2 diabetes. Insulin resistance associated with obesity is induced by adipokines, free fatty acids, and chronic inflammation in adipose tissue. Pancreatic β cells compensate for insulin resistance by hypersecretion of insulin. However, at some point, β-cell compensation is followed by β-cell failure, and diabetes ensues. (Reproduced with permission from Kasuga M: Insulin resistance and pancreatic β-cell failure. J Clin Invest 116:1756, 2006.)

Insulin Resistance

Insulin resistance is the failure of target tissues to respond normally to insulin. The liver, skeletal muscle and adipose tissue are the major tissues where insulin resistance manifests in abnormal glucose tolerance. Insulin resistance results in:

- Failure to inhibit endogenous glucose production (gluconeogenesis) in the liver, which contributes to high fasting blood glucose levels
- Failure of glucose uptake and glycogen synthesis to occur in skeletal muscle following a meal, which contributes to high post-prandial blood glucose level
- Failure to inhibit lipoprotein lipase in adipose tissue, leading to excess circulating free fatty acids (FFAs), which in turn, amplify the state of insulin resistance

A variety of functional defects have been reported in the insulin signaling pathway in states of insulin resistance. For example, reduced tyrosine phosphorylation of the insulin receptor and IRS proteins is observed in peripheral tissues, which compromises insulin signaling and reduces the level of the glucose transporter GLUT-4 on the cell

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