with additional factors such as obesity and family history compounding the risk. In addition, individuals with prediabetes also harbor a significant risk for cardiovascular complications.

Classification

Although all forms of diabetes mellitus share hyperglycemia as a common feature, the underlying abnormalities involved in the development of hyperglycemia vary widely. The previous classification schemes of diabetes mellitus were based on the age at onset of the disease or on the mode of therapy; in contrast, the current etiologic classification reflects our greater understanding of the pathogenesis of each variant (Table 24-6). The vast majority of cases of diabetes fall into one of two broad classes:

- ***Type 1 diabetes*** **is an autoimmune disease characterized by pancreatic β cell destruction and an absolute deficiency of insulin**. It accounts for approximately 5% to 10% of all cases, and is the most common subtype diagnosed in patients younger than 20 years of age.
- ***Type 2 diabetes*** **is caused by a combination of peripheral resistance to insulin action and an inadequate secretory response by the pancreatic β cells ("relative insulin deficiency").** Approximately 90% to 95% of diabetic patients have type 2 diabetes, and the vast majority of such individuals are overweight. Although classically considered "adult-onset," the prevalence of type 2 diabetes in children and adolescents has been increasing at an alarming pace due to the increasing rates of obesity in these age groups. One piece of encouraging news is that the incidence of obesity in the U.S. in children ages 2-5 years fell by over 40% during the period of 2004 to 2012, a tipping of the scales that may signal a reversal of a troubling trend.

The important similarities and differences between types 1 and 2 diabetes are summarized in Table 24-7.

A variety of monogenic and secondary causes are responsible for the remaining cases (discussed later). It should be stressed that while the major types of diabetes have different pathogenic mechanisms, the long-term complications affecting the kidneys, eyes, nerves, and blood vessels are the same, as are the principal causes of morbidity and death. The pathogenesis of the two major types is discussed separately. We will first briefly review normal insulin secretion and the mechanism of insulin action since these are critical to understanding the pathogenesis of diabetes.

Glucose Homeostasis

Normal glucose homeostasis is tightly regulated by three interrelated processes: glucose production in the liver; glucose uptake and utilization by peripheral tissues, chiefly skeletal muscle; and actions of insulin and counterregulatory hormones, including glucagon, on glucose uptake and metabolism.

Insulin and glucagon have opposing regulatory effects on glucose homeostasis. During fasting states, low insulin and high glucagon levels facilitate hepatic gluconeogenesis and glycogenolysis (glycogen breakdown) while decreasing glycogen synthesis, thereby preventing hypoglycemia.

Table 24-6 Classification of Diabetes Mellitus

Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
Immune-mediated
Idiopathic
Type 2 diabetes (combination of insulin resistance and β-cell dysfunction)
Genetic defects of β-cell function
Maturity-onset diabetes of the young (MODY), caused by mutations in:
Hepatocyte nuclear factor 4α (*HNF4A*), MODY1
Glucokinase (*GCK*), MODY2
Hepatocyte nuclear factor 1α (*HNF1A*), MODY3
Pancreatic and duodenal homeobox 1 (*PDX1*), MODY4
Hepatocyte nuclear factor 1β (*HNF1B*), MODY5
Neurogenic differentiation factor 1 (*NEUROD1*), MODY6
Neonatal diabetes (activating mutations in *KCNJ11* and *ABCC8*, encoding Kir6.2 and SUR1, respectively)
Maternally inherited diabetes and deafness (MIDD) due to mitochondrial DNA mutations (m.3243A→G)
Defects in proinsulin conversion
Insulin gene mutations
Genetic defects in insulin action
Type A insulin resistance
Lipoatrophic diabetes
Exocrine pancreatic defects
Chronic pancreatitis
Pancreatectomy/trauma
Neoplasia
Cystic fibrosis
Hemochromatosis
Fibrocalculous pancreatopathy
Endocrinopathies
Acromegaly
Cushing syndrome
Hyperthyroidism
Pheochromocytoma
Glucagonoma
Infections
Cytomegalovirus
Coxsackie B virus
Congenital rubella
Drugs
Glucocorticoids
Thyroid hormone
Interferon-α
Protease inhibitors
β-adrenergic agonists
Thiazides
Nicotinic acid
Phenytoin (Dilantin)
Vacor
Genetic syndromes associated with diabetes
Down syndrome
Klinefelter syndrome
Turner syndrome
Prader-Willi syndrome
Gestational diabetes mellitus

American Diabetes Association: Position statement from the American Diabetes Association on the diagnosis and classification of diabetes mellitus. Diabetes Care 31 (Suppl. 1): S55-S60, 2008.