417 Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology

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Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. In the United States, DM is the leading cause of end-stage renal disease (ESRD), nontraumatic lower extremity amputations, and adult blindness. It also predisposes to cardiovascular diseases. With an increasing incidence worldwide, DM will be likely a leading cause of morbidity and mortality in the future.

CLASSIFICATION

DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy (Fig. 417-1). There are two broad categories of DM, designated type 1 and type 2 (Table 417-1). However, there is increasing recognition of other forms of diabetes in which the pathogenesis is better understood. These other forms of diabetes may share features of type 1 and/or type 2 DM. Both type 1 and type 2 DM are preceded by a phase of abnormal glucose homeostasis as the pathogenic processes progress. Type 1 DM is the result of complete or near-total insulin deficiency. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM and have important potential therapeutic implications now that pharmacologic agents are available to target specific metabolic derangements. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

Two features of the current classification of DM merit emphasis from previous classifications. First, the terms *insulin-dependent diabetes mellitus* (IDDM) and *non-insulin-dependent diabetes mellitus* (NIDDM) are obsolete. Because many individuals with type 2 DM eventually require insulin treatment for control of

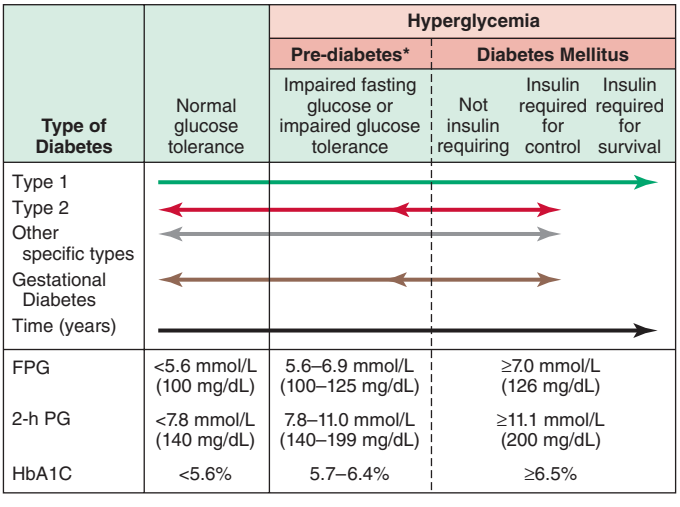

FIGURE 417-1 Spectrum of glucose homeostasis and diabetes mellitus (DM). The spectrum from normal glucose tolerance to diabetes in type 1 DM, type 2 DM, other specific types of diabetes, and gestational DM is shown from left to right. In most types of DM, the individual traverses from normal glucose tolerance to impaired glucose tolerance to overt diabetes (these should be viewed not as abrupt categories but as a spectrum). *Arrows* indicate that changes in glucose tolerance may be bidirectional in some types of diabetes. For example, individuals with type 2 DM may return to the impaired glucose tolerance category with weight loss; in gestational DM, diabetes may revert to impaired glucose tolerance or even normal glucose tolerance after delivery. The fasting plasma glucose (FPG), the 2-h plasma glucose (PG) after a glucose challenge, and the hemoglobin A_{1c} (HbA_{1c}) for the different categories of glucose tolerance are shown at the lower part of the figure. These values do not apply to the diagnosis of gestational DM. Some types of DM may or may not require insulin for survival. *Some use the term *increased risk for diabetes* or *intermediate hyperglycemia* (World Health Organization) rather than *prediabetes*. *(Adapted from the American Diabetes Association, 2014.)*

TABLE 417-1 ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

I. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)
   - A. Immune-mediated
   - B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Other specific types of diabetes
   - A. Genetic defects of beta cell development or function characterized by mutations in:
     1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)
     2. Glucokinase (MODY 2)
     3. HNF-1α (MODY 3)
     4. Insulin promoter factor-1 (IPF-1; MODY 4)
     5. HNF-1β (MODY 5)
     6. NeuroD1 (MODY 6)
     7. Mitochondrial DNA
     8. Subunits of ATP-sensitive potassium channel
     9. Proinsulin or insulin
     10. Other pancreatic islet regulators/proteins such as *KLF11, PAX4, BLK, GATA4, GATA6, SLC2A2* (GLUT2), *RFX6, GLIS3*
   - B. Genetic defects in insulin action
     1. Type A insulin resistance
     2. Leprechaunism
     3. Rabson-Mendenhall syndrome
     4. Lipodystrophy syndromes
   - C. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase
   - D. Endocrinopathies—acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma
   - E. Drug- or chemical-induced—glucocorticoids, vacor (a rodenticide), pentamidine, nicotinic acid, diazoxide, β-adrenergic agonists, thiazides, calcineurin and mTOR inhibitors, hydantoins, asparaginase, α-interferon, protease inhibitors, antipsychotics (atypicals and others), epinephrine
   - F. Infections—congenital rubella, cytomegalovirus, coxsackievirus
   - G. Uncommon forms of immune-mediated diabetes—"stiff-person" syndrome, anti-insulin receptor antibodies
   - H. Other genetic syndromes sometimes associated with diabetes—Wolfram's syndrome, Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome

IV. Gestational diabetes mellitus (GDM)

Abbreviation: MODY, maturity-onset diabetes of the young.

Source: Adapted from American Diabetes Association: Diabetes Care 37(Suppl 1):S14, 2014.