CHAPTER 1

DIABETES MELLITUS: CLASSIFICATION, ETIOLOGY, AND PATHOGENESIS

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1. What are the diagnostic criteria for diabetes mellitus and prediabetes?

Table 1.1 lists the diagnostic criteria for diabetes mellitus. In the absence of unequivocal hyperglycemia, the diagnosis requires two abnormal test results from the same sample or from two separate samples. If the test results are discordant, the abnormal one should be repeated. If the A1c is discordant, consider the presence of a hemoglobinopathy.

2. How common is diabetes mellitus?

Diabetes mellitus affected approximately 30 million people in the United States in 2020; prediabetes affected nearly 84 million. The prevalence was highest among those of Native American and Native Alaskan descent (~15%) and lowest among non-Hispanic Caucasians.

3. What are the different types of diabetes mellitus?

The most common types are type 1 diabetes and type 2 diabetes. Less common types include latent autoimmune diabetes in adults (LADA), pancreatic diabetes (type 3c), ketosis-prone type 2 diabetes, posttransplant diabetes, and maturity-onset diabetes of the young (MODY). Diabetes can also occur secondary to other diseases, such as Cushing's syndrome, acromegaly, glucagonoma, and pheochromocytoma.

Hyperglycemia or diabetes can also result from the use of medications, especially glucocorticoids, atypical antipsychotic drugs, statins, tyrosine kinase/vascular endothelial growth factor (VEGF) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, anaplastic lymphoma kinase (ALK) inhibitors, *BCR-ABL* inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors, and immune checkpoint inhibitors (especially programmed cell death protein 1 [PD-1] and programmed cell death protein 1 ligand [PD-L1] inhibitors). Most drug-induced hyperglycemia resembles or is type 2 diabetes, whereas immune checkpoint inhibitors more often cause what appears to be autoimmune or type 1 diabetes.

4. What is type 1 diabetes mellitus? What is the etiology and pathogenesis?

Type 1 diabetes mellitus is an autoimmune disease in which the immune system destroys pancreatic beta cells, causing absolute insulin deficiency. The disorder results from a genetic predisposition with a superimposed precipitating cause or event. The concordance for type 1 diabetes among identical twins is 30% to 70%, whereas the risk for a nonidentical twin or nontwin sibling of an affected person is 6% to 7%, and the risk for children of a parent with diabetes is 1% to 9%. Roughly 50% of the heritability can be linked to specific human leukocyte antigen (HLA) haplotypes (DR3 and DR4-DQ8), but over 60 non-HLA genes (mostly immune system genes) have also been associated with the risk for type 1 diabetes. Precipitating events that trigger the development of diabetes in genetically predisposed individuals are largely unknown; leading theories include diet in infancy, viral infections (especially enteroviruses), and alterations of the intestinal microbiome.

5. Describe the development of type 1 diabetes mellitus.

Type 1 diabetes develops in stages, starting with the appearance of islet-cell antibodies, followed by progressive loss of beta-cell mass and function. Type 1 diabetes is often diagnosed clinically when there has been a loss of at least 80% of beta-cell mass. Fig. 1.1 depicts the events occurring during the development of type 1 diabetes mellitus.

6. What tests are best to establish a diagnosis of type 1 diabetes mellitus?

Once diabetes is diagnosed according to the criteria outlined previously, identifying type 1 diabetes as the cause is best done by measuring serum C-peptide and two or more islet-cell autoantibodies. C-peptide is a breakdown product of proinsulin that is cosecreted with insulin and that serves as a marker of endogenous insulin secretion; C-peptide levels are low (for the ambient glucose level) or undetectable in people with type 1 diabetes. The islet-cell autoantibodies that are most commonly positive include antibodies to glutamine acid decarboxylase (GAD), insulin, islet antigen-2 (IA-2), and zinc transporter 8 (ZnT8). The presence of these antibodies can also predict the eventual development of type 1 diabetes in family members of an affected person. Those with only a single positive antibody often do not develop type 1 diabetes, but the presence of two or more positive antibodies in children confers an 84% risk of developing type 1 diabetes by adulthood.

Table 1.1 Diagnostic Criteria for Diabetes Mellitus

	DIABETES MELLITUS
Fasting plasma glucose	≥126 mg/dL (7.0 mmol/L)
2-hour plasma glucose[a]	≥200 mg/dL (11.1 mmol/L)
Hemoglobin A1c[b]	≥6.5% (48 mmol/mol)
Random plasma glucose	≥200 mg/dL (11.1 mmol/L) in a patient with symptoms of hyperglycemia or hyperglycemic crisis

[a]Two-hour oral glucose tolerance test: 75 g anhydrous glucose in water.
[b]Hemoglobin A1c: use a method certified by National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT).

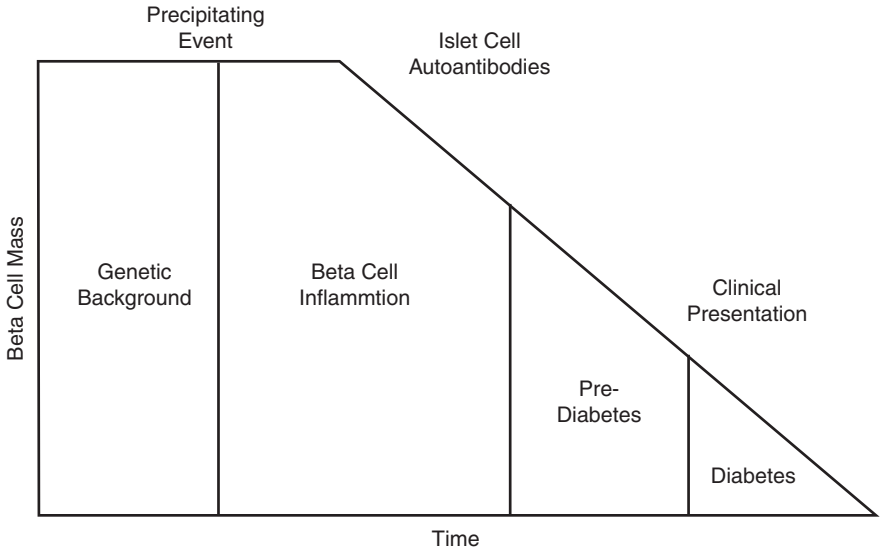

Fig. 1.1 Development of type 1 diabetes mellitus. (Redrawn from Eisenbarth GS. Type 1 diabetes mellitus. A chronic autoimmune disease. *N Engl J Med.* 1986;314:1360-1368.)

7. What is type 2 diabetes mellitus? What are the etiology and pathogenesis?

Type 2 diabetes mellitus has an even stronger genetic predisposition (~90% concordance rate for identical twins) but is clearly polygenic, and the highest-risk genes are still poorly defined. On this genetic background, superimposed acquired factors such as obesity, stress, pregnancy, and glucocorticoid use can precipitate the development of type 2 diabetes. The pathogenesis of type 2 diabetes is multifactorial and complex. The classical triad includes insulin resistance in the liver (excess hepatic glucose production), insulin resistance in muscle (impaired glucose uptake), and progressive beta-cell failure (relative insulin deficiency). The "ominous octet," described by Dr. Ralph DeFronzo in the 2009 Banting Lecture, added five additional abnormalities: fat cells (increased lipolysis), gastrointestinal tract (incretin hormone deficiency), pancreatic alpha cells (hyperglucagonemia), kidneys (increased glucose reabsorption), and brain (insulin resistance). Many of these defects are present, to a greater or lesser degree, in people with prediabetes and in nondiabetic people with a strong family history of type 2 diabetes.

8. Explain a recent classification suggesting that there are five main types of diabetes mellitus.

Using six variables (GAD antibodies, age, body mass index [BMI], A1c, homeostatic model assessment [HOMA] insulin sensitivity, HOMA beta-cell function), a recent data-driven cluster analysis identified five diabetes clusters, which are shown in Table 1.2. Whereas the traditional classification of diabetes into type 1 and type 2 has a

Table 1.2 Proposed Classification of Diabetes Into Five Distinct Clusters

Cluster 1 (severe autoimmune diabetes [SAID]): early onset, low BMI, poor control, insulin deficiency, GAD antibodies positive.
Cluster 2 (severe insulin-deficient diabetes [SIDD]): similar to cluster 1, but GAD antibodies negative.
Cluster 3 (severe insulin-resistant diabetes [SIRD]): high BMI and insulin resistance.
Cluster 4 (mild obesity-related diabetes [MOD]): high BMI but no insulin resistance.
Cluster 5 (mild age-related diabetes [MARD]): similar to cluster 4, but higher age and more modest metabolic derangements.

BMI, body mass index; *GAD*, glutamine acid decarboxylase.

Table 1.3 Diagnostic Criteria for Prediabetes

	PREDIABETES
Fasting plasma glucose	100–125 mg/dL (5.6–6.9 mmol/L)
2-hour plasma glucose[a]	140–199 mg/dL (7.8–11.0 mmol/L)
Hemoglobin A1c[b]	5.7%–6.4% (39–47 mmol/mol)

[a]Two-hour oral glucose tolerance test: 75 g anhydrous glucose in water.
[b]Hemoglobin A1c: use a method certified by National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT).

distribution of approximately 94% type 2 and 6% type 1 diabetes, this proposed classification suggests a distribution of 7.6% in cluster 1, 14.6% in cluster 2, 15.2% in cluster 3, 21% in cluster 4, and 41.7% in cluster 5.

9. What is prediabetes?

Prediabetes is the precursor to overt diabetes. The diagnostic criteria for prediabetes are shown in Table 1.3. Approximately 11% of people with prediabetes develop overt diabetes each year. People with polycystic ovary syndrome (PCOS), a history of gestational diabetes mellitus (GDM), and a history of steroid-induced hyperglycemia are also at high risk of eventually developing type 2 diabetes mellitus. A structured education program about diabetes and lifestyle modification (diet, exercise, weight loss) has been consistently and unequivocally effective in preventing the progression of prediabetes to diabetes. This approach is strongly endorsed in the Standards of Medical Care in Diabetes of the American Diabetes Association.

10. What is latent autoimmune diabetes of adults (LADA)?

LADA is autoimmune beta-cell destruction that occurs later in life, causing diabetes but often with some minimal residual beta-cell function. The diagnostic criteria are vague but include age >30 years, positive islet-cell antibodies, and significant beta-cell destruction but with some persistent insulin secretion that may allow patients to avoid insulin treatment for more than 6 months. Some experts consider this to be just one end of the spectrum of type 1 diabetes and not really a distinct entity. These authors agree with that view.

11. What is ketosis-prone type 2 diabetes mellitus?

Ketosis-prone type 2 diabetes mellitus often presents with diabetic ketoacidosis (DKA) as a result of a severe but reversible beta-cell (insulin) deficiency and partially reversible insulin resistance. Insulin therapy is required to treat DKA and to control hyperglycemia immediately after DKA but can eventually be stopped and replaced by more typical type 2 diabetes medications in most patients. Nonetheless, DKA can be recurrent. Islet-cell antibodies are absent, and the insulin secretory defect is transient. Insulin resistance is also reversible and may be partially attributable to initial glucose toxicity. This is likely just part of the spectrum of type 2 diabetes. Other names for this condition include *atypical type 2 diabetes, type 1.5 diabetes*, and *Flatbush diabetes*.

12. What is posttransplant diabetes mellitus?

Posttransplant diabetes mellitus occurs in 10% to 50% of people after organ transplantation and appears to result from an underlying disorder of glucose metabolism with superimposed systemic inflammation plus the effects of immunosuppressive medications. Insulin therapy is usually required. The condition worsens the prognosis for the transplanted tissue and overall patient survival. A previous name for this disorder was *new-onset diabetes after transplant* (NODAT), but the preferred term now is *posttransplant diabetes mellitus*.

13. What are the characteristics of diabetes caused by pancreatic insufficiency?

Chronic pancreatitis and surgical pancreatic resection, depending on the extent, can lead to both exocrine and endocrine pancreatic insufficiency. The development of diabetes in this setting has been referred to as *pancreatic, pancreatogenic, pancreatogenous*, and *type 3c diabetes mellitus*. Affected people tend to be very insulin sensitive and prone to hypoglycemia, related partly to their concomitant glucagon deficiency. Other risk factors for hypoglycemia may include coexisting liver disease, malabsorption, poor dietary intake, and alcohol abuse. Because of these individuals' higher hypoglycemia risk, target A1c values tend to be set higher in these individuals than in those with other types of diabetes.

14. Describe diabetes related to cystic fibrosis (CF).

Diabetes mellitus occurs in approximately 50% of people with CF after age 35. People with CF-related diabetes tend to produce adequate amounts of basal insulin but have reduced or delayed insulin secretion in response to meals, causing them to have significant postprandial hyperglycemia. Therefore an oral glucose tolerance test is usually employed to diagnose this condition. Because of their tendency to have pulmonary infections and require glucocorticoid treatment, many individuals have concomitant insulin resistance.

15. Explain MODY.

MODY is characterized by diabetes that is usually diagnosed at a young age (<25 years), with autosomal dominant transmission and lack of autoantibodies; it is the most common type of monogenic diabetes and accounts for 2% to 5% of all diabetes cases. Several different genetic abnormalities have been identified. The affected genes control pancreatic beta-cell development, function, and regulation; the mutations cause impaired glucose sensing and insulin secretion with minimal or no defect in insulin action. Table 1.4 lists the MODY subtypes with their frequencies and optimal treatment strategies.

16. What is checkpoint inhibitor-associated autoimmune diabetes mellitus (CIADM)?

CIADM is an insulin-deficient form of diabetes that can develop during or after treatment with immune checkpoint inhibitors; the most commonly implicated agents are PD-1 and PD-L1 inhibitors, such as nivolumab and pembrolizumab. It may develop within 3 months of initial PD-1/PD-L1 inhibitor exposure. This type of diabetes is much like typical type 1 diabetes, although preexposure antibody status has not yet been well studied. Although some affected people have positive islet-cell antibodies, others are antibody negative and lack the higher-risk HLA haplotypes. Antibody-positive individuals tend to have a more abrupt onset and a higher risk of DKA than those who are antibody negative. However, both antibody-positive and antibody-negative individuals exhibit beta-cell failure with severe insulin deficiency and require intensive insulin therapy. See Chapter 17, "Diabetes Management in Cancer Patients."

17. What is GDM?

GDM is defined by the American College of Obstetrics and Gynecology (ACOG) as a "condition in which carbohydrate intolerance develops during pregnancy." Women with GDM have an increased risk of later developing type 2 diabetes mellitus and cardiovascular disease. Adverse perinatal outcomes are also associated with GDM. It is currently recommended that all pregnant women be tested for GDM between weeks 24 and 28 of pregnancy. GDM is discussed in more depth in Chapter 16.

Key Points

1. Diabetes mellitus is diagnosed by any of the following criteria: fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L), hemoglobin A1c ≥6.5% (48 mmol per mol), or random plasma glucose ≥200 mg/dL (11.1 mmol/L) in a patient with symptoms of hyperglycemia or hyperglycemic crisis.

Table 1.4 Subtypes of Maturity-Onset Diabetes of the Young (MODY)

MODY TYPE	MUTATION	TREATMENT
Type 1 (<10%)	Hepatocyte nuclear factor 4 alpha	Sulfonylurea
Type 2 (15%–30%)	Glucokinase gene	Diet, lifestyle
Type 3 (50%–65%)	Hepatocyte nuclear factor 1 alpha	Sulfonylurea
Type 4 (rare)	Insulin promoter factor 1	
Type 5 (rare)	Hepatocyte nuclear factor 1 beta	Insulin
Type 6 (rare)	Neurogenic differentiation factor 1	Insulin

2. Prediabetes is diagnosed by any of the following criteria: fasting plasma glucose of 100 to 125 mg/dL (5.6–6.9 mmol/L), 2-hour plasma glucose of 140 to 199 mg/dL (7.8–11.1 mmol/L), and hemoglobin A1c of 5.7% to 6.4% (39–47 mmol per mol).
3. Type 1 diabetes mellitus is an autoimmune disease characterized by pancreatic beta-cell destruction, resulting in absolute insulin deficiency. It is best diagnosed by finding a low or undetectable C-peptide and one or more positive islet-cell antibodies: GAD antibodies, insulin antibodies, IA-2 antibodies, or ZnT8 antibodies.
4. Type 2 diabetes mellitus is a heterogeneous metabolic disorder characterized by the pathophysiologic triad of excessive hepatic glucose production, peripheral insulin resistance, and progressive beta-cell failure; other contributing features include increased lipolysis, excessive glucagon secretion, deficient incretin hormone secretion, increased renal glucose reabsorption, and insulin resistance in the brain.
5. Less common types of diabetes include posttransplant diabetes, diabetes resulting from pancreatic insufficiency or pancreatectomy, CF-related diabetes, MODY, and various types of medication-induced diabetes.

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