FUEL METABOLISM
CHAPTER 1

DIABETES MELLITUS: ETIOLOGY, CLASSIFICATION, AND DIAGNOSIS

Adnin Zaman and Cecilia C. Low Wang

1. What is diabetes mellitus?

Diabetes mellitus is a term that encompasses a heterogeneous group of metabolic disorders, all of which are characterized by elevated blood glucose levels.

2. What is the origin of the term diabetes mellitus?

Although diabetes has been described in literature as ancient as the Ebers Papyrus of Egypt by Hesy-Ra (1552 BCE), the word diabetes comes from Arateus and the Greek word “diabainein” which means “siphon,” because affected people excreted excessive amounts of urine. The term diabetes mellitus was coined by Thomas Willis of Oxford, England, in 1675, when it was discovered that the urine of people with diabetes was sweet rather than tasteless (insipidus).

3. What is the epidemiology of diabetes?

Approximately 1.5 million Americans are diagnosed with diabetes each year. Thirty million Americans, or nearly 9% of the population, had diabetes mellitus in 2015. Of this, 1.25 million children and adults had type 1 diabetes. However, evidence suggests that out of the 30 million adults with diabetes, 7.2 million remain undiagnosed. The number of individuals with prediabetes is roughly 84 million. American Indians and Alaskan Natives have the highest rate of diabetes (15.1%), whereas non–Hispanic whites have the lowest prevalence.

4. What is the underlying pathophysiology of the two most common types of diabetes?

Type 1 diabetes results from autoimmune destruction of pancreatic beta cells causing complete or nearly complete insulin deficiency. Type 2 diabetes is characterized by excessive hepatic glucose production, tissue insulin resistance, and relative insulin deficiency, resulting in insufficient beta cell insulin production to compensate for the increased insulin requirements. In both cases, it is ultimately the absolute or relative insulin deficiency that results in elevated blood glucose levels.

5. Why do people get diabetes?

Type 1 diabetes occurs in people who have an inherited susceptibility (genetic—HLA related) and later a superimposed environmental trigger (theories have focused on food exposures, viral infections, and alterations of the intestinal microbiome). Type 2 diabetes has an even stronger genetic influence (polygenic, but not yet well defined) and more established environmental triggers (obesity, physical inactivity, glucocorticoid therapy).

6. How is diabetes diagnosed?

Diabetes is diagnosed through laboratory testing; there are several criteria for the diagnosis of diabetes. Ideally, two tests on different occasions are needed to confirm the diagnosis:

- **Hemoglobin A\(_1c\)** (HbA\(_{1c}\)) $\geq 6.5\%$ (HbA\(_{1c}\) of 5.7%–6.4% establishes a diagnosis of prediabetes
- **Fasting plasma glucose** $\geq 126$ mg/dL. Fasting is defined as no caloric intake for at least 8 hours
- **Random plasma glucose** $\geq 200$ mg/dL in a patient with classic symptoms of hyperglycemia
- **Oral glucose tolerance test** with a 2-hour plasma glucose $\geq 200$ mg/dL after a 75-g load of anhydrous glucose dissolved in water

7. What is the current classification for different types of diabetes?

Previously, diabetes was classified as type 1, type 2, gestational, or “secondary” diabetes. The most current classification of diabetes includes type 1, type 2, type 3c (pancreatogenous), gestational (type 4), latent autoimmune diabetes of adulthood (LADA), and maturity-onset diabetes of the young (MODY), among many others.

European investigators have recently proposed that types of diabetes be divided into five relatively distinct groups, which may offer greater predictability for diabetes-related outcomes:

- **Cluster 1 (severe autoimmune diabetes)**—early-onset disease, low body mass index (BMI), poor metabolic control, insulin deficiency, glutamic acid decarboxylase antibody (GAD Ab) positive
- **Cluster 2 (severe insulin-deficient diabetes)**—similar to cluster 1, but GAD Ab negative
- **Cluster 3 (severe insulin-resistant diabetes)**—high BMI and insulin resistance
- **Cluster 4 (mild obesity-related diabetes)**—high BMI, but no insulin resistance
- **Cluster 5 (mild age-related diabetes)**—similar to cluster 4, but higher age at diagnosis, and with modest metabolic derangements
Another way to classify diabetes is to consider antibody status and beta cell function (Aβ±), which places all forms of diabetes along a spectrum. In this system, for example, type 1 diabetes would be reclassified as autoimmune positive and beta cell negative (A+/β−) to indicate that it is a disease of hyperglycemia in the presence of autoimmunity with no beta cell production of insulin. Similarly, one might think of LADA as A+/β+ (autoimmune disorder of pancreas but with continued beta cell function) and type 2 diabetes as A−/β+ and postpancreatectomy diabetes as A−/β− (Table 1.1).

8. What is the natural history of type 1 diabetes?
The natural history of type 1 diabetes involves lifelong requirement for insulin therapy. Soon after the diagnosis of type 1 diabetes is made, there is often a “honeymoon phase,” during which beta cells are still able to produce small amounts of insulin. Patients usually still require insulin during this time but at generally smaller doses than later in the course of their diabetes. Without insulin therapy, patients develop a life-threatening condition known as diabetic ketoacidosis (DKA; see Chapter 2). If hyperglycemia is not adequately controlled, patients may suffer from chronic complications of diabetes, such as retinopathy, diabetic kidney disease, and neuropathy.

9. What is the natural history of type 2 diabetes?
In individuals with type 2 diabetes, generally there is some degree of insulin resistance in the initial stages, but eventually, insulin deficiency develops and worsens over time. Diabetes (with hyperglycemia) does not develop until pancreatic beta cells become incapable of producing enough insulin to compensate for the individual’s insulin resistance. Noninsulin medications are often effective in restoring euglycemia initially, but multiple agents are often needed over time to maintain glycemic control. If patients are on several noninsulin agents but have not achieved their goal HbA1c, insulin can be added to the regimen. Some patients with type 2 diabetes may ultimately require basal-bolus insulin therapy (as with type 1 diabetes) to achieve glycemic control. Weight loss is an effective strategy to reduce insulin resistance and usually allows patients to reduce the number of medications needed to achieve and maintain their goal HbA1c.

10. Who develops ketosis-prone diabetes?
A less commonly encountered form of diabetes is characterized by a temporary lack of insulin production by pancreatic beta cells. Ketosis-prone diabetes disproportionately affects nonwhite individuals. Patients with DKA require insulin therapy to manage this condition and for a short time after resolution of DKA. However, in most individuals, beta cell function is eventually recovered, and insulin therapy can be tapered off within a few months. In fact, patients tend to become hypoglycemic within weeks of hospital discharge if maintained on their original basal-bolus regimen unless the clinician and patient closely monitor blood glucose values to scale back the insulin regimen. Once the immediate post-DKA period of glucose toxicity is overcome and beta cell function is regained, patients can typically be maintained on one or more noninsulin agents. Without lifestyle modifications and medication adherence, patients are at risk for a repeating cycle of DKA—glucose toxicity—insulin dependence—possible hypoglycemia—recovery.

11. What is LADA?
LADA is a form of autoimmune diabetes with onset later in life compared with typical type 1 diabetes. This was previously thought to be a rare cause of diabetes, and individuals were often misdiagnosed as having type 2 diabetes because of the later age of presentation. However, unlike patients with type 2 diabetes, patients with LADA have positive antibodies (usually GAD Ab). After their initial presentation, they may go through a “honeymoon phase,” during which noninsulin agents are sufficient to achieve and maintain glycemic control. However, as beta cell failure progresses, patients eventually require insulin and ultimately experience a course similar to those with type 1 diabetes.

12. What other causal factors should I be thinking about when I see a patient with high glucose?
When evaluating a patient with high blood glucose, a new diagnosis of diabetes or existing poorly controlled diabetes should always be at the forefront of consideration. However, there are other causes of hyperglycemia that ought to be considered. The most common non–diabetes-related cause is glucocorticoid administration. Although most individual do not develop hyperglycemia while on steroids, these medications (given via any route)
may precipitate hyperglycemia in those with underlying glucose intolerance. Critical illnesses and medical conditions, such as infections, may also cause hyperglycemia because of stress-induced increase in cortisol production. Similarly, hyperglycemia may develop in patients with endogenous hypercortisolism (Cushing syndrome)—either from overproduction of adrenocorticotropic hormone (ACTH) by a pituitary tumor or ectopic tumor or from overproduction of cortisol by an adrenal tumor. Other rare causes of hyperglycemia include acromegaly resulting from a growth hormone–secreting pituitary adenoma or a catecholamine-producing tumor, such as a pheochromocytoma or paraganglioma. In the inpatient setting, patients with glucose intolerance receiving intravenous dextrose as either maintenance fluid or with IV medications may also develop hyperglycemia. Those receiving enteral nutrition or total parenteral nutrition are at particularly high risk for developing hyperglycemia when nutrition is delivered in this nonphysiologic manner.

13. What is type 3c diabetes?
Also known as pancreatogenic or pancreatogenous diabetes, type 3c diabetes is a form of diabetes that develops when nonautoimmune disorders of the pancreas compromise pancreatic endocrine function, resulting in decreased insulin production. Patients who have recurrent acute pancreatitis or chronic pancreatitis; those who have sustained abdominal trauma, such as from a motor vehicle accident; and those who have undergone partial or complete pancreatectomy are most likely to develop type 3c diabetes.

14. Who should be screened for diabetes?
The United States Preventive Services Task Force (USPSTF) recommends screening for abnormal fasting plasma glucose levels in overweight and obese adults ages 40 to 70 years. People who have a family history of diabetes, those who have a history of gestational diabetes or polycystic ovarian syndrome, and those who are members of certain racial/ethnic groups (African American, American Indian or Alaskan Native, Asian American, Hispanic or Latino American, or Native Hawaiian/Pacific Islander in origin) may develop diabetes at a younger age or at a lower BMI and, therefore, should be screened earlier. The American Diabetes Association (ADA) has made similar recommendations and suggests screening every 3 years starting at age 45 years with a fasting plasma glucose test.

15. Can diabetes be prevented?
The Diabetes Prevention Program (DPP) has demonstrated the significant beneficial effects of intensive lifestyle modifications in patients with prediabetes to prevent progression to diabetes. Randomized controlled trials have shown that pharmacotherapy may also reduce the rates of progression to overt diabetes in individuals at high risk for type 2 diabetes, but the risks of these medications may outweigh their benefits in some patients. The ADA recommends pharmacotherapy for patients who are at high risk for progression to diabetes because of multiple risk factors at baseline and for those who have a persistently elevated HbA1c > 6% despite lifestyle modifications. Although numerous strategies have been evaluated in controlled clinical trials, no therapies have been demonstrated to effectively prevent the progression of type 1 diabetes.

16. What is monogenic diabetes?
Unlike type 1 and type 2 diabetes, which are multifactorial in etiology, monogenic diabetes results from single gene mutations causing pancreatic beta cell dysfunction or insulin signaling defects. Patients are typically young at the time of diagnosis, do not require insulin, and lack autoantibodies. Monogenic diabetes is often inherited in an autosomal dominant pattern, and it is common to have multiple generations of family members affected. Neonatal diabetes and MODY are the two more common forms of monogenic diabetes. Identification of the affected genes is beneficial from a therapeutic standpoint because the various forms of monogenic diabetes are treated differently. For example, MODY3 is caused by a mutation in the hepatocyte nuclear factor-1 alpha and is most effectively treated with sulfonylureas, whereas MODY2 results from a defect in the glucokinase gene and is best treated with dietary changes alone.

17. How can insulin resistance be assessed clinically?
Insulin resistance has a wide array of clinical manifestations, including acanthosis nigricans, skin tags, hirsutism, ovarian hyperandrogenism, and androgenic alopecia. Of these, acanthosis nigricans is the most commonly recognized sign and is described as symmetric, velvety, light brown to black, thickened plaques and accentuated skin marks that appear on knuckles and in intertriginous areas. The pathophysiology is thought to be stimulation of insulin growth factor-1 receptors in fibroblasts and keratinocytes by extremely high insulin levels, resulting in proliferation of these skin cells. Insulin resistance can be estimated in patients without diabetes by using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) score after measuring fasting blood glucose and serum insulin levels. Measurements of insulin resistance, such as the hyperinsulinemic euglycemic clamp, are used in the research setting but not in the clinical setting.

18. What is metabolic syndrome?
The diagnosis of metabolic syndrome requires at least 3 out of 5 of the following: hyperglycemia, hypertension, hypertriglyceridemia, low levels of high-density lipoprotein (HDL), or increased abdominal circumference. When present, metabolic syndrome is associated with significantly increased risk of heart disease, stroke, and diabetes (if not already present). Treatment to reduce the risk for cardiovascular events requires intensive lifestyle modification with dietary changes, exercise, and weight loss. Often, medications are needed to treat each individual component of metabolic syndrome.
• Diabetes results from absolute or relative insulin deficiency. In type 1 diabetes, beta cells are destroyed, resulting in complete insulin deficiency. In type 2 diabetes, beta cells cannot produce enough insulin to compensate for the underlying insulin resistance.

• Diabetes is diagnosed via blood testing and requires abnormal results on two separate occasions to confirm the diagnosis. The diagnostic criteria include HbA₁c ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL, random plasma glucose ≥ 200 mg/dL in addition to the typical symptoms of diabetes, or plasma glucose ≥ 200 mg/dL 2 hours after receiving a 75-g glucose load during an oral glucose tolerance test (OGTT).

• There are several ways to classify the types of diabetes. The first method involves classifying diabetes as type 1, type 2, type 3c, gestational (type 4), and “other.” Diabetes can also be conceptualized as falling on a spectrum of autoimmunity and beta cell function (A⁺/B⁻). More recently, some investigators have proposed that the types of diabetes be divided into five distinct groups, which may be more helpful in predicting diabetes-related outcomes.

• Patients with type 1 diabetes require lifelong insulin therapy, although there is often a short-lived initial “honeymoon phase” during which pancreatic beta cells are still able to produce a small amount of insulin. In comparison, the natural history of type 2 diabetes involves insulin resistance that develops before beta cell dysfunction, at which stage patients can be managed with noninsulin agents, but progressive insulin deficiency ensues. Approximately half the patients with type 2 diabetes in the United States are on insulin therapy with or without noninsulin agent(s).

• When evaluating a patient with hyperglycemia, a new diagnosis of diabetes or preexisting diabetes should be at the forefront of consideration. However, glucocorticoids, critical illness, or medical therapies, such as enteral or parenteral nutrition, may cause stress hyperglycemia. Acromegaly and pheochromocytoma are rare causes of hyperglycemia and diabetes.

**KEY POINTS**

**BIBLIOGRAPHY**


ABSTRACT
Diabetes mellitus is a term that encompasses a heterogeneous group of disorders that are all characterized by elevated blood glucose. The most common type is type 2 diabetes, which has a strong genetic component and environmental contributors, but there are many other types to be aware of including type 1 diabetes, gestational diabetes, and “secondary” forms of diabetes. This chapter provides a general overview of diabetes mellitus including the pathophysiology, classification, diagnosis, screening, and prevention. It also outlines a few of the key types of diabetes including types 1 and 2, latent onset autoimmune diabetes of adults and ketosis-prone diabetes, and monogenic diabetes, as well as features of insulin resistance and metabolic syndrome.

KEY WORDS
diabetes mellitus, beta cell function, autoimmune, diagnosis, insulin resistance, monogenic, metabolic syndrome