Classification of Diabetes: Not All Hyperglycemia is the Same

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Editor's note: This article is the 2nd in a 12-part series reviewing the fundamentals of diabetes care for physicians in training.

During internship and residency, physicians-in-training encounter a myriad of diseases and symptoms. As discussed in this space in the previous issue of *Clinical Diabetes*,[1] diabetes is a major issue in U.S. health care and is growing rapidly. Medical professionals can expect to spend a large portion of their time caring for diabetic patients in the inpatient and outpatient settings as the prevalence of this disease increases steadily. Central to the treatment of patients with diabetes is understanding the classification system used to describe diabetes.

Previously, physicians classified diabetes based on the treatment required to control the disorder (insulin-dependent versus non–insulin-dependent diabetes) or age at which the disorder develops (e.g., juvenile diabetes or late-onset autoimmune diabetes of adulthood). As our understanding of diabetes has deepened, the diagnostic criteria and classification scheme of diabetes has changed as well. Different therapies now target the underlying mechanisms of diabetes, such as insulin deficiency, insulin resistance, and other aspects of the disease process. To improve the health care of people with diabetes, the American Diabetes Association (ADA) no longer recommends classification of diabetes based on treatment of hyperglycemia, but rather on underlying mechanism.[2,3] The underlying mechanisms of diabetes were discussed in detail in the last issue;[1] this article will focus on the classification scheme for diabetes, which is important for several reasons.

In addition to offering expedient and up-to-date health care for patients, there are other important reasons to have a thorough understanding of the classification of diabetes. Diagnosis of diabetes can have a major impact on the cost of an individual's health insurance premium. In many situations, patients with diabetes may even be considered uninsurable, which limits their options for self-employment or in obtaining insurance for their family. There are also important ramifications in other areas, such as insulin use and application for commercial drivers' licenses, because the use of insulin makes it necessary to apply for a waiver to operate a commercial vehicle across state lines.[4] It is important, therefore, to avoid inappropriate diagnosis of diabetes.

ADA revised the criteria for diagnosis of diabetes in 1997.[2] This classification provides for diagnosis of diabetes based on both fasting and postprandial criteria. These criteria specify that individuals have diabetes if they have symptoms of diabetes, such as polyuria, polydipsia, or unexplained weight loss, and a random plasma glucose measurement $\geq$200 mg/dl, or a fasting plasma glucose > 126 mg/dl, or a 2-hour plasma glucose > 200 mg/dl after consumption of 75 g of glucose. It is important to note that these readings should be performed in a laboratory setting rather than with a handheld glucose meter because of the potential for error with handheld devices. It is also advisable to repeat the testing on a different day. The glucose tolerance test is not recommended for routine diagnosis of diabetes, in part because of the ease and higher degree of reproducibility of fasting glucose tests.

The hemoglobin A_{1c} (A1C) test, because of its lack of standardization and unreliability in the setting of hemoglobin variation, is not used to diagnose diabetes. It is, however, a useful tool to monitor glycemic control and the risk of complications.

Impaired Fasting Glucose and Impaired Glucose Tolerance

There also exists a large group of patients whose glucose is not sufficiently elevated to meet the diagnosis of diabetes by the above criteria, but whose glucose level is too high to be considered normal. These individuals have fasting glucose levels between 100 and 125 mg/dl or a 2-hour postprandial glucose reading of 140–199 mg/dl. These patients are considered to have "impaired fasting glucose" or "glucose intolerance," respectively.[2]

These patients may have normal A1C values and may be virtually normoglyemic but are at a high risk to develop overt diabetes. This risk may be reduced significantly by lifestyle changes or some medical therapies.[5] Patient who are developing type 1 diabetes also develop glucose intolerance followed by impaired fasting glucose before the presence of overt diabetes. To date, prevention strategies for type 1 diabetes have not been successful.

Type 1 Diabetes

As discussed in the previous issue of *Clinical Diabetes*,[1] type 1 diabetes is

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caused by an absolute deficiency in insulin production. It is thought to arise from autoimmune destruction of the β-cells of the pancreas in genetically susceptible individuals and constitutes ~ 10% of diabetes in the United States. Although this form of diabetes is more common in childhood, it can occur at any time in life. Adults misdiagnosed as having type 2 rather than type 1 diabetes may be expected to have very limited or transient response to oral agents and to progress rapidly to insulin therapy. Because these patients eventually develop an absolute deficiency of insulin, insulin is the mainstay of treatment. Progression to absolute deficiency is variable and tends to be rapid in children and slower in adults.

Several markers of autoimmunity can help identify people with type 1 diabetes, including anti-islet, anti-GAD_{65}, anti IA-2, and anti-insulin autoantibodies. Type 1 diabetes is further subclassified into type 1A diabetes if autoimmune markers are positive and type 1B diabetes if they are not. Approximately 90% of newly presenting patients will have at least one positive antibody titer. Positive status varies based on age, duration of diabetes, and ethnicity. Anti-GAD antibodies are positive in 70–80% of patients at the time of diagnosis. They are also more commonly positive in adults who develop type 1 diabetes and generally remain positive, whereas anti-insulin antibodies are not reliably measured after initiation of insulin therapy.[6] Other patients clearly have complete or near-complete insulin deficiency and other autoimmune diseases, such as autoimmune hypothyroidism, yet remain antibody negative. These patients are considered to have type 1B diabetes.

It is important to note that history of diabetic ketoacidosis is suggestive of, but not diagnostic for, type 1 diabetes because some patients with type 2 diabetes may also develop this complication. Type 1 diabetes may also present during pregnancy.[2,3] There is also evidence that early and intensive use of insulin in adults presenting with type 1 diabetes prolongs their ability to produce insulin, which further underscores the importance of early and accurate diagnosis of type 1 diabetes.[7]

Type 2 Diabetes

Type 2 diabetes is a heterogeneous group of conditions that constitute ~ 90% of diabetes in the United States. Previously, this group of conditions was known as non–insulin-dependent diabetes or adult-onset diabetes. Type 2 diabetes involves insulin resistance and relative insulin deficiency rather than an absolute insulin deficiency as seen in type 1 diabetes. Insulin resistance is thought to precede insulin deficiency in most patients, and autoimmune destruction of β-cells does not occur, although β-cell mass may be reduced. Because the insulin deficiency is relative rather than absolute, diabetic ketoacidosis occurs less frequently than in type 1 diabetes.

Therapy for type 2 diabetes varies considerably from that for type 1 diabetes. The majority of patients with this form of diabetes are clinically obese, and exercise and weight loss lead to improvements in the disease state and even clinical remission in some individuals. Pharmacotherapies directed toward increasing insulin sensitivity and increasing β-cell insulin production are useful in type 2, but not in type 1, diabetes. Unlike type 1 diabetes, there is a strong genetic predisposition to developing type 2 diabetes, and the presence of several family members with type 2 diabetes suggests the diagnosis.

Gestational diabetes mellitus (GDM) is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy." Unlike other forms of diabetes, GDM uses a different set of diagnostic criteria and screening because normal physiological levels of glucose are different during pregnancy. The pathophysiology and diagnostic criteria for GDM are discussed in detail elsewhere in this issue of *Clinical Diabetes* (p. 57). It is important to note that GDM is a powerful predictor of the development of type 2 diabetes later in life. Some studies have demonstrated that as many as 70% of women who experience GDM will develop type 2 diabetes within 10 years after delivery.[8]

Other Specific Types of Diabetes

The ADA recognizes > 56 other specific types of diabetes. Some of these are quite rare, whereas others are much more common. Understanding these different forms of diabetes is important because their treatment modalities sometimes differ significantly from those of other forms of diabetes.

Several other forms of diabetes are associated with insulin deficiency associated with non–immune-mediated injury to the β-cells of the pancreas or the pancreas as a whole. This group of disorders includes such diseases as cystic fibrosis, acute or chronic pancreatitis, trauma, partial or complete pancreatic resection (Whipple procedure), hemochromatosis, and other causes. The degree of diabetes is generally proportional to the amount of injury to the pancreatic β-cell mass, which is disproportionately located in the head of the pancreas. Certain individuals, such as those with early type 2 diabetes, may have limited β-cell reserve before pancreatic injury and therefore may develop diabetes after what appears to be minor loss of pancreatic tissue. Another clinically important aspect in caring for these patients is that they may be more susceptible to hypoglycemia if they have lost α-cells in addition to β-cells and therefore do not have normal glucagon secretion.

Several hormones oppose the action of insulin and are therefore diabetagenic if secreted in excess. Examples include cortisol (Cushing's syndrome), growth hormone (acromegaly), glucagon (pancreatic glucagonoma), and epinephrine (pheochromocytoma). Many of these hormones lead to hyperglycemia by increasing hepatic glucose production or decreasing insulin sensitivity. Conditions that cause excess secretion of these substances can result in glucose intolerance, elevated fasting glucose, or frank diabetes. It is important to note unusual

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physical stigmata of these diseases when evaluating patients for diabetes, especially if they are newly presenting, exhibit more rapid progression, or are resistant to therapy. Some estimates suggest that up to 3% of patients with poorly controlled glucose in diabetes clinics may have Cushing's syndrome.[9]

Several monogenetic defects in β-cell function have been described. They are collectively referred to as maturity-onset diabetes of the young (MODY). Typically, they manifest themselves in infancy or childhood, cause impaired insulin secretion with relatively normal insulin action, and are inherited in an autosomal-dominant fashion. There are also several genetic disorders that lead to abnormal insulin action. Examples include leprechaunism, type A insulin resistance, and Rabson-Mendenhall syndrome.[10]

Medical treatments of diabetes are becoming increasingly focused on specific forms of diabetes and on aspects of the diabetic state, such as insulin resistance, insulin deficiency, and increased hepatic glucose output. It is increasingly important to accurately diagnose patients with the correct form of diabetes to start with therapies that are concordant with their underlying defect. In the case of type 1 diabetes, early diagnosis and treatment can lead to prolonged ability to produce insulin endogenously and lower risk of microvascular complications.[7] Similarly, early recognition of impaired fasting glucose may delay or avert the development of type 2 diabetes.[5] Health care providers should strive to accurately diagnose glucose abnormalities to provide their patients the greatest chance for positive response to medication and continuing good health.

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