Diabetes: Magnitude and Mechanisms

Michael J. Fowler, MD

Editor's note: *This article is the first in an eight-part series reviewing the fundamentals of diabetes care for physicians in training. This series is an updated adaptation of a 12-part series published in* Clinical Diabetes *between 2006 and 2009. The previous series can be found online at the journal Web site (http://clinical.diabetesjournals.org).*

Like other aspects of medical practice, the scope of medical care changes because diseases, therapies, and prognoses are continuously in flux. One major source of change in the field of health care is in the treatment of diabetes, which is consuming an increasingly large portion of national health care expenditures and effort. Diabetes is, in many ways, a large part of the future of medicine in the United States and in many parts of the world. Its rapid growth will undoubtedly have a significant impact on the cost of any future public health care legislation.

The growing prevalence of diabetes, therefore, makes it increasingly important for medical practitioners to be able to treat diabetes effectively. Diabetes affects virtually every specialty and subspecialty of medical practice; even physicians who are not primary care providers need to be cognizant of potential complications and comorbidities caused by diabetes.

During the next 2 years, *Clinical Diabetes* will devote space in each issue to reviewing the fundamentals of diabetes care for physicians in training. The goal is to provide doctors in internships and residency programs, as well as other medical providers, with important information about diabetes and the care of patients who have it. We intend to focus on salient, practical information that can be rapidly used in the clinical setting. We begin by highlighting the scope of diabetes and key pathophysiological attributes of the four common types of diabetes.

Diabetes has become a major cause of morbidity and mortality in the United States and is increasing in the rest of the world. Seemingly everywhere, the prevalence of diabetes has increased steadily throughout the past several decades. The Centers for Disease Control and Prevention estimates that the prevalence of known diabetes in people > 18 years of age has increased from 5.1% in 1997 to 10.1% in 2009.[1] These statistics do not take into account people with undiagnosed diabetes. Perhaps even more alarming is that approximately one-third of diabetes is currently undiagnosed.[2]

Although the prevalence of diabetes is increasing, diabetes is not homogenously distributed throughout the population. The ongoing National Health and Nutrition Evaluation Survey (NHANES) has found that diabetes prevalence is considerably higher in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites. Age is also directly correlated with risk of diabetes, with 15.8% of the population > 65 years of age suffering from diabetes, compared to 6.5% for the total population. The higher prevalence of diabetes with age is present in all ethnic groups.[2]

The scope of those at risk for developing diabetes is equally, if not more, immense. Impaired fasting glucose (IFG), defined as a fasting plasma glucose (FPG) level of 100–125 mg/dl, is a precursor to diabetes.[3,4] NHANES has found that 26% of the total population of adults > 20 years of age have IFG. The relationship of increased IFG to age holds true for the general population, and Mexican Americans have significantly more IFG than non-Hispanic whites or non-Hispanic blacks. The magnitude of these numbers further emphasizes that diabetes will continue to affect the U.S. population for the foreseeable future.

The impact of diabetes is by no means limited to the United States, however. Increasing urbanization, aging populations, increasing obesity, and declining levels of physical activity are all contributing to increases in diabetes worldwide. It is believed that in 2000, the number of people with diabetes worldwide was ~ 171 million. India, China, and the United States have the highest numbers of people with diabetes in the world.[5] It has also been estimated that from 1995 to 2025, the number of people with diabetes in the world will increase by 122%. Furthermore, it is expected that the prevalence of

diabetes in developed countries will increase by 27% in adult populations, and the prevalence in underdeveloped countries will increase by 42%. Adjusted for population changes, this would constitute a 170% increase in the number of people with diabetes from 1995 to 2025.[6]

The economic impact of diabetes is profound. In 2007, the American Diabetes Association (ADA) estimated the direct and indirect costs of diabetes. The direct economic cost of diabetes for the people who have the disease in the United States was estimated to be $116 billion. When one considers the indirect costs of diabetes, such as loss of productivity, disability, and early mortality, the cost is even higher, approaching $174 billion in 2007. It is important to remember, however, that these estimates do not include the economic cost of undiagnosed diabetes, nor do they include the magnitude of immeasurable costs, such as human pain and suffering caused by the disease.[7]

Classifying diabetes has been a difficult undertaking. Diabetes is a heterogeneous group of diseases that, through various mechanisms, cause hyperglycemia. The ADA defines diabetes as "a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both." It is important to emphasize that the heterogenous group of diseases that are collectively known as diabetes have distinct pathophysiological mechanisms and therefore require different approaches to treatment.[3]

To further delineate these mechanisms, the ADA also offers a simple classification system for the various forms of diabetes. Previous classification systems have focused on the treatment rather than the cause of hyperglycemia. Previous terminology included distinctions such as "non-insulin-dependent diabetes," "insulin-requiring diabetes," and "late-onset diabetes." To promote better understanding and therefore better treatment of the disease, the ADA now recommends the use of four broad categories based on the etiology of diabetes. These categories include type 1 diabetes, type 2 diabetes, gestational diabetes mellitus (GDM), and other specific forms of diabetes.[8] It is important to understand which pathological process may be taking place in a particular patient because this will determine the necessary treatment to control the disease and predict potential outcomes.

Type 1 Diabetes

Absolute insulin deficiency caused by autoimmune-mediated destruction of pancreatic β-cells characterizes type 1 diabetes. Previously, this condition has been called "insulin-dependent diabetes" or "juvenile diabetes." It is thought to be caused by a combination of environmental factors, such as viral infection, superimposed on a genetic susceptibility. It accounts for ~ 10% of those with diabetes in the United States, but the prevalence may be increasing. The disorder may be further subclassified into type 1A if autoimmune markers are found, usually at the time of diagnosis.[3] Type 1B diabetes is an absolute insulin deficiency in which no autoimmune markers can be identified. Type 1B diabetes may be more common in people of Asian heritage.[9]

As mentioned above, type 1 diabetes is a multifactoral autoimmune disease thought to arise from a complex interaction between both genetic susceptibility and environmental insult(s). First, an individual is born with an immune system that is thought to be predisposed to developing type 1 diabetes. There is a strong association of type 1 diabetes with individuals who possess particular HLA haplotypes. HLA DR4-DQ8 and DR3-DQ2 are present in > 90% of children with type 1A diabetes, whereas it is generally only present in ~ 40–50% of Caucasian populations. Furthermore, 30–50% of patients with type 1A diabetes are heterozygotes for HLA DR4-DQ8 and DR3-DQ2, whereas this combination of alleles is only present in ~ 2.4% of the general population.[10] It is important to note, however, that these are associations and that most people with the above HLA alleles do not develop type 1 diabetes, demonstrating that other factors are involved in the development of the disease.

Many triggers have been proposed for the development of type 1 diabetes in genetically susceptible individuals. Viruses, such as enteroviruses, coxackie virus, and rubella, have been proposed as culprits but have not been definitively shown to induce type 1 diabetes.[11] Food additives or toxins, such as nitrosamines, have also been proposed as a cause of diabetes.[12] Some investigators have also implicated cow's milk as an initiating factor in the development of autoimmunity in type 1 diabetes.[13] None of these theories has evolved into a clear cause-and-effect initiator of diabetes.

By whatever initiating mechanism, the autoimmune destruction of β-cells leads to a progressive decline in the body's insulin secretory capacity. Eventually, this decline manifests itself in hyperglycemia after a large carbohydrate load, such as a meal or a glucose tolerance test. When ~ 80% of β-cells have been destroyed, patients develop the first clinical symptoms of diabetes. Interestingly, the rate of β-cell decline can vary based on age, with older patients who develop type 1 diabetes typically experiencing a much more gradual decline in β-cell mass.[14]

Type 2 Diabetes

Type 2 diabetes is a heterogeneous group of conditions that constitute ~ 90% of diabetes in the United States. Like type 1 diabetes, type 2 diabetes also involves both genetic susceptibility and environmental factors, although the genetic component may be greater than in type 1 diabetes. It is caused by a combination of insulin resistance and relative insulin deficiency with increased hepatic glucose production. It is important to note that some individuals experience predominantly insulin resistance and others insulin deficiency. Insulin resistance is generally thought to precede insulin deficiency.

Obesity is associated with increased insulin resistance and may be the reason type 2 diabetes is more common in obese individuals. The precise mechanism by which obesity leads to insulin resistance is not completely described but may be related to several biochemical factors, such as free fatty acids, leptin, tumor necrosis factor-α, and other substances. In addition, many genetic polymorphisms may play a part in insulin resistance, possibly through post-insulin receptor signal transduction mechanisms.[14]

What is well established, however, is that overweight and obesity are strongly associated with development of type 2 diabetes and may be responsible for the majority of the growing diabetes pandemic described above.[15] Furthermore, weight loss is strongly associated in prospective studies with decreased progression from IGT to type 2 diabetes.[16] This information leads to strong recommendations for health care providers to encourage weight reduction to prevent or control type 2 diabetes.

Insulin resistance alone, however, does not cause diabetes. Most obese people do not develop type 2 diabetes, despite increased insulin resistance.[17] For type 2 diabetes to emerge, there must also be relative insulin deficiency. Before type 2 diabetes develops, the pancreatic β-cells increase their production of insulin to compensate for increased insulin resistance. Studies have demonstrated that there is measurable β-cell hypertrophy present in obese subjects who do not have diabetes. For unclear reasons, β-cell secretory capacity gradually declines in some individuals, leading to the development of type 2 diabetes.

As β-cell insulin secretory capacity declines, type 2 diabetes begins to develop. Initially, hyperglycemia is only observed after large meals, as in type 1 diabetes. As β-cell function declines further, however, hyperglycemia becomes more severe. Studies have suggested that 40% of β-cell mass may be lost in individuals who have glucose intolerance, and ~ 60% may be lost when clinical type 2 diabetes develops.[18] Hepatic insulin resistance and relative insulin deficiency also lead to increased hepatic gluconeogenesis, which further worsens hyperglycemia. Eventually, the degree of hyperglycemia worsens and becomes virtually universal if left untreated.[14]

The cause of β-cell failure in type 2 diabetes is unknown. In addition to a genetic predisposition, studies have also demonstrated higher rates of apoptosis and decreased β-cell mass in patients with type 2 diabetes.[18] The U.K. Prospective Diabetes Study showed that insulin deficiency was a progressive condition that did not seem to be affected by whether a patient received sulfonylurea or metformin therapy.[19] There are also increased amounts of amyloid deposits in the isets of patients with type 2 diabetes.[20] Many authors speculate that increased insulin resistance may be a genetic trait that can be worsened by obesity and that β-cells compensate for this increased resistance. Some individuals, however, cannot maintain this compensation because of β-cell failure, which leads to the development of type 2 diabetes.

GDM

The ADA defines GDM as "any degree of glucose intolerance with onset or first recognition during pregnancy."[8] The ADA has proposed a classification system based on O'Sullivan's criteria, which were established in the 1960s.[21] There are also other acceptable criteria, and these classification systems will be discussed in greater detail in the next issue of *Clinical Diabetes.*

The prevalence of GDM varies based on the population studied. It complicates ~ 4% of pregnancies in the United States, or ~ 135,000 cases per year.[3] GDM is associated with an increased risk of preeclampsia, cesarean delivery, fetal macrosomia, and an increased risk of hypertension and diabetes after pregnancy.[22] It is also important to recognize that, infrequently, autoimmune (type 1) diabetes may present itself during pregnancy. Women who exhibit rapid progression of diabetes or experience diabetes that does not resolve after pregnancy should be screened for markers of diabetes autoimmunity.

Several factors are thought to contribute to the development of GDM. Chief among these is increased insulin resistance. Pregnancy is associated with marked increases in insulin resistance to levels typically associated with type 2 diabetes.[22] Insulin resistance increases in midpregnancy and throughout the third trimester. This increase in insulin resistance is thought to be caused by increased maternal adipose tissue, effects of placental hormones of pregnancy, and increased clearance of insulin by the placenta.[23] It is also important

to note that women who experience GDM tend to have greater insulin resistance than women without GDM after pregnancy. This suggests that women who develop GDM may be more insulin resistant at baseline and therefore also at higher risk for developing type 2 diabetes after pregnancy.[24]

GDM is a powerful predictor of type 2 diabetes later in life. Some studies have shown that as many as 70% of women who experience GDM will develop type 2 diabetes within 10 years after delivery. It is important to note, however, that the risk of diabetes varies markedly in different studies and in patients of different ethnic backgrounds.[25] This body of knowledge leads to recommendations that women who have been found to have GDM be screened regularly for diabetes after pregnancy and pursue aggressive lifestyle interventions that may prevent the development of type 2 diabetes.

Other Specific Forms of Diabetes

The ADA recognizes > 56 other specific types of diabetes. Although discussion of all of these forms is beyond the scope of this review, several are particularly relevant in general medical practice.

Diseases of the exocrine pancreas constitute one of the more common other forms of diabetes in general medical practice. This group of disorders includes such conditions as cystic fibrosis, pancreatitis, trauma, pancreatic resection, hemochromatosis, and other causes. These disorders cause insulin deficiency through destruction of the pancreatic β-cell. The degree of diabetes is generally proportionate to the amount of injury to the pancreas, although it is important to note that certain individuals may have limited β-cell reserve (such as those with early type 2 diabetes) before pancreatic injury and may therefore 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 diabetogenic if secreted in excess. Examples of such hormones include cortisol, growth hormone, glucagon, and epinephrine. 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 frank diabetes. Treatment, in addition to the usual care of diabetes, should be directed toward controlling the underlying hormonal excess, such as removing an endocrine tumor.

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 and cause impaired insulin secretion with relatively normal insulin action and are inherited in an autosomal-dominant manner. There are also several genetic disorders that lead to abnormal insulin action. Examples include leprechaunism, type A insulin resistance, and Rabson-Mendenhall syndrome.[8]

Physicians in training today can expect to treat many patients with diabetes during their career. It is important to note, as described above, that the number of patients who have diabetes will increase substantially in the foreseeable future as the population ages, becomes more ethnically diverse, and unless current trends are abated, becomes more obese. Furthermore, as the number of patients with diabetes grows, so will the pharmaceutical armamentarium used to control the disorder. These two factors make it important to focus a great deal of time and effort to understanding this disease during training because of its importance in many patients' lives and to society as a whole. During the next 2 years, *Clinical Diabetes* will help physicians in training master the core features of this disorder.

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Michael J. Fowler, MD, is an assistant professor of medicine in the Division of Diabetes, Endocrinology, and Metabolism, Vanderbilt Eskind Diabetes Clinic, at Vanderbilt University Medical Center in Nashville, Tenn. He is an associate editor of Clinical Diabetes.