THE NATURAL HISTORY OF TYPE 2 DIABETES

Implications for Clinical Practice

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Effective therapy of type 2 diabetes has been a challenge. Patients with type 2 diabetes face a chronic, progressive disease that leads to complications that profoundly affect both quality of life and longevity. Additionally, the clinician is challenged with a heterogeneous disorder that has a wide spectrum of complications that progress and responses to treatment that vary with each individual patient over time. The goal of this article is to acquaint the primary care provider with the pathogenesis of type 2 diabetes and how this condition progresses from an early asymptomatic stage with insulin resistance to mild postprandial hyperglycemia to frank diabetes requiring pharmacologic intervention. Understanding this natural history of type 2 diabetes helps guide the clinician in formulating an effective treatment regimen that reflects the pathologic differences between the various stages of this disease. The most successful treatment strategies hinge on this key point: the optimal regimen (particularly regarding medication choices) will change for each individual patient as the diabetes progresses. Clinicians now are able to make more sophisticated and effective management plans based on current knowl-

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edge gained from large clinical studies and the ever-growing number of medications available for the treatment of type 2 diabetes.

The term *impaired glucose tolerance* (IGT) or prediabetes was first coined in 1979 by the World Health Organization (WHO) and The National Diabetes Data Group (NDDG) to replace the terms *borderline, chemical,* and *asymptomatic diabetes mellitus*. In 1997, the American Diabetes Association's (ADA) Expert Committee recommended the following criteria for IGT: a normal fasting plasma glucose (less than 126 mg/dL) and a plasma glucose of 140 mg/dL or greater, but less than 200 mg/dL 2 hours after a 75 g oral glucose challenge. This stage of mild postprandial hyperglycemia is both an important area of clinical research and an extremely useful marker of patients at risk for developing of type 2 diabetes. Patients with IGT may benefit from timely patient education and perhaps even more aggressive forms of intervention such as diet, exercise, or medication. Clinical research interests have expanded beyond developing new ways to treat type 2 diabetes. Major efforts now are being made to determine who is at the highest risk for diabetes and to formulate cost-effective prevention strategies aimed at these individuals.

PATHOGENESIS OF IMPAIRED GLUCOSE TOLERANCE AND TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus is a heterogeneous disorder; three basic metabolic defects characterize the disease: insulin resistance, an insulin secretory defect that is not autoimmune mediated, and an increase in glucose production by the liver. The cause of these metabolic defects, and therefore the cause of type 2 diabetes, largely is unknown. Clearly, type 2 diabetes has a strong genetic component and is found more frequently in certain families and ethnic minority groups such as Hispanics, African Americans, Pacific Islanders, and Native American Indians. Furthermore, twin studies have shown that monozygotic twins have at least a twofold greater concordance in the incidence of diabetes compared with dizygotic twins.[30] Great effort has been made to find single or clustered genetic defects common to diabetics. The relative failure in finding candidate genes that lead to type 2 diabetes most certainly suggests that the disease is extremely heterogeneous, with probably multigenetic defects. Furthermore, many acquired factors have been identified that also play a role in the pathogenesis of the disease. Figure 1 depicts the sequence of events that occur before frank diabetes develops and the potential role of these genetic and acquired factors in the basic metabolic defects that characterize type 2 diabetes.

Although little headway has been made in attributing any specific underlying genetic defect to type 2 diabetes, considerable information is available on the underlying metabolic defects. As mentioned above, the defects are a triad of insulin resistance, β-cell dysfunction, and increased

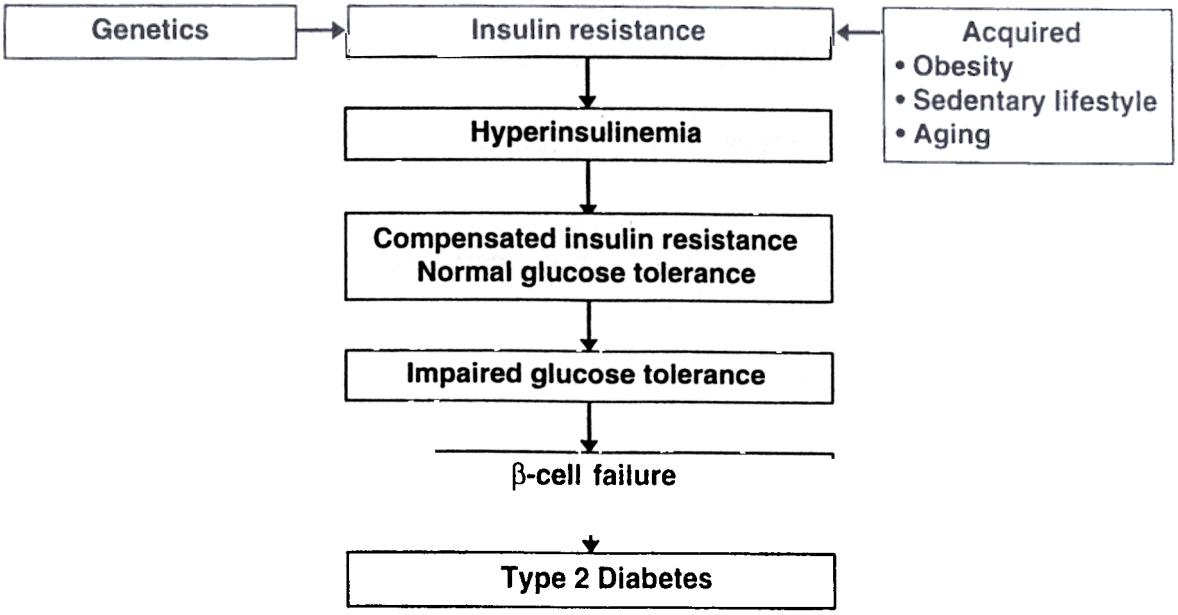

Figure 1. Progression to type 2 diabetes. The etiologic sequence of the development of Type 2 diabetes. FFA-free fatty acid.

hepatic glucose production. Some controversy still exists as to whether insulin resistance or inadequate insulin secretion occurs first in the pathogenesis of diabetes; a general consensus, however, has emerged that insulin resistance is the primary defect in type 2 diabetes.[9,33] Insulin resistance is characterized by a subnormal response to a given concentration of insulin. Insulin resistance is measured indirectly by a fasting insulin level (higher levels of insulin correspond to higher degrees of insulin resistance) or directly in a research setting using a euglycemic insulin-clamp technique.

The cause of pancreatic β-cell dysfunction, the second metabolic defect that appears in type 2 diabetics, is still a focus of intense research and debate. Several key pieces of information on the specific β-cell defects in type 2 diabetes, however, are well characterized.[22] Changes in the β-cell occur early in the pathogenesis of type 2 diabetes. In fact, in patients with insulin resistance, a measurable change occurs in the pulsatile secretory pattern of insulin release before diabetes or even IGT develop. The pathogenic and clinical relevance of this early defect is unclear. Later defects in glucose-stimulated insulin release occur that clearly play a role in the progression to diabetes and then continue to affect the course of diabetes itself. For example, the decline in insulin levels, and thus a decrease in insulin's inhibitory effects, allows for increased hepatic glucose production. Beta-cell exhaustion may be genetically mediated, termed *preprogrammed β-cell failure*, or result from hypothesized damage to the β-cell from chronic exposure to hyperglycemia (glucose toxicity model) or result from adverse affects of increased free fatty acids. Whatever the underlying causes and mechanisms it is clear that the full phenotypic expression of type 2 diabetes requires both insulin resistance and β-cell dysfunction.

PROGRESSION OF IMPAIRED GLUCOSE TOLERANCE TO MILD TYPE 2 DIABETES

The metabolic sequences that eventually lead to type 2 diabetes precede the development of hyperglycemia by years or even decades. As shown in Figure 2, studies have shown that 20% of type 2 diabetics have retinopathy at the time of diagnosis, a percentage that increases linearly with the duration of diabetes. Epidemiologists have extrapolated this data to estimate that the onset of detectable retinopathy probably occurs an average of 6.5 years before the clinical diagnosis of diabetes. Diabetic retinopathy does not develop until hyperglycemia persists for several years and thus the true onset of type 2 diabetes often is more than 10 years before the clinical diagnosis.

Insulin resistance, that is resistance to insulin's role in promoting glucose uptake by skeletal muscle and fat cells, is the initial metabolic defect. Figure 3 summarizes the natural history of this defect in the progression of IGT to frank type 2 diabetes. At first, the pancreatic β-cell is able to compensate by increasing insulin levels, leading to hyperinsulinemia. This compensation is able to keep glucose levels normalized for a period of time (up to several years), but IGT develops with mild postprandial hy-

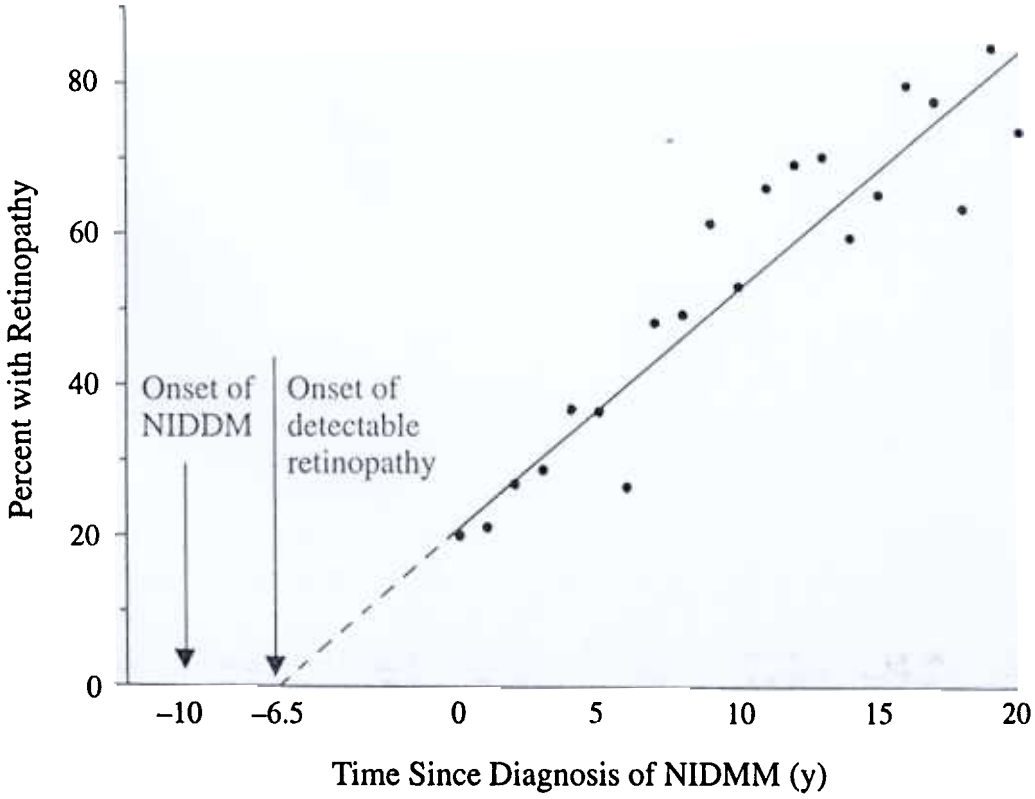

Figure 2. The prevalence of retinopathy at the time of diagnosis of type 2 diabetes. Extrapolation of the data indicates the time at which retinopathy first developed. Onset of type 2 diabetes often is several years before clinical evidence of retinopathy. (*From* Klien R: Hyperglycemia and microvascular and macrovascular disease in diabetes. Diabetes Care 18:258–268, 1995; with permission.)

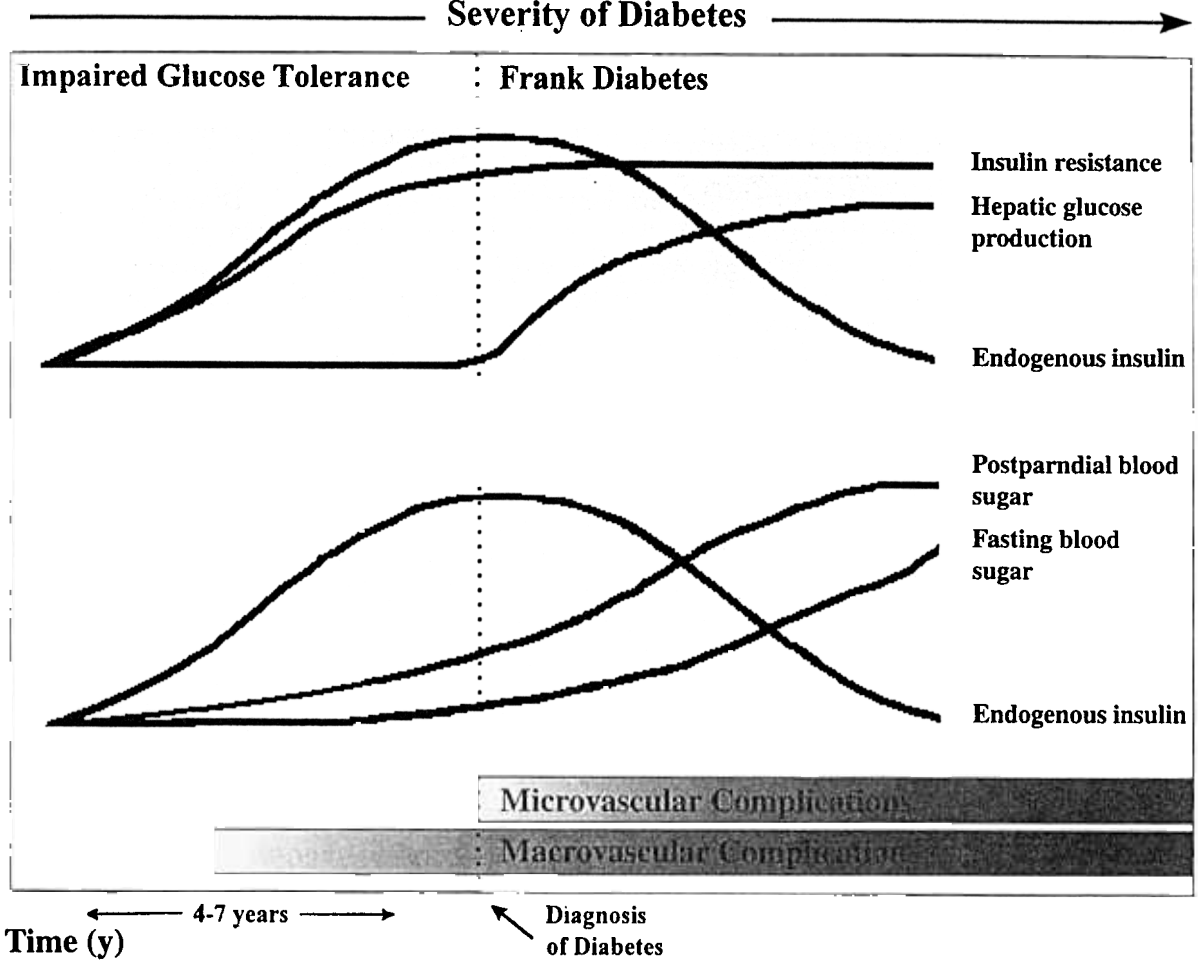

Figure 3. Natural history of type 2 diabetes. The prediabetic state of impaired glucose tolerance is characterized by increasing insulin resistance, compensatory hyperinsulinemia, and mild postprandial hyperglycemia. Initially, fasting blood glucose levels (FBG) are maintained in near normal ranges. The β-cell then begins to fail, resulting in higher postprandial glucose levels and, with further loss of insulin secretory capacity and impaired glucorecognition, FBG and hepatic glucose production increase.

perglycemia. As insulin resistance worsens, more global defects in insulin secretion occur that result in increased hepatic glucose production. These defects together lead to further elevations in the fasting blood sugar. The ADA has encouraged the use of the term *impaired fasting glucose* (IFG), which is defined as having a fasting plasma glucose (FPG) level of 110 mg/dL or greater but less than 126 mg/dL,[12] to denote this stage. Clinically IFG and IGT represent a similar point along the continuum between normal glucose tolerance and frank diabetes: an essentially asymptomatic, but still potentially pathologic stage characterized by mild hyperglycemia. Both IGT and IFG serve as markers for those who are at greatest risk for developing type 2 diabetes.

Numerous prospective and cross-sectional studies have determined the cumulative risk of developing type 2 diabetes once IGT is recognized.[7,30] Table 1 summarizes many of these studies. Depending on the duration of follow-up and the ethnic group studied, prospective clinical

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