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The Natural History of Type 2 Diabetes: Practical Points to Consider in Developing Prevention and Treatment Strategies

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Type 2 diabetes, previously referred to as *adult-onset* or *non-insulin-dependent diabetes,* progresses from an early asymptomatic stage with insulin resistance to mild postprandial hyperglycemia to frank diabetes requiring pharmacological intervention. Understanding this natural history of type 2 diabetes will guide primary care providers in formulating effective treatment regimens that reflect the pathological differences between these stages of the disease. The optimal medication regimen, when used in conjunction with dietary changes and exercise, will require modifications for each patient as the disease progresses.

The term *impaired glucose tolerance* (IGT) or *pre-diabetes* was first coined in 1979 by the World Health Organization and the National Diabetes Data Group to replace the terms *borderline, chemical,* and *asymptomatic diabetes mellitus*. In 1997, an expert committee of the American Diabetes Association recommended the following criteria for IGT: a normal fasting plasma glucose (<126 mg/dl) with a postprandial plasma glucose of ≥140 mg/dl but <200 mg/dl 2 h after a 75-g oral glucose challenge.[1]

This stage of mild postprandial hyperglycemia is an extremely useful marker of patients at risk for the eventual development 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. An estimated 15.7 million Americans have type 2 diabetes, representing 5.9% of the population. Only two-thirds of those affected are diagnosed and are being actively treated. Although these numbers are staggering, there are even more potential diabetic patients waiting in the wings: the prevalence of IGT is estimated to be 22 million cases in the United States.[2]

Pathogenesis of Impaired Glucose Tolerance and Type 2 Diabetes Mellitus

Type 2 diabetes 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, is largely 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 American Indians. Candidate genes have not yet been identified as the cause of type 2 diabetes, and it is likely that the disease is the result of multigenetic defects. Many acquired factors also play a role in the pathogenesis of the disease. Factors that contribute to insulin resistance include obesity, aging, and a sedentary lifestyle. Other acquired factors that may contribute to the insulin secretory defect include chronic glucotoxicity and elevated free fatty acid levels.

As mentioned above, the metabolic defects underlying type 2 diabetes are a triad of insulin resistance, β-cell dysfunction, and impaired hepatic glucose production. Some controversy still exists as to whether insulin resistance or inadequate insulin secretion occurs first in the pathogenesis of diabetes. However, a general consensus has emerged that insulin resistance is the primary defect in type 2 diabetes.[3] Insulin resistance is characterized by a subnormal response to a given concentration of insulin and can be measured indirectly by a fasting insulin level: higher levels of insulin correspond to higher degrees of insulin resistance.

The cause of pancreatic β-cell dysfunction, the second metabolic defect that appears in type 2 diabetes, is still a focus of intense research and debate.[4] Changes in the β-cell do occur early in the pathogenesis of type 2 diabetes. However, it is later defects in glucose-stimulated insulin release 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. β-Cell exhaustion may be genetically mediated or result from hypothesized damage to the β-cell from chronic exposure to hyperglycemia, or it may result from adverse effects 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. 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 1 summarizes the natural history of this defect in the progression of IGT to overt 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 hyperglycemia.

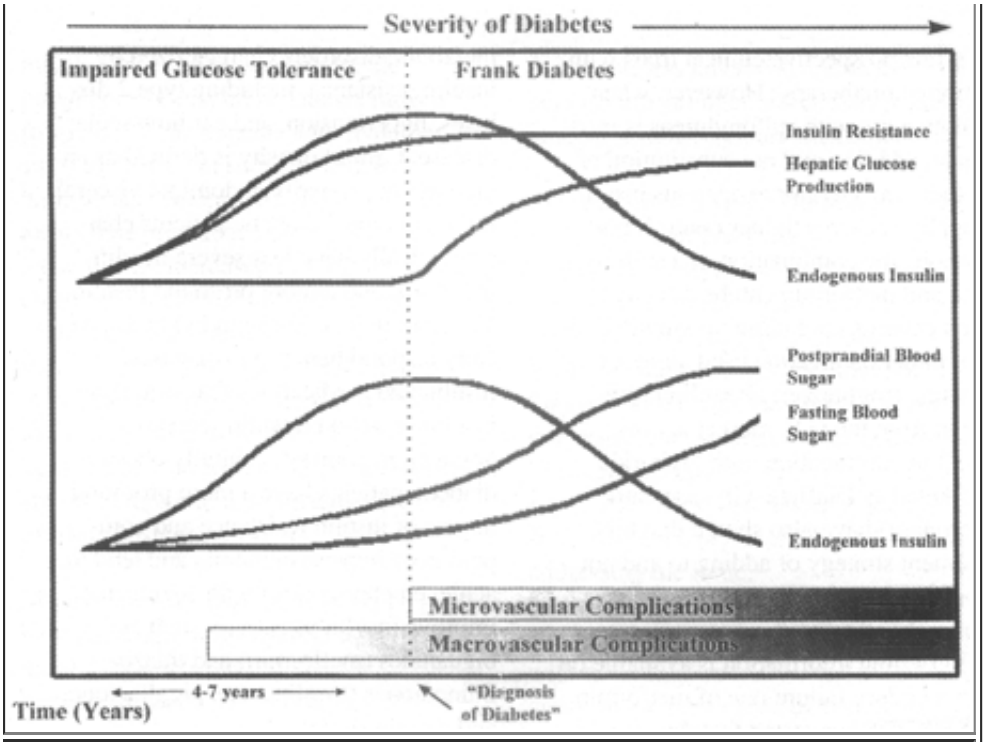

Figure 1. The natural history of insulin resistance, progressing from impaired glucose tolerance to overt type 2 diabetes.

As insulin resistance worsens, more global defects in insulin secretion occur that result in increased hepatic glucose production. Together these defects lead to further elevations in fasting blood glucose. The American Diabetes Association has encouraged the use of the term *impaired fasting glucose* (IFG) to denote this stage. IFG is defined as having a fasting plasma glucose level ≥110 mg/dl but <126 mg/dl.[1]

Clinically, IFG and IGT represent a similar point along the continuum between normal glucose tolerance and frank diabetes: an essentially asymptomatic but still potentially pathological 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 clinical studies have determined the cumulative risk of developing type 2 diabetes once IGT is recognized.[5] Depending on the duration of follow-up and the ethnic group studied, prospective clinical trials have shown that approximately one-third of individuals with IGT will progress to type 2 diabetes. African Americans, American Indians, Hispanics, and Pacific Islanders all have a higher-than-average incidence of both IGT and type 2 diabetes.

The progression from IGT to early type 2 diabetes is marked by a decrease in β-cell function and thus a decline in insulin secretion (see Fig. 1). It is the failure over time of the β-cell to compensate for insulin resistance with hyperinsulinemia that marks the beginning of type 2 diabetes. As long as the pancreatic β-cell is able to compensate for insulin resistance by increasing insulin production and secretion, glucose levels remain normal or near normal. However, eventually the β-cell begins to fail, and insulin secretion falls, resulting in hyperglycemia. Eventual failure of the pancreatic β-cell has been a predictable abnormality leading to

changes in a patient's response to various therapies.

Two additional pathophysiological changes become manifest during the transition from IGT to type 2 diabetes. Insulin resistance becomes more severe, a progression that may be due not only to full expression of genetic defects, but also to acquired factors such as obesity, decreased physical activity, and aging. The second change is an increase in basal hepatic glucose production. Although early type 2 diabetes may be as asymptomatic as IGT, the degree of hyperglycemia is now severe enough to start the clock for the development of microvascular complications.

Progression of Mild Type 2 Diabetes to Insulin-Requiring Type 2 Diabetes

Insulin resistance is the primary pathogenic insult underlying type 2 diabetes and remains a factor throughout the natural history of the disease. Yet, it is changes in β-cell function that determine both the onset of frank diabetes and the progression of the disease.

As outlined above, the transition from normal glucose tolerance to IGT is marked by hyperinsulinemia that reflects a quantitatively appropriate response on the part of the β-cell to insulin resistance and postprandial hyperglycemia. Over time, however, the β-cell becomes refractory to glucose, and although the cell continues to secrete supraphysiological amounts of insulin, a relative insulin deficiency develops, and hyperglycemia worsens to the point of frank diabetes. Later, the β-cell's secretory capacity further declines. An absolute insulin deficiency develops, and eventually the β-cell becomes unresponsive to interventions aimed at improving β-cell function such as insulin secretagogues (including sulfonylureas). By this point in the disease process, patients with type 2 diabetes will most likely require exogenous insulin or multiple oral agents used in combination to achieve adequate glucose control.

These stages in the natural history of type 2 diabetes are important to consider in choosing and modifying a treatment regimen. Different classes of antidiabetic agents appear to be effective at different stages. This concept has been demonstrated repeatedly in prospective clinical trials that determine the secondary failure rates for medications used in the treatment of type 2 diabetes. Failure of an intervention that was initially effective often indicates progression of the disease. The treatment plan must then be modified to regain glycemic control.

Secondary failure rates in the use of sulfonylureas have been studied, and these trials are particularly useful in understanding the role β-cell dysfunction plays in the progression of type 2 diabetes. One of these studies was conducted as part of the United Kingdom Prospective Diabetes Study (UKPDS).[6,7]

The UKPDS was a long-term, large-scale, prospective series of clinical trials designed to address issues involving effective therapy and micro- and macrovascular complications of type 2 diabetes and its treatments. In the UKPDS, more than 5,000 newly diagnosed type 2 diabetic patients were randomized to receive either chlorpropamide (Diabinese) or glibenclamide (not available in the United States), which are both sulfonylureas; metformin (Glucophage); or insulin. Failure of treatment was prospectively defined as a fasting plasma glucose >108 mg/dl.

The linear overall failure rate in the UKPDS of all treatment groups was an impressive 7% per year. By the end of the 11-year study, well over 50% of subjects had required additional therapy. Those subjects with the lowest level of β-cell function had the highest rate of treatment failure with sulfonylureas. These results support the general belief that sulfonylurea failure is due to declining β-cell function and not to some ill-defined effect of the medication itself.

The UKPDS also found an accelerated rate of sulfonylurea failures among the morbidly obese (individuals with a body mass index [BMI] $\geq$30 kg/m^2) as compared with the moderately obese (BMI between 25 and 30 kg/m^2). Obesity and duration of diabetes clearly have an impact on β-cell function beyond their effects on insulin resistance and, therefore, affect response to antidiabetic therapy.

As patients progress along the natural history of diabetes, multidrug combinations will most likely be required to achieve glycemic goals. There have been few prospective clinical trials with combination therapy. However, when monotherapy with sulfonylureas is inadequate, addition and not substitution of another oral agent or exogenous insulin typically achieves tighter control. For example, the combination of a sulfonylurea and metformin can be effective when patients are failing maximum doses of either medication used alone.[8] Trials using troglitazone (Rezulin [withdrawn from the U.S. market at press time]) in combination with glyburide (marketed as DiaBeta, Glynase, and Micronase) have also shown that this treatment strategy of adding to and not substituting for sulfonylureas can be extremely effective.[9]

Very little information is available on the secondary failure rate of metformin. The UKPDS suggested that the secondary failure rate for metformin would appear similar to what was seen with sulfonylureas. Information is now becoming available on the secondary failure rate of the newest class of insulin sensitizers, the thiazolidinediones, which include troglitazone, pioglitazone (Actos), and rosiglitazone (Avandia). These agents work mainly by improving peripheral insulin resistance in skeletal muscle and, to a lesser degree, by reducing excess hepatic glucose production. Thiazolidinediones' effect on the pancreatic β-cell is still being studied, but it clearly does not directly stimulate insulin secretion. Given that thiazolidinediones' primary effect is on insulin resistance, a pathogenic factor that is present throughout the continuum of IGT to mild type 2 diabetes to end-stage disease, it is anticipated that the secondary failure rate of this class of medication will be low relative to sulfonylurea therapy.[9]

Role of Obesity in the Pathogenesis and Treatment of Type 2 Diabetes

Obesity has a profound impact on the progression of the diabetic state and on patients' responses to any particular form of treatment. Central obesity often precedes the development of many metabolic disorders characterized by insulin resistance, including type 2 diabetes, hypertension, and cardiovascular disease. Central obesity is defined as an increase in primarily abdominal visceral fat. Lean type 2 diabetic patients characteristically have less severe insulin resistance and a more profound insulin secretory defect. These individuals typically respond better to exogenous insulin and medications that stimulate insulin secretion (insulin secretagogues). In contrast, centrally obese diabetic patients have a more profound

degree of insulin resistance and compensatory hyperinsulinemia and tend to achieve better control with agents that improve insulin sensitivity such as biguanides (metformin) and thiazolidinediones (troglitazone, pioglitazone, and rosiglitazone).

Relative Prevalence of Type 2 Diabetes, IGT, and Insulin Resistance: Implications for Intervention

The incidence of IGT and type 2 diabetes is rising annually because the major risk factors for these conditions are becoming more prevalent. These risk factors include obesity, an increase in the mean age of the population, and more sedentary lifestyles. However, the prevalence of IGT and type 2 diabetes is just the tip of the iceberg when one considers the prevalence of the major pathogenic lesion itself: insulin resistance. Insulin resistance is the featured defect in Syndrome X, a constellation of metabolic abnormalities that is even more common than type 2 diabetes and, like diabetes, is associated with an increased risk of cardiovascular disease.

Almost 900 subjects representing a cross-section of the general population, aged 40-79 years, were evaluated for the coexistence of insulin resistance and one of a number of metabolic disorders. These disorders included IGT, type 2 diabetes, dyslipidemia, hyperuricemia, and hypertension. When the investigators considered the prevalence of insulin resistance in each of the metabolic disorders separately, the prevalence of insulin resistance ranged from 58.0% (in subjects with hypertension) to 88.1% (in subjects with low high-density lipoprotein [HDL] cholesterol). The prevalence of insulin resistance further increased to 95.2% when clusters of metabolic disorders were considered, such as the coexistence of IGT or diabetes with low HDL, hyperuricemia, and hypertension. In addition, individuals who were obese (BMI >25 kg/m^2) and who had no other metabolic abnormalities had a prevalence of insulin resistance of 42%.

Macrovascular Disease and IGT

Few clinicians would doubt that type 2 diabetic patients have a threefold increased risk of coronary artery disease, but too few clinicians realize that IGT is associated with at least a twofold increased risk. IGT and insulin resistance are associated with low levels of HDL cholesterol, increases in triglycerides, and hypertension. These metabolic problems, in combination with changes in factors involved in the coagulation cascade, may result in accelerated atherosclerosis and early macrovascular complications.

Prospective studies have shown that cardiovascular risk factors are associated with a subsequent diagnosis of IGT, suggesting that there is overlap between the pathogenic mechanisms for macro-vascular disease and IGT.[10] Studies such as these underscore that early intervention in patients with IGT has the potential not only to delay progression to type 2 diabetes, but also to treat early macrovascular disease. Therefore, IGT should be treated as a disease entity itself, worthy of clinical screening and intervention.

Studies have shown that individuals can move in and out of IGT, suggesting that there are potentially reversible components of IGT that could be addressed before its progression to frank diabetes. It makes sense that the most opportune time to intervene is at the beginning of this process, when complications are fewer and less advanced and when patients are younger and possibly more amenable to lifestyle

modifications.

Prevention of Type 2 Diabetes With Diet and Exercise

Sedentary lifestyle and poor physical fitness are both risk factors for the progression of IGT to type 2 diabetes. Although these factors are interrelated, they are both reversible and are potential targets for preventive intervention. The same comments also apply to obesity, a risk factor that has been identified unequivocally in all clinical trials addressing the issue.

Several clinical trials have demonstrated the utility of diet or exercise, with or without specific weight loss goals, in the prevention of type 2 diabetes in high-risk individuals. Studies have also demonstrated that even modest amounts of weight loss have beneficial effects on glucose control.

The Malmo Feasibility Study involved a 6-year protocol during which a cohort of early, asymptomatic type 2 diabetic patients and subjects with IGT were given diet instructions and/or physical training. Weight loss of 2.33.7% was achieved and maintained in the treatment group (compared with 0.51.7% loss achieved by the two control groups, one composed of subjects with IGT and no intervention and the other composed of control subjects with normal glucose tolerance). In the treated group, glucose tolerance was normalized in >50% of those with IGT, and nearly 50% of the early diabetic patients were in remission at the end of the study period. Further analysis showed that weight loss and improved fitness were each beneficial to glucose tolerance, but that when taken together, the benefit was additive.[11]

Prevention of Type 2 Diabetes With Pharmacological Agents

Several classes of oral antidiabetic agents are now available for the treatment of type 2 diabetes; however, not all may be appropriate as preventive agents to prevent or delay the progression of IGT to diabetes. All forms of antidiabetic therapy, including sulfonylureas, can potentiate a partial reversal of insulin resistance due to improvement of the hyperglycemia-induced component of insulin resistance (peripheral glucose toxicity). For example, the improvement in insulin resistance that has been demonstrated in sulfonylurea-treated diabetic patients is likely secondary to the reduction in glycemia. Individuals with IGT do not have a significant degree of glycemia and, therefore, do not have a significant component of peripheral glucose toxicity. These individuals would not be expected to improve their insulin resistance with sulfonylurea therapy. There is also the risk of hypoglycemia and further weight gain with sulfonylureas.

Thiazolidinediones (troglitazone, rosiglitazone, and pioglitazone), and to a lesser extent, biguanides (metformin), act as insulin sensitizers and may well have a beneficial role in preventing type 2 diabetes in individuals with IGT and other additional risk factors for diabetes. Furthermore, these two types of oral antidiabetic agents do not act by stimulating insulin secretion and do not have the potential to cause hypoglycemia when used as monotherapy. Metformin also reduces insulin resistance. However, its main mechanism of action is through decreasing hepatic glucose production (HGP), and subjects with IGT do not have significantly increased HGP. Thiazolidinediones work mainly by improving peripheral insulin resistance and have been studied in subjects with IGT.[12] Approximately 80% of the subjects with IGT who underwent 12 weeks of troglitazone therapy reverted to

normal glucose tolerance.[13] Long-term clinical trials are currently underway to assess the benefits and efficacy of thiazolidinediones and biguanides in the prevention of type 2 diabetes.

Summary

The development of type 2 diabetes can be viewed as a continuum starting with the fully compensated insulin-resistant state and progressing to IGT and later, frank type 2 diabetes. A triad of metabolic defects characterize type 2 diabetes: insulin resistance, nonautoimmune β-cell dysfunction, and inappropriately increased HGP.

The natural history of type 2 diabetes directly reflects the interrelationships among these three defects. The primary and earliest pathogenic lesion is insulin resistance, and the β-cell is able to compensate for a variable length of time by secreting supraphysiological amounts of insulin. IGT is characterized by insulin resistance, compensatory hyperinsulinemia, and mild postprandial hyperglycemia. Over time, however, the β-cell begins to fail, and as relative insulin deficiency occurs, fasting hyperglycemia and full-blown type 2 diabetes develop. In addition, as insulin levels fall, the inhibitory effect of insulin on HGP decreases, and significant fasting hyperglycemia develops. Further progression of the disease is marked by an absolute insulin deficiency. Obesity, aging, weight gain in adulthood, and physical inactivity are some of the environmental factors that affect the natural history of diabetes, affecting its progression at all points in the continuum.

Screening patients for IGT is probably the best test to identify high-risk individuals, since postprandial hyperglycemia occurs typically before the onset of fasting hyperglycemia in the natural history of type 2 diabetes. However, IGT relies on an oral glucose tolerance test for diagnosis--a test that has largely been replaced by fasting plasma glucose in general clinical practice because of convenience and greater reproducibility. This change in practice patterns underscores the importance of the new impaired fasting glucose criteria (i.e., glucose between 110 and 126 mg/dl) in the clinical setting to identify people with glucose intolerance at an earlier stage in the natural history of the disease. The presence of both IFG and IGT indicate an increased risk for other syndromes associated with insulin resistance, such as hypertension and dyslipidemia, which also require an aggressive diagnostic and therapeutic plan.

Understanding the natural history of type 2 diabetes aids clinicians in identifying those patients most at risk for developing diabetes and in developing an effective treatment plan for those who already have the disease. The available classes of oral antidiabetic agents have different mechanisms of action and are, therefore, potentially most effective at different stages in the continuum from IGT and IFG to frank diabetes. Given that insulin resistance is the major pathogenic factor in the *pre-diabetic* state of IGT and continues to persist in frank diabetes, thiazolidinediones and biguanides (insulin sensitizers) may be extremely useful as first-line agents in the early treatment of diabetes and in its prevention.

The potential benefits of intervening before the onset of diabetes and aggressively treating once the disease becomes manifest are tremendous. Identifying and treating individuals with IGT will most likely reduce the incidence of macrovascular disease and type 2 diabetes. Early intervention in type 2 diabetes reduces the incidence of

macro- and microvascular disease and will most likely slow the progression of the disease itself. Primary care providers are uniquely poised to promote and provide early prevention and to have a substantial impact on lessening the burden placed on individuals and society by type 2 diabetes.

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