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-
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. 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
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.\textsuperscript{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.\textsuperscript{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. Extrap-
olation 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 glucoregulation, FBG and hepatic glucose production increase.

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, 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. Table 1 summarizes many of these studies. Depending on the duration of follow-up and the ethnic group studied, prospective clinical
Table 1. INCIDENCE OF TYPE 2 DIABETES IN PERSONS WITH IMPAIRED GLUCOSE TOLERANCE

<table>
<thead>
<tr>
<th>Population with IGT</th>
<th>Mean Age (y)</th>
<th>No. of Subjects</th>
<th>Duration of Follow-up † (y)</th>
<th>Average Annual Incidence of Type 2 Diabetes* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nauruans</td>
<td>38</td>
<td>51</td>
<td>6.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Pima Indians</td>
<td>32</td>
<td>384</td>
<td>3.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Maltese</td>
<td>35–74</td>
<td>75</td>
<td>6.0</td>
<td>5.1</td>
</tr>
<tr>
<td>French</td>
<td>44–55</td>
<td>486</td>
<td>2.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Colorado</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanics</td>
<td>20–74</td>
<td>128</td>
<td>4.0</td>
<td>8.7</td>
</tr>
<tr>
<td>Non-Hispanic whites</td>
<td>20–74</td>
<td>128</td>
<td>4.0</td>
<td>5.3</td>
</tr>
<tr>
<td>South African Indians</td>
<td>49</td>
<td>128</td>
<td>4.0</td>
<td>12.6</td>
</tr>
<tr>
<td>San Antonio, TX</td>
<td>25–64</td>
<td>211</td>
<td>8.0</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*World Health Organization guidelines were used for the diagnostic criteria of IGT and type 2 diabetes in each study.
†Duration of follow up are mean values.


Trials have shown that approximately one third of individuals with IGT progress to type 2 diabetes. The role of race and ethnicity in the incidence of progression to diabetes cannot be overemphasized. African Americans, Native American Indians, Hispanics, and Pacific Islanders all have a higher than average incidence of both IGT and type 2 diabetes. For example, the incidence of IGT is 17.6 per 1000 person-years in non-Hispanic whites and 32.6 per 1000 person-years in Hispanics. Furthermore, in a Colorado-based study, Hispanics with IGT had an 8.7% annual incidence of type 2 diabetes, whereas non-Hispanic whites with IGT had an incidence of 5.3% per year of 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. 3). 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. So 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. 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 other additional pathophysiologic changes become manifest during the transition from IGT to type 2 diabetes. Insulin resistance becomes more severe, a progression that may not be caused only by full expression of genetic defects, but also by acquired factors such as obesity, decreased physical activity, and aging. As discussed in more detail later
and summarized in the box below, all of these factors have been identified epidemiologically as risk factors for type 2 diabetes and have the potential to be causally related to the appearance and progression of insulin resistance.8,9,10,14,29 The second change is an increase in basal hepatic glucose production (HGP). Although early type 2 diabetes may be as asymptomatic as the preceding stage of IGT, the degree of hyperglycemia is now severe enough to start the clock for the development of microvascular complications.

<table>
<thead>
<tr>
<th>Increased age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity (urbanization/westernization)</td>
</tr>
<tr>
<td>Hispanic, African American, Native American Indian, and Pacific Islander</td>
</tr>
<tr>
<td>Family history of diabetes</td>
</tr>
<tr>
<td>Central obesity (moderate and morbid)</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
</tr>
<tr>
<td>History of gestational diabetes</td>
</tr>
<tr>
<td>Impaired glucose tolerance or impaired fasting glucose</td>
</tr>
<tr>
<td>Elevated blood pressure*</td>
</tr>
<tr>
<td>Elevated triglycerides*</td>
</tr>
<tr>
<td>Low high density lipoprotein (HDL)</td>
</tr>
<tr>
<td>*This has not proven to be an independent risk factor in all studies.</td>
</tr>
</tbody>
</table>

**PROGRESSION OF MILD TYPE 2 DIABETES MELLITUS TO INSULIN-REQUIRING TYPE 2 DIABETES MELLITUS**

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 the changes in β-cell function that determines both the onset of frank diabetes and the progression of the disease once established. 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 supraphysiologic 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, in terms of maximum secretory response, pulsatility, and overall plasma insulin levels.22 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, the type 2 diabetic most likely requires 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) (See article by Baldeweg and Yudkin elsewhere in this issue.) In the UKPDS, over 5000 newly diagnosed type 2 diabetics were randomized to receive either chlorpropamide or glibenclamide (both sulfonylureas), metformin, or insulin and were then followed for 11 years. Failure of treatment was prospectively defined as a fasting plasma glucose greater than 108 mg/dL. The linear overall failure rate in the UKPDS of all treatment groups was an impressive 7% per year (Fig. 4). Previous smaller-scale studies have estimated failure rates of 1.4% to 5.6% per year. By the end of the 11-year study, well over 50% of subjects required additional therapy (Fig. 4). 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 caused by declining β-cell function, not by an ill-defined effect of the medication itself. This study also found an accelerated rate of sulfonylurea failures among younger diabetics (i.e., subjects less than 54 years of age at the time of diagnosis) and among the morbidly obese (i.e., those individuals with a body mass index [BMI] of 30 kg/m² or greater), compared with the moderately obese (i.e., those patients with a BMI between 25–30 kg/m²). Obesity and duration of diabetes clearly have an impact on β-cell function, beyond their affects on insulin resistance and, therefore, impact response to antidiabetic therapy. The role of obesity in the natural history of Type 2 diabetes is discussed in more detail later.

Studies focused on secondary failure rates of therapeutic interventions can be very useful, but several caveats must be considered when trying to apply such studies to actual clinical practice. These studies use medication failure as an endpoint, whereas in the practical treatment of diabetes, therapeutic intervention is needed as soon as the medication becomes inadequate in achieving ideal glucose control. Microvascular and macrovascular complications begin to develop in patients with baseline fasting plasma glucose levels much lower than those values used to determine secondary treatment failure in many clinical studies. For example, the initial 6-year data on sulfonylurea secondary failure rates among 1300 diagnosed diabetics in the UKPDS relied on a fasting plasma glucose of greater than 270 mg/dL as the definition for treatment failure.

As patients progress along the natural history of diabetes, multidrug combinations most likely are required to achieve glycemic goals. Pro-
Figure 4. Secondary failure rates in the United Kingdom Prospective Diabetes Study (UKPDS). Fasting plasma glucose (FPG, A) and HbA₁c (B) during the 11-year UKPDS. Subjects in the intensive treatment group (open circles), who were randomized to either insulin, metformin, or sulfonylurea, had an initial decrease in the FPG and HbA₁c. Both conventional (solid circles) and intensive treatment groups, however, had similar rates of deterioration in glycemic control for the remainder of the study. (From UK Prospective Diabetes Study Group: intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352:837–853, 1998; with permission.)

spective clinical trials with combination therapy are few in number; however, when monotherapy with sulfonylureas is inadequate, addition, not substitution, of another oral agent or exogenous insulin typically achieves improved control. For example, the combination of a sulfonylurea and metformin can be effective when patients are failing maximum doses of either medication used alone.³ In the US Pivotal trials, addition of met-
formin to the regimens of type 2 diabetics failing maximum doses of glyburide led to a significant improvement in FPG levels. There was no therapeutic benefit, however, in replacing glyburide with metformin in these same subjects. Trials using troglitazone in combination with glyburide also have shown that this treatment strategy of adding, not substituting, for sulfonylureas can be extremely effective.

Very little information is available on the secondary failure rate of metformin. Early studies have reported a failure rate of 5% to 10% per year, similar to the failure rates of sulfonylureas. The UKPDS provided indirect evidence supporting these earlier reports and suggested that the secondary failure rate for metformin would appear similar to what was seen with sulfonylureas (Fig. 4). The UKPDS data applicable to metformin as monotherapy, however, are difficult to determine because so few patients remained on metformin alone for the duration of the study.

Information is now becoming available on the secondary failure rate of the newest insulin sensitizer, troglitazone. This agent works mainly by improving peripheral insulin resistance in skeletal muscle and, to a lesser degree, by reducing excess hepatic glucose production. Troglitazone’s effect on the pancreatic β-cell is still being studied, but clearly it does not directly stimulate insulin secretion. Given that troglitazone’s primary affect 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 medication will be low relative to sulfonylurea therapy. It appears from several extension trials with troglitazone as monotherapy and in combination with sulfonylureas or insulin that the secondary failure rate for troglitazone is low. Figure 5 demonstrates the secondary failure rate in the troglitazone/sulfonylurea combination extension study (116 weeks); the subjects recruited for this study had diabetes for an average of 8 years before initial randomization.

ROLE OF OBESITY IN INSULIN RESISTANCE AND TYPE 2 DIABETES

Obesity has a profound impact on the progression of the diabetic state and on the patient’s response to any particular form of treatment. For example, lean type 2 diabetics characteristically have a 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, obese diabetics 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).

In the early 1980s, it became clear that 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 an increase primarily in visceral fat in the ab-
domen. Although this clinical association between insulin resistance and central obesity has been clear for some time, whether one condition causes the other or whether they develop concurrently still is controversial. It generally is agreed that the specific distribution of the increased adipose tissue, not just the presence of increased fat mass, is more important to the relationship between insulin resistance and obesity. A striking example of this point is a study comparing active and retired Japanese Sumo wrestlers. Sumo wrestlers still engaged in the sport have large amounts of subcutaneous abdominal fat and are quite insulin sensitive. Retired, inactive Sumo wrestlers and Japanese who have emigrated to the United States appear to redistribute their fat mass to visceral deposits, demonstrate clinically significant levels of insulin resistance, and have an increased incidence of type 2 diabetes and cardiovascular disease.

RELATIVE PREVALENCE OF TYPE 2 DIABETES MELLITUS, IMPAIRED GLUCOSE TOLERANCE, AND INSULIN RESISTANCE: IMPLICATIONS FOR INTERVENTION

The incidence of IGT and type 2 diabetes is rising annually because many of the major risk factors for these conditions are becoming more...
prevalent (e.g., obesity, an increase in the mean age of the population, more sedentary lifestyles). Based on data from the National Health and Nutrition Examination Surveys (NHANES II and III), type 2 diabetes is on its way to becoming the most common chronic disease in the United States. An estimated 16 million Americans have type 2 diabetes, representing more than 11% of the population. Only half of those affected actually are diagnosed and actively being treated. Approximately 600,000 new cases of type 2 diabetes present each year in the United States. Although these numbers are staggering, the prevalence of IGT is estimated to be 22 million cases in the United States. Among American adults under 74 years of age, 11% have IGT.16,17,27

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. Recall that 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. The prevalence of insulin resistance in the general population was the focus of a cross-sectional study, The Bruneck Study.2 Almost 900 subjects representing a cross-section of the general population, aged 40 to 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 HDL). 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 as defined by a BMI greater than 25 kg/m² and who had no other metabolic abnormalities had a prevalence of insulin resistance of 42%. Clearly, insulin resistance is extremely prevalent and, given its pathologic potential, may itself become a target for therapeutic intervention in the future.

Significantly more clinical research attention is being paid to the non-obese, insulin resistant individual as someone who may benefit from early, preventative treatment. The term metabolically obese, normal weight individual (MONW) has been coined to describe the person with hyperinsulinemia, insulin resistance, and hypertriglyceridemia who is predisposed to premature coronary heart disease and type 2 diabetes.31 As the Bruneck study suggests, the MONW patient is probably quite commonly encountered. Most likely, MONW represents one end of the spectrum of syndrome X, just as IGT represents one end of the continuum leading to diabetes. Careful studies involving MONW subjects suggest that they have had small amounts of weight gain in adulthood; an increase of 4 to 5 kg has been shown to be associated with clinically significant increases in the prevalence of diabetes and cardiovascular disease risk factors. Certainly, these patients may benefit from diet, exercise, and perhaps pharmacologic intervention early in the course of their metabolic disease.
MACROVASCULAR DISEASE AND IMPAIRED GLUCOSE TOLERANCE

Current research efforts in the prevention of type 2 diabetes reflect a growing interest in also addressing the pathologic consequences of the prediabetic state, IGT. Few clinicians doubt that type 2 diabetics 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. The NHANES II documented an increased prevalence of several cardiovascular findings in IGT subjects when compared with rates found in normal glucose tolerant individuals. Many of these findings—hypertension, angina, abnormal heart findings, and medical histories of arteriosclerosis and stroke—are signs or symptoms of macrovascular disease. As early as the 1970s, it has been clear that IGT is not itself associated with microvascular disease; the incidence of retinopathy and nephropathy correlate with the severity of hyperglycemia and duration of frank diabetes. In contrast, IGT is associated with an increased incidence of macrovascular disease and its complications. Impaired glucose tolerance 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. In fact, prospective studies have since shown that cardiovascular risk factors are associated with a subsequent diagnosis of IGT, suggesting that there is overlap between the pathogenic mechanisms for macrovascular disease and IGT. Studies such as these underscore that early intervention in patients with IGT has the potential to delay progression to type 2 diabetes, but to treat early macrovascular disease actively.

To underscore the association between insulin resistance and macrovascular disease, many have proposed that syndrome X or the insulin resistance syndrome are not adequate terms. These phrases do not emphasize that cardiovascular disease and type 2 diabetes are clinically the most important complications of insulin resistance in terms of morbidity and mortality. A newly coined term cardiovascular dysmetabolic syndrome has been proposed. The diagnostic criteria are dyslipidemia, insulin resistance, obesity, and high blood pressure (DROP).

INTERVENTIONS TO ALTER THE NATURAL HISTORY OF TYPE 2 DIABETES

As interest grows to investigate and promote clinical interventions to prevent the onset of type 2 diabetes and its vascular complications, some argue that IGT is not just a risk factor for type 2 diabetes but may also be a disease in itself, with associated complications of macrovascular disease. Impaired glucose tolerance, therefore, should be treated as a disease that is worthy of clinical screening and intervention. Furthermore, studies have shown that patients can move in and out of IGT. Between 30% to 50% of patients with IGT who were followed for 2 to 17 years reverted
back to normal glucose tolerance. Therefore, there are potentially reversible components of IGT that could be addressed before the progression of IGT 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. Early recognition of diabetes and identification of those with risk factors such as IGT allows the clinician and the patient to initiate treatments to both decrease the progression of diabetes or perhaps even delay the onset of diabetes.

PREVENTION OF TYPE 2 DIABETES WITH DIET AND EXERCISE

Sedentary lifestyle and poor physical fitness are risk factors for the progression of IGT to type 2 diabetes. Although these factors are interrelated, both are potential targets for preventative 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 prospectively studied the use of diet or exercise with or without specific weight loss goals in the prevention of type 2 diabetes in high risk individuals. In a small-scale study of 136 morbidly obese individuals with IGT, all but 27 of the subjects underwent bariatric surgery for weight loss and were then followed over 2 to 10 years for the progression of their IGT state to type 2 diabetes. Compared with the control group of 27, the treated group experienced approximately 50% reduction in excess body weight and a 30-fold reduction in the incidence of diabetes. A second study demonstrated that even modest amounts of weight loss had beneficial effects on glucose control. The Malmo Feasibility Study involved a 6-year protocol during which a cohort of early, asymptomatic type 2 diabetics and subjects with IGT were given diet instructions or physical training or both. Weight loss of 2.3% to 37% was achieved and maintained in the treatment group (compared with 0.5%–1.7% loss achieved by the two control groups: one group composed of subjects with IGT and no intervention and the second group composed of controls with normal glucose tolerance). In the treated group, glucose tolerance was normalized in more than 50% of those with IGT and nearly 50% of the early diabetics were in remission at the end of the study period. Most of the improvement in weight and glucose control was achieved in the first 2 years. Further analysis showed that weight loss and improved fitness when considered alone were each beneficial to glucose tolerance, but the benefit was additive when they were considered together.

PREVENTION OF TYPE 2 DIABETES WITH PHARMACOLOGIC AGENTS

Several classes of oral antidiabetic agents are available for the treatment of type 2 diabetes. Not all, however, may be appropriate as agents
to prevent or delay the progression of IGT to diabetes. All forms of anti-diabetic therapy, including sulfonylureas, can potentiate a partial reversal of insulin resistance caused by 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 diabetics likely is secondary to the reduction in glycemia. Individuals with IGT do not have a significant degree of hyperglycemia, therefore they do not have a significant component of glucose toxicity. These individuals would not be expected to improve their insulin resistance with sulfonylurea therapy. There also is 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 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 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. Troglitazone, a thiazolidinedione, works mainly by improving peripheral insulin resistance and has been studied in subjects with IGT. Approximately 80% of the subjects with IGT who underwent 12 weeks of troglitazone therapy reverted to normal glucose tolerance.1,28 As shown in Figure 6, the improvement in blood glucose levels was accompanied by a substantial improvement in insulin resistance as demonstrated by a marked reduction in basal and postprandial hyperinsulinemia.

THE DIABETES PREVENTION PROGRAM

An ongoing, multicenter, prospective, clinical trial in the United States initiated by the National Institutes of Health is attempting to prevent or delay the progression of IGT to frank diabetes. The trial is referred to as the Diabetes Prevention Program (DPP). Subjects at high risk for diabetes, that is, those with IGT, have been randomized to either lifestyle modifications or metformin. To keep the focus of the study on high risk populations, recruitment of participants emphasized the elderly (at least 20% of the subjects are 65 years of age or older), women with a history of gestational diabetes, minority groups with a high prevalence of diabetes (at least 50% of subjects are members of high risk minority groups), and those with obesity. All groups have received standard lifestyle recommendations, but the intensive lifestyle intervention group will have the goal of achieving and maintaining a 7% reduction in body weight and an increase in caloric expenditure of 700 kcal per week throughout the study period. The pharmacologic intervention arm is double blinded and placebo controlled. This large-scale study will help to answer the fundamental and crucial question of whether intensive lifestyle modifications or metformin can delay or prevent the development of type 2 diabetes. Other
large prevention trials that consider the role of acarbose (STOP NIDDM STUDY) and troglitazone in preventing the progression of IGT to type 2 diabetes are being conducted. The latter study is referred to as the *Diabetes Prevention Study with Troglitazone in Subjects with Impaired Glucose Tolerance*.

**SUMMARY**

Type 2 diabetes is at one end of the continuum represented by the fully compensated insulin resistant state to IGT to frank type 2 diabetes. A triad of metabolic defects characterize type 2 diabetes: insulin resistance, nonautoimmune β-cell dysfunction, and inappropriately increased hepatic glucose production. The natural history of type 2 diabetes directly reflects the interrelationships between these three defects (see Fig. 3). 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 supraphysiologic amounts of insulin. Impaired glucose tolerance is characterized
by insulin resistance, compensatory hyperinsulinemia, and mild postprandial hyperglycemia. Over time, the β-cell begins to fail and as relative insulin deficiency occurs, fasting hyperglycemia and full blown type 2 diabetes develop. 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 influence the natural history of diabetes and affect its progression at all points in the continuum.

Diabetes prevention trials, including the DPP, have prioritized using criteria for IGT (i.e., postprandial hyperglycemia) and not IFG as the diagnostic litmus test for subjects at high risk for developing diabetes. Screening subjects for IGT probably is the best test to identify high-risk individuals because postprandial hyperglycemia occurs typically before the onset of fasting hyperglycemia in the natural history of type 2 diabetes. Impaired glucose tolerance, however, relies on an oral glucose tolerance test for diagnosis, a diagnostic 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 IFG criteria (i.e., glucose between 110–126 mg/dL) in the clinical setting to pick up people with glucose intolerance at an earlier stage in the natural history of the disease. The presence of IFG and IGT both 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 the clinician in identifying those patients most at risk for developing diabetes and in developing an effective treatment plan for those who already have the disease. Each of the available classes of oral antidiabetic agents have different mechanisms of action and, therefore, are 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 prediabetic 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 patients with IGT most likely will reduce the incidence of macrovascular disease and type 2 diabetes. Early intervention of type 2 diabetes certainly reduces the incidence of macro and microvascular disease and most likely will slow the progression of the disease itself. Large-scale clinical studies currently are underway to quantify the benefits expected from early recognition and preventative treatment. Armed with the strategies that will result from these trials, the primary care provider is 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.
References

THE NATURAL HISTORY OF TYPE 2 DIABETES


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