Impaired Fasting Glucose and Impaired Glucose Tolerance

Implications for care

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Type 2 diabetes is now epidemic. In the U.S., there has been a 61% increase in incidence between 1990 and 2001 (1). There are currently 1.5 million new cases per year, and the prevalence in 2005 was almost 21 million (2). The epidemic has affected developed and developing countries alike, and the worldwide prevalence of diabetes is projected to increase dramatically by 2025 (3). The increase in type 2 diabetes is related to lifestyle changes that have resulted in overweight, obesity, and decreased physical activity levels. These environmental changes, superimposed on genetic predisposition, increase insulin resistance, which, in concert with progressive β-cell failure, results in rising glycemia in the nondiabetic range. In addition to the risk for diabetes, insulin resistance and impaired insulin secretion are accompanied by a host of major cardiovascular disease (CVD) risk factors including hypertension and dyslipidemia. Further reduction in insulin secretion over time results in increasing glycemia and the development of diabetes, which in turn is associated with the development of microvascular and cardiovascular complications.

The transition from the early metabolic abnormalities that precede diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), to diabetes may take many years; however, current estimates indicate that most individuals (perhaps up to 70%) with these pre-diabetic states eventually develop diabetes (4–10). During the pre-diabetic state, the risk of a CVD event is modestly increased (11–22). With the development of diabetes, however, there is a large increase in risk for CVD, as well as for long-term complications affecting the eyes, kidneys, and nervous system. The complications of diabetes, which are the cause of major morbidity and mortality, are related to its duration, chronic level of glycemia, and other risk factors.

Although clinical trials have demonstrated the effectiveness of intensive glycemic and blood pressure control to reduce the long-term complications of diabetes, the public health burden of the disease remains enormous. The magnitude of the epidemic, coupled with complex treatment requirements that are difficult and costly to implement, make the prevention of diabetes a critical public health goal. Between 1997 and 2006, eight major clinical trials examined whether lifestyle or pharmacologic interventions would prevent or delay the development of diabetes in populations at high risk by virtue of having IFG and/or IGT (4,5,23–28). The study populations often had other recognized risk factors for diabetes including obesity, a prior history of gestational diabetes, or a positive family history of diabetes. All of these trials demonstrated reductions in the development of diabetes of 25–60% over the period of follow-up. The largest reductions (~60%) were accomplished with lifestyle interventions aimed at weight loss and increasing physical activity and with thiazolidinediones (4,5,24,25,27). Lesser degrees of reduction (25–30%) have been achieved with other drugs (5,23,24,28).

The availability of interventions that have been shown to decrease the development of diabetes has stimulated consideration whether such interventions should be recommended and implemented, in whom, and under what circumstances. To address these issues, the American Diabetes Association convened a consensus development conference on 16–18 October 2006 focusing on the pre-diabetic states of IFG and IGT. Following the presentations of invited speakers and in-depth discussions, a seven-member panel of experts in diabetes, endocrinology, and metabolism developed this consensus position based on the questions below. The expert members were also asked to note where additional information or studies would be necessary to answer these questions.

QUESTION 1: What are IFG and IGT, and what is their natural history? — How much does IFG, IGT, or the combination of both conditions increase the risk for subsequent development of diabetes? Does IFG and/or IGT increase the development of cardiovascular disease? If so, are the effects of IFG and/or IGT independent of associated known cardiovascular risk factors including the subsequent development of diabetes?

IFG and IGT represent intermediate states of abnormal glucose regulation that exist between normal glucose homeostasis and diabetes. IFG is now defined by an elevated fasting plasma glucose (FPG) concentration (≥100 and <126 mg/dl) (29). IGT is defined by an elevated 2-h plasma glucose concentration (≥140 and

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Panel disclosures can be found on p. 757.

Abbreviations: CVD, cardiovascular disease; DPP, Diabetes Prevention Program; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc07-9920

Table 1—*Classification of glucose tolerance states*

State	FPG level (mg/dl)	2-h plasma glucose in OGTT (mg/dl)*
IFG	100–125	<200
Isolated IFG	100–125	<140
IGT	<126	140–199
Isolated IGT	<100	140–199
Combined IFG/IGT	100–125	140–199
NGT	<100	<140

*Standard 75-g OGTT.

<200 mg/dl) after a 75-g glucose load on the oral glucose tolerance test (OGTT) in the presence of an FPG concentration <126 mg/dl (29,30).

With the definitions above, there is overlap between the two groups. To study the separate characteristics of IFG and IGT, classifications of isolated IFG and isolated IGT that are mutually exclusive have been created (isolated IFG = FPG of 100–125 mg/dl with the 2-h value <140 mg/dl; isolated IGT = 2-h value of 140–199 mg/dl with the fasting level <100 mg/dl). The combined characteristics of IFG and IGT have been studied by identifying populations that fulfill both criteria (FPG = 100–125 mg/dl and 2-h value = 140–199 mg/dl). Conversely, normal glucose tolerance (NGT) is defined as FPG <100 mg/dl and 2-h plasma glucose <140 mg/dl (Table 1).

IFG was defined in 1997 by the American Diabetes Association as a means of classifying individuals who had fasting glucose levels between normal and diabetes (30). It was meant to be analogous to IGT as an intermediate metabolic state between normal and diabetes, but based on the FPG. The original FPG range (110–125 mg/dl) was changed in 2003 to 100–125 mg/dl so that the population risk of developing diabetes with IFG would be similar to that with IGT (29). The change in the cut point increased the overall prevalence of IFG approximately three- to fourfold. It is clear, however, that IGT and IFG do not define the same individuals.

The prevalence of IFG and IGT varies widely, with recent data from the U.S. indicating the prevalence of IFG to be ~26% and somewhat older data showing a 15% prevalence of IGT (2). Both are expected to increase in the foreseeable future. The prevalences of IFG and IGT vary considerably among different ethnic groups (30–34). IFG and IGT also differ significantly in their age and sex distribution; the prevalences of both metabolic disorders increase with advancing age. IGT is more frequent in women than in men (34–36). Unfortunately, most of the published literature on IFG is based upon the older cut point (110–125 mg/dl).

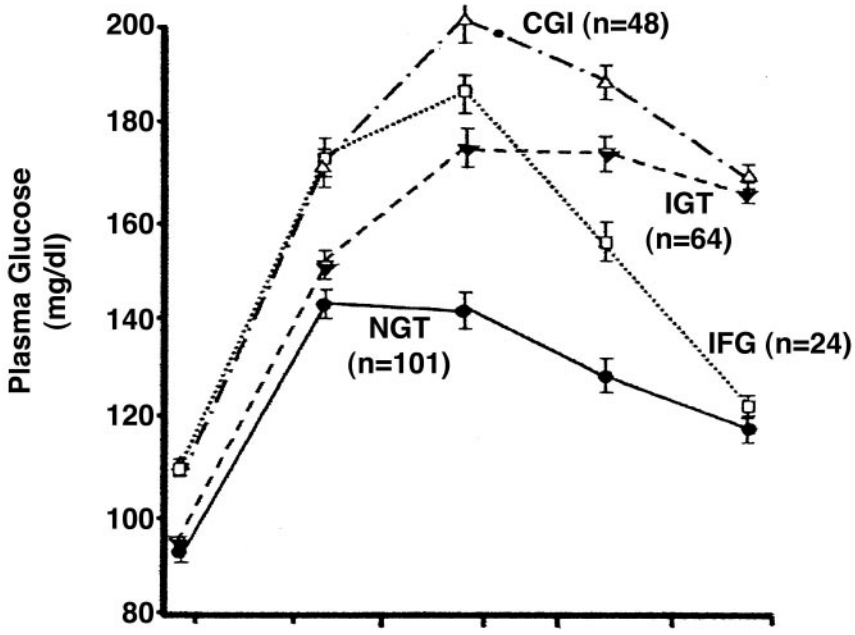

Figure 1—*Plasma glucose concentration during an OGTT performed in subjects with IFG, IGT, NGT, or combined IFG/IGT (CGI). Adapted with permission from ref. 54.*

The natural history of both IFG and IGT is variable, with ~25% progressing to diabetes, 50% remaining in their abnormal glycemic state, and 25% reverting to NGT over an observational period of 3–5 years (9,37–38). Individuals who are older, overweight, and have other diabetes risk factors are more likely to progress. Moreover, low insulin secretion and severe insulin resistance identify individuals more likely to progress to diabetes (39). With longer observation, the majority of individuals with IFG or IGT appear to develop diabetes.

Both IFG and IGT have a heterogeneous pathogenesis, and this may contribute to different rates of progression to diabetes. Also, the poor precision and accuracy of glucose measurements (40) and the poor reproducibility of the glucose tolerance test itself (41–43) contribute to the difficulty of defining the natural history of IFG/IGT in any one individual. Individuals with both IFG and IGT have approximately double the rate of developing diabetes compared with individuals with just one of them. However, with recent changes in the cut point defining IFG, the risk of developing diabetes associated with IFG needs to be reevaluated.

Numerous longitudinal studies indicate that both IFG and IGT are associated with a modest increase in the hazard ratio (~1.1–1.4) for CVD, with IGT being a slightly stronger risk predictor (11–22). The majority of this risk appears to be conferred by progression to diabetes, when the risk of CVD increases two- to fourfold. Many cardiovascular risk factors (e.g., low HDL cholesterol, hypertension, and elevated triglycerides) are prevalent in IFG and IGT, but it is unclear whether they occur more frequently in one state than the other (44–49). However, after adjustment for known cardiovascular risk factors, both IFG and IGT remain as independent, albeit weak, risk factors for CVD in some studies but not in others (11–22). Even so, it is unclear whether the CVD risk associated with IFG or IGT can be attributed to the development of diabetes during follow-up or whether these states per se convey such risk (37,50,51).

QUESTION 2: What is known about the pathogenesis of IFG and IGT?

— The epidemiologic differences between IFG and IGT suggest that different pathophysiologic mechanisms contribute to these disturbances in glucose homeostasis (52–55). During a standard 75-g OGTT, people with isolated IGT have, by definition, FPG levels that are similar to those with

NGT. However, following glucose ingestion the plasma glucose concentration rises excessively at all time points and remains elevated (by definition ≥140–199 mg/dl) after 120 min (Fig. 1). On the other hand, in isolated IFG, the FPG is higher (by definition 100–125 mg/dl) than in NGT and isolated IGT, and the plasma glucose concentrations at 30–60 min in the OGTT are greater than in both NGT and isolated IGT. Thereafter, the plasma glucose concentration in IFG declines to near-baseline values at 120 min. These two very distinct oral glucose tolerance curves reflect different pathophysiologic disturbances in glucose homeostasis in isolated IFG and isolated IGT. The plasma glucose curves in people with both IFG and IGT reflect the characteristics of both.

Although both isolated IFG and isolated IGT are insulin-resistant states, they differ in their site of insulin resistance (51,54). People with isolated IFG predominantly have hepatic insulin resistance and normal muscle insulin sensitivity, whereas individuals with isolated IGT have normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance. Not surprisingly, individuals with both IFG and IGT manifest both muscle and hepatic insulin resistance.

The pattern of insulin secretion also differs between IFG and IGT. People with isolated IFG have a decrease in first-phase (0–10 min) insulin secretory response to intravenous glucose and a reduced early-phase (first 30 min) insulin response to oral glucose. However, the late-phase (60–120 min) plasma insulin response during the OGTT is normal in isolated IFG. Isolated IGT also has a defect in early-phase insulin secretion in response to an oral glucose load and in addition has a severe deficit in late-phase insulin secretion.

The combination of hepatic insulin resistance and defective insulin secretion in isolated IFG results in excessive fasting hepatic glucose production accounting for fasting hyperglycemia. The impairment in early insulin response in combination with hepatic insulin resistance results in the excessive early rise of plasma glucose in the 1st hour of the OGTT. However, the preservation of late insulin secretion combined with normal muscle insulin sensitivity allows glucose levels to return to the preload value in isolated IFG. In contrast, in isolated IGT the defective late insulin secretion, combined with muscle and hepatic insulin resistance, results in prolonged hyperglycemia after a glucose load.

QUESTION 3: How do we define the natural history of IFG/IGT, and can we alter it?

— At the simplest level, the natural history of both IFG and IGT can be defined in terms of progression to diabetes. As discussed earlier, the majority of people with IFG/IGT will develop progressive hyperglycemia and eventually meet criteria for diabetes. A definition of natural history based on glucose levels has the advantage of being relatively easy to measure and quantitate.

A second definition of the natural history could be based on the underlying pathophysiological abnormalities associated with the development of hyperglycemia. A progressive decline in insulin secretion or increase in insulin resistance could be used to define the natural history. A natural history definition based on pathophysiologic parameters might be more sensitive to and discriminate better among the various effects of particular interventions than changes in glycemia. On the other hand, a nonglycemic definition of the natural history is more complicated, more expensive to measure, and less easily translatable to clinical practice, and its long term consequences may be more difficult to interpret.

A third possible definition of "natural history" could be based on the complications of hyperglycemia, including microvascular and macrovascular disease. Because the relative risk of developing these complications is low as long as individuals remain in the IFG/IGT glycemic range, studies that use this definition are likely to be impractical.

Just as there are different potential definitions of the natural history of IFG and IGT, there are different ways in which the natural history can be altered. The progression to diabetes is a time-dependent phenomenon; one possible alteration is simply to "reset the clock" without changing the rate of the deterioration. It is possible that some interventions will lower glycemia initially but do nothing to change the subsequent rate of rise of glycemia. This mechanism will delay crossing the glycemic threshold that defines diabetes.

A second possible way to alter the natural history is based on changes in the underlying rate of deterioration in the pathophysiologic abnormalities. Thus, if we defined the natural history in terms of a progressive decline in β-cell function or increased insulin resistance, an intervention that improved these pathophysiologic disturbances would also slow the rate of progression to diabetes.

A wide variety of interventions have been shown to alter the natural history of IFG/IGT progression to diabetes. All of the controlled clinical trials to date have measured changes in glycemia as their primary outcome. None of the completed studies allow us to determine definitively whether the interventions "reset the clock" or altered the rate of progression. Of note, the results of published studies (25,56) support a beneficial effect on the underlying pathophysiology, specifically a reduction in insulin resistance and an improvement in relative insulin secretion.

There clearly is a need for further studies that quantitate changes in β-cell function/mass and insulin sensitivity over time in response to interventions. Such studies may discover specific effects of different interventions on the underlying pathogenesis of the disease. Since studies to demonstrate improvements in hard outcomes (e.g., changes in the incidence of micro- or macrovascular disease) may not be feasible, future research studying the effect(s) of interventions on the pathophysiology of IFG, IGT, and diabetes might establish important therapeutic targets.

QUESTION 4: Do interventions that prevent the progression from IFG/IGT to diabetes also prevent the development/worsening of diabetes-related microvascular complications, cardiometabolic risk factors (e.g., hypertension and dyslipidemia), or CVD events?

— The prevention or delay of diabetes should lead to a decrease in duration-dependent diabetes-related microvascular complications; however, direct data are not available to determine whether this occurs. Published trials have not been sufficiently powered to show a reduction in these hard outcomes. One of the other major reasons to recommend therapeutic interventions for individuals with IFG/IGT is the potential to reduce the long-term increased risk of CVD associated with diabetes. The potential for achieving this goal can be assessed by evaluating three distinct outcomes: cardiovascular risk factors, surrogate

markers of atherosclerosis, or clinically significant cardiovascular events. Interventions that similarly reduce the progression from IFG/IGT to diabetes may have different effects on the CVD outcomes above. An example of dissociation between diabetes delay/prevention and reduction in CVD risk factors is seen by comparing the effects on blood pressure of intensive lifestyle change versus metformin, both of which reduced diabetes development in the Diabetes Prevention Program (DPP) (58). Intensive lifestyle change was associated with no increase in incident hypertension compared with a significant increase in the metformin and placebo arms. On the other hand, in the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, rosiglitazone both decreased the development of diabetes and reduced blood pressure (27).

Of the usual surrogate measures of atherosclerosis, only carotid intima-media thickness has been studied in diabetes prevention trials. In both the TRIPOD (Troglitazone in Prevention of Diabetes) study (25) and STOP-NIDDM (Study to Prevent Non–Insulin-Dependent Diabetes Mellitus) (23), treatment with troglitazone and acarbose, respectively, was associated with a reduced rate of increase in carotid intima-media thickness over time compared with placebo.

The only study to show a significant beneficial effect of an intervention on CVD events was the STOP-NIDDM study (57). Acarbose treatment was associated with a 49% relative risk reduction of the composite CVD outcome ($P = 0.03$), an unexpected finding given the relatively small number of CVD events (15 in the treated group, 32 in the placebo group). Conversely, in the DREAM study (27), a significant increase in congestive heart failure events was seen with rosiglitazone compared with placebo (0.5 vs. 0.1%, $P = 0.01$), although the total number of congestive heart failure events was small (14 vs. 2 events).

In summary, intensive lifestyle interventions can have substantial effects on diabetes delay/prevention and modest, albeit statistically significant, effects on CVD risk factors. Whether these changes will translate into meaningful reductions in CVD events remains to be demonstrated. The impact on CVD risk factors or events when pharmacologic agents are used to prevent/delay diabetes is even less clear and may differ depending on the medication used.

QUESTION 5: Are there adequate data to recommend interventions to prevent or delay diabetes in IFG/ IGT at this time?

— The epidemic increase in diabetes and its serious long-term consequences strongly support efforts to prevent its occurrence, with the expectation that morbidity and mortality will be decreased. Even in the absence of direct data regarding the benefits of diabetes prevention on long-term complications, the Panel believes in principle that early intervention is justified based on the following: the goal of delaying the onset of diabetes and postponing its requirement for treatment, which is often complex; the prospect of preserving β-cell function; and the likelihood that microvascular, and perhaps cardiovascular, complications will be delayed or prevented.

The strong association between diabetes and obesity suggests that our first priority is maintenance of healthy weight and obesity prevention. All individuals who are overweight or obese, regardless of their blood glucose value, should be intensively counseled to lose weight and to exercise. In addition, interventions at the community level, such as changes in school-based meals and exercise programs, community infrastructure changes conducive to increasing exercise frequency, and legislation that promotes a healthy lifestyle, are required.

As mentioned above, a number of well-designed and executed clinical trials have demonstrated the value of lifestyle modification or pharmacological therapy to prevent or delay the onset of diabetes. These completed prevention trials indicate that an intensive lifestyle intervention provides the greatest reduction in the occurrence of diabetes, along with a modest reduction in CVD risk factors, and has a favorable safety profile. The lifestyle modification studies were associated with virtually no serious untoward effects. In addition, lifestyle modification is likely to have other beneficial health-related effects (4,5,58).

For all of these reasons, lifestyle modification therapy emphasizing modest weight loss (5–10% of body wt) and moderate-intensity physical activity (~30 min daily) is the treatment of choice for individuals with IFG/IGT. While it is likely that the population enrolled in the clinical trials may not exactly mirror the general population, it seems very likely that lifestyle modification would benefit all people with IFG/IGT.

A more difficult issue is whether drug therapy is warranted to delay/prevent diabetes in individuals with IFG/IGT. Although several drugs successfully slowed progression to diabetes, there are many issues that need to be considered before medications can be recommended.

Metformin was the first drug shown to be effective (5). Although its effectiveness was about half that achieved with lifestyle modification (31 vs. 58%), substantially greater benefit was seen in a subset of younger and obese individuals. The drug is inexpensive and has a long history of use showing virtually no long-term serious side effects and only a low prevalence (5–10%) of modest side effects, such as nausea and gastrointestinal disturbances.

Acarbose appears to be as effective as metformin, but many patients cannot tol-

Table 2—*Treatment recommendation for individuals with IFG, IGT, or both*

Population	Treatment
IFG or IGT	Lifestyle modification (i.e., 5–10% weight loss and moderate intensity physical activity ~30 min/day)
Individuals with IFG *and* IGT *and* any of the following: ● <60 years of age ● BMI ≥35 kg/m^2 ● Family history of diabetes in first-degree relatives ● Elevated triglycerides ● Reduced HDL cholesterol ● Hypertension ● A1C >6.0%	Lifestyle modification (as above) and/or metformin*

*Metformin 850 mg twice per day.

erate its gastrointestinal side effects, and it is relatively costly. Orlistat is similar to acarbose in effectiveness and is also poorly tolerated, but because it is now an over-the-counter drug, it should be less costly. Of note, however, the study showing the effectiveness of orlistat was not designed as a prevention trial (28); therefore, the effect of the drug in diabetes prevention is not as clearly established as with the other drugs.

Most recently, the results of the DREAM Study (27) indicated that rosiglitazone was as effective in delaying/preventing diabetes as lifestyle modification in the Finnish or DPP studies (4,5). However, rosiglitazone is costly and was associated with a sevenfold increase in heart failure, although the number of such cases was small.

Based on this synopsis of the available trial results, the Panel recommends that only metformin be considered as drug therapy for individuals with IFG/IGT. In the DPP, the subsets of the study cohort that had substantially increased benefit from metformin were those participants <60 years of age and those who had a BMI ≥35 kg/m^2. Therefore, the Panel also recommends that metformin be limited to such individuals. Since individuals with associated risk factors for diabetes, e.g., family history in first-degree relatives, elevated triglycerides, low HDL cholesterol, and hypertension, are more likely to progress to diabetes, the presence of one or more of these factors may contribute to the decision to treat with metformin. In addition, to better target a population likely to benefit from metformin therapy, an unpublished analysis of data from the DPP (see QUESTION 6) suggests that an A1C ≥6.0% approximately doubles the rate of progression to diabetes in an IFG/IGT population.

A summary of these recommendations is shown in Table 2. Future recommendations may include other medications if they prove to be effective, have a good safety profile, are tolerable, and are of relatively low cost.

QUESTION 6: Who should be screened and with what methods and frequency to prevent/delay the adverse consequences of IFG/IGT?

— Screening for IFG/IGT is fundamentally no different from screening for diabetes. The same risk factors associated with diabetes are, not surprisingly, associated with IFG/IGT. Thus, the population to be screened for IFG/IGT should be the same as currently recommended for screening for diabetes. At present, FPG and 2-h OGTT are the tests of choice to identify all states of hyperglycemia (59). Either test is suitable, and each has advantages and disadvantages, such as convenience, cost, and reproducibility. Identification of individuals with IGT, which is recommended in order to institute metformin therapy, can be made only with a 2-h OGTT, while identification of FPG requires measurement of the plasma glucose concentration after an overnight fast.

If only lifestyle modification is planned, a confirmatory test is not required. On the other hand, the Panel recommends that metformin therapy be considered in individuals similar to those included in the DPP with confirmed IFG and IGT who had the greatest benefit with metformin (see QUESTION 5) Therefore, both abnormalities (IFG and IGT) must be documented if metformin is to be used.

The most efficient sequence of testing is an FPG first (currently recommended as the preferred test to detect diabetes) followed by the 2-h OGTT on a subsequent day to demonstrate the presence of combined IFG/IGT. If individuals with IFG/IGT are treated with metformin, the Panel recommends that routine moni-

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toring should be performed with A1C testing semi-annually. If not on drug therapy, the patient should be seen annually.

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