Follow-up Report on the Diagnosis of Diabetes Mellitus

THE EXPERT COMMITTEE ON THE DIAGNOSIS AND CLASSIFICATION OF DIABETES MELLITUS*

In 1997, an International Expert Committee was convened to reexamine the classification and diagnostic criteria of diabetes, which were based on the 1979 publication of the National Diabetes Data Group (1) and subsequent WHO study group (2). As a result of its deliberations, the Committee recommended several changes to the diagnostic criteria for diabetes and for lesser degrees of impaired glucose regulation (IFG/IGT) (3). The following were the major changes or issues addressed.

1) The use of a fasting plasma glucose (FPG) test for the diagnosis of diabetes was recommended, and the cut point separating diabetes from nondiabetes was lowered from FPG ≥140 mg/dl (7.8 mmol/l) to ≥126 mg/dl (7.0 mmol/l). (All glycemic values represent venous plasma.) This change was based on data that showed an increase in prevalence and incidence of diabetic retinopathy beginning at approximately a FPG of 126 mg/dl, as well as on the desire to reduce the discrepancy that existed in the number of cases detected by the FPG cut point of ≥140 mg/dl and the 2-h value in the OGTT (2-h plasma glucose [2-h PG]) of ≥200 mg/dl (11.1 mmol/l).

2) Normal FPG was defined as <110 mg/dl (6.1 mmol/l).

3) The use of HbA_{1c} (A1C) as a diagnostic test for diabetes was not recommended. The primary reason for this decision was a lack of standardized methodology resulting in varying nondiabetic reference ranges among laboratories.

4) Although the OGTT (which consists of an FPG and 2-h PG value) was recognized as a valid way to diagnose diabetes, the use of the test for diagnostic purposes in clinical practice was discouraged for several reasons (e.g., inconvenience, less reproducibility, greater cost). The diagnostic category of impaired glucose tolerance (IGT) was retained to describe people whose FPG was <126 mg/dl but whose 2-h PG after a 75-g oral glucose challenge was 140–199 mg/dl.

5) The range of FPG levels between "normal" and that diagnostic for diabetes was named "impaired fasting glucose" (IFG). IFG identified people whose FPG ranged from 110 mg/dl (6.1 mmol/l) to 125 mg/dl (6.9 mmol/l). This construct was established so that there would be a fasting category analogous to IGT.

The WHO consultation (4) also adopted most of the above conclusions. The two significant differences were that, whenever feasible, individuals with IFG should receive an OGTT to exclude the presence of diabetes, and the adoption of different criteria for the diagnosis of gestational diabetes.

Since the 1997 Expert Committee report, many new data related to the diagnosis of diabetes have been published. First, many analyses of both old and new epidemiological data have examined the equivalence of the FPG and the 2-h PG to predict diabetes, and questions have been raised about the preference of the FPG test over the 2-h PG to diagnose diabetes (5–7). Second, the IGT category has now been associated with cardiovascular disease (CVD) risk factors (8–10) and CVD events (10,11), whereas IFG is much less strongly associated with CVD events and CVD mortality (10,11). Third, the National Glycosylated Hemoglobin Standardization Program (NGSP) has now ensured that most laboratories in the U.S. perform the assays using standardized controls and report glycated hemoglobin results in a manner traceable to the assay used in the Diabetes Control and Complications Trial (DCCT) (12). These developments have improved assay performance and now allow caregivers and patients to compare reported results obtained among laboratories. Additional studies have suggested that the A1C may assist in diagnosing diabetes (13–17). Finally, data from major clinical trials that tested whether the progression from IGT to diabetes could be delayed or prevented by a treatment intervention have produced concordant results: intensive lifestyle modification (nutritional and exercise interventions) (18,19), metformin (19,20), and acarbose (20,21) were effective to variable degrees. In addition, a thiazolidinedione drug (troglitazone) reduced the incidence of diabetes in high-risk women with prior gestational diabetes (22).

An inherent difficulty in the diagnosis of diabetes is the present lack of an identified unique qualitative biological marker that separates all people with diabetes from all nondiabetic individuals. The closest such characteristic for practical purposes is diabetic retinopathy, but this suffers from the obvious defect that in most diabetic patients, retinopathy usually becomes evident years after the recognized onset of diabetes. The lack of a suitable, unique marker of diabetes has led to reliance on the metabolic abnormality historically associated with the disease, i.e., hyperglycemia (as measured by the FPG or 2-h PG) as the most useful diagnostic test. The selection of diagnostic cut points for these tests rests on two

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Abbreviations: 2-h PG, 2-h plasma glucose; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; DECODE, Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGSP, National Glycosylated Hemoglobin Standardization Program; NHANES III, Third National Health and Examination Survey.

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

observations: the bimodality of the distribution of both glucose values in some populations (23,24), albeit with overlap of normal and diabetic levels, and the ability of FPG and 2-h PG to predict the presence of diabetic retinopathy or the risk of developing it in the future (3).

In light of the new information, a reconstituted International Expert Committee met to evaluate these issues and make revisions to the previous criteria where appropriate. This report summarizes the deliberations.

Question 1: Should the cut point of FPG ≥126 mg/dl (≥7.0 mmol/l) or the cut point for the 2-h PG of ≥200 mg/dl (11.1 mmol/l) for the diagnosis of diabetes, or both, be changed?

The diagnostic levels of glucose, both FPG and 2-h PG, are largely predicated on their association with the risk of having or developing retinopathy. Based on the data reviewed in the 1997 report (3), the incidence of retinopathy increases above an FPG of ≥126 mg/dl, rather than above 140 mg/dl. Although one recent study (49) suggests that an even lower FPG cut point would be appropriate, in the absence of supporting data from additional populations, no new cut point can be recommended. Similarly, there are no new cogent data favoring a change in the 2-h PG cut point for the diagnosis of diabetes per se. If all-cause mortality or CVD mortality were to be used as the criterion to define a risk threshold, the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study reports that a 2-h PG of ~180 mg/dl would provide a similar risk cutoff as an FPG of 126 mg/dl (11).

The 2-h criterion of 200 mg/dl identifies a larger fraction of the population as having diabetes than the previous fasting criterion of 140 mg/dl. To eliminate, or at least reduce this discrepancy, the Expert Committee in 1997 recommended lowering the fasting criterion to 126 mg/dl.

It was believed at the time that this change would justify de-emphasizing the OGTT, since some of the individuals previously identifiable only by this test would have fasting values between 126 and 139 mg/dl and would thus be identified by the new fasting criterion. It was also believed at the time that these new recommendations would have a minimal impact on prevalence estimates. The current World Health Organization (WHO) criterion for diagnosing diabetes in epidemiological studies is an FPG ≥126 mg/dl (7.0 mmol/l) or a 2-h PG ≥200 mg/dl (11.1 mmol/l) in the OGTT (4). Using the 2-h PG criterion, compared with the 1997 ADA criterion of FPG ≥126 mg/dl alone (5), the average difference in prevalence of diabetes in 16 European populations from eight countries (totaling 26,190 people) was +0.5%, with a range of −4 to +13%. Based on the Third National Health and Examination Survey (NHANES III) data discussed in the 1997 Report (3), the difference in prevalence compared with the previous criterion of FPG ≥140 mg/dl or 2-h PG ≥200 mg/dl was −2.0% (26). Thus, overall, no consistent difference in the prevalence of diabetes across populations has been observed by employing the 1997 FPG criterion.

In the same studies, it was noted that although the FPG criterion of ≥126 mg/dl and the 2-h PG criterion of ≥200 mg/dl sometimes identify the same individuals, they often do not coincide. In the European DECODE study (5), of 1,517 people with diabetes by either criterion alone or by both criteria, only 28% met both criteria. A total of 40% met the fasting criterion only, and 31% met the 2-h PG criterion only. Among those who met the 2-h PG criterion, 51% did not meet the fasting criterion, and 59% of those who met the fasting criterion did not meet the 2-h PG criterion. In the NHANES III study of previously undiagnosed diabetic adults age 40–74, 44% met both the 2-h PG and FPG criteria, 14% met the FPG criterion but not the 2-h PG criterion, and 41% met the 2-h PG criterion alone (27). The discrepancy between the European and U.S. distributions may be explained by the fact that the U.S. study population was more obese and, therefore, more likely to have an elevated FPG and did not include elderly people (age ≥75 years) who are more likely to have an elevated 2-h PG.

The differences in the prevalence of diabetes by one criterion versus the other could be interpreted as indicating that there might be two metabolically distinct early forms of type 2 diabetes. However, the data are too scant to subclassify type 2 diabetes formally into two distinct diseases, based on the use of FPG or 2-h PG. It should be stressed that all these epidemiologic studies are based on a single glucose measurement, while the full criteria for the diagnosis of diabetes require a confirmatory test in asymptomatic subjects. Differences in prevalence by the two different criteria could therefore also result from the large day-to-day variability in the tests. In conclusion, we recommend that the cut points for the diagnosis of diabetes by FPG and 2-h PG should remain as in our 1997 report. (Table 1)

Question 2: Should the lower limit for IFG be reduced from 110 mg/dl?

The category IFG was introduced to designate the zone between the upper limit of normal FPG and the lower limit of diabetic FPG, much as IGT designates the zone between the upper limit of normal 2-h PG and the lower limit of diabetic 2-h PG. The ideal method of selecting the lower limit of IFG would be the identification of a threshold of FPG at which the risk of a clinical or metabolic outcome rises sharply. Data from Mauritius (28) indicate that such a threshold of FPG does not exist for cardiovascular risk factors, all-cause mortality, or future diabetes. Also, the DECODE study recently reported that there was no glycemic threshold for either FPG or 2-h PG above which mortality increases sharply (11). Both very low and high FPG were associated with an increased risk of death, whereas the 2-h PG was a continuous risk factor for mortality. On the other hand, data

Table 1—*Diagnostic thresholds for diabetes and lesser degrees of impaired glucose regulation*

	Test	
Category	FPG	2-h PG
Normal	<100 mg/dl (<5.6 mmol/l)	<140 mg/dl (<7.8 mmol/l)
IFG	100–125 mg/dl (5.6–6.9 mmol/l)	—
IGT	—	140–199 mg/dl (7.8–11.0 mmol/l)
Diabetes*	≥126 mg/dl (≥7.0 mmol/l)	≥200 mg/dl (≥11.1 mmol/l)

When both tests are performed, IFG or IGT should be diagnosed only if diabetes is not diagnosed by the other test. *A diagnosis of diabetes needs to be confirmed on a separate day.

from the Pima Indians show that the risk of diabetes does increase markedly at FPG concentrations above ~100 mg/dl (26).

Thus, the selection of a lower limit of IFG and 2-h PG is likely to be somewhat arbitrary. The upper limit of normal in the FPG (110 mg/dl) was taken from clinical laboratory experience, although recently a value of 106 mg/dl has been reported to be the upper limit (95th percentile) of the normal range established from measurements made in a large population of apparently healthy people (29,30). The rationale for establishing the intermediate categories of impaired glucose regulation was based on their ability to predict future diabetes. However, as pointed out in the 1997 report (3), the range of FPG values that defines IFG (110–125 mg/dl) includes a much lower proportion of the population than is included in the IGT category. This has been confirmed in eight population studies reviewed by Unwin et al. (31). Of those who had IFG and/or IGT, 16% had both, 23% had IFG alone, and 60% had IGT alone (31), with significant age and gender differences among the glucose intolerance categories. Although it may be desirable for IFG and IGT to be equivalent (i.e., to represent similar proportions of the population or even better the same individuals), if the two tests are measuring somewhat different metabolic states, then any discrepancy is not necessarily a "flaw" in one of the tests.

The predictive powers of IFG and IGT alone for development of diabetes over several years are similar in some but not all populations. The sensitivity of IFG as originally defined is less than that of IGT in most populations (31), but the specificity of IFG may be somewhat greater, as was found in a population from Mauritius (28). IGT identifies a larger number of individuals who will ultimately develop diabetes, largely because IGT is more common than IFG in most populations. These differences between the predictive abilities of IFG and IGT were shown, at least among Pima Indians, to be entirely a function of different cut points rather than differences in FPG or 2-h PG as predictive tests (26). When categorized in groups containing equal frequencies of the population, abnormalities of FPG or 2-h PG had the same predictive values for subsequent diabetes (26).

The receiver operator characteristic (32) curve of the ability of various baseline levels of FPG to predict diabetes, later diagnosed by a FPG ≥126 mg/dl or 2-h PG ≥200 mg/dl, have been recently analyzed by the Expert Committee in four populations (data unpublished). The FPG value at the point on the receiver operator characteristic curve closest to the ideal of 100% sensitivity and 100% specificity over the glycemic range of 81–126 mg/dl (4.5–7.0 mmol/l) was 103 mg/dl (5.7 mmol/l) in a Dutch population, 97 mg/dl (5.4 mmol/l) in a Pima Indian population, 94 mg/dl (5.4 mmol/l) in a Mauritius population, and 94 mg/dl (5.2 mmol/l) in a San Antonio population. These values suggest that 110 mg/dl was inappropriately high as a lower limit for IFG. Thus, changing the IFG cut point to 100 mg/dl (5.6 mmol/l) would optimize its sensitivity and specificity for predicting future diabetes. Of course, decreasing the lower limit of IFG will also have the virtue of increasing the proportion of those with IGT who can be identified by a FPG test. In addition, such a change will considerably increase the absolute number of people with IFG and, thereby, affect the relative proportion of people with IFG or IGT.

While the choice of a lower cut point can be made on the basis of the epidemiologic predictive data as described above, other factors that should influence the choice of the cut point are not currently known for IFG. For example, we do not yet know the total benefit or the total cost to an individual who is designated at risk for diabetes by either test, by any criterion. The higher the ratio of benefit to cost, the lower the optimal cut point that should be selected. Inasmuch as most (~80%) of the participants in the Diabetes Prevention Program (19) with IGT also had an FPG of 100–125 mg/dl, an intensive lifestyle intervention may also be beneficial in delaying or preventing diabetes in individuals with IFG by the proposed new definition. However, another much less intensive lifestyle intervention has not been shown to reduce the risk in subjects selected by an FPG criterion alone (33). At the same time, it must be acknowledged that a benefit similar to that shown in the DPP has not yet been proven by a clinical trial for people with FPG of 100–125 mg/dl who do not also have IGT. Finally, it should be noted that the lower cut point of 140 mg/dl that currently defines IGT was itself selected on arbitrary criteria.

In summary, the data we reviewed, on balance, suggest that the cut point for IFG should be reduced from 110 mg/dl to 100 mg/dl, and that IFG should be redefined as an FPG of 100–125 mg/dl (5.6–6.9 mmol/l). We also recommend that the cut point for IGT remain as a 2-h PG value between 140–199 mg/dl (7.8–11.0 mmol/l).

Question 3: Should the HbA_{1c} (A1C) level be included as a criterion for the diagnosis of diabetes?

Soon after the introduction of the glycohemoglobin assay as an index of glycemia, its use for the diagnosis of diabetes was considered. Measurement of glycohemoglobin (A1C) for this purpose has numerous advantages.

1) A1C measures average glycemic levels in a time scale of weeks, whereas plasma glucose varies greatly within any given day and from day to day. Thus, an elevated A1C indicates a chronic state of hyperglycemia, while hyperglycemia as measured by the FPG or 2-h PG may be transitory.

2) The patient does not have to fast or otherwise prepare, and a blood sample can be drawn any time of day.

3) In reference laboratories, the precision of A1C measurement is similar to the measurement of plasma glucose (29,34).

4) A test that can be used to diagnose diabetes and evaluate the results of treatment is an attractive measurement, as compared with our current situation, which calls for using different tests to diagnose the disease and then monitor treatment.

5) There is a threshold level of A1C associated with risk for retinopathy, as there is for FPG and 2-h PG (3). A graph showing the risk of diabetic microvascular complications based on A1C levels is superimposable on similar graphs, in which glycemia is expressed by the FPG or 2-h PG levels.

6) A recent meta-analysis showed that when using a statistical cut point of 2 SDs above the nondiabetic mean A1C value to diagnose diabetes, as defined by the 2-h PG, a variety of A1C assays had a mean sensitivity of 66% and a specificity of 98%, which compares favorably to the FPG (13).

On the other hand, measurement of A1C for the diagnosis of diabetes still has disadvantages.

1) A profusion of assay methods has led to different nondiabetic reference ranges because different glycated hemoglobin fractions have been measured (30). This problem has been reduced in the U.S. because of the efforts of the NGSP. Although the NGSP has succeeded in standardizing ~95% of the laboratories in the U.S., with results certified as "traceable to the DCCT A1C assay," (12) the level of precision and accuracy of the A1C test may still not be sufficient in all laboratories to allow the assay to be used to diagnose diabetes. Moreover, in many countries, A1C assays are not widely available and no A1C standardization program has even begun. Newer methods for measuring A1C by mass spectrometry, although not practical for clinical use, have the potential to provide better standardization across all A1C assays.

2) A chemical preparation to create uniform calibration standards has only recently been established (30). This preparation however has not yet been widely adopted.

3) A1C values may be affected by other conditions (e.g., hemoglobinopathy, pregnancy, uremia, blood transfusion, and hemolytic anemia), and depending on the laboratory method used, this may confound the diagnosis of diabetes.

On balance, therefore, it seems best to continue to use the A1C test as a monitor for the effectiveness of glycemic therapy and as an indicator for when therapy needs to be modified. In conclusion, the Committee believes that it is still premature to add A1C to the group of tests used for the definitive diagnosis of diabetes.

Question 4: What is the value of the 2-h PG in addition to the FPG?

In the 1997 report, we indicated that "although the OGTT is an acceptable diagnostic test. . . it is not recommended for routine use" (3). This statement resulted in reports expressing concern that many individuals who would have been diagnosed only by the 2-h PG would now be missed. Other reports noted that the 2-h PG is superior to the FPG because it would detect individuals at increased risk for CVD and that these individuals would not be identified by the FPG (31). In addition, several major studies have now documented the ability to prevent or delay the onset of diabetes in individuals with IGT, only identifiable by definition using an OGTT. Thus, we now have several potential reasons to do a test of glycemia: to either diagnose diabetes or impaired glucose regulation or to indicate increased risk for CVD. The question arises: which test of hyperglycemia, the FPG or 2-h PG, is most appropriate?

We think it helpful to frame the following discussion of diabetes tests on the basis of generic criteria that one might use for choosing any diagnostic tests. *1*) Are the tests measuring an important feature of the disease in question? 2) What are the relative advantages and disadvantages of the tests to detect the condition in question? 3) What are the comparative features of the tests insofar as ease of use, reproducibility of results, and cost to perform? *4*) What are the adverse consequences in terms of any "lost opportunity" if one test versus the other is used?

How does the FPG or 2-h OGTT relate to the condition to be detected?

The FPG and 2-h PG are both single point-in-time measures of glycemia. Both are associated with adverse outcomes that result from chronic hyperglycemia. Although they are not entirely interchangeable, since the FPG alone does not always detect people with IGT and the 2-h PG does not always detect people with IFG, both tests are useful in terms of their ability to detect hyperglycemia and the consequences of disordered glucose metabolism.

What are their relative advantages and disadvantages?

A discussion of the sensitivity and specificity of a test mandates comparison to some objective "gold standard." In this regard, the FPG test is compromised since it is usually compared with the 2-h PG, which has de facto been considered the "gold standard." By this standard, the FPG has, of course, less sensitivity. The OGTT was originally designed to detect an abnormality in glucose metabolism in patients with normal FPG levels by perturbing homeostasis with a glucose challenge. The 2-h PG result from the OGTT subsequently became a convenient way to detect glycemic abnormalities in individuals, even when they were tested in a nonfasting state. Early studies took advantage of the combination of the greater metabolic sensitivity of the OGTT with the conveniences of measuring plasma glucose at a postchallenge standard time point at any time of day. The results of these studies led to the ascendancy of the 2-h PG as the "gold standard test." However, if in the early studies only fasting values had been reported, and the FPG test was viewed as the "gold standard," then attention today would likely be focused on the decreased sensitivity and specificity of the 2-h PG to detect diabetes (i.e., some people meeting FPG criteria for diabetes would be missed by the 2-h PG alone, and some people nondiabetic by FPG would be "falsely" diagnosed by the 2-h PG).

Neither the FPG nor 2-h PG cut point denotes end-organ damage per se. Rather, they indicate future risk for microvascular and perhaps macrovascular complications (35–42,49). Indeed, there is a superimposable, continuous relationship between the fasting and 2-h values and the risk of diabetic microvascular complications above a threshold for each (3,49).

By lowering the cut point for IFG (as recommended above), the IFG population will now include a greater percentage of individuals who also have IGT (~30% of those with IFG will have IGT). Of note, even with an IFG cut point of 100 mg/dl, there will be individuals who have IFG but not IGT and vice versa. The clinical significance of either discrepancy is not completely known, but each condition, even in the absence of the other, is a risk factor for subsequent diabetes.

Most (25,42–48), but not all (39,49–52), longitudinal observational studies have reported that an elevated 2-h PG value (but below that diagnostic of diabetes) is a better predictor of all-cause mortality or CVD morbidity/mortality than an elevated FPG value. From that finding, it is inferred that the 2-h PG value is a better test to employ for the diagnosis of diabetes or impaired glucose regulation. All of the studies, however, have one or more of the following shortcomings that make it difficult to conclude that the 2-h PG is the better test.

First, in many reports, the ability of FPG and 2-h PG to predict CVD and total mortality was evaluated using categorical groupings, e.g., those with or without IFG were compared with those with IGT, rather than studying the predictive power of each test over the entire range of its possible values. The categorical analyses affect the comparison between the tests because, for example, the "window" of

plasma glucose (in mg/dl) is much larger for IGT than it is for IFG. However, in some studies, the 2-h PG was better than the FPG for predicting mortality across the range of plasma glucose values.

Second, in none of the studies was the relationship between IFG and IGT and the incident adverse outcome adjusted for incident diabetes that may have already occurred first during the follow-up period. Thus, it is unclear to what extent the development of diabetes (or other CVD risk factors that developed during follow-up, such as hypertension) influenced the end point adverse outcome. This shortcoming may be important, since in longitudinal analyses (49,53), only individuals who progressed from NGT or IGT to diabetes during follow up had increased all-cause and CVD mortality compared with those who did not progress to diabetes. Therefore, IGT and IFG per se may not be the causative factor for CVD, but rather they are risk factors for developing diabetes, which is then associated in some fashion with the pathogenesis of CVD.

Third, although these cohort studies generally performed baseline adjustments for numerous well-known CVD risk factors, none adjusted for all known CVD risk factors or for recently recognized causal/associative factors such as plasminogen activator inhibitor 1 or C-reactive protein. This is an important consideration because two recent studies found that the 2-h PG added relatively little (51) or nothing (52) for identifying CVD risk if other traditional risk factors were considered, although this has not been a consistent finding (45).

Even if there is an independent relationship between IFG or IGT and all-cause or CVD related outcomes, there is incomplete evidence that a glycemic intervention benefits patients by preventing CVD. In most of the diabetes prevention trials (18–20), the participants were not followed long enough to determine whether any clinical outcome was affected. In the UKPDS (U.K. Prospective Diabetes Study) (54), the evidence was inconclusive that lowering glucose per se in people with diabetes will favorably impact macrovascular disease. Alternatively, a recent secondary analysis of the data from the STOP-IDDM trial indicated that IGT subjects (most of whom also had IFG or diabetes by FPG criteria) had a significantly reduced risk of CVD (55). However, since acarbose is also associated with a significant reduction in body weight, blood pressure, and triglyceride levels, the drug may be exerting a CVD benefit by a mechanism other than through its glucose-lowering effect per se. In addition, the secondary analysis may be confounded by some study design factors and limitations in the statistical analysis, as the authors acknowledged. Thus, although there is growing evidence that glucose lowering in patients with impaired glucose regulation may reduce CVD, a definitive clinical study is needed before such a treatment recommendation can be made.

In some patients, a 2-h PG value diagnostic of diabetes in an individual with a normal FPG or IFG might trigger pharmacologic glucose-lowering therapy. However, in the vast majority of these patients, the pretreatment A1C level will be <6.5% (56), and the extent to which such patients would benefit from such drug therapy is not known. On the other hand, a 2-h PG value diagnostic of diabetes mandates lower blood pressure and lipid goals compared with nondiabetic individuals (57), although no clinical trial has focused specifically on the benefits of treating such patients to these targets. Among individuals with IFG, there will be some in whom the 2-h PG, if performed, will identify diabetes. Thus, performing a 2-h PG might be considered in subjects with IFG, as recommended by the WHO consultation (4).

Much has been written on the pathogenesis of diabetes (58–61), with considerable data indicating that resistance to insulin action in peripheral tissues is an early feature, followed by or simultaneous with progressive β-cell dysfunction. Both ultimately contribute to the development of diabetes. It has been suggested that insulin resistance and/or compensatory hyperinsulinemia convey an elevated risk of CVD (62,63). If this proves to be true, and an elevated 2-h PG is a marker for early-stage insulin resistance, it might be useful to identify individuals at particularly high risk for CVD who might then benefit from intervention. However, other parameters related to the metabolic syndrome (64–67) may be more relevant to CVD risk, and here too, we do not as yet have clinical trial evidence showing that lowering insulin resistance per se in those with IGT, or even in those with diabetes, actually reduces CVD events.

In summary, there are reasons why a 2-h PG might be the preferred test for the added information it may provide. However, questions still remain regarding the ultimate clinical impact or value of detecting diabetes or IGT when the FPG is normal. These uncertainties have led to opposing editorial positions (68,69) on which test to use. The evidence still precludes definitively declaring either test more advantageous than the other.

What other features are related to either test?

The measurement of FPG is less expensive and less intrusive than the 2-h PG. Although both tests require overnight fasting for at least 8 h, the 2-h PG frequently results in an extended office visit for the patient, potentially resulting in more lost wages or an inability to engage in other desired activities. A minority of patients cannot tolerate the glucose challenge drink, making the results of the test uninterpretable because the full glucose load was not ingested. On the other hand, some patients will not have actually fasted, potentially resulting in a falsely elevated FPG, whereas the impact of nonfasting on the 2-h PG value may be less.

The FPG test is more reproducible than the 2-h PG. The day-to-day intraindividual coefficients of variation range from 6.4 to 11.4% for FPG and 14.3 to 16.7% for the 2-h PG (70–73). In addition, the overall test retest reproducibility using the OGTT is unsatisfactory (74). The San Antonio group (75) reported that patients diagnosed with diabetes exclusively on the basis of the 2-h PG were five times more likely to revert to nondiabetic status after 7–8 years of follow-up than those meeting the 126 mg/dl FPG diagnostic criteria. In the Paris Prospective Study (76), 72% of those in whom diabetes was diagnosed by the 2-h PG value alone reverted to nondiabetic status after 30 months of follow-up compared with 42% of the patients diagnosed with diabetes by FPG. Thus, the FPG test is more reliable (at least for the diagnosis of diabetes) and less costly than the 2-h PG.

Is there a "lost opportunity" by doing one test versus the other?

Is there evidence that choosing the "wrong" test will have adverse consequences? If individuals who develop abnormalities of one glucose test (FPG or 2-h PG) eventually develop an abnormal value in the other, then the only disadvantage of restricting testing to a single glu-

cose test is delayed diagnosis for those in whom the "wrong" test was chosen. At present, there is no evidence that such delayed diagnosis is critical. Conversely, it may be true that some or many individuals with diabetes by 2-h PG or FPG will never develop diabetes as measured by the other test. In that case, the diagnosis of diabetes by either test might be worthwhile. For either scenario, we have no data to inform our choice of test. The OGTT offers the obvious advantage that a FPG and 2-h PG are both measured, whereas when measuring FPG alone, no information about the 2-h PG value is known. As previously noted (11), all-cause mortality is increased in people with normal FPG but who are diabetic based on the 2-h PG; however, it is not known whether treating this state of asymptomatic diabetes will in fact reduce mortality.

Is it possible to identify people likely to have IFG/IGT using other characteristics?

Models to predict prevalent IGT, incident diabetes, or CVD without employing a measure of glucose intolerance (52,77–80) have been developed. Some of the models have excluded any measurement of glycemia (78–80), while others have included FPG (52,77). Such models are invariably more effective in the population from which they were derived than in independent confirmation datasets from other populations. In those few studies where the model was derived from one population and tested in another (78,79), it did not perform sufficiently well to obviate the need for blood glucose testing. Although these models hold promise, confirmatory independent testing across various populations must be performed in order to demonstrate sufficient utility for their widespread use.

In summary, there is currently inadequate clinical evidence that either test is superior. Given the methodological features of the FPG test, it remains the test of choice in clinical practice where cost, convenience, and reproducibility are important considerations. For research studies or in clinical situations in which it is important, to the extent possible, to rule in or out every case of diabetes or every case of IFG/IGT, the FPG and 2-h PG should be performed. It is important to keep in mind that confirmatory testing is recommended to diagnose diabetes.

Conclusions

Based on the data that have appeared in the literature since the 1997 Expert Committee report, we recommend that the criteria to diagnose diabetes should remain as previously defined. However, the lower cut point defining IFG should be reduced from ≥110 mg/dl to ≥100 mg/dl (≥5.6 mmol/l). Thus, "normal" would now be defined as a FPG <100 mg/dl. The revised thresholds are shown in Table 1. In addition, the Committee concludes that the FPG and 2-h PG (but not the A1C test) remain the tests of choice for the diagnosis of both their respective impaired states, as well as for the diagnosis of diabetes. There are arguments in favor of either test. The 2-h PG, because of the currently defined cut points for diabetes, is a more sensitive assay in most populations. But the FPG is more reproducible, less costly, and likely to be more convenient.

There are obviously many aspects regarding the specific measurements of glycemia that are still unclear. Further research is needed to improve our understanding and approach toward detecting IFG, IGT, or diabetes. For example, more work needs to be done to standardize the A1C assay worldwide, so that this measure could be routinely employed for diagnosing diabetes. Second, we need to better understand the pathophysiology and risks associated with IFG and IGT. Do they represent distinct metabolic abnormalities or to what extent are they part of a continuum? What are the true adverse outcomes associated with either? Will measurement of factors other than plasma glucose identify populations that would benefit from prevention strategies demonstrated to be effective in clinical trials? Finally, to what extent can future CVD be ameliorated if the cut points for IFG, IGT, or diabetes are changed and treatment of glycemia is initiated earlier? The answers to these and other questions will necessitate regular surveillance and reconsideration of new data that may lead to appropriate revisions to the diagnostic and classification criteria for diabetes over time.

Acknowledgments— The committee greatly appreciates the Hoorn Study Research Group (Drs. L.M. Bouter, J.M. Dekker, R.J. Heine, G. Nijpels, and C.D.A. Stehouwer) who provided data from the Hoorn study. We also thank Dr. K. Williamson (San Antonio) and Dr. R.L. Hanson and S. Kobes (Phoenix) for performing the receiver operating curve analysis.

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