HbA_{1c} Measurement Improves the Detection of Type 2 Diabetes in High-Risk Individuals With Nondiagnostic Levels of Fasting Plasma Glucose

The Early Diabetes Intervention Program (EDIP)

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OBJECTIVE — Whereas new diagnostic criteria based on a fasting plasma glucose (FPG) of >126 mg/dl (7.8 mmol/l) have improved the detection of diabetes, multiple reports indicate that many people with diabetes diagnosed by 2-h oral glucose tolerance test (OGTT) glucose measurements of ≥11.1 mmol/l (200 mg/dl) would remain undiagnosed based on this FPG criteria. Thus, improved methods to detect diabetes are particularly needed for high-risk individuals. We evaluated whether the combination of FPG and HbA_{1c} measurements enhanced detection of diabetes in those individuals at risk for diabetes with nondiagnostic or minimally elevated FPG.

RESEARCH DESIGN AND METHODS — We analyzed FPG, OGTT, and HbA_{1c} data from 244 subjects screened for participation in the Early Diabetes Intervention Program (EDIP).

RESULTS — Of 244 high-risk subjects studied by FPG measurements and OGTT, 24% of the individuals with FPG levels of 5.5–6.0 mmol/l (100–109 mg/dl) had OGTT-diagnosed diabetes, and nearly 50% of the individuals with FPG levels of 6.1–6.9 mmol/l (110–125 mg/dl) had OGTT-diagnosed diabetes. In the subjects with OGTT-diagnosed diabetes and FPG levels between 5.5 and 8.0 mmol/l, detection of an elevated HbA_{1c} (>6.1% or mean + 2 SDs) led to a substantial improvement in diagnostic sensitivity over the FPG threshold of 7.0 mmol/l (61 vs. 45%, respectively, $P = 0.002$). Concordant FPG levels ≥7.0 mmol/l (currently recommended for diagnosis) occurred in only 19% of our cohort with type 2 diabetes.

CONCLUSIONS — Diagnostic criteria based on FPG criteria are relatively insensitive in the detection of early type 2 diabetes in at-risk subjects. HbA_{1c} measurement improves the sensitivity of screening in high-risk individuals.

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In 1997, the American Diabetes Association (ADA) expert committee adopted revised criteria for the diagnosis of diabetes (1). In short, these guidelines included lowering the diagnostic threshold for fasting plasma glucose (FPG) from 7.8 to 7.0 mmol/l and de-emphasized the use of the oral glucose tolerance test (OGTT) (2–4). Indeed, surveys have shown that practicing physicians seldom obtain an OGTT to diagnose diabetes (2) because the OGTT is construed as being cumbersome (3) and highly variable. In an attempt to provide a simple and effective method of diagnosis, the ADA recommended using the FPG level as the preferred test for the screening and diagnosis of diabetes (1).

Diabetes is defined by circulating glucose levels associated with increased risk of developing diabetic microvascular complications, such as retinopathy and nephropathy. Epidemiological studies suggest that a plasma glucose level of 11.1 mmol/l 2 h after a glucose challenge represents a threshold at which that risk increases substantially (5,6). Hence, a postchallenge plasma glucose level of 11.1 mmol/l is the basis for the formulation of the diagnostic criteria recommended by both the ADA (7) and the World Health Organization (8) for the diagnosis of diabetes. However, the FPG level associated with this same risk of microvascular disease is less clear. Because epidemiological data suggest that an FPG level of 7.0 mmol/l closely corresponds to a postglucose challenge level of 11.1 mmol/l (9,10), the expert committee recommended an FPG level of 7.0 mmol/l (confirmed on a separate occasion) as the diagnostic criterion of choice for diabetes. Data are available, however, suggesting that many individuals demonstrate abnormal responses to glucose challenges well before the onset of fasting hyperglycemia (11,12). Indeed, numerous reports have indicated that up to 50% of patients with diabetes who were diagnosed by OGTT criteria would have been missed by current FPG criteria (13–17).

The goal and premise of diabetes management is the prevention of diabetes-associated complications, and this goal is best achieved when the disease is

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Abbreviations: ADA, American Diabetes Association; EDIP, Early Diabetes Intervention Program; FPG, fasting plasma glucose; IFG, impaired fasting glucose; OGTT, oral glucose tolerance test.

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

diagnosed at an early stage. In this regard, the ADA expert committee created a new diagnostic class to identify a population at risk for diabetes. This new category, defined as individuals exhibiting FPG levels between 6.1 and 6.9 mmol/l, is called impaired fasting glucose (IFG). Although this new classification is helpful in alerting physicians to patients at risk, the guidelines did not specify a diagnostic strategy for this at-risk group. This is an important point, because epidemiological data suggest that up to two-thirds of the individuals with IFG may have diabetes or impaired glucose tolerance, as diagnosed by formal OGTT screening (14,18,19). To establish more sensitive diagnostic criteria, particularly as applied to a population at risk for diabetes, we analyzed data obtained from subjects who were screened or enrolled in the Early Diabetes Intervention Program (EDIP).

EDIP

The EDIP is a 5-year prospective double-blinded randomized study funded by the National Institutes of Health and Bayer Pharmaceuticals. This study is a collaboration between Indiana University, Indianapolis, Indiana, and Washington University, St. Louis, Missouri. The driving hypothesis of this study is that postprandial hyperglycemia, which is the most prominent disturbance of glucose homeostasis in patients with type 2 diabetes in its very early stage, contributes significantly to β-cell failure. The study will test whether control of postprandial glucose excursions with acarbose, an α-glucosidase inhibitor, will delay the worsening of fasting hyperglycemia, preventing β-cell deterioration and diabetes-associated complications in patients with "early" diabetes, operationally defined as patients exhibiting FPG levels between 5.5 and 7.8 mmol/l and 2-h post–glucose load plasma glucose levels ≥11.1 mmol/l.

RESEARCH DESIGN AND METHODS

— A total of 215 patients have been enrolled between the two sites. Recruitment for the study was performed via direct mailing, local newspaper and radio advertisements, and campus fliers directed toward individuals who were at risk for diabetes but who had not been previously diagnosed. Individuals with obesity (BMI ≥24 kg/m^2), a history of gestational diabetes, or a family history of diabetes were specifically recruited, as were those who had been told they had "a touch of sugar," "borderline diabetes," or "glucose intolerance." Exclusion criteria included *1*) age <24 years; *2*) pregnancy; *3*) cancer treatment within the past 5 years; *4*) HIV or tuberculosis; *5*) myocardial infarction, coronary bypass grafting, or coronary angioplasty within the past 6 months; *6*) congestive heart failure; *7*) third-degree atrioventricular heart block; *8*) uncontrolled hypertension (i.e., systolic and diastolic blood pressure >180 and >105 mmHg, respectively); *9*) serum aspartate aminotransferase or alanine aminotransferase >1.8 times the upper limits of normal; *10*) serum creatinine >120 mmol/l in men or >115 μmol/l in women; *11*) hematocrit <40% in men or <35% in women; and *12*) fasting plasma triglycerides >6.8 mmol/l.

After informed consent, subjects underwent FPG determination. Those with FPG levels <5.5 mmol/l or >8.0 mmol/l were informed of the results and referred to their primary care physician for further care. Subjects with FPG measurements between 5.5 and 8.0 mmol/l proceeded to a single OGTT using 75 g dextrose. Those with a 2-h postload plasma glucose measurement ≥11.1 mmol/l were considered as having diabetes and were enrolled into the EDIP trial. These subjects were randomized in a double-blind fashion to receive either acarbose or a placebo. The second FPG was measured 1–6 weeks after the first, just before randomization.

Study design

Following baseline studies, dietary assessment was performed, and all subjects underwent counseling for weight reduction or weight-maintaining diets according to the ADA practice guidelines (20). Subjects were informed of the potential side effects of acarbose, and to minimize gastrointestinal effects, dosage of the study drug was titrated upward slowly, starting at 25 mg/day with an eventual goal of 100 mg three times a day with the first bite of each meal. For those suffering significant gastrointestinal side effects, the dose was reduced until symptoms abated. The placebo was prescribed in an identical fashion.

Outcome measures

The primary outcomes of this study are the development of diabetes (by fasting criteria of FPG ≥7.0 mmol/l) in those subjects who had nondiagnostic FPG levels at baseline and the progression of FPG levels in those who had baseline levels between 7.0 and 7.8 mmol/l. Secondary outcomes include the development and/or progression of diabetes-associated micro- and macrovascular complications. The former are assessed by periodic retinal photographs for evidence of retinopathy using methods previously described (21), 24-h urine albumin excretion, and monofilament testing for crude evidence of sensory neuropathy. Macrovascular complications are assessed by history of cardiac events, periodic electrocardiogram interpretation, and serial measurements of carotid intimal wall thickness by B-mode and Doppler carotid ultrasonography. Tertiary outcomes are the effects of acarbose on weight, serum lipids, apoprotein B, insulin secretion and sensitivity (as determined by the hyperglycemic clamp technique), and meal tolerance. Comorbidities (e.g., hypertension, dyslipidemia, etc.) are treated according to current guidelines by the primary care physician.

Measurements

For this report, we analyzed data from the baseline OGTT and HbA_{1c} measurements, as well as from repeat FPG measurements obtained 1–6 weeks after enrollment into the study. Plasma glucose was measured by a glucose analyzer (YSI, Yellow Springs, OH). HbA_{1c} levels were determined by immunoturbidimetric immunoassay (Unimate; Roche Diagnostics, Indianapolis, IN) with a normal range of 4.5–6.1%.

Statistical methods

Data are presented as means ± SD. Accuracy of the diagnostic criteria was compared using McNemar's test and is expressed as percentages and 95% confidence intervals of the percentages. Ordinary least-squares regression was used to evaluate the relationships between continuous variables.

RESULTS

FPG and OGTT screening in an at-risk population

As of the writing of this article, 950 volunteer subjects with risk factors for diabetes but without known diabetes have been screened by FPG measurements. Of these subjects, 678 had FPG levels <5.5 mmol/l, 28 had FPG levels >8.0 mmol/l, and 244 subjects had FPG levels between

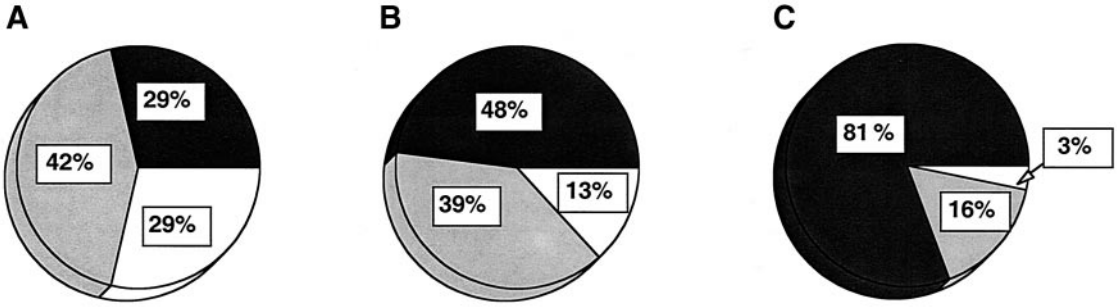

Figure 1—*Incidence of normal glucose tolerance (□), impaired glucose tolerance (▨), and diabetes (■) (defined by OGTT criteria) in individuals with normal* (A)*, impaired* (B)*, and abnormal* (C) *FPG as defined by current ADA guidelines* (n = *84, 98, and 62, and FPG = 5.5–6.0, 6.1–6.9, and 7.8–8.0 mmol/l, respectively).*

5.5 and 8.0 mmol/l. Each of the 244 subjects with FPG levels of 5.5–8.0 mmol/l underwent an OGTT, and 49.5% (121 subjects) were found to have diabetes based on 2-h OGTT criteria (i.e., 2-h plasma glucose level ≥11.1 mmol/l). Figure 1 compares the diagnostic classifications of this group, as defined by OGTT criteria, to the FPG classifications set forth by the ADA. Of 84 subjects with FPG levels of 5.5–6.0 mmol/l, 24 (28%) had diabetes by OGTT criteria, and 47 of 98 subjects (48%) with IFG (i.e., FPG levels of 6.1–6.9 mmol/l) also had diabetes as defined by OGTT criteria. Thus, 50% of subjects with risk factors for diabetes who exhibited IFG actually had diabetes as determined by a single positive OGTT.

Regression analysis between FPG and 2-h OGTT glucose levels indicates that a significant relationship exists between the two measures of glucose homeostasis ($r = 0.52$; $P < 0.001$) (Fig. 2). According to this model, 6.7 mmol/l is the FPG that best correlates to the 2-h post–glucose load level of 11.1 mmol/l. Lowering the diagnostic threshold for FPG from 7.0 to 6.7 mmol/l identified only a small additional number of subjects with OGTT-diagnosed diabetes, but 62 of the 121 subjects (51% of the patients with OGTT-diagnosed diabetes) remained unidentified.

Relationships among FPG, 2-h post-OGTT, and HbA_{1c} in patients with early diabetes

Of the 121 subjects with OGTT-diagnosed diabetes, complete data were available for 101, and these data are used in the remainder of the analysis. Of the 20 subjects with missing data, 8 had no data recorded because they refused consent and 12 had samples that were misplaced or improperly handled. We have analyzed the whole

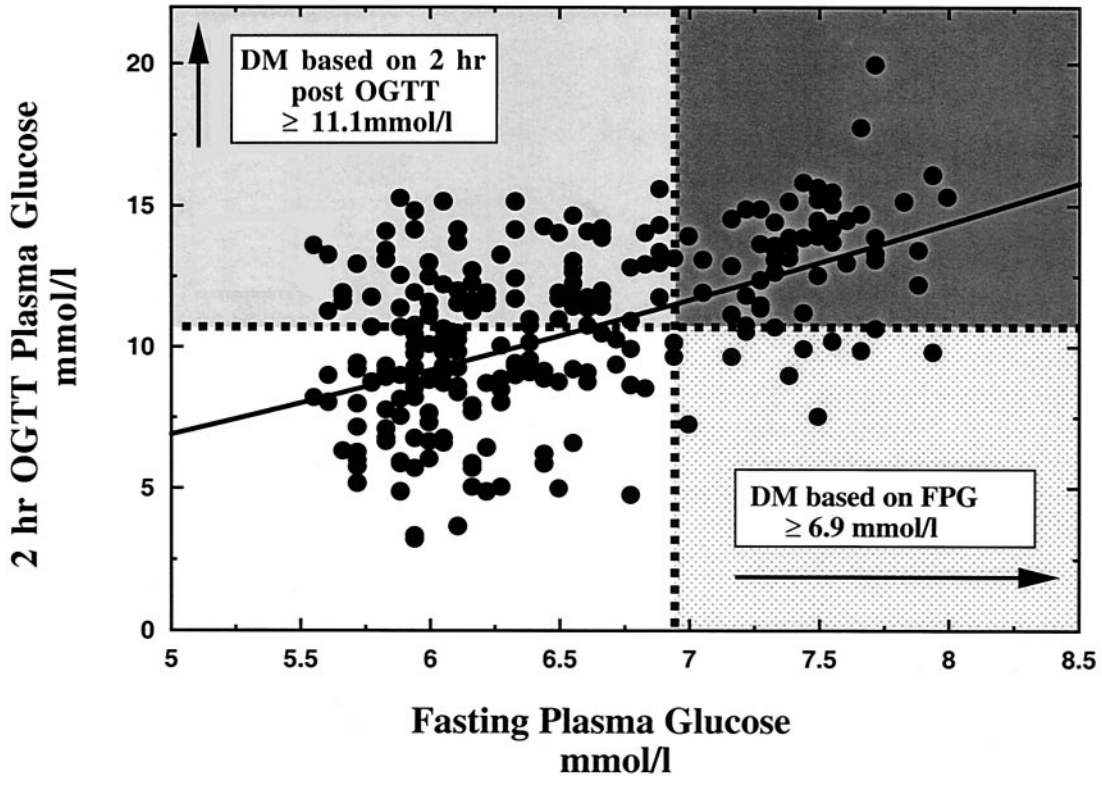

Figure 2— *Relationship between FPG and 2-h post-OGTT plasma glucose.*

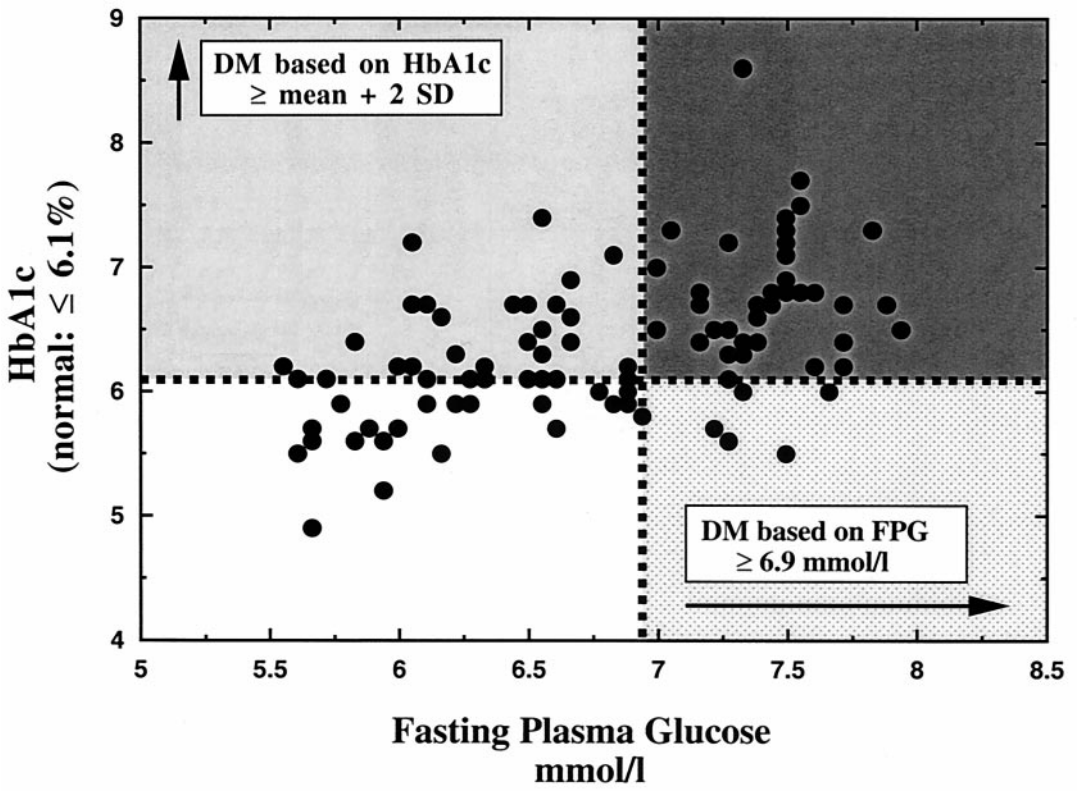

Figure 3— *Correlation of FPG and HbA$_{1c}$ levels.*

data set on the assumption that these were random occurrences; thus, they should not lead to bias in the results. Demographic data for this group are as follows: 68% women, 78% Caucasian, 18% African-American, 2% Hispanic, 2% Asian, age 53.6 ± 11.4 years, weight 98.8 ± 9.3 kg, and BMI 35.2 ± 7.4 kg/m^2. Figure 3 illustrates the distribution of FPG levels and correlates FPG values to measurements of HbA$_{1c}$. Only 45 of the 101 subjects (45%) with OGTT-diagnosed diabetes exhibited initial FPG levels ≥7.0 mmol/l, and the rest had normal FPG levels. In contrast, using HbA$_{1c}$ levels >2 SDs above mean as the criteria for our assay, we identified 62 of the 101 subjects (62%) as having diabetes. The ability of an elevated HbA$_{1c}$ measurement to detect diabetes was significantly greater than that of FPG measurements in our cohort of high-risk subjects (61% CI 51–71 vs. 45% CI 35–55, respectively; $P = 0.002$). It is noteworthy that of the 56 subjects with FPG levels between 5.0 and 6.9 mmol/l, 24 (43%) exhibited an elevated HbA$_{1c}$. Therefore, a substantial percentage of our high-risk cohort with OGTT-diagnosed diabetes who were not identified on the basis of current FPG criteria were correctly detected on the basis of an elevated HbA$_{1c}$.

Figure 4 illustrates the results of repeat FPG testing in our cohort of subjects with diabetes diagnosed by OGTT criteria. Of the 45 subjects who had FPG levels ≥7.0 mmol/l on initial testing, only 19 (42%) had diagnostic values on repeat FPG testing. Thus, repeat FPG testing in this population resulted in reduced diagnostic sensitivity. In contrast, 34 (76%) of the subjects had elevated HbA$_{1c}$ levels. Within the entire group of 101 subjects with OGTT-diagnosed diabetes, the combination of a single FPG test and an elevated HbA$_{1c}$ (>2 SDs above mean) showed better diagnostic sensitivity than two concordant FPG measurements ≥7.0 mmol/l for the diagnosis of diabetes (76% CI 66–86 vs. 42% CI 32–52, respectively; $P = 0.0015$).

CONCLUSIONS — Previous reports comparing the diagnostic classifications of diabetes based on FPG and OGTT criteria have been epidemiological (i.e., population-based). Our study differs in that it is based on a population comprised solely of subjects who have risk factors for type 2 diabetes but who have not been previously diagnosed with diabetes. This is an important distinction, because our data are not representative of the population at large and thus cannot directly serve to develop screening strategies for populations. However, our population is highly representative of individuals at risk for diabetes (i.e., those most likely to be recommended for diabetes screening); therefore, results obtained from this study should lead to clinically relevant analyses and discussion. We defined the diagnosis of diabetes on the basis of results from a single OGTT, which is a similar approach to many previous epidemiological studies that studied the prevalence, incidence, and burden of diabetes (14,18,22,23). This is not in keeping with the current ADA guidelines, which require either two tests to be abnormal or one test to be positive on two separate occasions. This approach, though not optimal, is representative of the practice situation and has provided meaningful data (14,18,22,23).

The results from this study allow us to make several observations. First, this study provides strong evidence that individuals with risk factors for diabetes and FPG levels between 5.5 and 8.0 mmol/l

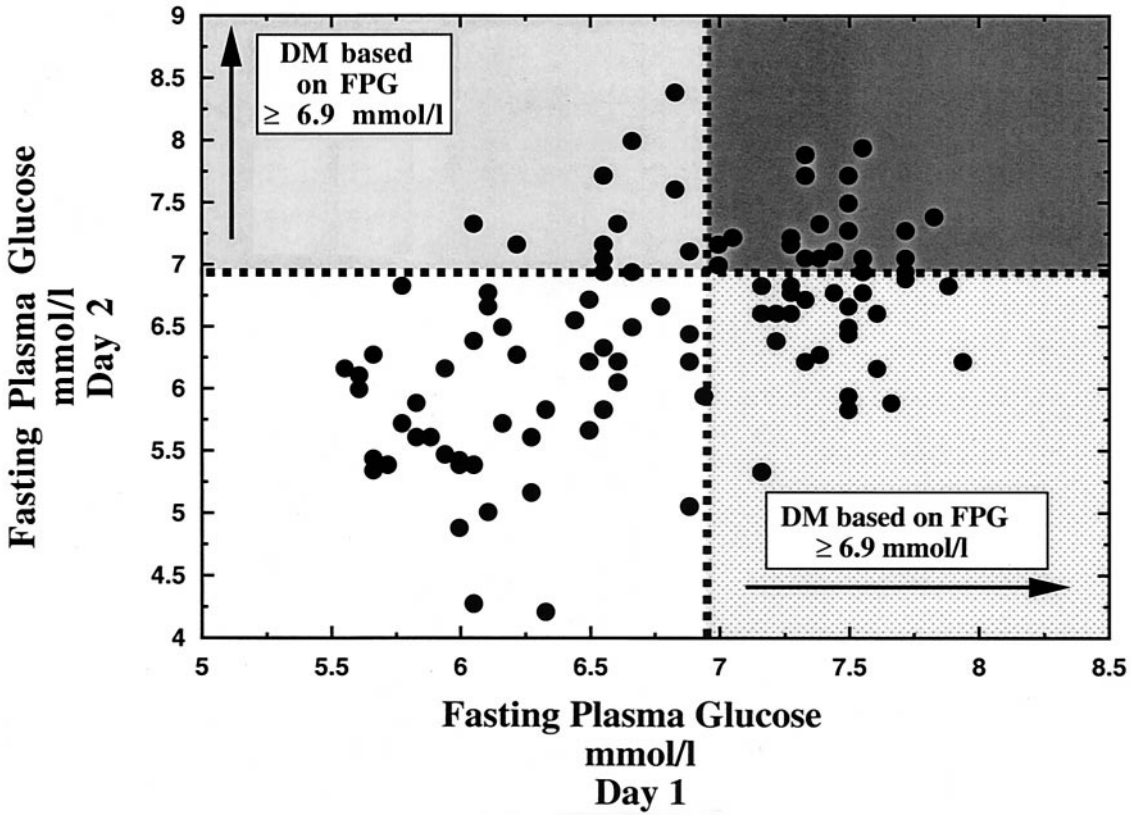

Figure 4— *Lack of reproducibility of FPG measurements.*

have a 50% chance of actually having diabetes, as diagnosed by OGTT criteria. Moreover, our results suggest that nearly half of those with both risk factors for diabetes and IFG (FPG levels of 6.1–6.9 mmol/l) actually have diabetes by OGTT criteria. Second, our data suggest that measuring HbA_{1c} in at-risk individuals enhances the ability to diagnose diabetes in its early stage. Third, the data suggest that the diagnostic criterion requiring two concordant FPG measurements ≥7.0 mmol/l to diagnose diabetes in at-risk individuals with FPG levels between 7.0 and 8.0 mmol/l results in a dramatic loss of sensitivity. Together, the data indicate that the current diagnostic criteria maximize the specificity of diagnosis rather than the sensitivity of screening. However, the current diagnostic criteria appear to have an inadequate ability to detect diabetes in at-risk populations, particularly those with IFG.

Results from this study extend the findings of previous population-based reports indicating that FPG measurements are not sufficiently sensitive to detect diabetes in previously undiagnosed individuals. A single FPG measurement ≥7.0 mmol/l identified only 45% of our cohort with early type 2 diabetes. Data from 480 Japanese subjects with diabetes indicated that a diagnostic FPG value of 7.0 mmol/l provides a sensitivity of 52% (24). Epidemiological data from Modan and Harris (25) suggest that an FPG level of 6.6 mmol/l in Americans and Israelis allows for sensitivities of 54 and 65%, respectively. Other studies estimate that 40–70% of patients with diabetes, diagnosed by OGTT criteria, have fasting glucose levels <7.0 mmol/l (13,26–28). The currently recommended "confirmatory" test after the discovery of a single elevated FPG value (≥7.0 mmol/l) is a repeat FPG measurement or OGTT; however, most physicians repeat the FPG (1). Our data and those from other studies (16,28,29) suggest that requiring two FPG measurements ≥7.0 mmol/l for the diagnosis of diabetes only compounds the insensitivity of a single FPG test. A recent study of newly diagnosed subjects with type 2 diabetes found that 95% of FPG measurements varied by ±15% on a daily basis (29). Manucci et al. (28) reported that concordant FPG values >7.0 mmol/l occur in merely 55% of obese diabetic subjects. Only 42% of our subjects with OGTT-diagnosed diabetes who demonstrated initial FPG levels of 7.0–8.0 mmol/l had diabetic-range FPG levels on repeat testing. Requiring two FPG levels >7.0 mmol/l to diagnose diabetes provided an overall sensitivity of 19% in our cohort of 101 subjects with early type 2 diabetes.

The usefulness of HbA_{1c} in the screening and diagnosis of diabetes has been widely debated (30–32), and it is criticized primarily for its lack of sensitivity and for the confounding aspects of assay and reference-range standardization and of inadequate quality control (33,34). The issues with the technical aspects of the assay were highlighted by studies in which samples for the measurement of HbA_{1c} were split between assays, yielding extreme variability in the results (35,36). Indeed, large epidemiological studies have suggested that HbA_{1c} testing is less sensitive than FPG measurement in terms of its diagnostic capabilities (37,38). However, data from the present study (obtained in a well-defined at-risk population) and data from previous reports (obtained in more general populations)

(39,40) indicate that the combination of FPG and HbA_{1c} measurements is more predictive than either parameter alone.

A diagnostic approach using FPG and HbA_{1c} measurements very similar to those described in our study was recently proposed by Davidson et al. (41). Their suggestion, in contrast to ours, is to use an HbA_{1c} value of 7.1% (or 1% above the upper limit of normal) as the diagnostic threshold for diabetes. The choice of this HbA_{1c} value was based on current treatment goals and was not for diagnostic purposes. This approach increases the specificity rather than the sensitivity of diagnosis. Because the mean ± 2 SDs value for any test is, by convention, a definable normal range (5.3 ± 0.8% for our assay), any level that is above the normal range in any given assay should be considered abnormal (>6.1% for our assay). Little et al. (42) suggested that an HbA_{1c} value >2 SDs above the mean was highly specific for diabetes. Wiener (43) suggested that an HbA_{1c} value >6.2% (reference range 3.8–5.5%) had 100% specificity for the diagnosis of diabetes. Recent evaluation of data from the Third National Health and Nutrition Examination Survey has also indicated that HbA_{1c} measurements are highly specific (>97%) for the diagnosis of diabetes (41). Thus, patients with elevated HbA_{1c} values—even those in whom the FPG measurements are nondiagnostic—are overwhelmingly likely to have diabetes.

It is noteworthy that our subjects were aware that their OGTT indicated diabetes before they returned for the second FPG measurement. Although they were not specifically instructed to do so, it is possible that subjects initiated lifestyle modifications between the time of OGTT and the second FPG measurement, giving rise to reduced concordance between measurements. Arguably, it is also likely that this scenario occurs in the clinical setting after patients have been instructed that their screening FPG suggests the diagnosis of diabetes and that a second sample is required for confirmation.

In conclusion, in patients with risk factors for diabetes and FPG levels ≥5.5 mmol/l—and in particular in patients with FPG values ≥6.1 mmol/l but below the current diagnostic threshold—the HbA_{1c} level appears helpful in identifying those with early diabetes. Individuals with elevated HbA_{1c} values but nondiagnostic FPG levels are overwhelmingly likely to have diabetes. Finally, for patients with a single FPG between 7.0 and 8.0 mmol/l, obtaining an HbA_{1c} measurement appears to be of greater value than repeat FPG testing in confirming the diagnosis of diabetes in at-risk individuals.

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