Plasma Glucose and Prediction of Microvascular Disease and Mortality

Evaluation of 1997 American Diabetes Association and 1999 World Health Organization criteria for diagnosis of diabetes

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OBJECTIVE — The 1997 American Diabetes Association (ADA) and 1999 World Health Organization (WHO) criteria for diabetes and hyperglycemia were evaluated and compared with respect to prediction of microvascular and macrovascular disease and mortality.

RESEARCH DESIGN AND METHODS — The prevalence of retinopathy and nephropathy at baseline and during the subsequent 10 years and mortality rates were examined in relation to baseline fasting plasma glucose (FPG) and 2-h postload plasma glucose (2-h PG) among 5,023 Pima Indian adults and in relation to the cut points defined by the ADA and WHO criteria.

RESULTS — The frequencies of retinopathy and nephropathy were directly related to baseline FPG and 2-h PG with approximate thresholds near or below the current diagnostic criteria for diabetes (FPG ≥7.0 and 2-h PG ≥11.1 mmol/l). The rates of retinopathy were 4.7% in impaired fasting glucose (IFG) and 20.9% in diabetes by ADA criteria; 1.6% for impaired glucose tolerance (IGT) and 19.7% for diabetes by 1985 WHO criteria; and 1.2% for IGT and 19.2% for diabetes by the 1999 WHO criteria. Mortality rates from cardiovascular-renal–related diseases were higher in diabetic individuals (FPG ≥7.0 or 2-h PG ≥11.1 mmol/l) than in those with normal FPG and 2-h PG but were not elevated in those with IFG or IGT.

CONCLUSIONS — Retinopathy and nephropathy were directly related to higher FPG or 2-h PG. FPG, which identifies those at high risk of microvascular disease and mortality, can be used to predict these outcomes and to diagnose diabetes when oral glucose tolerance testing is not practical.

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Since the 1997 recommendation of the American Diabetes Association (ADA) to modify the diagnostic criteria for diabetes (1), there have been many comparisons of those who would be diagnosed by these and by the previous 1985 World Health Organization (WHO) criteria (2–5). Most previous reports, however, have not evaluated the underlying measurements—fasting plasma glucose (FPG) and 2-h postload plasma glucose (2-h PG) concentrations—or considered the balance between sensitivity and specificity in predicting adverse outcomes and in selection of diagnostic levels.

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Abbreviations: 2-h PG, 2-h postload plasma glucose; ADA, American Diabetes Association; FPG, fasting plasma glucose; IFG, impaired fasting glucose; ROC, receiver operating characteristic; WHO, World Health Organization.

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

The best criteria for hyperglycemia for the diagnosis of diabetes should not be determined by comparing how many people are diagnosed by 1 criterion when evaluated against another. Instead, they should be based on a nonglucose reference (such as retinopathy) of clinical importance that is directly related to the disease process (6). In several studies, FPG and 2-h PG during an oral glucose tolerance test were strongly predictive of retinopathy and nephropathy and nearly equivalent in their predictive abilities (1,6,7). This finding, together with the simplicity of measurement of FPG, resulted in the ADA recommendation that diabetes could be diagnosed by FPG (if ≥7.0 mmol/l) rather than 2-h PG, which is more costly to determine and is not widely used in routine clinical practice (1).

The ADA also introduced the category of impaired fasting glucose (IFG), defined as FPG ≥6.1 but <7.0 mmol/l (1). The long-term relationships of IFG to cardiovascular disease and mortality or its ability to predict diabetes are not well known. Comparisons between FPG and 2-h PG and between the ADA and WHO criteria for diabetes in predicting the development of retinopathy, nephropathy, and mortality are presented in this article using longitudinal data from the Pima Indian population study.

RESEARCH DESIGN AND METHODS

Subjects and measures

The methods are described in a previous publication (8). The present analyses are restricted to 5,023 individuals not taking insulin or oral hypoglycemic agents in whom FPG, 2-h PG, and retinopathy were assessed at the baseline examination. Diabetes was defined by ADA criteria (1) and WHO criteria of 1985 (2) and 1999 (9). These criteria are as follows: *1*) ADA criteria: FPG ≥7.0 mmol/l (i.e., the criterion recommended for determining the prevalence and incidence of the disease); *2*) 1985 WHO criteria: FPG ≥7.8 mmol/l or 2-h PG ≥11.1 mmol/l; and

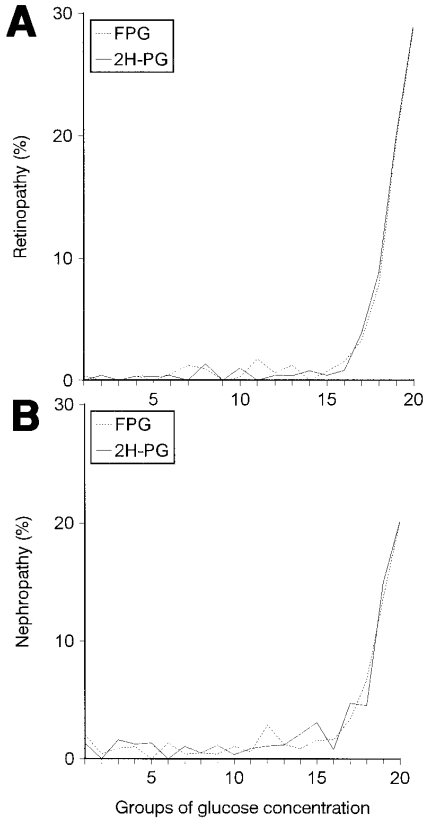

Figure 1—*Period prevalence of retinopathy (*A*) and nephropathy (*B*) in 5,023 Pima Indians divided into 5-percentile groups of the distribution of FPG and 2-h PG. For FPG, the 16th group consists of 5.8–5.9, the 17th group 6.0–6.4, the 18th group 6.5–7.8, the 19th group 7.9–13.4, and the 20th group 13.5–27.2 mmol/l. For 2-h PG, the 16th group consists of 8.2–8.5, the 17th group 9.0–10.6, the 18th group 10.7–14.9, the 19th group 15.0–21.9, and the 20th group 22–39.1 mmol/l.*

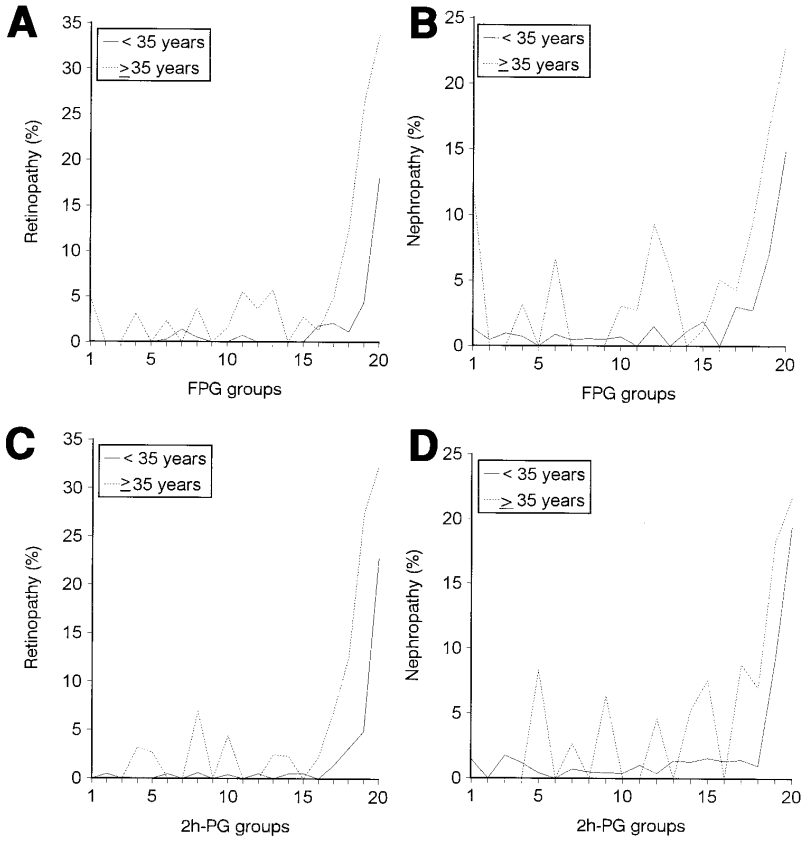

Figure 2—*Period prevalence (%) of retinopathy (*A and C*) or nephropathy (*B and D*) in individuals younger or older than 35 years at baseline divided into 5-percentile groups of the distribution of FPG (*A *and* B*) and 2-h PG (*C *and* D*). The boundaries of the percentile groups, based on subjects of all ages, are the same as those in Fig. 1.*

3) 1999 WHO criteria: FPG ≥7.0 mmol/l or 2-h PG ≥11.1 mmol/l. Among people nondiabetic by each criterion, IGT is defined by 2-h PG ≥7.8 to <11.1 mmol/l, and by ADA and 1999 WHO criteria, IFG is defined by FPG ≥6.1 to <7.0 mmol/l.

The biennial research examinations include direct ophthalmoscopic examination through dilated pupils by an examiner unaware of the glucose tolerance or presence of diabetes of the subject. Urinary total protein and creatinine concentrations were measured, and the urine protein-to-creatinine ratio was determined (10). Urine protein data were missing for 76 subjects.

Microvascular complications were defined as follows: *1*) retinopathy—the presence of at least 1 hemorrhage, microaneurysm, or proliferative retinopathy; and *2*) nephropathy—urine protein-to-creatinine ratio ≥1.0 mg protein/mg creatinine, a ratio equivalent to a total protein excretion rate of ~1 g/day (10).

Mortality was analyzed in individuals with baseline examinations between 1975 and 1994, with follow-up through 31 December 1994. They were restricted to people aged ≥35 years because of the small number of deaths (mostly accidental) below this age. The underlying cause of death was determined by review of all available inpatient and outpatient medical records, death certificates, autopsy findings, and medical examiner reports (11). The ninth revision of the *International Classification of Disease* was used to classify cardiovascular-, renal-, and diabetes-related causes (herein referred to as cardiovascular-renal mortality) as codes 250, 401–459, or 580–587, respectively (12).

Statistical analysis

Period prevalence of retinopathy and nephropathy. Subjects with or without a diagnosis of diabetes, retinopathy, and nephropathy and with measurements of FPG and 2-h PG at baseline were included. The outcome measure was the presence of retinopathy or nephropathy at baseline examination or at the last biennial examination conducted within 10 years. Three groups of individuals were included this analysis: those who had an examination at baseline only, those with follow-up within 5 years, and those with follow-up within 10 years. Rates were adjusted for follow-up time by the direct method, and 95% CIs were computed (13). The resultant period prevalence rates were analyzed by baseline FPG or 2-h PG.

Receiver operating characteristics. Receiver operating characteristic (ROC) curves were used to compare the ability of FPG and 2-h PG to discriminate between those with and those without retinopathy. The ROC curve describes the diagnostic properties of a test by plotting sensitivity as a function of 1 − specificity. Sensitivity and specificity of glucose levels to detect retinopathy were computed at diagnostic thresholds or cutoff points over a range of FPG and 2-h PG. Sensitivity is the fraction of individuals with a value greater than or

Table 1—*Period prevalence of retinopathy and number of people at risk according to combined baseline FPG and 2-h PG categories*

	2-h PG (mmol/l)			
	<7.8	7.8–11.0	≥11.1	Total by FPG
FPG (mmol/l)				
<6.1	0.3 (0.2–0.5)	0.6 (0–1.2)	17.6 (8.0–27.2)	0.6 (0.4–0.9)
n	3,499	537	60	4,096
6.1–6.9	3.3 (0–6.9)	4.1 (0.6–7.7)	6.9 (1.5–12.3)	4.7 (2.3–7.0)
n	93	126	79	298
≥7.0	0	14.9 (1.4–28.5)	21.8 (18.5–25.1)	20.9 (17.7–24.0)
n	16	29	584	629
Total by 2-h PG	0.4 (0.2–0.6)	1.7 (0.8–2.7)	19.9 (17.0–22.7)	—
n	3,608	692	723	5,023

Data are % (95% CI) or *n*.

equal to the cutoff point among those who have the outcome (retinopathy) within 10 years (i.e., the ability to identify individuals having or developing retinopathy). Specificity is the fraction of individuals with a value less than the cutoff point among those without retinopathy. The ROC curve allows comparison of the diagnostic characteristics of continuous variables (such as plasma glucose) over the range of possible values rather than just at 1 arbitrary point (14). The area under a ROC curve represents the probability that a subject chosen at random from the group with the outcome of interest had a higher test value than one without.

Mortality. Death rates were calculated as the number of deaths divided by the person-years of follow-up from the date of the first examination until death or 31 December 1994. Death rates were stratified by FPG and 2-h PG at the first examination at age ≥35 years. Death rates were age- and sex-adjusted by the direct method using the age-sex distribution of all subjects aged ≥35 years at baseline as the reference population, and CIs were computed (13). Statistical significance of differences in age- and sex-stratified mortality rates were assessed between groups (15).

RESULTS

Microvascular disease

At baseline, there were 96 prevalent cases of retinopathy and 84 of nephropathy. Adding those present at follow-up, the period prevalence was composed of 168 cases of retinopathy and 151 of nephropathy. The associations of the period prevalence of retinopathy and nephropathy with 5-percentile groups of baseline FPG and 2-h PG are shown in Fig. 1. The FPG and 2-h PG curves are very similar. ROC curve analyses showed that there were no significant differences in the associations of retinopathy with FPG (area under the ROC curve = 0.89) or 2-h PG (area = 0.90) or of nephropathy with FPG (area = 0.79) or 2-h PG (area = 0.80). There was an increase in retinopathy (Fig. 1*A*) and nephropathy (Fig. 1*B*) beginning in the groups with FPG = 6.0–6.4 mmol/l and 2-h PG = 9.0–10.6 mmol/l and continuing with higher levels of baseline FPG and 2-h PG. When using only the cases of retinopathy or nephropathy prevalent at baseline, the prevalence of these complications also increased at the same levels of FPG or 2-h PG, and the 2 measures of glycemia were indistinguishable by ROC curve analysis. Because the period prevalence is based on more cases and results in more stable estimates, the results are presented only for period prevalence.

The effects of age on the relationships between FPG and 2-h PG and microvascular disease are shown in Fig. 2. At almost all plasma glucose levels, the rates of retinopathy and nephropathy were higher in those ≥35 years of age at baseline. Thresholds of FPG and 2-h PG associated with increasing rates of retinopathy or nephropathy appear to be lower in older individuals.

The period prevalence of retinopathy is shown in Tables 1 and 2 according to the categories of FPG and 2-h PG specified in the ADA and WHO criteria. The rates of retinopathy in diabetic subjects were 19.2–20.9%, depending on which criteria for diabetes were used; 3.7–4.7% in IFG; 1.2–1.6% in IGT; and 0.3% in individuals with FPG <6.1 and 2-h PG <7.8 mmol/l at baseline. Although the estimated rates in some of the categories are imprecise because of small sample sizes, they are higher in the IFG than in the IGT groups. For example, the period prevalence of retinopathy was 3.3% in the 93 people with IFG but normal 2-h PG, which is much higher than the 0.6% in the 537 with IGT but normal FPG. As with retinopathy, rates of nephropathy were much higher in individuals with diabetes by any definition and higher in individuals with IFG than with IGT (Tables 3 and 4).

Sensitivity and specificity for retinopathy are plotted over a wide range of FPG cut points as a ROC curve in Fig. 3. The points on the curve representing several FPG values are indicated along with the percentages, in parentheses, of the baseline population with values at or above these points. Also shown (as triangles) are points corresponding to 2-h PG of 7.8 or 11.1 mmol/l. They lie almost on the curve for FPG, i.e., their predictive values are almost identical to the FPG values corresponding to the same fraction of the population. The squares represent diabetes by the 1985 WHO criteria (i.e., FPG ≥7.8 mmol/l or 2-h PG ≥11.1 mmol/l) and the 1999 WHO criteria (i.e., FPG ≥7.0 mmol/l or 2-h PG ≥11.1 mmol/l). Both these points lie slightly above the curve, indicating that at these specificities, they have higher sensitivities than the points based on FPG alone. The difference between any of the points based on 2-h PG and the curve, however, is very small.

Table 2—*Period prevalence of retinopathy and number of people at risk according to American Diabetes Association and World Health Organization diagnostic categories*

Classification	ADA	WHO-1985	WHO-1999
IGT	—	1.6 (0.7–2.6)	1.2 (0.4–2.0)
n	—	684	663*
IFG	4.7 (2.3–7.0)	—	3.7 (1.2–6.1)
n	298	—	219*
Diabetes	20.9 (17.7–24.0)	19.7 (16.8–22.5)	19.2 (16.4–21.9)
n	629	733	768

Data are % (95% CI) or *n*. *Includes 126 people with IFG and IGT. ADA, classification by ADA (1997) criteria for FPG only; WHO-1985, classification by WHO (1985) criteria; WHO-1999, classification by WHO (1999) criteria.

Table 3—*Period prevalence of retinopathy and number of people at risk according to combined baseline FPG and 2-h PG categories*

	2-h PG (mmol/l)			
	<7.8	7.8–11.0	≥11.1	Total by FPG
FPG (mmol/l)				
<6.1	1.0 (0.6–1.3)	2.3 (1.0–3.5)	9.2 (1.6–16.8)	1.2 (0.9–1.6)
n	3,450	531	58	4,039
6.1–6.9	6.4 (1.5–11.2)	3.6 (0.2–7.0)	2.8 (0–6.7)	4.1 (1.8–6.3)
n	92	125	77	294
≥7.0	0	11.5 (0–24.2)	15.3 (12.4–18.2)	14.6 (11.8–17.4)
n	16	29	569	614
Total by 2-h PG	1.1 (0.8–1.4)	2.8 (1.6–4.0)	13.4 (10.9–15.9)	14.6 (11.8–17.4)
n	3,558	685	704	4,947

Data are % (95% CI) or *n*. Sample sizes are smaller than those in Table 1 because of missing data on nephropathy.

Mortality

During 13,069 person-years of follow-up in the 1,370 Pima Indian adults aged ≥35 years, there were 285 deaths from all causes, and 241 from nontraumatic causes. Of these 241 deaths, 69 were from cardiovascular-renal causes, and the remaining 172 were from other nontraumatic causes. Table 5 shows age- and sex-adjusted nontraumatic mortality and cardiovascular-renal mortality rates according to FPG or 2-h PG. There were too few subjects to allow reliable estimation of age- and sex-adjusted mortality rates in all groups formed by combinations of FPG and 2-h PG.

Mortality rates from all nontraumatic or cardiovascular-renal causes were substantially higher in individuals with diabetes (FPG ≥7.0 mmol/l or 2-h PG ≥11.1 mmol/l) but were not related to plasma glucose at lower levels. For example, mortality rates due to cardiovascular-renal causes were 6.6 deaths/1,000 person-years in people with FPG ≥7.0 mmol/l and 3.0 deaths/1,000 person-years in people with FPG <7.0 mmol/l ($P < 0.001$), but there was no significant difference between the groups with FPG <6.1 mmol/l (3.1 deaths/1,000 person-years) and FPG 6.1–6.9 mmol/l (2.5 deaths/1,000 person-years). Similar relationships of cardiovascular-renal deaths were seen with 2-h PG. By contrast, neither FPG nor 2-h PG was related to rates of death from other nontraumatic causes.

CONCLUSIONS

Microvascular complications

The microvascular complications of retinopathy and nephropathy, considered hallmarks of diabetes, were related to both baseline FPG and 2-h PG above thresholds of ~6.0 mmol/l for FPG and 9.0 mmol/l for 2-h PG. In older subjects, retinopathy and nephropathy were more frequent at almost all levels of FPG or 2-h PG, and the apparent thresholds for the increase in retinopathy or nephropathy were lower. Older individuals may have had higher FPG and 2-h PG for a longer duration at the time of the baseline examination or glycemia may have increased more rapidly. Retinopathy may also occur more frequently at a given glucose level at older ages because of additional factors such as higher blood pressure. Nevertheless, these findings argue against the suggestion, reviewed by West (16), that diagnostic levels for diabetes should be set higher in older individuals.

Levels of hyperglycemia lower than those diagnostic of diabetes are used to define IFG and IGT. IFG identifies a smaller number of people who are at greater risk of diabetes than those with IGT (8) and have a higher prevalence of retinopathy (Tables 1 and 2) and nephropathy (Tables 3 and 4) at baseline or within 10 years.

The ROC curve (Fig. 3) illustrates sensitivities and specificities over a wide range of FPG. The FPG criteria of ≥7.8 or ≥7.0 mmol/l identify fewer individuals at risk of retinopathy than the 1985 WHO criteria (2-h PG ≥11.1 mmol/l), and their sensitivities are lower. There is little difference in the sensitivity and specificity of the 1985 and 1999 WHO criteria. The FPG cutoff point for the prediction of retinopathy that corresponds best to a 2-h PG level of 11.1 mmol/l is 6.6 mmol/l, with a sensitivity of 81%, compared with 85% for 2-h PG. If the FPG cutoff point for the diagnosis of diabetes were lowered from 7.0 to 6.6 mmol/l, the same percentage of subjects (14%) would be identified as by a 2-h PG cutoff point of ≥11.1 mmol/l.

Cardiovascular mortality

In addition to the well-known effects of diabetes on mortality, lesser degrees of hyperglycemia, such as IGT, have been associated with increased mortality from all causes or from cardiovascular diseases in some studies (17–19) but not in others (20,21). In the Rancho Bernardo (U.S.) Study, FPG was linearly associated with mortality from ischemic heart disease in men, and the rates in women were elevated at FPG ≥6.7 mmol/l (22). Among Norwegian men, cardiovascular mortality rates were 50% higher among those with FPG levels 4.9–6.0 mmol/l than among those with lower FPG concentrations (23). In the Funagata Diabetes Study in Japan, all-cause and cardiovascular mortality rates were significantly higher in IGT than in normal glucose tolerance by 1985 WHO criteria, and they were slightly, but not significantly, higher in the smaller group of people with IFG by ADA criteria (24).

Among the Pima Indians, age- and sex-adjusted mortality rates from nontraumatic or cardiovascular-renal causes were higher in individuals who met either ADA or WHO

Table 4—*Period prevalence of retinopathy and number of people at risk according to American Diabetes Association and World Health Organization diagnostic categories*

Classification	ADA	WHO-1985	WHO-1999
IGT	—	2.7 (1.5–3.9)	2.5 (1.3–3.6)
n	—	677	656*
IFG	4.1 (1.8–6.3)	—	4.8 (2.0–7.7)
n	294	—	217*
Diabetes	14.6 (11.8–17.4)	13.3 (10.9–15.8)	13.0 (10.6–15.3)
n	629	714	749

Data are % (95% CI) or *n*. Sample sizes are smaller than those in Table 1 because of missing data on nephropathy. *Includes 126 people with IFG and IGT. ADA, classification by ADA (1997) criteria for FPG only; WHO-1985, classification by WHO (1985) criteria; WHO-1999, classification by WHO (1999) criteria.

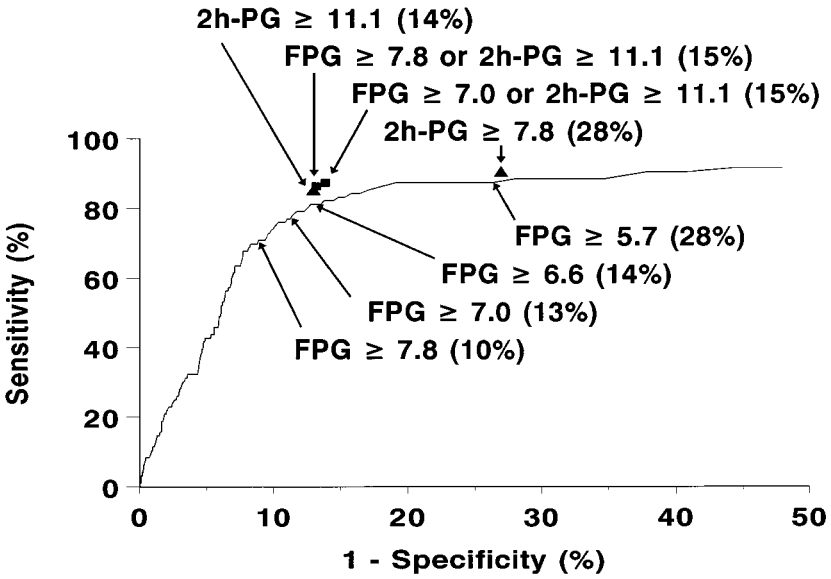

Figure 3—*The ROC curve for FPG in predicting retinopathy. The sensitivity is plotted as a function of 1 − specificity. The points on the curve representing 4 FPG values are marked with arrows. The percentages of the baseline population with values at or above these points are shown in parentheses. For comparison, the 2 points corresponding to 2-h PG of 7.8 or 11.1 mmol/l are shown (▲). ■, The 1985 and 1999 WHO criteria for diabetes.*

diagnostic criteria for diabetes but were not higher in those with IFG or IGT. All of the excess mortality in the diabetic subjects was due to cardiovascular-renal causes; mortality from other nontraumatic causes was unrelated to either FPG or 2-h PG.

Selecting a test and diagnostic level

FPG and 2-h PG have similar abilities to predict the adverse outcomes of diabetes and, among nondiabetic individuals, to predict the development of diabetes (8). The approximate thresholds in the relationships of plasma glucose and microvascular disease (Figs. 1 and 2) are close to the currently recommended diagnostic levels (1,9). Evidence for glycemic thresholds for macrovascular disease and mortality is lacking, however, because their relationships with glucose may be more linear and vary among populations. Selection of diagnostic levels based on outcomes that do not have clear thresholds is more complicated and involves balancing higher sensitivity with lower specificity, greater medical and social costs of overdiagnosis, and potential harm from treatment.

Suggestions that the 2-h PG is more sensitive than FPG in detecting individuals at risk of diabetes, cardiovascular disease, or other adverse outcomes resulted from equating the sensitivity of a particular diagnostic category with the sensitivity inherent in the measurement itself (25–27). In some situations, the combination of FPG and 2-h PG may be a slightly better predictor than either alone. For example, diagnostic levels based on both measures have slightly better sensitivity for retinopathy at the same specificity than either measure alone (Fig. 3). In the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe Study, the combination based on categorical definitions predicted cardiovascular mortality better than either measure alone (26). As shown in the present article, almost equivalent sensitivities and specificities can be obtained by setting equivalent diagnostic cut points for FPG and 2-h PG. Thus, the sensitivity to predict retinopathy (Fig. 3) or, among those initially nondiabetic, to predict subsequent diabetes (8), can be improved not only by measuring 2-h PG, but also by using the FPG alone with a lower cutpoint.

These observations raise the serious question of when oral glucose tolerance tests should be performed for clinical purposes. An oral glucose tolerance test can identify additional people with abnormal glycemia only in those with normal FPG, who form the vast majority of most populations. It is unclear whether the small increase in sensitivity obtained by the combination of FPG and 2-h PG is worthwhile. The major published evidence for a beneficial effect of aggressive treatment of hyperglycemia in type 2 diabetes comes from the U.K. Prospective Diabetes Study, in which eligibility was based on FPG ≥6.1 mmol/l but not on 2-h PG (28). In the U.S. Diabetes Prevention Program, which will assess treatments for IGT, eligibility requires an elevated FPG (≥5.3 mmol/l) and hence will provide limited data on people with normal FPG (29). Without evidence that lowering blood glucose in people with normal FPG is beneficial, the value of detecting abnormalities of 2-h PG in such individuals is not established but requires further research.

In summary, FPG and 2-h PG are associated with retinopathy and nephropathy, with approximate thresholds near or below the current diagnostic criteria for diabetes (FPG ≥7.0 mmol/l and 2-h PG ≥11.1 mmol/l). Among Pima Indians, mortality rates were elevated in diabetic individuals but not in individuals with IFG or IGT. Measurement of FPG is more convenient and reproducible (30) than 2-h PG, and

Table 5—*Age- and sex-adjusted cause-specific mortality rates at ages ≥35 years according to baseline FPG and 2-h PG categories in Pima Indians*

	Cause of death		
	Nontraumatic	Cardiovascular-renal	Other nontraumatic
FPG (mmol/l)			
<6.1	13.5 (10.9–16.1)	3.1 (1.9–4.4)	10.4 (8.1–12.6)
6.1–6.9	12.9 (7.5–18.3)	2.5 (0.5–4.4)	10.4 (5.4–15.4)
≥7.0	18.2 (14.4–21.9)	6.6 (4.4–8.8)	11.6 (8.5–14.6)
2-h PG (mmol/l)			
<7.8	12.4 (9.6–15.2)	2.6 (1.3–3.9)	9.8 (7.4–12.3)
7.8–11.0	15.5 (10.2–20.8)	2.6 (0.7–4.5)	12.9 (7.9–17.8)
≥11.1	18.1 (14.6–21.6)	6.8 (4.7–8.9)	11.3 (8.5–14.1)

Data are number of deaths/1,000 person-years (95% CI).

FPG is highly predictive of retinopathy, nephropathy, and mortality. In addition to its ability to predict diabetes (8), FPG is a suitable test for identifying those at high risk of microvascular disease and mortality, and therefore for diagnosing diabetes.

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