Comparison of Fasting and 2-Hour Glucose and HbA₁c Levels for Diagnosing Diabetes

Diagnostic criteria and performance revisited

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OBJECTIVE — Nearly two decades ago, the National Diabetes Data Group (NDDG) and the World Health Organization (WHO) Expert Committee on Diabetes Mellitus published diagnostic criteria for diabetes. We undertook this study to compare the performance of three glycemic measures for diagnosing diabetes and to evaluate the performance of the WHO criteria.

RESEARCH DESIGN AND METHODS — In a cross-sectional population-based sample of 1,018 Egyptians ≥20 years of age, fasting and 2-h glucose and HbA₁c levels were measured, and diabetic retinopathy was assessed by retinal photograph. Evidence for bimodal distributions was examined for each glycemic measure by fitting models for the mixture of two distributions using maximum likelihood estimates. Sensitivity and specificity for cutpoints of each glycemic measure were calculated by defining the true diabetes state (gold standard) as 1) the upper (diabetic) component of the fitted bimodal distribution for each glycemic measure, and 2) the presence of diabetic retinopathy. Receiver operating characteristic (ROC) curves were constructed to determine the performance of the glycemic measures in detecting diabetes as defined by diabetic retinopathy.

RESULTS — In the total population, the point of intersection of the lower and upper components that minimized misclassification for the fasting and 2-h glucose and HbA₁c were 7.2 mmol/l (129 mg/dl), 11.5 mmol/l (207 mg/dl), and 6.7%, respectively. When diabetic retinopathy was used to define diabetes, ROC curve analyses found that fasting and 2-h glucose values were superior to HbA₁c ($P < 0.01$). The performance of a fasting glucose of 7.8 mmol/l (140 mg/dl) was similar to a 2-h glucose of 12.2–12.8 mmol/l (220–230 mg/dl), and the performance of a 11.1 mmol/l (200 mg/dl) 2-h glucose was similar to a fasting glucose of 6.9–7.2 mmol/l (125–130 mg/dl).

CONCLUSIONS — Optimal cutpoints for defining diabetes differ according to how diabetes itself is defined. When diabetes is defined as the upper component of the bimodal population distribution, a fasting glucose level somewhat lower than the current WHO cutpoint and a 2-h glucose level somewhat higher than the current WHO cutpoint minimized misclassification. When diabetic retinopathy defines diabetes, we found that the current fasting diagnostic criterion favors specificity and the current 2-h criterion favors sensitivity. These results should prove valuable for defining the optimal tests and cutpoint values for diagnosing diabetes.

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The National Diabetes Data Group (NDDG) and the World Health Organization (WHO) Expert Committee on Diabetes Mellitus published diagnostic criteria for diabetes mellitus in 1979 and 1980 (1,2). These recommendations were similar and have been widely accepted by clinicians and researchers. The worldwide consensus has allowed the comparison of results from diabetes studies carried out in different countries and continents. However, both reports anticipated that criteria might need revision as research and knowledge advanced.

In the development of diagnostic criteria for diabetes, studies of the frequency distribution of glucose measurements were carefully examined. Although most populations had a single distribution skewed to higher levels (3,4), a bimodal pattern was observed in the Pima Indian (5–7) and Nauruan (8) populations. In these populations, the lower component characterized the distribution in individuals with normal glucose tolerance, and the upper component characterized the distribution in individuals with diabetes. A fasting blood glucose of approximately 7.8 mmol/l (140 mg/dl) divided the lower and upper components. The lower component of the 2-h glucose value (after a 75-g oral load) had an upper bound of approximately 11.1 mmol/l (200 mg/dl). Further supporting the hypothesis that the upper component characterized individuals with diabetes was the finding that the prevalence of diabetic retinopathy was low among individuals whose 2-h glucose values were in the lower component, and was higher among individuals whose values were in the upper component (5).

Glycemic measures for the diagnosis of diabetes have been extensively reviewed (9–14). Current fasting and 2-h glucose cutpoints are not equivalent in detecting individuals who meet WHO criteria for diabetes. Indeed, in the second National Health and Nutrition Examination Survey (NHANES II), about 75% of those with 2-

h glucose values diagnostic for diabetes had fasting values below that diagnostic for diabetes (15). More recently, McCance et al. (9) found fasting glucose and glycated hemoglobin levels to be acceptable alternatives to 2-h glucose values in predicting diabetic retinopathy (9).

In a recent population-based study of diabetes in Egypt (16), we performed oral glucose tolerance tests (OGTT), tested HbA$_{1c}$ levels, and took retinal photographs. With this information, we were able to examine the distribution of glycemic measures and their relationship to retinopathy. The purposes of this study were to *1*) examine the performance of current diagnostic criteria and other cutpoints for diagnosing diabetes using the bimodal distributions of three glycemic measures to define the true diabetes state (gold standard), *2*) examine the relationship between diabetic retinopathy and each glycemic measure, and *3*) examine current diagnostic criteria and other cutpoints and compare the performance of three glycemic measures for diagnosing diabetes using the presence of diabetic retinopathy as the true diabetes state (gold standard).

RESEARCH DESIGN AND METHODS

Survey
The methods and preliminary results of the Diabetes in Egypt Project have been reported elsewhere (16). In summary, between 1991 and 1994, a population-based survey was conducted in metropolitan Cairo and in three rural agricultural villages in Kaliubia, a delta region approximately 30 miles north of Cairo. Household census listings were provided by the Egyptian Central Agency for Public Mobilization and Statistics; 6,052 randomly selected households were eligible (occupants were Egyptian and had resided there for ≥6 months). All household residents ≥20 years of age were enumerated in each sampled household; then, using Kish's selection tables (17), one person was randomly selected to participate in the study (regardless of whether the person was at the home during the field visit or had diabetes). After obtaining informed consent, field workers measured random capillary whole blood glucose levels of participants with a portable reflectance meter (One Touch II, Lifescan, Milpitas, CA). Of eligible households, 4,620 (76%) randomly selected participants had capillary glucose levels

measured. All participants (100%) at higher risk for diabetes (random capillary glucose ≥5.6 mmol/l [≥100 mg/dl], including those with a history of diabetes) and a random sample (20% in most areas; although early in the study, in a few areas, as a result of uncertainty as to the response rate, either 10% or 100%) of those at lower risk for diabetes (random capillary glucose <5.6 mmol/l [<100 mg/dl]) were invited for a medical and laboratory exam. Of the 2,021 (1,351 at high risk, 670 at low risk) invited for the exam, 1,451 (72%; 976 [72%] at high risk, 475 [71%] at low risk) had glucose and HbA$_{1c}$ levels measured after an overnight fast and glucose measured 2 h after a 75-g oral glucose load. Participants received no formal dietary preparation. Individuals receiving antihyperglycemic medications were instructed not to take those medications on the morning of the OGTT. All participants who underwent OGTTs received eye examinations (dilated pupil) by an ophthalmologist and had a bilateral retinal photograph taken of the fundus through dilated pupils.

We measured serum glucose by the glucose oxidase method (CV 3.8%) with a dry chemistry analyzer (Kodak DT-60; Eastman Kodak, Rochester, NY) and HbA$_{1c}$ using affinity chromatography (CV 6.0%; Pierce Scientific, Rockford, IL). The University of Wisconsin Reading Center staff graded the retinal photographs with a modified Airlie House classification scheme for diabetic retinopathy (18). We considered retinopathy to be present when there were retinal microaneurysms either alone or with nonproliferative changes (hard or soft exudates, intraretinal microangiopathy, or retinal hemorrhages), preproliferative or proliferative changes, or vitreous hemorrhage.

In the previous study (16), we used WHO criteria to determine whether diabetes was present (fasting glucose ≥7.8 mmol/l [≥140 mg/dl] or 2-h glucose ≥11.1 mmol/l [≥200 mg/dl]) (2). After applying sampling weights to account for the unequal probability of selection for each participant, we estimated that 9.3% of the population ≥20 years of age had diabetes.

Of the 1,451 individuals who underwent clinical and laboratory examinations, 1,018 (70%) had fasting and 2-h glucose levels, HbA$_{1c}$ levels, and gradable retinal photograph; this group was included in this analysis. Individuals not included in this analysis tended to be older (mean age,

51 vs. 45 years; $P < 0.01$) but were similar with respect to sex (37% vs. 41% male; $P = 0.25$), mean BMI (30.4 vs. 30.6 kg/m^2; $P = 0.67$), and mean 2-h glucose value (183 vs. 184 mg/dl; $P = 0.88$). In the group included in this analysis, 277 individuals had diagnosed diabetes (251 [91%] of whom were receiving antihyperglycemic medication [48, insulin; 195, oral antihyperglycemic medication; and 8, both]) and 85 had previously undiagnosed diabetes. Compared with the 111 individuals with diabetes who were not receiving antihyperglycemic medication (26 diagnosed and 85 previously undiagnosed), the 251 who were receiving medication had substantially higher mean fasting glucose (12.3 vs. 10.7 mmol/l [222 vs. 193 mg/dl] ; $P < 0.01$), 2-h glucose (18.6 vs. 16.3 mmol/l [337 vs. 293 mg/dl]; $P < 0.01$) and HbA$_{1c}$ (9.1 vs. 8.1%; $P < 0.01$) values.

Some previous reports of the distributions of glycemic levels and bimodality have included individuals with diagnosed diabetes (6,8). Some have included those with diagnosed diabetes who were receiving medication (19–22), and others have excluded them (9,10,23). Excluding those diagnosed and receiving treatment (medication or dietary) eliminates the treatment effect, but can dramatically change the characteristics of the population with diabetes. Including diagnosed individuals or those on treatment maintains the population-based characteristics of the sample, but may allow some treatment-induced effect on the glycemic measures. We performed analyses with and without inclusion of individuals who were receiving antihyperglycemic medication.

Statistical analyses
To determine the cutpoints between the lower and upper components, we modeled the frequency distribution of each glycemic measurement (log base 10 of mg/dl units for glucose and log base 10 of the percent HbA$_{1c}$) as a mixture of two normal distributions, as has been done previously with other populations (5,6,19–22). The model for a mixture of two normal distributions is as follows:

$$f(y) = \alpha f_1(y|\mu_1,\sigma_1) + (1 - \alpha)f_2(y|\mu_2,\sigma_2)$$

In this model, y is the measured blood glucose value, and f_1 and f_2 are the normal probability density functions for the lower and upper components, with means μ_1 and μ_2 and standard deviations σ_1 and σ_2.

Alpha (α) and $1 - \alpha$ are the mixture proportions that predict the size of the lower and upper components—that is, they describe the probability of being in one of the components versus the other. We obtained maximum likelihood estimates (MLE) of the parameters using the expectation-maximization algorithm for mixtures (24,25). To determine whether a mixture of two normal distributions fit the data better than a single normal distribution, we compared twice the difference in log likelihood values from both models with the χ^2 distribution (6 df) (25). The cutpoint between the two distributions was selected to minimize misclassification, as previously described (22). The intersection of the two distributions between the means (i.e., where the probability density functions of the two distributions were equal) when the diabetic component ($1-\alpha$) accounts for 9.3% of the total population (i.e., the estimated prevalence during the Diabetes in Egypt Project [16]) yields the cutpoint at which the overlap and misclassification is at its minimum. Using previously described methods (26), we also modeled the bimodal distribution, controlling for antihyperglycemic medication use.

We determined the prevalence of retinopathy by deciles of each glycemic measure. To compare the ability of fasting and 2-h glucose and HbA_{1c} measurements to detect the presence or absence of retinopathy over a range of values, we calculated receiver operating characteristic (ROC) curves and compared the areas under the curves (27). Because the ROC curves were derived from the same cases and were thus correlated, we used bootstrap methods (28) to correct for this correlation when assessing the statistical significance of differences in the areas.

The sensitivity of a specific glycemic cutpoint was defined as its ability to correctly identify individuals who have diabetes; its specificity was defined as its ability to correctly identify individuals who do not have diabetes. Because we were attempting to examine diagnostic criteria for diabetes, there needed to be an objective clinical state (or gold standard) against which the various glycemic measures could be evaluated. Using the upper component of the bimodal distribution to define the diabetes state (gold standard), the proportion of the upper (diabetic) component above the intersection point between the upper and lower components defined sensitivity, and the proportion of the lower

(nondiabetic) component below the intersection point defined specificity. Using retinopathy to define the diabetes state (gold standard), sensitivity for a glycemic cutpoint was the probability that individuals with diabetic retinopathy had equal or greater glycemic values, and the specificity was the probability that individuals with no retinopathy had glycemic values less than the selected cutpoint.

All calculations relating to mixture distributions were programmed in GAUSS Version 3.2 (Aptech Systems, Maple Valley, WA). Logistic regression models were fitted with S-Plus Version 3.3 (Statistical Sciences, Seattle, WA).

RESULTS

Bimodality of glycemic measures
The frequency distributions of the fasting and 2-h glucose and the HbA_{1c} values all suggested that two components were present for each measure (Fig. 1). When modeled, the MLEs for each measure fit the mixture of two distributions (with unequal variance) significantly better ($P < 0.001$) than a single distribution. The mean values of the first component for the fasting and 2-h glucose and percent HbA_{1c} were 5.0 mmol/l (90 mg/dl; 95% CI 88.7–91.2), 5.8 mmol/l (104 mg/dl; 95% CI 100–107), and 5.2% (95% CI 5.1–5.2), respectively; of the second component, they were 10.8 mmol/l (195 mg/dl; 95% CI 181–212), 17.5 mmol/l (316 mg/dl; 95% CI 293–335), and 7.7% (95% CI 7.4–8.4), respectively. In the study population, the points of intersection of the first and second components that minimized misclassification for the fasting and 2-h glucose and percent HbA_{1c} were 7.2 mmol/l (129 mg/dl; 95% CI 124–135), 11.5 mmol/l (207 mg/dl; 95% CI 191–224) and 6.7% (95% CI 6.5–6.9), respectively. These intersection points minimized the overlap of the components of the bimodal distributions. The sensitivities for the fasting and 2-h glucose and HbA_{1c} intersection points were 84%, 90%, and 68%, respectively; the specificities were 99.7%, 99.5%, and 99.6%, respectively. The sensitivity and specificity of a 7.8 mmol/l (140 mg/dl) fasting glucose cutpoint were 79% and 100%, respectively; for the 11.1 mmol/l (200 mg/dl) 2-h glucose cutpoint, they were 92% and 99%, respectively.

A model that controlled for the effect of antihyperglycemic medication found a similar bimodal distribution, with intersection
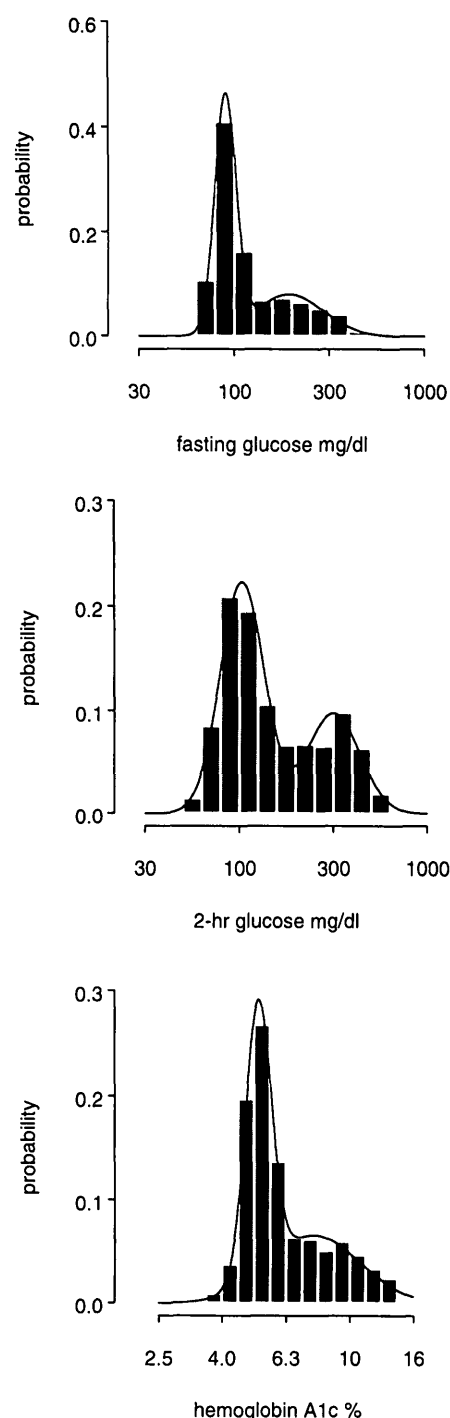
Figure 1—*Histograms of fasting and 2-h glucose values and percent HbA_{1c} (▫) and the fitted model (——) for the mixture of two distributions.*

points similar to those for the entire population (fasting glucose, 7.1 mmol/l [127 mg/dl]; 2-h glucose, 11.3 mmol/l [204 mg/dl]; and HbA_{1c}, 6.7%). However, when all individuals receiving antihyperglycemic medication were excluded, the two components were not well separated.
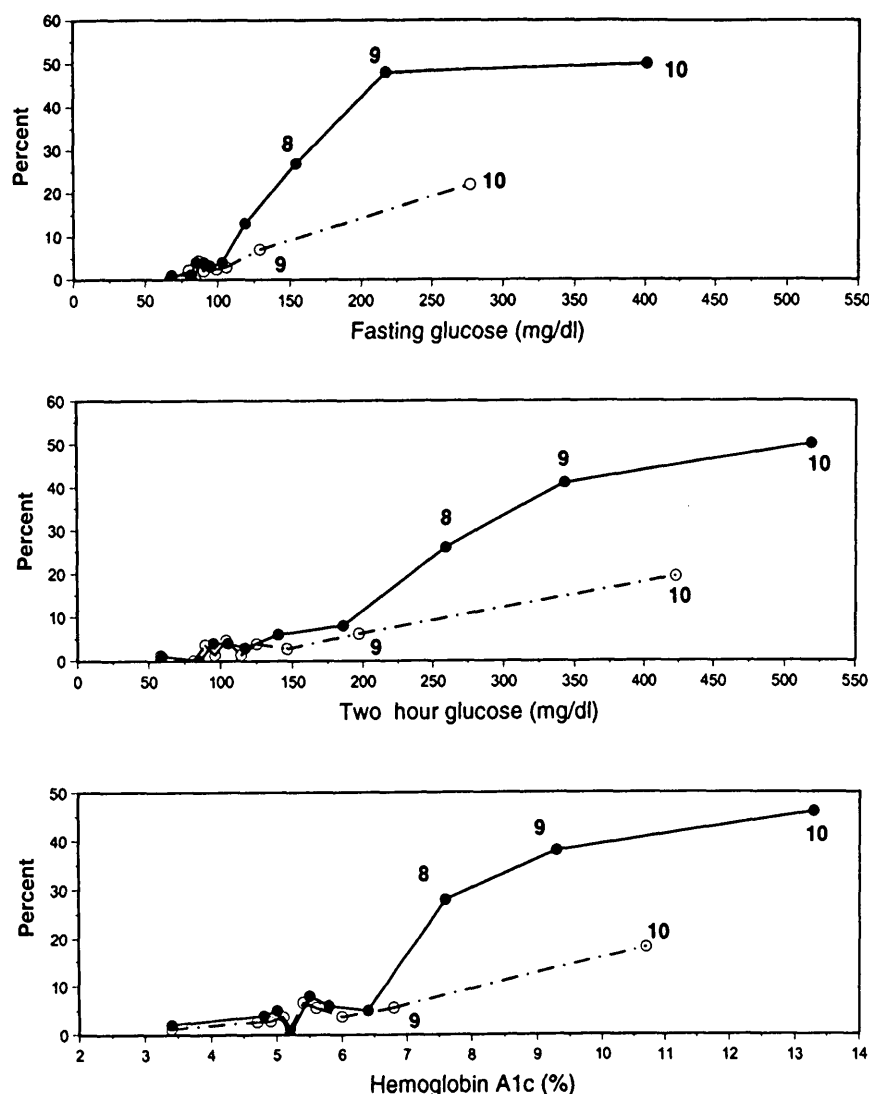
Figure 2—*Prevalence of retinopathy by decile (8th–10th are labeled) of fasting and 2-h glucose values and percent HbA₁c for total population (———) and the population excluding 251 individuals who were receiving antihyperglycemic medication (— · —).*

Retinopathy and glycemia

In the total population, the prevalence of retinopathy markedly increased above the sixth decile for fasting glucose values and above the seventh decile for the 2-h glucose and HbA₁c values (Fig. 2). In the sixth decile of fasting glucose, the prevalence of retinopathy was 4% and the median glucose value was 5.7 mmol/l (103 mg/dl; range 98–108 mg/dl); in the seventh decile of fasting glucose, the prevalence of retinopathy was 13% and the median glucose value was 6.6 mmol/l (119 mg/dl; range 108–130 mg/dl). In the seventh decile of the 2-h glucose and HbA₁c levels, the prevalence of retinopathy was 8% and 5%, respectively, and the median glycemic values were 10.3

mmol/l (186 mg/dl; range 155–217 mg/dl) and 6.4% (range 6.0–6.8%), respectively. In the eighth decile for the 2-h glucose and HbA₁c levels, the prevalence of retinopathy was 26% and 28%, respectively, and the median glycemic values were 14.4 mmol/l (259 mg/dl; range 218–301 mg/dl) and 7.6% (range 6.9–8.4%), respectively.

Overall, the prevalence of retinopathy for those whose glycemic values were above the sixth decile for fasting glucose or above the seventh decile for 2-h glucose or HbA₁c levels was 33%, 39%, and 38%, respectively. In contrast, the prevalence of retinopathy for those whose glycemic values were in the first through sixth deciles for fasting glucose or in the first through seventh deciles

for 2-h glucose and HbA₁c levels was 3%, 4%, and 4%, respectively. Thus those with glycemic values equal to or greater than these cutpoints were 8–12 times more likely to have diabetic retinopathy than those with values below the cutpoints.

Analyses that excluded those receiving antihyperglycemic medication found that the level of retinopathy increased between the ninth and tenth decile for each measure. The glycemic levels at this transition from low to high prevalence were slightly higher than the levels in the analyses that included with the entire population (Fig. 2). In the ninth decile of fasting and 2-h glucose and HbA₁c levels, the prevalence of retinopathy was 7.1%, 6.5%, and 5.6%, respectively, and the median values were 7.2 mmol/l (129 mg/dl; range 110–147 mg/dl), 10.9 mmol/l (197 mg/dl; range 160–234 mg/dl), and 6.8% (6.2%–7.4%), respectively. In the tenth decile of fasting and 2-h glucose and HbA₁c levels, the prevalence of retinopathy was 22, 19, and 18%, respectively, and the median values were 15.4 mmol/l (277 mg/dl; range 148–406 mg/dl), 23.5 mmol/l (423 mg/dl; range 235–612 mg/dl), and 10.7% (range 7.5%–14.0%), respectively.

To compare the performance of each measure over the entire range of measures, we plotted ROC curves. We found similar areas under the fasting and 2-h glucose curves (0.85 vs. 0.86; P = 0.63) (Fig. 3A). However, the area under the HbA₁c curve was significantly smaller than the area under the glucose curves (fasting glucose vs. HbA₁c: 0.85 vs. 0.82, P < 0.01; 2-h glucose vs. HbA₁c: 0.86 vs. 0.82, P < 0.01). Excluding individuals who received antihyperglycemic medication reduced the area under the ROC curves (Fig. 3B). In this subgroup analysis, the areas under the curves for each glycemic measure were not significantly different (fasting vs. 2-h glucose: 0.79 vs. 0.76, P = 0.46; fasting glucose vs. HbA₁c: 0.79 vs. 0.72, P = 0.06; 2-h glucose vs. HbA₁c, 0.76 vs. 0.72, P = 0.44).

To determine the ability of each glycemic measure to predict the presence of diabetic retinopathy over the range of measured values, we calculated the sensitivity and specificity for various cutpoints for the total population and the subpopulation excluding those receiving antihyperglycemic medication (Table 1). In both the total population and subpopulation, the performance (in terms of sensitivity and specificity) of a fasting glucose cutpoint of 7.8 mmol/l (140 mg/dl) was similar to that
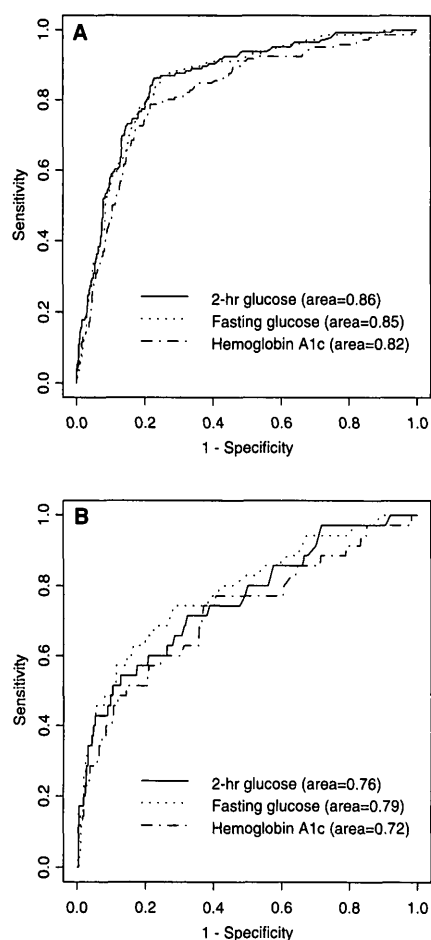
Figure 3—*Receiver operating characteristic curves for fasting and 2-h glucose and HbA₁c measures for predicting the presence of diabetic retinopathy for the total population (A) and the population excluding 251 individuals who were receiving antihyperglycemic medication (B).*

Table 1—*Performance of various cutpoints in detecting the presence and absence of retinopathy for the total sample population and the subpopulation of those not receiving antihyperglycemic medication*

Glycemic measure	Cutpoint	Total sample population (n = 1,018) Sensitivity (%)	Specificity (%)	Subpopulation not receiving antihyperglycemic medication Sensitivity (%)	Specificity (%)
Fasting glucose (mg/dl)					
	120	85	76	57	88
	125	84	77	57	88
	130	82	79	51	90
	135	79	80	49	91
	140	79	81	49	91
	150	76	82	49	92
2-h glucose (mg/dl)					
	180	87	75	54	86
	190	86	76	51	88
	200	86	78	51	89
	210	83	78	46	90
	220	81	79	46	91
	230	79	80	43	91
HbA₁c					
	6.4	80	74	51	84
	6.5	79	75	51	86
	6.6	79	76	49	87
	6.7	79	77	49	87
	6.9	78	78	49	88
	7.1	75	80	46	89

of a 2-h glucose cutpoint of 12.2–12.8 mmol/l (220–230 mg/dl). The performance of a 2-h glucose cutpoint of 11.1 mmol/l (200 mg/dl) was similar to that of a fasting glucose cutpoint of 6.9–7.2 mmol/l (125–130 mg/dl). In the total population, the sensitivity and specificity were approximately equal for the fasting and 2-h glucose and HbA₁c cutpoints of 7.8 mmol/l (140 mg/dl), 12.8 mmol/l (230 mg/dl), and 6.9%, respectively.

CONCLUSIONS — Several recent reports have addressed issues related to the diagnosis of diabetes (9–14). Controversy has revolved around two key questions: *1*) What is the optional definition of diabetes? Is it the upper component of a bimodal distribution or susceptibility to levels of glycemia associated with microvascular and neuropathic complications? and 2) What is

the optimal diagnostic test and what is the optimal cutpoint value for that test? The performance of glycemic measures can be assessed and compared against various defined diabetic states (gold standards), but selecting the optimal test and the optimal cutpoint value must go beyond these calculations and consider several other elements. The misclassification (false-positive and false-negative) rates must be considered in light of the importance placed on misclassifying individuals at high risk for developing diabetic complications as not having diabetes, or conversely, misclassifying individuals at low risk of developing complications as having diabetes. In addition, the effect of misclassification on the individual and society, specifically with respect to costs, must be considered.

In this study, the intersection points for the lower and upper components of the bimodal distribution were 7.2 mmol/l (129 mg/dl), 11.5 mmol/l (207 mg/dl), and 6.7% for the fasting and 2-h glucose and HbA₁c, respectively. These cutpoints changed little after controlling for antihy-

perglycemic medication use. Based on the fitted model for the whole population, these cutpoints would best differentiate individuals with and without diabetes. These cutpoints are slightly lower than those reported by others for both the fasting (9,20) and 2-h (8,9,19,20,22) glucose distributions, and were lower than the NDDG and WHO fasting glucose cutpoint of 7.8 mmol/l (140 mg/dl), although they were similar to the NDDG and WHO 2-h glucose cutpoint of 11.1 mmol/l (200 mg/dl).

In detecting retinopathy in the entire population or in the population excluding those who were receiving antihyperglycemic medication, a fasting glucose cutpoint of 7.8 mmol/l (140 mg/dl) and a 2-h glucose cutpoint of 12.2–12.8 mmol/l (220–230 mg/dl) had roughly equal performance in terms of sensitivity and specificity. The 2-h glucose value of 11.1 mmol/l (200 mg/dl) tended to favor sensitivity and had similar performance to a fasting value of 6.9–7.2 mmol/l (125–130 mg/dl).

The difference in the performance of

the NDDG and WHO fasting and 2-h glucose diagnostic criteria in populations is apparent and has been recognized (1,2). Roughly 75% of subjects who participated in the NHANES II with diagnostic 2-h values had fasting values <7.8 mmol/l (<140 mg/dl) (15). We found the same relationship in this population. The fasting criterion favors specificity, whereas the 2-h criterion favors sensitivity.

The ROC curve analyses in the total population found that the 2-h and fasting glucose measures performed equally well in detecting retinopathy, with both outperforming HbA_{1c}. This suggests that the fasting and 2-h glucose measures may be superior to HbA_{1c} for diagnostic purposes. In contrast, we did not find the glucose measures to be significantly better than HbA_{1c} when individuals receiving antihyperglycemic medications were excluded. However, compared with the glucose measures, the trend of a smaller area under the HbA_{1c} curve persisted and nearly reached statistical significance when compared with the fasting glucose measure.

The findings from this study that glucose measures may detect retinopathy better than HbA_{1c} contrast with findings from other reports (9,10), possibly because of two reasons: The first reason is that, for this study, affinity chromatography was used to assay HbA_{1c} levels, whereas high-performance liquid chromatography methods were used by others (9,10). A second explanation may be provided by results of the Diabetes Control and Complications Trial (29). In both conventional and intensive treatment groups, an increase in the HbA_{1c} level resulted in an increased risk for retinopathy. However, the increased risk was not equal in the two groups. At any HbA_{1c} level, the conventional treatment group had a higher risk for development or progression of retinopathy compared with the intensive treatment group. Because unequal excursion above and below the mean glucose level can result in the same HbA_{1c} level (30), the difference in the risk might be due to greater variation in the glucose level in the conventional compared with the intensively treated group. Therefore, use of the glucose measurements may perform better than HbA_{1c} for predicting retinopathy and, thus, diagnosing diabetes.

The current study had a number of limitations. Development of diabetic retinopathy depends on the duration of diabetes, the level of hyperglycemia, and the presence of comorbidities (e.g., hyper-

tension). The present evaluation was cross-sectional and did not account for the duration or level of hyperglycemia prior to the study. However, the majority of individuals with diabetes in the general population have NIDDM, which may have existed several years before detection (31,32). Thus, even if the time of clinical diagnosis is known, it is difficult to know with certainty the duration of the diabetes. In addition, the precise level of hyperglycemia during the undiagnosed period, or even during the diagnosed period, is generally not known.

The current study population included individuals with diagnosed diabetes who were taking antihyperglycemic medication. Including individuals on medication for analyses maintains the population-based sample of individuals with diabetes. Antihyperglycemic medication will have the effect of lowering the fasting and 2-h glucose and HbA_{1c} levels. Not surprisingly, and as in other cross-sectional studies (33–35), we found that the mean glycemic values were significantly higher for the population of individuals with WHO-defined diabetes who were receiving antihyperglycemic medications compared with those not receiving such medication. Thus excluding all individuals currently receiving antihyperglycemic medication would tend to bias the upper component to represent only individuals with mild glucose intolerance, not the entire diabetic population. The net effect would result in the shifting of the second component closer to the first. In the extreme case, when treatment normalizes glucose, there may be no evidence of a second component. However, the extent to which treatment of hyperglycemia changed the characteristics of the upper component or lowered the glycemic levels of individuals with retinopathy cannot be determined directly.

Further, treatment of hyperglycemia may not affect the bimodal distributions for each glycemic measure equally. Fasting and HbA_{1c} values depend on the metabolic environment for several hours (in the case of fasting values) or months (in the case of HbA_{1c}), whereas the 2-h value represents the more immediate metabolic environment. Participants did not take their diabetes medication the morning of the OGTT, and thus the effect on the 2-h value was likely minimized.

To examine this effect of antihyperglycemic treatment, we did analyses on both the entire population and on the pop-

ulation excluding those receiving antihyperglycemic medication. We found that, after excluding individuals receiving antihyperglycemic medications, the distribution of glycemic measures fit a mixture distribution of glycemic values with components that were not well separated. Further analyses found that the absolute performance (in terms of either the sensitivity and specificity of a cutpoint or the area under the ROC curve for a glycemic measure) was lower when the diabetic population on antihyperglycemic treatment was excluded. However, the relative patterns and performance for each glycemic measure in the subpopulation, which excluded those receiving antihyperglycemic medications, was comparable with the total population. Thus this suggests that these comparisons and conclusions are valid.

More quantitative information about the performance of glycemic measures for detecting diabetes is needed. Currently, little information is available to guide discussions surrounding the issue of diagnostic criteria for diabetes. We have described the performance of the current diagnostic criteria for diabetes and the utility of three glycemic measures in detecting retinopathy. These results should be compared with other population-based studies examining this issue, and should prove valuable for determining the optimal tests and cutpoint values for diagnosing diabetes.

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