Which Test for Diagnosing Diabetes?

DAVID R. MCCANCE, MD, MRCP
ROBERT L. HANSON, MD, MPH
MARIE-ALINE CHARLES, MD, MPH
LENNART T.H. JACOBSSON, MD, PHD
DAVID J. PETTITT, MD, MPH
PETER H. BENNETT, MB, FRCP
WILLIAM C. KNOWLER, MD, DRPH

Hyperglycemia, measured by both fasting levels and the oral glucose tolerance test (OGTT), is the accepted means of defining diabetes. Demonstration of the bimodal frequency distributions of fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG), and later glycated hemoglobin (GHb), along with the observed increase in complications at the point of separation of the distributions gave clinical and prognostic relevance to the current definition of this disease. The present consensus on diagnostic criteria was reached ~15 years ago (1).

The inconvenience, variability, and nonphysiological nature of the OGTT are well recognized (2). In spite of these limitations, the 2-h postload plasma glucose measurement has remained the gold standard against which all other tests have been evaluated. This short commentary seeks to remind the reader that the ultimate evaluation of any test depends on a reference or standard by which to judge the alternative test. The specific microvascular complications of diabetes offer one such objective endpoint. Three alternative measures of glycemia are examined in this perspective.

COMPARISON OF 2hPG, FPG, AND GHb AS DIAGNOSTIC TESTS

— We have recently published a comparison, summarized herein, of the ability of plasma glucose, fasting and 2 h after a 75-g load, and GHb to predict the specific microvascular complications of non-insulin-dependent diabetes (3). The 5-year incidence and prevalence of retinopathy and nephropathy were examined in 960 Pima Indian subjects aged 25 and older who were not receiving insulin or oral hypoglycemic treatment at the baseline examination. Thus, the sample included nondiabetic and newly diagnosed diabetic subjects and those previously diagnosed but not receiving pharmacological treatment. Retinopathy was defined by the presence of at least one microaneurysm or hemorrhage or proliferative retinopathy, and nephropathy by a urine protein-to-creatinine ratio of ≥1.0 (corresponding to a total protein excretion rate of ~1 g/day).

Frequency distributions of the logarithms of the three glucose variables in the cross-sectional study were bimodally distributed, with the prevalence of retinopathy and nephropathy being, respectively, 12.0–26.7 and 3.9–4.2 times as high above as below cutoff points that minimized overlap. The 2hPG measurement was more sensitive than the two other variables but was less specific than GHb or fasting glucose concentration for both complications.

The 5-year incidence and prevalence of retinopathy by decile of each of the three test variables is shown in Fig. 1. All three variables were predictive of retinopathy ($P < 0.0001$; log rank statistic), with evidence of a threshold between the 80th and 90th percentiles below which retinopathy was absent or rare and above which the incidence was high. The association of glycemia with nephropathy was also significant but less strong than that with retinopathy. Receiver-operating characteristic curves showed that 2hPG was superior to FPG ($P < 0.05$) for prevalent cases of retinopathy, but otherwise no variable had a significant advantage over any other test for detecting incident or prevalent cases of either complication (3).

DIAGNOSTIC CUTOFF POINTS

— Cutoff points allow the comparison of a dichotomy of a test variable against a relevant clinical endpoint. A test result should be considered diagnostic of diabetes not because it exceeds an arbitrarily selected value but because it separates those at low and high risk for clinically important outcomes such as specific microvascular complications. This inherent risk (for retinopathy as demonstrated in epidemiological studies) was the rationale behind the derivation of the 2-h 11.1 mmol/l criterion. The 2hPG and FPG values defined as diagnostic of diabetes by the World Health Organization (WHO) (1) are not equivalent: approximately three quarters of subjects with diagnostic 2hPG concentrations (≥11.1 mmol/l) have fasting glucose values below the level defined as diagnostic by the WHO (7.8 mmol/l) (4).

From the Diabetes and Arthritis Epidemiology Section, Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases; and the National Institute of Musculoskeletal and Skin Diseases (L.T.H.J.), Phoenix, Arizona.

Address correspondence and reprint requests to David R. McCance, MD, MRCP, Sir George E. Clark Metabolic Unit, Royal Victoria Hospital, Belfast BT12 6BA, U.K.

Received for publication 23 February 1995 and accepted 27 February 1995.

2hPG, 2-h plasma glucose; FPG, fasting plasma glucose; GHb, glycated hemoglobin; OGTT, oral glucose tolerance test; WHO, World Health Organization.

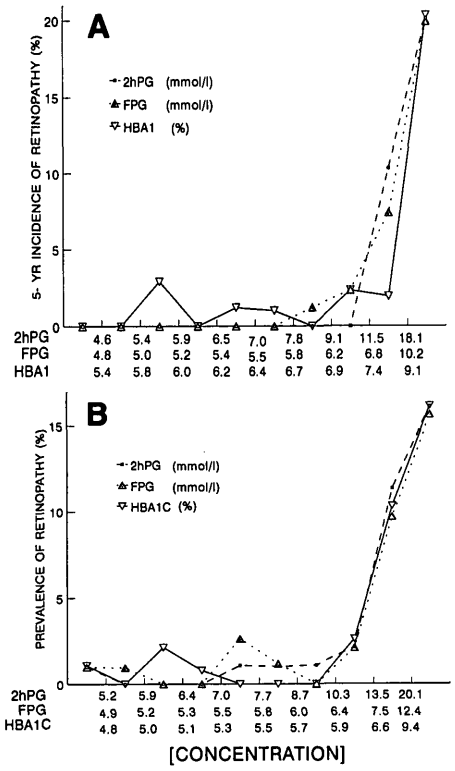

Figure 1—*Five-year cumulative incidence (A) and prevalence (B) rates of retinopathy in relation to deciles of FPG, 2hPG, and HbA_1/HbA_{1c}. Decile values of the corresponding glycemic variables are shown in the abscissae. From McCance et al. (3).*

The lack of equivalence of the FPG and 2hPG levels in the WHO criteria, however, was deliberate. The 2hPG value for the diagnosis of diabetes, which can only be measured if an OGTT is performed, was chosen to approximate the optimal point for separating those at higher and lower risk of developing complications, thus optimizing sensitivity and specificity of the test. On the other hand, the fasting value was chosen to have a high degree of specificity for diabetes. This was believed to be appropriate as it could then be used in clinical settings without the need to perform an OGTT. The fasting value, therefore, represents a level of glycemia that provides a high level of clinical certainty that the patient does indeed have diabetes if it is elevated on two occasions. With this as a criterion, it was felt that the OGTT would only be needed clinically if the fasting values fell below the suggested diagnostic level and grounds to suspect that the patient might have diabetes remained.

The selection of diagnostic points, based on any of these measures of glycemia, depends on considerations that include the beneficial and adverse effects of diagnosis and treatment. The point of maximum separation of frequency distributions and the relationship with microvascular complications offer two independent approaches to distinguishing subjects with diabetes. An alternative is the point that maximizes the sum of sensitivity and specificity. Values for FPG and GHb that are equivalent to that of the 11.1 mmol/l WHO 2hPG criterion may also be derived from those points with similar ratios of sensitivity to specificity (Table 1) (3). Undue significance cannot be attached to these individual values, which are highly dependent on the measures and means chosen to define them. The similar prevalence of diabetes for the three variables by the various methods is further evidence of their equivalence for classification and perhaps for diagnostic purposes.

NO GLYCEMIC MEASUREMENT IS CLEARLY SUPERIOR

These data show that when 2hPG, FPG, and GHb measures are examined in relation to what may be the most relevant clinical endpoint—that of the long-term complications of diabetes—each of the three variables has a similar association with the prevalence and 5-year incidence of these complications. These findings suggest that the choice of a measure of glycemia for diagnostic purposes might favor GHb or FPG, which are more readily obtained than a glucose tolerance test. However, an acceptable standardization of laboratory methods for measuring GHb must still be reached.

Our results pertain to a population with a high prevalence of diabetes, which facilitates the analysis of distribu-

Table 1—***Sensitivities and specificities for prevalent cases of retinopathy and percentage of subjects with levels above antimodal cutoff points, those equivalent to the WHO 2hPG (11.1 mmol/l) criterion, and cutoff points maximizing the sum of sensitivity and specificity (see DIAGNOSTIC CUTOFF POINTS)***

	2hPG (mmol/l)	FPG (mmol/l)	HbA_{1c} (%)
Antimodal			
Cutoff point	12.6	9.3	7.8
Sensitivity	87.5	68.8	65.6
Specificity	80.2	87.7	87.8
Subjects above cutoff point (%)	22.0	14.2	14.0
WHO equivalent			
Cutoff point	11.1	6.8	6.1
Sensitivity	87.5	81.2	81.3
Specificity	75.8	77.1	76.8
Subjects above cutoff point (%)	26.3	24.9	25.3
Maximum sensitivity plus specificity			
Cutoff point	13.0	7.2	7.0
Sensitivity	87.5	81.3	78.1
Specificity	81.4	80.4	84.7
Subjects above cutoff point (%)	20.9	21.7	17.4

From McCance et al. (3).

tions. We have no reason, however, to suspect that the equivalence of the three glycemic measures cannot be generalized to other populations, given that complications in the Pima Indian population are qualitatively indistinguishable from those in other populations and risk factors for their development are similar. This hypothesis requires confirmation in other populations.

CONCLUSIONS — These results suggest that from consideration of the risk of microvascular complications, measurement of GHb or FPG concentrations may be just as useful as measurement of 2hPG concentrations for diagnostic purposes. Given the improvements in accuracy of laboratory methods for the measurement of plasma glucose during the past 15 years and the establishment of GHb as a biologically important index of glycemia, the currently used methods and criteria for the diagnosis of diabetes should be reconsidered.

References

1. World Health Organization: *WHO Expert Committee on Diabetes Mellitus. Second Report.* Geneva, World Health Org., 1980 (Tech. Rep. Ser., no. 646) p. 9–14
2. McDonald GW, Fisher GF, Burnham C: Reproducibility of the oral glucose tolerance test. *Diabetes* 14:473–480, 1965
3. McCance DR, Hanson RL, Charles MA, Jacobsson LTH, Pettitt DJ, Bennett PH, Knowler WC: Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *Br Med J* 308:1323–1328, 1994
4. Harris MI, Hadden WC, Knowler WC, Bennett PH: Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20–74 yr. *Diabetes* 36:523–534, 1987