Diagnosing Diabetes With Glucose Criteria: Worshipping a False God

In this issue of Diabetes Care, Dr. David Sacks has nicely delineated the pros and cons of the measurements of glucose concentrations and A1C levels and the resulting effects on using each to diagnose diabetes (1). With the continued improvement in A1C assays, the balance seems to increasingly favor using A1C levels. This commentary will examine an issue that has received scant attention in the past, i.e., what is the actual evidence upon which the current glucose criteria for diagnosing diabetes mellitus is based?

Glucose concentrations in almost all populations (except those with very high prevalences of diabetes, e.g., Pima Indians), are distributed unimodally with a rightward skew (2,3), making the choice of a diagnostic value for diabetes arbitrary. If glucose concentrations are log-transformed to minimize the rightward skewness, a bimodal distribution has been noted (4–8). However, cutoff values defining the two distributions have ranged from 200–307 mg/dL, mostly depending on the ages of the population surveyed (3–8).

Prior to 1979, at least six different sets of criteria diagnosed diabetes (9). In 1979, the National Diabetes Data Group (NDDG) resolved this issue by establishing one set of criteria (10). They selected these criteria based on glucose concentrations that allegedly predicted the development of diabetic retinopathy, a specific microvascular complication of diabetes. Three prospective studies (11–13) were available to the NDDG on which to base their decision. A total of 1,213 patients were followed for 3 to 8 years after oral glucose tolerance tests (OGTTs), 77 of whom developed retinopathy. There was no further evaluation of their glycemic status after the original OGTT, although it was very likely that the 77 people who developed retinopathy in the studies used by the NDDG to establish the diagnostic criteria had increasing glycemia in the years between the test and the identification of retinopathy. However, on the basis of these 77 individuals, the NDDG selected a fasting plasma glucose (FPG) concentration of ≥140 mg/dL or a 2-h value after 75 g oral glucose of ≥200 mg/dL to diagnose diabetes. Thus, the “gold standard” 2-h value on an OGTT for diagnosing diabetes rests on fewer than 100 individuals whose glycemic status was unknown for years prior to the development of retinopathy. A description of the three studies used for their decision is available (14).

In the mid-1990s, the American Diabetes Association (ADA) convened an Expert Committee (15) to reexamine the diagnosis of diabetes in light of any new information available since the NDDG report. An overriding goal of the committee was to make the FPG concentration and the 2-h glucose concentration on the OGTT equivalent for the diagnosis of diabetes, that is, if one criterion was met, the other would likely be met as well (15,16). With the NDDG criteria, ~95% of patients whose FPG concentrations were 140 mg/dL had 2-h glucose concentrations ≥200 mg/dL on the OGTT (17), but only one-quarter to one-half of patients with 2-h values on the OGTT ≥200 mg/dL had FPG concentrations ≥140 mg/dL (17–19). The Expert Committee decided to retain the 2-h glucose concentration of ≥200 mg/dL as a diagnostic criterion because changing it “would be very disruptive” considering the large number of epidemiological studies using that value to define diabetes (15).

The FPG concentration that gave a prevalence of diabetes equivalent to the 2-h value of ≥200 mg/dL on an OGTT was ~126 mg/dL (7.0 mmol/L) (5,15,20,21) and was selected by the Expert Committee (15). They sought to justify the new lowered FPG criterion of ≥126 mg/dL for the diagnosis of diabetes by linking levels of glycemia with diabetic retinopathy in populations of Pima Indians (n = 960) (5), Egyptians (n = 1,081) (22), and a randomly selected cohort in the Third National Health and Nutrition Examination Survey (NHANES III) (n = 2,821) (15). FPG, 2-h OGTT glucose, and A1C levels were divided into deciles and plotted against the prevalence of retinopathy in each decile. The values reported by the Expert Committee (15) for the first decile with an increase in retinopathy in the three studies were, respectively, as follows: FPG 136, 130, and 120 mg/dL; 2-h glucose 244, 218, and 195 mg/dL; and A1C 6.7, 6.9, and 6.2%. These values are very misleading, however, because they were the lowest glycemic level of each initial decile in which the prevalence of retinopathy increased. Although the individual values of these patients with retinopathy were unknown, it is extremely unlikely that most of them congregated at the lower end of the decile. Using the values at the bottom of the decile for diagnosis certainly increases the sensitivity of the glucose criteria but at the usual expense of decreasing the specificity. Unfortunately, the lowest values of these deciles have been used to support the current glucose criteria for the diagnosis of diabetes (23,24). It is much more likely that the mean/median glycemic values of the decile more truly represent the patients with retinopathy. These mid-decile values (25) were, respectively: FPG 167, 155, and 165 mg/dL; 2-h glucose 298, 252, and 292 mg/dL; and A1C 7.8, 7.5, and 7.4%. Thus, since most people agree that the microvascular complication of retinopathy is the basis upon which glucose criteria for the diagnosis of diabetes should be chosen, the diagnosis in many individuals using the current glucose criteria are false-positives.

Further evidence that the present glucose criteria are too low if retinopathy is used to identify the glycemic levels by which to diagnose diabetes is the relationship among the microvascular complications of diabetes, glucose concentrations, and A1C levels. Five longitudinal studies in over 2,000 diabetic patients followed from 4 to 9 years demonstrated very little development or progression of diabetic retinopathy or nephropathy if the average A1C levels were maintained between 6 and 7% and none if they were kept in the normal range below 6% (26–30). Yet, if the current glucose criteria are used, many people who are diagnosed with diabetes have normal A1C levels. For instance, in the NHANES III population with no history of diabetes, 61% and 19% of those with FPG concentrations of 126–139 mg/dL and ≥140 mg/dL,
respectively (25), and 69% and 41% of those with 2-h glucose concentrations on an OGTT of 200–239 mg/dL and ≥240 mg/dL, respectively (31), had normal A1C levels. Given that bona fide diabetic retinopathy is not seen in people with normal A1C levels (5,15,22,23,32), do we really want to diagnose diabetes in such individuals?

In contrast to the three studies (5,15,22) allegedly supporting the current glucose criteria, three subsequent ones (33) could not confirm threshold values for FPG or 2-h glucose concentrations on an OGTT for retinopathy. On the other hand, threshold values for A1C levels have been confirmed (23,32).

As already pointed out (1,23), there are a number of advantages to using A1C levels to diagnose diabetes, e.g., less variability of the assay compared with glucose, removal of preanalytic modifying factors, much less day-to-day variability (<2%) compared with FPG (12–15%), and better reflection of long-term glycemia. On the other hand (1,23), there are potential disadvantages, e.g., interference by hemoglobinopathies, influence of iron status (34) and erythrocyte turnover, and increased levels in African Americans (35–37) and Latinos (37) independent of glucose concentrations. These are not insurmountable barriers. Regarding hemoglobinopathies, in the 20 different Diabetes Control and Complications Trial (DCCT) aligned assays in use, HbS, HbC, and HbE interfere with only four and HbD with only two (38). In the NHANES 1999–2006 population without known diabetes, mean A1C levels were equal or 0.1% higher in iron-deficient women and men, respectively, compared with their iron-sufficient counterparts (39). The iron status might be evaluated in young menstruating women with A1C levels ≥6.5% before making the diagnosis of diabetes. Finally, since increased glycation is one cause of diabetes complications (40), the slightly higher A1C levels in minorities might have pathological significance.

In conclusion, the weakness of the evidence for the current glucose criteria to diagnose diabetes strongly supports Dr. Sacks’ contention based on measurement considerations that if A1C assays aligned with the DCCT assay (38) are available, the diagnosis of diabetes should be made by A1C levels ≥6.5% (24). In addition to the measurement issues, the rationale for this conclusion is that 1) the distribution of glucose concentrations in most populations is unimodal with no consistent cut point with which to diagnose diabetes; 2) bona fide retinopathy, a specific complication of diabetes, is not seen in people whose A1C levels are <6.5% (23,32); 3) raised A1C levels cause the microvascular complications of diabetes, and lowering levels is beneficial (26,27,41); and 4) increased glycation of proteins is one of the causes of diabetes complications, supplying a direct link between the diagnosis and the complications (40). If a DCCT-aligned A1C assay is not available, glucose criteria can be used to diagnose diabetes. Confirmation of diagnostic values should utilize the same test to avoid confusion whereby individuals have diabetes by one criterion but not by another.

MAYER B. DAVIDSON, MD

From Charles R. Drew University, Los Angeles, California.

Corresponding author: Mayer B. Davidson, mayerdavidson@cdrewu.edu.

DOI: 10.2337/dc10-1689

© 2011 by the American Diabetes Association. Readers may use this article as long as the work is cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/for details.

Acknowledgments—M.B.D. has received support from the National Institutes of Health grants U54 RR02613 and U54 CA143931, and from ADA. No potential conflicts of interest relevant to this article were reported.

References

1. Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care 2011;34:518–523

2. Gordon T. Glucose tolerance of adults, United States, 1960-1962: diabetes prevalence and results of glucose tolerance test, by age and sex. Vital and Health Statistics. Series 11, No.2. Washington, DC, US Government Printing Office, 1964

3. Hayner NS, Kjelsberg MO, Epstein FH, Francis T Jr. Carbohydrate tolerance and diabetes in a total community, Tecumseh, Michigan. I. Effects of age, sex, and test conditions on one-hour glucose tolerance in adults. Diabetes 1965;14:413–423

4. Zimmet P, Whitehouse S. Bimodality of fasting and two-hour glucose tolerance distributions in a Micronesian population. Diabetes 1978;27:793–800

5. McCance DR, Hanson RL, Charles MA, et al. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ 1994;308:1323–1328

6. Raper LR, Taylor R, Zimmet P, Milne B, Balkau B. Bimodality in glucose tolerance distributions in the urban Polynesian population of Western Samoa. Diabetes Res 1984;1:19–26

7. Rosenenthal M, McMahan CA, Stern MP, et al. Evidence of bimodality of two hour plasma glucose concentrations in Mexican Americans: results from the San Antonio Heart study. J Chronic Dis 1983;38:5–16

8. Fan J, May SJ, Zhou Y, Barrett-Connor E. Bimodality of 2-h plasma glucose distributions in whites: the Rancho Bernardo study. Diabetes Care 2005;28:1451–1456

Valeron AJ, Eschwege E, Papoz L, Rosselin GE. Agreement and discrepancy in the evaluation of normal and diabetic oral glucose tolerance test. Diabetes 1975;24:585–593

10. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039–1057

11. Jarrett RJ, Keen H. Hyperglycaemia and diabetes mellitus. Lancet 1976;2:1009–1012

12. Sayegh HA, Jarrett RJ. Oral glucose-tolerance tests and the diagnosis of diabetes: results of a prospective study based on the Whitehall survey. Lancet 1979;2:431–433

13. Pettiti DJ, Knowler WC, Lisse JR, Bennett PH. Development of retinopathy and proteinuria in relation to plasma-glucose concentrations in Pima Indians. Lancet 1980;2:1050–1052

14. Davidson MB, Peters AL, Schriger DL. An alternative approach to the diagnosis of diabetes with a review of the literature. Diabetes Care 1996;18:1065–1071

15. Expert Committee. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997;20:1183–1197

16. Davidson MB. Correction to the 2010 report on the diagnosis and classification of diabetes. Diabetes Care 2010;33:e57

17. Peters AL, Davidson MB, Schriger DL, Hasselblad V. Meta-analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels. A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. JAMA 1996;276:1246–1252

18. 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 1987;36:523–534

19. Modan M, Harris MI. Fasting plasma glucose in screening for NIDDM in the U.S. and Israel. Diabetes Care 1994;17:436–439

20. Finch CF, Zimmet PZ, Alberti KGMM. Determining diabetes prevalence: a rational basis for the use of fasting plasma
Editorial

21. Koehler C, Temelkova-Kurktschiev T, Henkel E, Schaper F, Fuecker K, Hanefeld M. Is the newly suggested fasting plasma glucose cut-off point for the diagnosis of diabetes the right one? Diabetologia 1999;42:635–636

22. Engelgau MM, Thompson TJ, Herman WH, et al. Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes. Diagnostic criteria and performance revisited. Diabetes Care 1997;20:785–791

23. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334

24. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1):S62–S69

25. Davidson MB, Schriger DL, Peters AL, Lorber B. Revisiting the oral glucose tolerance test criterion for the diagnosis of diabetes. J Gen Intern Med 2000;15:551–555

26. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986

27. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103–117

28. Krolewski AS, Laffel LMB, Krolewski M, Quinn M, Warram JH. Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. N Engl J Med 1995;332:1251–1255

29. Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tohjima T, Kawamori R. Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. Diabetes Care 1998;21:116–120

30. Warram JH, Scott LJ, Hanna LS, et al. Comparison of fasting and 2-hour glucose concentrations? Diabet Med 1990;7:603–610

31. Davidson MB, Schriger DL, Peters AL, Lorber B. Relationship between fasting plasma glucose and glycated hemoglobin: potential for false-positive diagnoses of type 2 diabetes using new diagnostic criteria. JAMA 1999;281:1203–1210

32. Wong TY, Liew G, Tai ES, et al. Relationship between glycated haemoglobin and microvascular complications: is there a natural cut-off point for the diagnosis of diabetes? Diabetologia 2000;43:1279–1289

33. Wong TY, Liew G, Tapp RJ, et al. Relationship between fasting glucose and retinopathy for diagnosis of diabetes: three population-based cross-sectional studies. Lancet 2008;371:736–743

34. Brooks AP, Metcalfe J, Day JL, Edwards MS. Iron deficiency and glycosylated haemoglobin A. Lancet 1980;2:141

35. Saaddine JB, Fagot-Campagna A, Rolla D, et al. Distribution of HbA1c levels for children and young adults in the U.S.: Third National Health and Nutrition Examination Survey. Diabetes Care 2002;25:1326–1330

36. Herman WH, Ma Y, Uwaifo G, et al.; Diabetes Prevention Program Research Group. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007;30:2453–2457

37. Davidson MB, Schriger DL. Effect of age and race/ethnicity on HbA1c levels in people without known diabetes mellitus: implications for the diagnosis of diabetes. Diabetes Res Clin Pract 2010;87:415–421

38. HbA1c methods and hemoglobin variants (HbS, HbC, HbE and HbD traits) [online]. National Glyco Standardization Program. Available from http://www.ngsp.org/interf.asp. Accessed 2 June 2010

39. Kim C, Bullard KM, Herman WH, Beckles GL. Association between iron deficiency and A1C levels among adults without diabetes in the National Health and Nutrition Examination Survey, 1999–2006. Diabetes Care 2010;33:780–785

40. Goh S-Y, Cooper ME. Clinical review: The role of advanced glycation end products in progression and complications of diabetes. J Clin Endocrinol Metab 2008;93:1143–1152

41. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853 [Erratum, Lancet 1999;354:602]