

# 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  $\geq 140$  mg/dL or a 2-h value after 75 g oral glucose of

$\geq 200$  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,  $\sim 95\%$  of patients whose FPG concentrations were 140 mg/dL had 2-h glucose concentrations  $\geq 200$  mg/dL on the OGTT (17), but only one-quarter to one-half of patients with 2-h values on the OGTT  $\geq 200$  mg/dL had FPG concentrations  $\geq 140$  mg/dL (17–19). The Expert Committee decided to retain the 2-h glucose concentration of  $\geq 200$  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  $\geq 200$  mg/dL on an OGTT was  $\sim 126$  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  $\geq 126$  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  $\geq 140$  mg/dL,

respectively (25), and 69% and 41% of those with 2-h glucose concentrations on an OGTT of 200–239 mg/dL and  $\geq 240$  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  $\geq 6.5\%$  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  $\geq 6.5\%$  (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.

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