Perhaps diabetes is a bit like obscenity: We know it when we see obvious cases, but it is difficult to develop one definition that encompasses the entire spectrum of disease. Hyperglycemia exists on a continuum, and persons destined to develop type 2 diabetes progress along this continuum over time, from having blood glucose concentrations that are typical, to those in some intermediate but asymptomatic range, to glucose concentrations that are frankly increased and often associated with acute symptoms and chronic complications of the disease. But at what point does an individual have blood glucose concentrations, or other measures of glycemia, that cross the line from no diabetes to diabetes?

Several decades ago, the National Diabetes Data Group (NDDG)\(^2\) developed consensus diagnostic criteria for diabetes that were based on population distributions of glucose concentrations (even though for most populations there is not a bimodal distribution for glucose clearly dividing diseased from nondiseased individuals) and based on the relative risk of decompensation to overt or symptomatic diabetes. These criteria, including a fasting plasma glucose (FPG) concentration of 140 mg/dL (7.8 mmol/L) or greater and a 2-h plasma glucose concentration during a 75-g oral glucose tolerance test (OGTT) of 200 mg/dL (11.1 mmol/L) or greater, became the worldwide standard for diagnosing diabetes. Even in 1979, however, the NDDG noted that “there is no clear division between [those with diabetes] and [those without diabetes] in the FPG concentration or their response to an oral glucose load” and acknowledged that the cutpoints chosen were arbitrary (1).

In 1997, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus was convened to revisit the criteria for diagnosing diabetes. This group examined population data for retinopathy in 3 distinct populations and noted that for FPG, 2-h postload glucose (PG), and hemoglobin A\(_{1c}\) (Hb A\(_{1c}\)), the relatively specific diabetes complication of retinopathy was absent at lower levels of the glycemic measures and that its prevalence increased linearly above a certain cutpoint. The group verified that the 2-h PG cutpoint of 200 mg/dL (11.1 mmol/L) appeared to be appropriate for determining the emergence of retinopathy but recognized that the NDDG FPG cutpoint of 140 mg/dL (7.8 mmol/L) was less sensitive—diagnosing far fewer people—than the 2-h PG cutpoint. The FPG cutpoint of 140 mg/dL (7.8 mmol/L) was also significantly above the point at which retinopathy prevalence was observed to increase. This group recommended 126 mg/dL (7.0 mmol/L) as the FPG cutpoint to diagnose diabetes, and this concentration subsequently became the worldwide FPG standard for a diagnosis of diabetes (2).

Neither the 1997 expert committee nor a subsequent group in 2003 recommended the use of the Hb A\(_{1c}\) test to diagnose diabetes, in part because of the lack of standardization and also because of a lack of consensus on the appropriate diagnostic cutpoint for identifying diabetes. In 2009, however, another international expert committee was convened, and it recommended that Hb A\(_{1c}\), with a cutpoint of 6.5% or greater, be used to diagnose diabetes (3). The American Diabetes Association, in its 2010 Clinical Practice Recommendations, added an Hb A\(_{1c}\) cutpoint of 6.5% or greater to the glucose-based criteria as an option for diagnosing diabetes (4).

Why the change to the inclusion of Hb A\(_{1c}\) as appropriate for the diagnosis of diabetes? The expert committee of 2009 examined data on retinopathy prevalence and glycemic measures from 9 populations (including the 3 examined in 1997) and determined that an Hb A\(_{1c}\) value of 6.5% appears to identify the cutpoint at which any retinopathy, or the even more specific moderate diabetic retinopathy, begins to occur at increasing frequency in populations (3). Hb A\(_{1c}\) appears to be at least as good as FPG or 2-h PG for showing a cutpoint for retinopathy. The Hb A\(_{1c}\) assay is now almost universally standardized and traceable to the Diabetes Control and Complications Trial assay in the US and many other countries, thanks to the work of the National Glycohemoglobin Standardization Program, the manufacturers, and the laboratories. Worldwide standardization efforts are moving forward.
with the development of a common standard. On the contrary, glucose is not a standardized analyte, and a number of issues of calibrator accuracy leading to bias have been noted (5). Surveys by the College of American Pathologists have shown that glucose values show substantial variation between methods. The observed variation indicates that one-third of the time an individual’s glucose sample run in 2 different laboratories could produce results that differ by >14%. The preanalytical stability of glucose can also be a problem because of glycolysis, even in tubes containing sodium fluoride (6).

One critically important measure of a test used to determine the presence (or absence) of a chronic disease is an acceptably low level of intra-individual variation—i.e., the test should give a similar result when it is repeated for the same patient within a short period of time. The 2-h PG test, termed by some the “gold standard” for diagnosing diabetes, performs poorly on this measure. Analyses from the National Health and Nutrition Examination Survey (NHANES) III Second Examination substudy, in which testing of a nationally representative sample of adults without diagnosed diabetes was repeated 2 weeks later, showed a within-person CV of 17% for the 2-h PG, compared with 5.7% for FPG and 3.6% for Hb A1c. When individuals who had a 2-h PG result diagnostic of diabetes had the test repeated 2 weeks later, only 72% of the time was diabetes confirmed. For FPG, 70% of the repeat tests were still diagnostic of diabetes, and for Hb A1c at a cutpoint of 6.5%, 83.3% were (7).

Other practical clinical considerations are important to the discussion. Hb A1c testing does not require the patient to fast or undergo any special preparation, making it more convenient for opportunistic screening in the usual clinical setting. For a disease in which an estimated 25% of patients with the disease are undiagnosed, especially in poor and minority communities, the ability to diagnose diabetes at any time is likely to increase the proportion of people who are screened and diagnosed. And unlike the glucose concentration, the Hb A1c concentration is not influenced by short-term stressors such as hospitalization and acute illness.

What are the downsides to adding Hb A1c to our menu of diagnostic tests? The 3 tests (FPG, 2-h PG, and Hb A1c) are not perfectly concordant—they identify slightly different populations with disease. Sensitivity and specificity depend on which test and which cutpoint are termed the gold standard, but NHANES analyses suggest that if all undiagnosed people were tested and evaluated with the 2010 cutpoints, the 2-h PG assay would diagnose more people than FPG, and FPG more than Hb A1c. In the real world, more people would likely move from undiagnosed to diagnosed with the availability of a more convenient and more widely applied test, as was the case when the FPG test was termed “preferred” over the more sensitive but less convenient OGTT.

The Hb A1c test is more expensive than the FPG test but not more so than the OGTT. Some hemoglobin traits interfere with some Hb A1c assay methods, although the majority of methods now correct for the most common hemoglobin traits (http://www.ngsp.org/interf.asp). As is the case when the test is used for monitoring diabetes control, any state of altered red cell turnover (hemolytic anemias, major blood loss, transfusions, pregnancy) will alter the relationship of Hb A1c to chronic glycemia, and in these patients glucose-based diagnostic testing should be used.

Some studies (8) suggest that African Americans have, on average, higher Hb A1c values for given glycemia levels. These data are intriguing and suggest possible deliberation for those just above the diagnostic cutpoint of 6.5%; however, no one yet has advocated race-specific Hb A1c cutpoints for monitoring diabetes. Moreover, population studies suggest that Hb A1c has a higher predictive value for diabetes complications than FPG (9) and that so-called rapid glycators are at an increased risk of diabetes complications (10). Is an Hb A1c level just above the diagnostic threshold a false positive in an African American, or is an FPG value just under the diagnostic threshold a false negative?

Given that there is no perfect cutpoint for either glucose or Hb A1c, it is important to recognize that values on the margin for any of the diagnostic tests need to be confirmed by repeat testing, and results need to be interpreted in the context of the uncertainty that exists whenever we establish a dichotomous diagnosis on the basis of a continuous variable. A patient with glucose or Hb A1c values just below diagnostic cutpoints requires careful follow-up and support to adopt healthy lifestyle changes, as does a patient just at or above the diagnostic cutpoints. Which tests clinicians choose to use matters less than ensuring that people at risk are appropriately tested so that clinicians can implement evidence-based interventions for primary or secondary prevention. Only then can we hope to turn the tide on the global diabetes epidemic.

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