EDITORIAL (SEE EXPERT COMMITTEE, P. 1327)

Redefining the Diagnosis of Diabetes Using Glycated Hemoglobin

The worldwide epidemic of type 2 diabetes continues unabated. Despite extensive efforts to educate providers, patients, and even the public at large as to the advantages of early identification and treatment to prevent complications, a large number of patients remain undiagnosed. A serious barrier to an enhanced detection of diabetes has been inadequate screening using tests somewhat inconvenient to patients and clinicians and therefore often not optimally implemented. In this issue of *Diabetes Care*, a joint American Diabetes Association, International Diabetes Federation, and European Association for the Study of Diabetes International Expert Committee examines diagnostic testing for diabetes, specifically, the role of A1C, and makes significant new recommendations. While this report has not yet been endorsed as a guideline by either of the associations (or other organizations), it does represent a step in that direction and thus deserves attention.

Clearly, no clinical diagnostic test is perfect. However, to be clinically useful, a test must be accurate, specific, standardized (or easily standardizable), handy, and, ideally, inexpensive. While plasma glucose testing meets some of these criteria, its use has been dogged by the need to obtain a sample in the fasting state (most people attend their outpatient visits in the fed state) or under standard carbohydrate challenge conditions, i.e., the oral glucose tolerance test. There also continues to be a degree of uncertainty concerning the diagnostic performance of fasting glucose testing versus that of the oral glucose tolerance test—the latter done rarely in clinical practice for obvious reasons: inconvenience and cost. In addition, considerable variability not only in 2-h postglucose load values but also in fasting glucose has been a problem. Appropriately, clinicians have long wondered why they cannot use another diagnostic index, such as A1C, an inherently attractive option because it recapitulates long-term ambient glycemia as opposed to a single point in time. With the recent introduction of the standardized global assay for the measurement of A1C (1), greater accuracy and precision than achieved with plasma glucose have been predicated. The overall edge of A1C over plasma glucose is accurately summarized in Table 1 of the International Expert Committee's report.

Importantly, the relation of A1C to average glucose levels, while good, is not perfect. On the other hand, it is conceivable that this "glycation gap" (2) may actually offer an advantage in that it might better predict the risk of complications in individuals more susceptible to nonenzymatic glycation of a variety of proteins, including those fundamentally important to vascular biology. Nevertheless, we expect a significant amount of controversy in this regard.

Cost and lack of standardization of the A1C test in some countries are likely to be additional contentious issues following the recommendations of the committee. The experts do, however, recognize the difficulty and therefore envision a reasonably balanced approach: for those unable to obtain a standardized A1C test (or an affordable one), to continue to use the well-established methods of glucose testing—fasting and postchallenge glucose—the older diagnostic criteria of which will remain in place. A similar approach should apply to individuals with hemoglobinopathies or other disorders of red cell life span, particularly common in certain ethnic groups, because A1C measurement here may be unreliable (3).

There is likely to be some initial debate concerning the cut point—A1C of 6.5%—chosen to define diabetes. This is, of course, a problem whenever one coerces a diagnosis, which by definition must be dichotomous, from a continuous variable. Yet, one might argue that even the fasting glucose threshold of 126 mg/dl (7 mmol/l), while not entirely arbitrary, represents a point along a continuum of metabolic derangement. Concern will be compounded by the fact that the upper limit of normal for A1C is 6.0%, leaving something of a gray zone between this value and the 6.5% cut point for diabetes. Values herein are not quite normal and yet not high enough to qualify as diabetes. This will predictably create the same confusion that may have arisen in individuals in the categories of impaired fasting glucose and impaired glucose tolerance using the current guidelines. Moreover, the sensitivity of the A1C test in this specific range may be less than optimal. (In this context, it is also very important to recognize that point-of-care testing is not recommended; the standardized assay, which makes the new recommendations feasible, is only available through a clinical laboratory.)

The International Expert Committee is indeed careful to point out that the threshold does not identify an A1C level below which risk is nil but, instead, one below which risk is lower: an inflection point in a continuous positive relationship rather than a true step function. However, the outcome used is retinopathy, i.e., one of the microvascular complications. It is natural to wonder whether a different threshold might have been chosen if the outcome considered had been atherosclerotic cardiovascular disease (CVD). Available data on the relationship between A1C and CVD risk may be less defined than those relating to retinopathy (4–6), but CVD events are more prevalent than microvascular events in type 2 diabetes (7–8). Admittedly, recent trial results showing an uncertain link between lowering glucose and macrovascular complications add to the complexity of defining risk using solely one feature (i.e., glucose) of a multidimensional metabolic disease (9–11). It would be reassuring if a critical analysis of the evidence converged on the same—or very close to the same—A1C level to be posited as the diabetes diagnostic threshold carrying definite risk for both micro- and macroangiopathy.

The lack of an A1C value for a formal definition of "pre-diabetes" is likely to raise further and related concerns. Here again, other methods, including the use of glucose values, may be helpful, but there continues to be little consensus on the best test to use in predicting diabetes. A variety of mathematical models, questionnaires, and risk engines can be used to define risk of diabetes as well as risk of cardiovascular disease, including one available on the American Diabetes Association Web site (http://www.diabetes.org/

diabetesphd). Furthermore, progression rates of people with mildly abnormal tests of glucose in the pre-diabetes range are highly variable (12) and dysglycemia may sometimes regress to normal without intervention. Even so, we expect considerable debate to follow with calls for a more robust diagnostic option to detect at-risk individuals. This is of particular importance when pharmacological therapy is being considered. Critics may reason that a diagnostic test for population-based and societal interventions to eat healthy, increase physical activity, and optimize body weight is not necessary. Yet, we would argue that when dealing with an individual patient, the conversation regarding risk reduction, whether it is attempted with diet or drugs, will be facilitated with concrete numbers with which a condition and its response to intervention can be measured.

Finally, that the A1C diagnostic threshold now being defined at 6.5% while the recommended target for most diabetic patients remains at 7% will be viewed by some as untidy—if not a contradiction of sorts. However, good clinical judgment suggests that for many patients it may be appropriate to start at least lifestyle interventions whenever the diagnosis is made, irrespective of A1C. Whether this threshold should now be considered one for the initiation of metformin therapy (or other agents) will be extremely, and appropriately, controversial. The argument will not be settled until we have randomized clinical trials that better inform our clinical decisions in patients with such mild degrees of hyperglycemia. Such data are sorely lacking at this point. Indeed, clinical research in this arena may be easier to conduct now that the new criteria have been suggested, given that cases will be easier to identify at this early stage.

In summary, the adoption of the A1C test as a diagnostic criterion is a reasonable proposition on the practical grounds analyzed by the report. Its worldwide feasibility is, at present, limited. In addition, anchoring the diagnostic threshold solely to microvascular risk, leaving a diagnostic hiatus in the A1C range 6.1–6.5%, and choosing an A1C threshold different from the treatment target recommended by most guidelines (7%) are problematic aspects carried over from the glucose-based diagnostics. Perhaps further analysis and relevant new evidence will be considered before the findings and arguments of the International Expert Committee can be transposed into widely endorsed recommendations.

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DOI: 10.2337/dc09-9034

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

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