

The Diagnosis of Diabetes Is Changing: How Implementation of Hemoglobin A_{1c} Will Impact Clinical Laboratories

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The earliest known description of diabetes mellitus is in the Papyrus of Ebers by Hesy-Ra in 1552 BC. Since then, we have learned that diabetes consists of a group of metabolic disorders, all of which produce hyperglycemia. The relatively specific complications of diabetes (affecting the eyes, kidneys, and nervous system) and the high prevalence (estimated at approximately 40×10^6 in the US and approximately 250×10^6 worldwide) combine to make it a substantial public health problem. Our comprehension of the pathophysiology of the disease is limited, however, and no biological marker is known to be unique to diabetes. Diagnosis has been based exclusively on the demonstration of increased glucose concentrations, initially in urine and subsequently in the blood. Therefore, the recent publication of the International Expert Committee report on the diagnosis of diabetes (1), which recommends the use of hemoglobin A_{1c} (Hb A_{1c})² rather than glucose for the diagnosis of diabetes, represents a dramatic change that deserves reflection.

Hyperglycemia has been the sole diagnostic criterion for diabetes since the development of blood glucose assays 100 years ago. Measurement of the response to a metabolic challenge in the form of the oral glucose tolerance test (OGTT) was initially used. The cutoff was 2 SDs above the mean glucose concentration in healthy individuals. This strategy was limited by a lack of standardization in both the performance and the interpretation of the test and its poor reproducibility. In 1979, the National Diabetes Data Group proposed criteria that were derived from the distribution of glucose concentrations in populations with a high prevalence of diabetes (2). The diagnostic criteria were (a) classic symptoms of diabetes with an unequivocal increase in plasma glucose, (b) a venous fasting plasma

glucose (FPG) concentration ≥ 7.8 mmol/L (140 mg/dL), or (c) a 2-h and an earlier sample during an OGTT with glucose concentrations ≥ 11.1 mmol/L (200 mg/dL) (2). The National Diabetes Data Group criteria were adopted widely and were endorsed in 1980 by the WHO.

With time, flaws became apparent in these criteria, and they were revised about 20 years later (3, 4). The entire focus was altered to a more pragmatic approach, with diagnosis based on the development of complications. Analysis of several epidemiologic studies revealed that the prevalence of retinopathy increased substantially above a glycemic threshold. Remarkably, FPG, 2-h postload glucose (during an OGTT), and Hb A_{1c} values all exhibit a distinct and identifiable threshold (3). On the basis of these data, the Expert Committee recommended that the cutoff for diagnosis with FPG measurement be lowered from 7.8 mmol/L (140 mg/dL) to 7.0 mmol/L (126 mg/dL), which is equivalent to a 2-h postload glucose concentration of 11.1 mmol/L (200 mg/dL). Thus, the diagnostic criteria recommended were (a) FPG ≥ 7.0 mmol/L (126 mg/dL), (b) 2-h postload glucose concentration ≥ 11.1 mmol/L (200 mg/dL) during an OGTT, or (c) symptoms of diabetes plus a casual plasma glucose value ≥ 11.1 mmol/L (200 mg/dL), with “casual” indicating that the blood is drawn without regard to the time of the preceding meal. In the absence of unequivocal hyperglycemia, confirmation is required through repeat testing on a subsequent day if any of these criteria is met. The WHO proposed an essentially identical scheme (4). The only difference is that the American Diabetes Association recommended analysis of FPG as the preferred test, whereas the WHO favored the OGTT.

Despite being the gold standard for diagnosis of diabetes for many years, measurement of blood glucose is subject to several limitations. For example, bias among instruments can misclassify as many as 12% of patients (1). Diurnal variation and the large biological variation in FPG values further contribute to possible misclassification. In addition, preanalytical factors, particularly glycolysis in vitro, further limit the diagnostic value of FPG.

Although the incorporation of Hb A_{1c} into diabetes diagnosis is a marked change, it has been considered—and rejected—previously. Lack of assay standardization was the reason Hb A_{1c} was not incorporated by the 1997

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Received June 23, 2009; accepted June 26, 2009.

Previously published online at DOI: 10.1373/clinchem.2009.132704

² Nonstandard abbreviations: Hb A_{1c}, hemoglobin A_{1c}; OGTT, oral glucose tolerance test; FPG, fasting plasma glucose.

Expert Committee (3) or the 2003 follow-up report. The 2009 International Expert Committee concluded that the advances in instrumentation and standardization make the accuracy and precision of the Hb A_{1c} assay at least as good as those of glucose assays. These improvements eliminate the major impediments to the use of Hb A_{1c} for diagnosis.

Hb A_{1c} has several appealing features as a diagnostic test for diabetes, including low preanalytical and biological variation; concentrations correlate with the risk for the development of microvascular complications; values reflect overall glycemic exposure; and there is no requirement that the patient be fasting. The last factor has considerable practical value because it eliminates the need for patients to return for phlebotomy after an overnight fast. On the basis of the prevalence of moderate retinopathy, an Hb A_{1c} value of $\geq 6.5\%$ was selected as the decision point (1). Diagnosis should be confirmed by repeating the Hb A_{1c} measurement on a different day unless clinical symptoms and glucose values > 11.1 mmol/L (200 mg/dL) are both present. Analysis should be performed on central-laboratory instruments, not with point-of-care devices, which have not been shown to be sufficiently accurate or precise for diagnosis (1).

Glucose measurement is no longer recommended for establishing the diagnosis of diabetes in nonpregnant individuals. Measurement of glucose with previously recommended methods (3) should be used only in pregnancy or when Hb A_{1c} testing cannot be used (e.g., in situations in which Hb A_{1c} assays are not available or are contraindicated). Conditions that preclude Hb A_{1c} testing include altered red blood cell turnover (e.g., hemolytic anemia, major blood loss, or blood transfusion). Some hemoglobin traits, such as Hb AS, Hb AC, Hb AE, or Hb AD, interfere with some methods of Hb A_{1c} analysis. Nevertheless, Hb A_{1c} can be measured accurately in almost all of the individuals with these variant hemoglobins by selecting an appropriate method of analysis (see <http://www.NGSP.org>). Mixing different methods for diagnosis should be avoided. Therefore, in situations for which glucose measurement is necessary, diagnosis should be confirmed by a second glucose measurement according to the criteria established in 1997 (3).

Another important decision by the International Expert Committee is the recognition that Hb A_{1c} concentrations of 6.0%–6.4% indicate individuals at high risk of developing diabetes (1). Repeat Hb A_{1c} testing is not required for persons who fall into this range. These individuals should be identified and receive counseling for exercising and achieving a healthy weight. Pharmacologic intervention can also be considered for these persons. The rationale for identifying a high-risk group, termed “subdiabetic hyperglycemia,” is that interventions

can substantially delay—or even prevent—the development of diabetes in these persons. Moreover, individuals with higher Hb A_{1c} values in the subdiabetic range are at increased risk of cardiovascular disease.

The clinical laboratory community will perform a vital role in implementing these changes. The number of requests for Hb A_{1c} measurement is likely to increase substantially. Currently the American Diabetes Association advocates that all individuals at high risk for diabetes be screened at least every 3 years. All persons ≥ 45 years of age are at high risk (5). According to census data, approximately 110×10^6 people in the US are ≥ 45 years of age, and these people should be screened every 3 years (equivalent to 37×10^6 persons per year). This number is likely an underestimate of those who should be screened because it does not include overweight adults who have additional risk factors, such as physical inactivity, hypertension, or belonging to a high-risk ethnic group [see (5) for complete list]. In responding to the increased demand for Hb A_{1c} testing, it is essential that laboratories do not compromise quality. Accurate assays with minimal bias and low imprecision are essential to avoid misclassifying individuals. Accuracy will be particularly important near the diagnostic thresholds, namely Hb A_{1c} concentrations of approximately 6%–7%. Inspection of the College of American Pathologists survey GH2-A 2009 reveals that approximately 95% of participants use methods that have CVs of $\leq 5\%$ at these Hb A_{1c} concentrations. Manufacturers of Hb A_{1c} methods will need to maintain accurate assays. In addition, laboratories will have to ensure that they use methods appropriate for the local population and avoid those that exhibit interference with hemoglobin variants that are common locally.

The International Expert Committee had members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation. At the time of writing, none of these organizations had officially endorsed these recommendations. The report is being considered by the relevant committees of each of these groups. Although the specific details of the recommendations to be proposed by these bodies have not been decided, it appears highly likely that all of the major clinical diabetes organizations will adopt Hb A_{1c} measurement for the diagnosis of diabetes.

The recommendation to measure Hb A_{1c} rather than glucose for the diagnosis of diabetes is a major departure from all prior guidelines. Nevertheless, the diagnosis remains indirect and based on a consequence of the underlying pathophysiology (namely, increased glucose in the blood), not the cause. An enhanced understanding of the molecular mechanisms underlying the insulin resistance and the secretory defects of the pancreas that occur in type 2 diabetes is necessary if we

are to identify a unique biological marker for diabetes. Until this goal is achieved, the diagnosis of diabetes will continue to be directed toward the sequelae of the metabolic derangements that occur in the disease.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors' Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.

Consultant or Advisory Role: D.B. Sacks, Bio-Rad Laboratories.

Stock Ownership: None declared.

Honoraria: D.B. Sacks, Bio-Rad Laboratories.

Research Funding: None declared.

Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

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