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Assessing the Utility of Glycated Hemoglobin

The recent article by Kilpatrick et al. (1) questioned the use of glycated hemoglobin (HbA_{1c}) for diabetes screening and monitoring. The authors concluded that "glycated hemoglobin measurements will always be of limited value as a test for diagnosing diabetes." While periodic critical assessments of laboratory measures are prudent, we feel that this effort should be objective and balanced before making such definitive conclusions.

To determine if the biological performance of HbA_{1c} renders it an inferior screening measure, it is necessary to compare it simultaneously to the performance of fasting plasma glucose (FPG), which is the currently recommended method of diagnosing diabetes in the U.S. (2). We agree with the authors that a series of measures is better than a single measure to diagnose diabetes. However, this conclusion applies to HbA_{1c} and FPG. We also agree that low cutoffs of HbA_{1c} may not distinguish between people with impaired glucose tolerance (IGT) and diabetes. However, the newly proposed diabetes diagnostic criteria essentially eliminate the classification of IGT, so this issue is less relevant. Third, the authors mention that HbA_{1c} can be impacted by erythrocyte survival and glycation rates. However, it must be equally recognized that FPG may be subject to the unquantified impact of physical fitness, physical activity the morning of the measure, and inaccuracies in reported fasting times. Information such as symptoms or future genetic markers could also influence a clinician's interpretation of HbA_{1c} or FPG to diagnose diabetes.

If one accepts the premise that the biological performance of FPG makes it superior to HbA_{1c} for screening, other concerns still remain. The strong conclusions in this paper are based on data from 12 subjects. All but one subject was under the age of 45. Only 25% of subjects had a BMI >25, and only 1 in 12 had a BMI >30. A larger population-based sample is required to assess the intra- and interindividual variance of HbA_{1c}. It would also be informative to conduct this analysis among those who would typically be at higher risk of having type 2 diabetes, namely those who are older or more obese.

This paper relies heavily on a statistical measure known as an index of individuality (IOI), which was developed in 1974 to judge "the appropriateness of applying a conventional normal range to an individual measurement of some biochemical constituent" (3). It is not clear, however, that the IOI should be applied to the distribution of HbA_{1c} values. Others have suggested that the HbA_{1c} distribution is bimodal in populations that include individuals with type 2 diabetes (4).

Aside from the statistical question about the robustness of the IOI, a practical assessment is indicated for a situation described in the paper that involves two theoretical nondiabetic subjects. The argument is stated that these two individuals have significantly different HbA_{1c} distributions in the normal range. The paper suggested that an HbA_{1c} value from the first subject, who has a mean HbA_{1c} of ~3.7%, would need to deviate much more to be classified in the diabetic range than a value from the second subject, who has a mean HbA_{1c} of ~4.5%. While it is not surprising that some people could have mean differences in the nondiabetic range of HbA_{1c}, the relevance of this difference must be considered with the fact that both means appear to be much lower than the mean HbA_{1c} value (~7.0%) among people with diagnosed diabetes in the U.S. (5).

Finally, the paper also states that setting HbA_{1c} targets among people with diabetes may not be appropriate. This conclusion is made with no data presented for people with diabetes. While the use of well-standardized HbA_{1c} measures to screen for diabetes has not been firmly established, it seems that more complete work is needed before a final judgment is made. Likewise, conclusions regarding the biological properties of HbA_{1c} among individuals with diabetes should include some data obtained from people with this condition.

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Response to Roubicek et al. and Eberhardt and Flegal

We thank Roubicek et al. (1) and Eberhardt and Flegal (2) for their interest in our article (3). The views of both letters center around whether glycated hemoglobin (HbA_{1c}) could still be a better diagnostic test for diabetes than fasting and/or 2-h plasma glucose values. However, it was not our intention to compare plasma glucose and HbA_{1c} as screening tests for diabetes. What we showed was that nondiabetic subjects with similar glycemia could consistently have HbA_{1c} values different from one another. Thus, as long as we continue to use hyperglycemic cutoffs to define diabetes (as has recently been reaffirmed by the American Diabetes Association), glycated hemoglobin measurements will

indeed always be of limited value when screening for type 2 diabetes

Roubicek et al. feel that instead of using glucose cutoffs, a single HbA_{1c} cutoff could be more appropriate for identifying subjects at high risk of developing long-term diabetic complications. We have reservations about applying this to every individual because, again, our study demonstrated that subjects with similar glycemia can have markedly different HbA_{1c} values and, presumably, vice versa. Indeed, if our findings are applied to the Diabetes Control and Complications Trial (DCCT) assay, then two subjects with the same glucose control may have HbA_{1c} values that differ by 2%. Thus, a patient with an HbA_{1c} of 7% (as found in the DCCT "intensively treated" group) could well have the same glycemic control as someone with an HbA_{1c} of 9% (whom we consider to be "conventionally treated").

Conversely, if, as has been suggested, we take 7% HbA_{1c} as a threshold for diagnosing diabetes (4), we may assume that the former individual will be significantly more hyperglycemic at an HbA_{1c} of 7% than the latter.

Do both subjects have the same risk of microvascular complications at 7% HbA_{1c}? If exposure to hyperglycemia is the main determinant of complication risk, then the answer is no. Even if, as Roubicek et al. suggest, we take a leap of faith and consider glycation to be the main determinant, then we still have to be sure that glycation of hemoglobin is an unerring reflection of glycation in small vessel tissues. Our concern is that this may not be the case, since glycated hemoglobin values can be influenced by many factors that are independent of glycemia, e.g., variations in red cell survival, which do not apply to vascular tissue.

Eberhardt and Flegal correctly state that we were speculating (albeit plausibly) when we applied our findings to diabetic patients, but they fail to mention that our findings are entirely consistent with DCCT clinical data (5) that demonstrated that diabetic patients with similar glycemia can also have markedly different HbA_{1c} values. They also state that our nondiabetic HbA_{1c} values are much lower than the mean of ~7.0% HbA_{1c} found in newly diagnosed patients. However, our assay was clearly not the DCCT assay, where the quoted reference range of 4.05–6.05% is much closer to the 7% value mentioned. Because we were examining biological (and not analytical) variation, we have no reason to believe that our data would not be equally applicable to this and other HbA_{1c} methods. Like Eberhardt and Flegal, we would also like to have included more subjects in our study, but given the unequivocal nature of our results, it seems very unlikely that our conclusions would change with increasing numbers. Likewise, if we took the advice of Eberhardt and Flegal and included more elderly and obese subjects in our study, the interindividual variance of HbA_{1c} would be likely to increase rather than decrease, since HbA_{1c} is known to rise with subject age in nondiabetic individuals (6).

Diagnosing diabetes using an HbA_{1c} cutoff is appealing because of its simplicity. However, we must remember that glycated hemoglobin is only a surrogate marker of both hyperglycemia and small-vessel glycation. As such, we feel clinicians should still be cautious that they do not overestimate the usefulness of HbA_{1c} testing.

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Agreement Between Old and New Diagnostic Criteria in Postpartum Testing of Women With Gestational Diabetes

Women with gestational diabetes should be retested postpartum to reclassify their glucose tolerance status. Previous American Diabetes Association (ADA) guidelines suggested that the 75-g oral glucose tolerance test (OGTT) should be performed at 6 weeks postpartum using the World Health Organization's diagnostic criteria (1). The recent report by the ADA's Expert Committee on the Diagnosis and Classification of Diabetes Mellitus has suggested a number of important changes to the diagnostic criteria of diabetes (2). The most significant changes are the reduction of the fasting blood glucose criterion for diabetes and the introduction of a new intermediate category of impaired fasting glucose, so that the sensitivity of the fasting blood glucose for the diagnosis of glucose intolerance is comparable to that of the 2-h value, making the OGTT redundant. These changes could be of particular value after childbirth because attendance for the postpartum OGTT is often poor. In our clinic, about one-third of women with gestational diabetes fail to undergo a postpartum OGTT.

We have evaluated the agreement between the old and new diagnostic criteria in a population that includes ethnic groups with a high incidence of type 2 diabetes (Polynesian and Asian). In a consecutive series of 475 women with gestational diabetes completing a postpartum OGTT, we have categorized the results according to the new fasting plasma glucose criteria: normal (≤6.0 mmol/l), intermediate (impaired fasting glucose) (6.1–6.9 mmol/l), or diabetes (≥7.0 mmol/l). Similarly, the results were categorized according to the old criteria: normal (fasting and 2-h, ≤7.7 mmol/l), intermediate (impaired glucose tolerance) (fasting, ≤7.7 mmol/l, and 2-h, 7.8–11 mmol/l), or diabetes (fasting, ≥7.8 mmol/l, and/or 2-h, ≥11.1 mmol/l). Thus, there were nine potential groups into which individuals could be classified (Table 1). The results were examined for concordance within diagnostic groups and for the overall presence of glucose intolerance (Table 1).