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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