

COMMENTS AND
RESPONSES

We conclude that renal damage is common in African-Americans with diabetes, even in recently diagnosed patients without hypertension. Our criteria for albuminuria are standard, but even a cutoff of 50 mg/g would identify an 11% prevalence of microalbuminuria among normotensive patients with duration of diabetes <1 year. The presence of renal damage in our analysis is comparable to that in a European population with type 2 diabetes (3). However, the basis for the discrepancy between these results and those of Chaiken et al. remains unclear. Harris et al. (4) estimate that diabetes may begin 9–12 years before diagnosis; the observations by Chaiken et al. could reflect earlier diagnosis in New York than in Atlanta or Denmark. The discrepancy could also reflect genetic differences in susceptibility to diabetic nephropathy. Clearly, aggressive screening is needed to permit early detection and appropriate treatment.

LEONARD M. THALER, MD
IMAD M. EL-KEBBI, MD
DAVID C. ZIEMER, MD
DANIEL L. GALLINA, MD
VIRGINIA G. DUNBAR, BS
LAWRENCE S. PHILLIPS, MD

From the Division of Endocrinology and Metabolism, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.

Address correspondence to Leonard M. Thaler, MD, Emory University School of Medicine, Diabetes Unit, 69 Butler St. SE, Atlanta, GA 30303. E-mail: lthaler@emory.edu.

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Use of HbA_{1c} in
Screening for
Diabetes

We wish to comment on the report by Kilpatrick et al. that appeared in the February 1998 issue of *Diabetes Care* (1).

The concepts of screening and cutoff levels are being used in clinical medicine for the purpose of detecting individuals with a particular risk, present or future, of having or developing a certain disease. In the case of diabetes, the risk to search for is the development of long-term complications. The threshold or cutoff value is fixed arbitrarily according to the purpose of the study: to identify all or almost all subjects at risk, or only those whose risk is great. Feasibility and economic factors are also taken into account. The cutoff levels for HbA_{1c} used in various studies were based on the undisputed fact that above a certain level, the risk of developing chronic diabetic complications increases markedly (2–4). In the hypothetical example given by Kilpatrick et al. of two people whose intraindividual HbA_{1c} levels occupy both extremes of the normal population distribution curve, what really matters is not whether they are more or less close to the threshold. The relevant issue is that if they reach or cross the threshold, their risks for developing complications will become comparably high. While it is true that the subject whose HbA_{1c} levels were closer to the cutoff point has a greater probability for this occurring than the one with the lower HbA_{1c} values, what screening means is to find those individuals who already have that risk at the time the test is made to offer them the appropriate counseling on further diagnostic testing or preventive measures.

We wonder if the authors of the report have done a similar evaluation with the fasting plasma glucose values taken simultaneously with the HbA_{1c} measurements, since the fasting glucose has been recommended for screening purposes in the recent report of the American Diabetes Association Expert Committee on Diagnosis and Classification of Diabetes Mellitus

(5). We suspect that the variation and indexes of individuality might be quite similar to those of HbA_{1c}. If that was not the case, it is remarkable that it was not mentioned in the paper.

Finally, we ask ourselves whether, with the authors' reasoning, we would have to question most screening methods that use threshold values to pinpoint individuals at risk for various diseases, such as serum cholesterol levels (there are normal subjects with mean levels of 150 mg/dl and others with 195 mg/dl) or blood pressure (normal subjects with 90/50 and others with 135/85).

We feel that despite the theoretical data presented by Kilpatrick et al., the idea of determining a particular threshold value of HbA_{1c} for screening purposes is valid, as has been shown in practice by several field studies (3,6). Efforts should continue to reach a consensus about the best methods and cutoff levels to be recommended for high-risk populations.

MARTIN ROUBICEK, MD
GLORIA VIÑES, MD
ALICIA GONZÁLEZ SANGUINETI

From the Endocrinology Division (M.R., G.V.) and the Clinical Laboratory Division (A.G.S.), Hospital Privado de Comunidad, Mar del Plata, Argentina.

Address correspondence to Martin Roubicek, MD, Servicio de Endocrinología, Hospital Privado de Comunidad, Córdoba 4545, 7600 Mar del Plata, Argentina. E-mail: roubicek@satlink.com.

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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.

MARK S. EBERHARDT, PHD
KATHERINE M. FLEGAL, PHD

From the Office of Analysis, Epidemiology, and Health Promotion (M.S.E.) and the Division of Health Examination Statistics (K.M.F.), the National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland.

Address correspondence to Mark S. Eberhardt, PhD, Office of Analysis, Epidemiology, and Health Promotion, National Center for Health Statistics, Centers for Disease Control and Prevention, 6525 Belcrest Rd., Room 730, Hyattsville, MD 20782.

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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