Are There Clinical Implications of Racial Differences in HbA_{1c}? Yes, to Not Consider Can Do Great Harm!

William H. Herman

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Studies that have compared HbA_{1c} levels by race have consistently demonstrated higher HbA_{1c} levels in African Americans than in whites. These racial differences in HbA_{1c} have not been explained by measured differences in glycemia, sociodemographic factors, clinical factors, access to care, or quality of care. Recently, a number of nonglycemic factors and several genetic polymorphisms that operate through nonglycemic mechanisms have been associated with HbA_{1c}. Their distributions across racial groups and their impact on hemoglobin glycation need to be systematically explored. Thus, on the basis of evidence for racial differences in HbA_{1c}, current clinical guidelines from the American Diabetes Association state: "It is important to take. . .race/ethnicity. . .into consideration when using the A1C to diagnose diabetes." However, it is not clear from the guidelines how this recommendation might be actualized. So, the critical question is not whether racial differences in HbA_{1c} exist between African Americans and whites; the important question is whether the observed differences in HbA_{1c} level are clinically meaningful. Therefore, given the current controversy, we provide a Point-Counterpoint debate on this issue. In the point narrative below, Dr. Herman provides his argument that the failure to acknowledge that HbA_{1c} might be a biased measure of average glycemia and an unwillingness to rigorously investigate this hypothesis will slow scientific progress and has the potential to do great harm. In the counterpoint narrative that follows Dr. Herman's contribution, Dr. Selvin argues that there is no compelling evidence for racial differences in the validity of HbA_{1c} as a measure of hyperglycemia and that race is a poor surrogate for differences in underlying causes of disease risk.

—William T. Cefalu
Editor in Chief, *Diabetes Care*

In the 1990s and early 2000s, studies that compared HbA_{1c} levels by race in people with type 2 diabetes consistently demonstrated higher HbA_{1c} levels in African Americans than in whites. In a 2006 meta-analysis, Kirk et al. (1) reported mean HbA_{1c} levels by race in U.S. adults with type 2 diabetes. All eleven studies that assessed HbA_{1c} levels in African Americans and whites demonstrated higher HbA_{1c} levels in African Americans (1). The mean difference ranged from 0.2 to 2.0%, and the mean between-group difference was ~0.65% (1).

Until the mid-2000s, the observed differences in HbA_{1c} by race were universally attributed to health disparities, that is, preventable differences in health indicators in different population groups. More recently, differences in HbA_{1c} were demonstrated in African American and white adults who were selected to have the same fasting and post–glucose load glucose levels. In the Diabetes Prevention Program (DPP), eligibility was based on both impaired fasting glucose (glucose levels of

Department of Internal Medicine and Department of Epidemiology, University of Michigan, Ann Arbor, MI

Corresponding author: William H. Herman, wherman@umich.edu.

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95–125 mg/dL) and impaired glucose tolerance (2-h post–glucose load glucose levels of 140–199 mg/dL). Despite having comparable fasting and post–glucose load glucose levels, African Americans had significantly higher HbA_{1c} levels than whites in the DPP (6.2 ± 0.6% vs. 5.8 ± 0.4%, $P < 0.0001$) both before and after adjusting for age, sex, BMI, blood pressure, fasting glucose, glucose area under the curve, corrected insulin response, and insulin sensitivity (2). Similarly, in A Diabetes Outcome Progression Trial (ADOPT), eligibility was based on short-duration, drug-naïve type 2 diabetes and fasting glucose levels between 126–180 mg/dL (3). HbA_{1c}, adjusted for age, sex, and BMI, was 8.0 ± 1.1% in African Americans and 7.3 ± 0.8% in whites ($P < 0.0001$) despite comparable fasting glucose levels (153 mg/dL vs. 151 mg/dL) and lower 30-min post–glucose load glucose levels in African Americans than in whites (233 mg/dL vs. 245 mg/dL) (3). These observations suggested that unknown factors associated with race might impact HbA_{1c} independent of glycemia (Table 1).

More recent studies that have compared HbA_{1c} by race and have statistically adjusted for access to care and quality of care while controlling for sociodemographic and clinical factors have not been able to explain these racial differences in HbA_{1c}. For example, in an analysis of data from the Health and Retirement Study, Heisler et al. (4) reported a 0.9% higher HbA_{1c} in African Americans compared with whites with diabetes. Even after adjustment for time spent with diabetes care providers, antihyperglycemic treatments, medication adherence, perceived quality of diabetes care, and diabetes self-efficacy, in addition to age, sex, education, income, insurance, diet, physical activity, diabetes duration, diabetes distress, diabetes comorbidities, and depression, HbA_{1c} remained higher in African Americans than in whites (4). Adjustment explained only about 15% of the difference in HbA_{1c} by race (4).

Recent studies that have compared HbA_{1c} by race within organized systems of care and have statistically adjusted for potential confounders have also not been able to explain the observed differences in HbA_{1c} by race. Adams et al. (5) examined racial differences in HbA_{1c} in insured, managed-care patients with type 2 diabetes who had comparable access to care and who were initiating antihyperglycemic treatment. At initiation of therapy, African Americans had higher average HbA_{1c} levels than whites (9.8 vs. 8.9%), and after 1 year of treatment, after adjusting for baseline HbA_{1c}, number of physician visits, treatment intensification, medication and test strip use, and medication adherence, as well as age, sex, BMI, hypertension, dyslipidemia, and comorbidities, the African American–white difference in HbA_{1c} remained 0.5% (5). It thus appears that racial differences in HbA_{1c} levels occur independently of glycemia across the spectrum of glucose tolerance and cannot be explained by access to care, quality of care, sociodemographic characteristics, or clinical characteristics.

Table 1—Proposed explanations for differences in HbA_{1c} by race and the weight of evidence supporting those explanations

Factors proposed to explain difference	Weight of evidence	References
Age, sex, education, income	Weak	2,3,4
BMI and/or insulin secretion/insulin sensitivity	Weak	2,3,5
Fasting or postprandial glucose levels	Weak	2,3,21
Diet and/or physical activity	Weak	4,6
Dietary fat	Moderate	7
Alcohol consumption	Moderate	8
Smoking	Strong	9
Insurance, access to care, quantity or quality of care	Weak	4,5
Antihyperglycemic therapy, treatment intensification, medication adherence	Weak	4,5
Diabetes distress, self-efficacy, depression	Weak	4
SNPs related to red blood cell biology	Strong	10,11
SNPs related to hemoglobin	Moderate	12
SNPs related to hemoglobin deglycation	Moderate	11,13,14

Clearly, one can hypothesize that unmeasured differences in diet and physical activity between African Americans and whites might result in unmeasured differences in fasting and postprandial glucose levels. In reality, however, studies such as the National Health and Nutrition Examination Survey that have systematically assessed diet and physical activity in African American and white adults have not demonstrated differences in diet that might explain the observed findings (6). Other carefully performed studies have suggested that lifestyle factors such as dietary fat (7), alcohol (8), and even cigarette smoking (9) may impact HbA_{1c} levels independent of glycemia. Additional studies are warranted to assess the independent contribution of these factors to racial differences in HbA_{1c}.

In addition to lifestyle factors, racial differences in red cell phenotypes may potentially account for racial differences in HbA_{1c}. Approximately a dozen single nucleotide polymorphisms (SNPs) have been associated with HbA_{1c}, and more than half of them appear to operate through "nonglycemic" mechanisms related to erythrocyte biology (10). Although some evidence suggests that these polymorphisms may contribute little to the variation in HbA_{1c} observed on a population basis (11), more recent studies have cast doubt on this assertion. A recent report from the African Genome Variation Project identified a novel locus associated with HbA_{1c} levels in the *HBA2* gene on chromosome 16 ($P = 6.9 \times 10^{-19}$) (12). This 3.8-kb deletion has been previously associated with the alpha thalassemia trait and is common among Africans in whom the minor allele frequency has been reported to be 25% as compared with less than 1% in Europeans (12). Its potential impact on hemoglobin glycation warrants further investigation (12). Similarly, three enzymes have been described that deglycate HbA_{1c}. Two of the three appear not to be present in humans, but the third, fructosamine 3-kinase, is present in the erythrocyte and has shown significant genome-wide association with HbA_{1c} in both Europeans and Asians (11,13,14). This polymorphism warrants further investigation in African American populations. Although research to date has not definitively identified polymorphisms that might explain nonglycemic

differences in HbA_{1c} between African Americans and whites, the data are clearly not sufficient to dismiss the possibility that such polymorphisms exist.

Finally, it has been argued that because diabetic complications occur more frequently in African Americans than in whites and because there are no racial differences in the association between HbA_{1c} and diabetic complications, there is no reason not to treat African Americans and whites to the same target HbA_{1c} levels. There are, however, at least three problems with this argument.

First, although it is clear that diabetic complications occur more frequently in African Americans than in whites, it is also clear that the major cause is not the difference in glycemia between African Americans and whites but the differences in income, education, access to care, quality of care, cardiovascular risk factor treatment, and risk factor control (15). The greater unadjusted prevalence of diabetic complications in African Americans compared with whites is attenuated by adjustment for the more frequent occurrence of nonglycemic risk factors for diabetic complications in African Americans (15).

Second, it has been argued that the association between HbA_{1c} and diabetic complications and comorbidities do not differ by race. Many of the studies purporting to demonstrate this lack of association between HbA_{1c} and complications across racial groups have assessed differences in the adjusted odds of diabetic complications and comorbidities between racial groups by calculating a *P* value for interaction (15,16). Failing to observe a significant *P* value for interaction, the authors have concluded that the association between HbA_{1c} and outcomes do not differ by race (15,16). A plausible alternative explanation for the failure to observe a significant interaction between African Americans and whites is insufficient statistical power, not the absence of an effect. Indeed, larger and more robust studies have demonstrated that the adjusted risk of diabetic complications, comorbidities, and death increase with HbA_{1c} and are greater in whites than in African Americans within HbA_{1c} categories $\geq$7% (17–19). This suggests that at any given HbA_{1c} level $\geq$7.0%, glycemic exposure is greater in whites compared with African Americans or, conversely, that glycemic exposure is lower in African Americans than in whites at any given HbA_{1c} level.

The third problem with promoting a "one size fits all" HbA_{1c} target and ignoring potential racial differences in the association between glucose levels and HbA_{1c} is that such a policy might result in a greater incidence of hypoglycemia in African Americans. For over a decade, diabetes quality of care measures focused on the prevention of hyperglycemia and rewarded HbA_{1c} lowering to achieve target HbA_{1c} levels $<$7%. This, combined with a desire to eliminate health disparities, resulted in a progressive diminution and indeed eradication of racial differences in HbA_{1c} in the U.S. between 1998 and 2010 (20). Yet, achieving the same target HbA_{1c} levels in whites and in African Americans may predictably result in lower blood glucose levels in African Americans than in whites. Findings from the DURAbility of Basal versus Lispro mix 75/25 insulin Efficacy (DURABLE) trial illustrate this point (21). In that trial, mean 7-point glucose profiles were assessed by self-monitoring of blood glucose. In post hoc analyses, a mean 7-point glucose profile of 100 mg/dL corresponded to an HbA_{1c} of 7.2% in whites and 7.6% in African Americans (21). Extrapolating from the same data set, a mean HbA_{1c} of 7.0% would correspond to a mean 7-point glucose profile of 89 mg/dL in whites and a mean 7-point glucose profile of 68 mg/dL in African Americans (21).

Data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which was designed to achieve HbA_{1c} levels $<$6% in the intensive treatment group and 7.0–7.9% in the standard treatment group, demonstrated an annual study-wide incidence of hypoglycemia requiring medical assistance of 3.14% in the intensive treatment group and 1.03% in the standard treatment group (22). Strikingly, however, the hazard ratio for hypoglycemia requiring medical assistance was 1.43 (1.20–1.71, $P < 0.0001$) for African Americans compared with whites after adjusting for multiple risk factors including age, sex, duration of diabetes, BMI, and renal disease (22). Other studies have demonstrated that rates of hospital emergency department visits for hypoglycemia are approximately twofold higher in African Americans than in whites (23). It thus appears that because at any given HbA_{1c} level, glucose levels are lower in African Americans compared with whites, the risk of severe hypoglycemia is increased in African Americans when efforts are made to treat African Americans and whites to the same target HbA_{1c} levels (24).

In summary, consistent differences in mean HbA_{1c} levels have been observed by race. These differences cannot be entirely explained by measured differences in glycemia, differences in sociodemographic or clinical factors, or differences in access to care or quality of care. It is wrong to conclude that the observed differences in HbA_{1c} between African Americans and whites must not exist because we cannot explain them. Differences in the distribution of nonglycemic factors associated with hemoglobin glycation such as dietary fat, alcohol consumption, and cigarette smoking, should be explored across racial groups. In addition, genetic polymorphisms associated with HbA_{1c} that operate through "nonglycemic" mechanisms, their distributions across racial groups, and their impact on hemoglobin glycation need to be more systematically explored. Our current failure to identify and characterize these polymorphisms is not sufficient to dismiss the possibility that they exist. Finally, focusing on the greater rate of diabetic complications and comorbidities in African Americans compared with whites and single-mindedly focusing on glycemia as the cause neglects the contribution of nonglycemic risk factors and diverts attention from the need to address and control them. Focusing on a "one size fits all" target for HbA_{1c} while neglecting direct measures of glycemia such as the results of self-monitoring of blood glucose presents a real likelihood for harm. Although the evidence does not currently exist to state unequivocally that race alters HbA_{1c} independently of glycemia, the lack of direct evidence does not negate that possibility. As scientists, we must be willing to accept the possibility that there are alternative explanations for established dogma. The failure to acknowledge alternative hypotheses will slow scientific progress and has the potential to do great harm.

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