Studies that have compared HbA1c levels by race have consistently demonstrated higher HbA1c levels in African Americans than in whites. These racial differences in HbA1c 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 HbA1c. 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 HbA1c, 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 HbA1c exist between African Americans and whites; the important question is whether the observed differences in HbA1c 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 HbA1c 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 HbA1c as a measure of hyperglycemia and that race is a poor surrogate for differences in underlying causes of disease risk.

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In the 1990s and early 2000s, studies that compared HbA1c levels by race in people with type 2 diabetes consistently demonstrated higher HbA1c levels in African Americans than in whites. In a 2006 meta-analysis, Kirk et al. (1) reported mean HbA1c levels by race in U.S. adults with type 2 diabetes. All eleven studies that assessed HbA1c levels in African Americans and whites demonstrated higher HbA1c levels in African Americans (1). The mean difference ranged from 0.2 to 2.0%, and the median between-group difference was ~0.65% (1).

Until the mid-2000s, the observed differences in HbA1c by race were universally attributed to health disparities, that is, preventable differences in health indicators in different population groups. More recently, differences in HbA1c 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...
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 HbA1c 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). HbA1c, 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 HbA1c independent of glycemia (Table 1).

More recent studies that have compared HbA1c 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 HbA1c. For example, in a population-based study (11), more recent studies have suggested that potential confounders have also not been able to explain the observed differences in HbA1c by race. Adams et al. (5) examined racial differences in HbA1c 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 HbA1c levels than whites (9.8 vs. 8.9%), and after 1 year of treatment, after adjusting for baseline HbA1c, 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 HbA1c remained 0.5% (5). It thus appears that racial differences in HbA1c 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 HbA1c 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 glycation                                       | 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 HbA1c levels independent of glycemia. Additional studies are warranted to assess the independent contribution of these factors to racial differences in HbA1c.

In addition to lifestyle factors, racial differences in red cell phenotypes may potentially account for racial differences in HbA1c. Approximately a dozen single nucleotide polymorphisms (SNPs) have been associated with HbA1c, 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 HbA1c 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 HbA1c levels in the HBB2 gene on chromosome 16 (P = 6.9 × 10−15) (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 HbA1c. 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 HbA1c 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 HbA1c 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 there are no racial differences in the association between HbA1c and diabetic complications, there is no reason not to treat African Americans and whites to the same target HbA1c 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 HbA1c and diabetic complications and comorbidities do not differ by race. Many of the studies purporting to demonstrate this lack of association between HbA1c 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 HbA1c 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 HbA1c, and are greater in whites than in African Americans within HbA1c categories ≥7% (17–19). This suggests that at any given HbA1c level ≥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 HbA1c level.

The third problem with promoting a “one size fits all” HbA1c target and ignoring potential racial differences in the association between glycemia and HbA1c 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 HbA1c lowering to achieve target HbA1c levels <7%. This, combined with a desire to eliminate health disparities, resulted in a progressive diminution and indeed eradication of racial differences in HbA1c in the U.S. between 1998 and 2010 (20). Yet, achieving the same target HbA1c 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 HbA1c of 7.2% in whites and 7.6% in African Americans (21). Extrapolating from the same data set, a mean HbA1c 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 86 mg/dL in African Americans (21).

Data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which was designed to achieve HbA1c 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 HbA1c 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 HbA1c levels (24).

In summary, consistent differences in mean HbA1c 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 HbA1c 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 HbA1c 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 HbA1c 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 HbA1c 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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