Are There Clinical Implications of Racial Differences in HbA_{1c}? A Difference, to Be a Difference, Must Make a Difference

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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 preceding point narrative, 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 below, 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
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In a major change to clinical practice guidelines, the International Expert Committee first recommended the use of hemoglobin A_{1c} (HbA_{1c}) for the diagnosis of diabetes in 2009 (1). This recommendation was codified in the American Diabetes Association's *Clinical Practice Recommendations* in 2010 (2) and has been adopted by the World Health Organization and numerous other professional groups across the globe (3,4). Given the long-standing use of HbA_{1c} for diabetes control and its strong link to complications, the use of HbA_{1c} in diagnosis of diabetes seemed advisable and advantageous. Nevertheless, the 2009 recommendations for the use of HbA_{1c} as a diagnostic test for diabetes were met with considerable controversy (5). Central to this controversy has been the interpretation of racial differences in HbA_{1c} levels. The relevance of racial differences in HbA_{1c} for its use in screening, diagnosis, and management of diabetes is the focus of this commentary.

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See accompanying articles, pp. 1299 and 1458.

RACIAL DIFFERENCES IN RISK OF DIABETES AND ITS COMPLICATIONS

In the U.S., racial and ethnic minority groups are disproportionately burdened by adverse social and economic conditions that can profoundly influence disease risk. Society-level factors such as social position, residence, material conditions (including wealth), social connections, environment, and food and physical insecurity are particularly important factors influencing risk of obesity and diabetes (6,7). There are well-documented racial disparities in the risk of diabetes, with African Americans approximately twice as likely to develop diabetes as compared with their white counterparts (8). Racial and ethnic minority groups are also disproportionately burdened by the complications of diabetes including retinopathy (9,10), chronic kidney disease (11), and lower-extremity peripheral vascular disease (12,13), with an especially high risk of amputation (14). Indeed, racial differences in end-stage renal disease represent one of the most striking racial disparities in health in the U.S. (15,16).

RACIAL DIFFERENCES IN HbA_{1c}

In numerous cohorts and in national data, it has been shown that blacks have higher HbA_{1c} values than whites in both the presence and absence of diabetes (17–21). Mexican Americans have values of HbA_{1c} that are intermediate between blacks and whites (9,22). Comparisons of HbA_{1c} in other racial/ethnic groups and non-U.S. populations are scarce but suggest higher nondiabetic levels of HbA_{1c} in some groups, e.g., South Asians, black Brazilians, and Inuit populations, compared with whites or Caucasians (23–25). It is unclear what factors might be driving these differences.

Racial differences in HbA_{1c} have been widely cited as a potential shortcoming of HbA_{1c} testing for diagnosis of diabetes (26–29). 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" (29). However, it is not clear from the guidelines how this recommendation might be actualized. Some argue that racial differences are nonglycemic in nature, i.e., a result of factors that influence HbA_{1c} via pathways independent of glucose or hyperglycemia, and have suggested that HbA_{1c} is "invalid" or "misleading" as a diagnostic test in African Americans (30,31). Clearly this claim is not trivial: HbA_{1c} is widely considered the gold standard measure of chronic hyperglycemia in diabetes care. Treatment and diagnostic decisions are routinely based on HbA_{1c} levels. If the higher HbA_{1c} in blacks compared with whites is primarily due to nonglycemic factors, then HbA_{1c} is falsely high in blacks. If this claim is substantiated, it suggests potential disparities in diabetes care may not be real, efforts to reduce hyperglycemia in blacks may be unwarranted and could cause harm, and that we might need race-specific diagnostic and treatment thresholds.

The debate is not whether racial differences in HbA_{1c} exist: they do. What is not clear is why levels of HbA_{1c} are somewhat higher in blacks compared with whites.

WHAT MIGHT EXPLAIN RACIAL DIFFERENCES IN HbA_{1C}?

Nonglycemic Factors

HbA_{1c} is an indirect measure of hyperglycemia (32–35), but it is well established that the primary determinant of HbA_{1c} is circulating glucose level (33). It has been postulated that racial differences in HbA_{1c} might be explained by differences in hemoglobin-related factors. Red cell turnover may be the most important unmeasured nonglycemic determinant of HbA_{1c} (36), but there is currently no direct evidence of racial differences in red cell turnover that might explain racial differences in HbA_{1c}. The impact of red cell turnover on HbA_{1c} in the general population is not well understood because of major difficulties in its measurement (37). Certain conditions such as glucose-6-phosphate dehydrogenase deficiency and specific hemoglobin variants (e.g., sickle cell) are more common in African Americans than in whites. Glucose-6-phosphate dehydrogenase deficiency causes hemolysis and can result in a lowering of HbA_{1c}, and sickle cell trait (and other hemoglobin variants) can falsely lower or raise HbA_{1c} or may have no effect depending on the method of HbA_{1c} measurement (38).

Glycemic Factors

The racial differences we see in HbA_{1c} levels across populations may reflect real differences in circulating average (nonfasting) glucose that are reflected in HbA_{1c} but not (or not as much) in fasting glucose or 2-h glucose. Given the considerable black–white disparities in risk of diabetes and other major health conditions, perhaps it is not so surprising that there are racial differences in HbA_{1c} even after adjusting for fasting glucose. A single measurement of fasting glucose or 2-h glucose does not fully reflect average glycemia and would not account for possible differences in true circulating average glucose between races. Differences in body composition, physical activity, diet, lifestyle, stress, and/or environmental and neighborhood-level factors might affect circulating nonfasting glucose levels and contribute to the racial differences in HbA_{1c}. Such parameters may not be fully captured by standard assessments in large epidemiologic studies, leaving open the possibility that racial disparities in HbA_{1c} are not artifactual but reflect black–white differences in true circulating nonfasting glucose.

Importantly, the higher levels of HbA_{1c} are also seen for other biomarkers of chronic hyperglycemia, specifically fructosamine and glycated albumin (39–42). Because fructosamine and glycated albumin are unaffected by the hematologic factors that might affect HbA_{1c}, racial differences in erythrocyte turnover or hemoglobin glycation cannot explain racial differences in these hemoglobin-independent serum biomarkers of hyperglycemia. The racial differences in fructosamine and glycated albumin support a difference in glycemia itself.

Genetic Factors

Genetic differences undoubtedly contribute to both glycemic and nonglycemic variation in measures of hyperglycemia including HbA_{1c}. The clinical significance of a nonglycemic genetic contribution is uncertain, particularly in persons without genetic hemoglobin abnormalities. We have previously shown that genetic ancestry does not contribute substantially ($<1\%$) to variability in HbA_{1c} among African Americans (43). Furthermore, no known genetic variants differ substantially enough between persons of African compared with Caucasian ancestry to

explain racial differences in HbA_{1c} in the general population (44–46). Although the current evidence does not rule out the possibility of genetic nonglycemic determinants of HbA_{1c}, there is no clear evidence that genetic differences contribute substantially to racial differences in HbA_{1c}. Race is primarily a social construct (47,48), and the literature does suggest that we should not treat race like a biological factor that should be used to adjust HbA_{1c} values.

The cause or causes of racial disparities in HbA_{1c} are incompletely understood, and we cannot rule out a small but systematic nonglycemic difference. Research is needed to understand the full determinants of HbA_{1c}, particularly the impact of red cell turnover on differences across population subgroups. Nonetheless, we should recognize that, in the diabetic range, the primary determinant of HbA_{1c} is circulating ambient glucose; other factors are likely to have a relatively small influence.

Are there nonglycemic determinants of HbA_{1c}? Certainly. Do these nonglycemic determinants play a large role at diagnostic or higher (diabetic) levels of HbA_{1c} in most of the population? Probably not. Are there studies that provide direct evidence that nonglycemic factors explain racial differences in HbA_{1c}? No. The question is then not whether there are racial differences in HbA_{1c} as an accurate index of chronic hyperglycemia. The important question now is: Are the observed racial differences in HbA_{1c} level clinically meaningful?

PROGNOSTIC VALUE OF HbA_{1c} IN DIFFERENT RACIAL/ETHNIC GROUPS

A major justification for using HbA_{1c} as a diagnostic test for diabetes is the strong evidence linking it to future diabetes and major clinical complications in ethnically diverse populations (19,49–54). If the observed systematically higher HbA_{1c} levels in African Americans as compared with whites stem from racial differences not in glucose exposure but from nonglycemic factors, then HbA_{1c} should be a weaker predictor of diabetic complications in African Americans, especially compared with fasting glucose. The current diabetes diagnostic cut point of HbA_{1c} 6.5% is supported by epidemiologic evidence for a high prevalence of retinopathy beginning above this threshold (1,55,56), with key studies in multiethnic U.S. study populations (56,57), Malay adults in Singapore (58), and Australian (59), Pima Indian (60), Egyptian (55,61), Korean (62), Chinese (63), and Japanese (64,65) populations. In analyses of data from the National Health and Nutrition Examination Survey (NHANES), investigators have directly compared the prognostic value of clinical categories of HbA_{1c} in populations of Mexican Americans, African Americans, and whites. These analyses found no evidence for racial/ethnic differences in the relative association of HbA_{1c} with prevalent retinopathy, suggesting that current diabetes clinical cut points should be interpreted similarly in whites, African Americans, and Mexican Americans (9,10). Randomized clinical trials in persons with diabetes have further demonstrated that lowering HbA_{1c}

Table 1—Adjusted hazard ratios (95% CI)* of peripheral vascular disease, chronic kidney disease, cardiovascular disease, and all-cause mortality according to categories of HbA_{1c} and fasting glucose at baseline in blacks and whites without diagnosed diabetes, the ARIC Study (1990–1992), $N = 11,018$

	HbA_{1c} <5.0%	HbA_{1c} 5.0–5.6%	HbA_{1c} 5.7–6.5%	HbA_{1c} ≥6.5%
Peripheral vascular disease, $n = 279$ events				
White	1.25 (0.70–2.23)	1 (ref)	1.63 (1.20–2.22)	3.22 (1.93–5.38)
Black	2.06 (0.74–5.69)	1 (ref)	1.24 (0.66–2.33)	2.73 (1.24–6.02)
Chronic kidney disease, $n = 1,550$ events				
White	0.97 (0.76–1.22)	1 (ref)	1.30 (1.13–1.49)	1.84 (1.41–2.42)
Black	2.15 (1.40–3.30)	1 (ref)	1.56 (1.22–2.01)	1.82 (1.28–2.60)
Cardiovascular disease, $n = 2,205$ events				
White	0.99 (0.81–1.20)	1 (ref)	1.51 (1.35–1.69)	1.94 (1.55–2.44)
Black	0.78 (0.47–1.29)	1 (ref)	1.36 (1.09–1.70)	2.28 (1.68–3.08)
All-cause mortality, $n = 2,999$ deaths				
White	1.19 (1.01–1.40)	1 (ref)	1.37 (1.24–1.50)	1.72 (1.39–2.12)
Black	1.41 (1.03–1.93)	1 (ref)	1.14 (0.96–1.36)	1.36 (1.05–1.78)
	Fasting glucose <90 mg/dL	Fasting glucose 90–99 mg/dL	Fasting glucose 100–125 mg/dL	Fasting glucose ≥126 mg/dL
Peripheral vascular disease, $n = 279$ events				
White	0.79 (0.42–1.51)	1 (ref)	0.99 (0.72–1.35)	1.26 (0.74–2.17)
Black	0.71 (0.21–2.45)	1 (ref)	0.68 (0.37–1.25)	1.55 (0.72–3.33)
Chronic kidney disease, $n = 1,550$ events				
White	1.07 (0.84–1.36)	1 (ref)	1.04 (0.91–1.18)	1.25 (0.98–1.59)
Black	1.14 (0.71–1.84)	1 (ref)	1.16 (0.90–1.50)	1.61 (1.14–2.27)
Cardiovascular disease, $n = 2,205$ events				
White	1.27 (1.04–1.55)	1 (ref)	1.12 (1.00–1.25)	1.40 (1.15–1.71)
Black	0.88 (0.57–1.35)	1 (ref)	0.89 (0.71–1.11)	1.38 (1.01–1.87)
All-cause mortality, $n = 2,999$ deaths				
White	1.01 (0.85–1.21)	1 (ref)	1.10 (1.00–1.21)	1.54 (1.29–1.83)
Black	1.17 (0.87–1.59)	1 (ref)	0.89 (0.75–1.07)	1.06 (0.81–1.38)

*Adjusted for age, sex, LDL cholesterol, HDL cholesterol, log-transformed triglycerides, BMI, waist-to-hip ratio, hypertension, family history of diabetes, education, drinking status, cigarette smoking status, and physical activity index.

reduces the risk of microvascular disease, regardless of race/ethnicity (66).

For this report we conducted analyses of two population-based studies, the community-based Atherosclerosis Risk in Communities (ARIC) Study and the nationally representative NHANES, to compare associations of diagnostic categories of HbA_{1c} and fasting glucose with major long-term diabetic complications in black, Mexican American, and white persons. We analyzed HbA_{1c} and fasting glucose data from 11,018 participants aged 48–68 years with no history of cardiovascular disease who attended the second examination of the ARIC Study from 1990 to 1992. During a median of approximately 20 years of follow-up, there were 279 peripheral vascular disease events, 1,550 cases of chronic kidney disease, 2,205 cardiovascular (coronary heart disease or stroke) events, and 2,999 deaths. Comparing the hazard ratios across clinical categories of HbA_{1c} and fasting glucose reveals that, in general, HbA_{1c} is more strongly associated with future clinical outcomes as compared with fasting glucose and the relative risk associations appear similar in blacks and whites (Table 1). NHANES III, which is linked to national mortality data (but not nonfatal outcomes), also included measurements of HbA_{1c} and fasting glucose in non-Hispanic black, non-Hispanic white, and Mexican American adults. Thus, similar analyses can be conducted in this nationally representative cohort. In an analysis of 12,722 NHANES III (1988–1994) participants aged 20 years or older with HbA_{1c} measurements (and 5,676 with fasting glucose), there were 804 total deaths of which 363 were from cardiovascular causes during a median of approximately 19 years of follow-up. In NHANES III, clinical categories of HbA_{1c} in non-Hispanic blacks were similarly or more strongly associated with cardiovascular and all-cause mortality as compared with non-Hispanic whites (Table 2).

These data from ARIC and NHANES demonstrate that $HbA_{1c} \geq 6.5\%$ is a risk factor for future development of peripheral vascular disease, kidney disease, cardiovascular disease, and death across racial/ethnic groups. We see patterns of association of HbA_{1c} diagnostic categories that are generally similar or stronger than those for fasting glucose; our results do not support the contention that HbA_{1c} is a weaker predictor of outcomes compared with fasting glucose in African Americans compared with whites. These results extend and update prior publications (18,19,53,67–69), and, taken as a whole, the current literature demonstrates that race-specific HbA_{1c} cut points for diagnosis of diabetes would not be consistent with long-term risk associations.

In other studies in ARIC, we also observed that associations of nontraditional biomarkers of hyperglycemia (fructosamine and glycated albumin) with clinical outcomes were also similar in blacks and whites (39). Ultimately, the literature suggests that HbA_{1c} is a similarly valid diagnostic and prognostic tool in persons of different races/ethnicities and supports recommendations for using the same HbA_{1c} diagnostic cut points across racial/ethnic groups (10,70). To quote a saying commonly attributed to Gertrude Stein: "A difference, to be a difference, must make a difference."

CONCLUSIONS

As with any clinical test, the strength and limitations of HbA_{1c} need to be understood and communicated. Each HbA_{1c} test result needs to be interpreted in the context of the individual patient. Although population-level evidence is critical to guide individual decision-making, diabetes clinical practice guidelines have increasingly recognized the need for individualization of diabetes treatment (71–73). To most effectively address the diabetes epidemic, we need to improve our approaches to preventing and treating diabetes and tailor these approaches to each individual.

Table 2—Adjusted hazard ratios (95% CI)* of cardiovascular and all-cause mortality according to categories of HbA_{1c} and fasting glucose† at baseline in persons without diagnosed diabetes, by race/ethnicity group, U.S. adults aged 18 years or older (NHANES III, 1988–1994), $N = 12{,}722$

	HbA_{1c} <5.0%	HbA_{1c} 5.0–5.6%	HbA_{1c} 5.7–6.5%	HbA_{1c} ≥6.5%
Cardiovascular mortality, $n = 804$ deaths				
Non-Hispanic white	0.74 (0.38–1.41)	1 (ref)	1.13 (0.83–1.53)	1.39 (0.77–2.51)
Non-Hispanic black	0.94 (0.45–1.96)	1 (ref)	1.10 (0.78–1.56)	2.25 (0.89–5.64)
Mexican American	0.60 (0.18–1.98)	1 (ref)	1.15 (0.63–2.10)	3.90 (1.86–8.17)
All-cause mortality, $n = 3{,}415$ deaths				
Non-Hispanic white	1.18 (0.91–1.54)	1 (ref)	1.12 (0.96–1.32)	1.50 (1.09–2.05)
Non-Hispanic black	1.27 (0.88–1.81)	1 (ref)	1.14 (0.98–1.32)	2.00 (1.40–2.85)
Mexican American	0.99 (0.60–1.63)	1 (ref)	1.15 (0.84–1.58)	1.74 (1.13–2.67)
	Fasting glucose <90 mg/dL	Fasting glucose 90–99 mg/dL	Fasting glucose 100–125 mg/dL	Fasting glucose ≥126 mg/dL
Cardiovascular mortality, $n = 363$ deaths†				
Non-Hispanic white	0.96 (0.51–1.80)	1 (ref)	1.43 (0.87–2.35)	1.82 (0.98–3.36)
Non-Hispanic black	0.77 (0.29–2.05)	1 (ref)	0.97 (0.45–2.07)	1.60 (0.42–6.13)
Mexican American	1.96 (0.86–4.47)	1 (ref)	1.11 (0.55–2.24)	1.22 (0.39–3.84)
All-cause mortality, $n = 1{,}536$ deaths†				
Non-Hispanic white	0.96 (0.76–1.21)	1 (ref)	1.16 (0.97–1.38)	1.47 (1.04–2.08)
Non-Hispanic black	1.09 (0.71–1.66)	1 (ref)	1.16 (0.85–1.59)	2.40 (1.50–3.84)
Mexican American	0.84 (0.46–1.53)	1 (ref)	0.97 (0.61–1.52)	1.48 (0.69–3.17)

*Adjusted for age, sex, lipids, BMI, waist-to-hip ratio, education, smoking status, hypertension, and physical activity; †Subsample of 5,676 participants who attended the morning examination and had measurements of fasting plasma glucose.

The evidence from population-based studies suggests that HbA_{1c} is a useful and valid test of hyperglycemia across racial/ethnic groups. Indeed, studies using modern HbA_{1c} assays have now shown that HbA_{1c} is more strongly associated with outcomes as compared with fasting glucose or 2-h postprandial glucose (19,54). There is robust evidence that HbA_{1c} is associated with microvascular and macrovascular outcomes in diverse populations. There is no compelling evidence that the validity of HbA_{1c} as a measure of hyperglycemia and the prognostic value of clinical categories of HbA_{1c} differ substantially according to race.

Certainly more work needs to be done to understand the causes of racial differences in HbA_{1c} and the contribution of nonglycemic factors. But race is a poor surrogate for differences in underlying causes of disease risk, and suggestions for racially based medical decisions are disquieting. If anything, we need less emphasis on using race to define health and guide medical decision making. With respect to HbA_{1c}, we need to understand what might be causing disparities lest we inappropriately withhold a useful and prognostic test from a subgroup of the population known to be at high risk for diabetes and its complications. There is no evidence that HbA_{1c} testing will lead to "overdiagnosis" of diabetes in African Americans. There is, however, a real concern that recommendations to avoid or interpret HbA_{1c} results differently in racial/ethnic minority populations may actually increase health disparities.

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