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## Association of Sickle Cell Trait With Hemoglobin A<sub>1c</sub> in African Americans

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## Abstract

**IMPORTANCE**—Hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) reflects past glucose concentrations, but this relationship may differ between those with sickle cell trait (SCT) and those without it.

**OBJECTIVE**—To evaluate the association between SCT and HbA<sub>1c</sub> for given levels of fasting or 2-hour glucose levels among African Americans.

**DESIGN, SETTING, AND PARTICIPANTS**—Retrospective cohort study using data collected from 7938 participants in 2 community-based cohorts, the Coronary Artery Risk Development in Young Adults (CARDIA) study and the Jackson Heart Study (JHS). From the CARDIA study, 2637 patients contributed a maximum of 2 visits (2005–2011); from the JHS, 5301 participants contributed a maximum of 3 visits (2000–2013). All visits were scheduled at approximately 5-year intervals. Participants without SCT data, those without any concurrent HbA<sub>1c</sub> and glucose measurements, and those with hemoglobin variants HbSS, HbCC, or HbAC were excluded. Analysis of the primary outcome was conducted using generalized estimating equations (GEE) to examine the association of SCT with HbA<sub>1c</sub> levels, controlling for fasting or 2-hour glucose measures.

**EXPOSURES**—Presence of SCT.

**MAIN OUTCOMES AND MEASURES**—Hemoglobin A<sub>1c</sub> stratified by the presence or absence of SCT was the primary outcome measure.

**RESULTS**—The analytic sample included 4620 participants (mean age, 52.3 [SD, 11.8] years; 2835 women [61.3%]; 367 [7.9%] with SCT) with 9062 concurrent measures of fasting glucose and HbA<sub>1c</sub> levels. In unadjusted GEE analyses, for a given fasting glucose, HbA<sub>1c</sub> values were statistically significantly lower in those with (5.72%) vs those without (6.01%) SCT (mean HbA<sub>1c</sub> difference,  $-0.29\%$ ; 95% CI,  $-0.35\%$  to  $-0.23\%$ ). Findings were similar in models adjusted for key risk factors and in analyses using 2001 concurrent measures of 2-hour glucose and HbA<sub>1c</sub> concentration for those with SCT (mean, 5.35%) vs those without SCT (mean, 5.65%) for a mean HbA<sub>1c</sub> difference of  $-0.30\%$  (95% CI,  $-0.39\%$  to  $-0.21\%$ ). The HbA<sub>1c</sub> difference by SCT was greater at higher fasting ( $P = .02$  for interaction) and 2-hour ( $P = .03$ ) glucose concentrations. The prevalence of prediabetes and diabetes was statistically significantly lower among participants with SCT when defined using HbA<sub>1c</sub> values (29.2% vs 48.6% for prediabetes and 3.8% vs 7.3% for diabetes in 572 observations from participants with SCT and 6877 observations from participants without SCT;  $P < .001$  for both comparisons).

**CONCLUSIONS AND RELEVANCE**—Among African Americans from 2 large, well-established cohorts, participants with SCT had lower levels of HbA<sub>1c</sub> at any given concentration of fasting or 2-hour glucose compared with participants without SCT. These findings suggest that HbA<sub>1c</sub> may systematically underestimate past glycemia in black patients with SCT and may require further evaluation.

Hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) is a practical measure of average glucose levels during the preceding 2 to 3 months.<sup>1-4</sup> In 2009, after review of available evidence, an International Expert Committee recommended the use of HbA<sub>1c</sub> to diagnose diabetes.<sup>5</sup> Extensive work has been done by the NGSP (formerly, the National Glycohemoglobin Standardization Program) to standardize methods for measuring HbA<sub>1c</sub> and to identify methods that provide accurate HbA<sub>1c</sub> measurement even in the presence of hemoglobin variants.<sup>6</sup>

Sickle cell trait (SCT) is the most common hemoglobin variant in the United States, with 8% to 10% of black people affected by SCT compared with less than 1% of white people.<sup>7,8</sup> Red blood cells of individuals with normal hemoglobin contain approximately 97% HbA, whereas red blood cells of individuals with SCT contain approximately 60% to 70% HbA and 30% to 40% HbS.<sup>9</sup> Although data are limited, it is hypothesized that the presence of HbS results in a shorter lifespan for red blood cells.<sup>9-12</sup> This would result in less available time for hemoglobin glycation, which in turn may influence the interpretation of HbA<sub>1c</sub> in relationship to the glucose values they intend to represent. Correct interpretation of HbA<sub>1c</sub> values in individuals with SCT is important because it directly affects efforts that use HbA<sub>1c</sub> for screening, diagnosis, and monitoring of diabetes and prediabetes. Accordingly, the objectives of this study were to (1) examine the association between HbA<sub>1c</sub> and SCT while controlling for other measures of glucose (fasting and 2-hour glucose) levels, (2) compare the prevalence of prediabetes and diabetes by SCT status, and (3) determine if SCT modifies the discriminative ability of HbA<sub>1c</sub> to identify individuals with prediabetes or diabetes.

## Methods

### Study Population

This retrospective study pooled data from participants who self-identified as African American from 2 established community-based cohorts, the Coronary Artery Risk Development in Young Adults (CARDIA) study and the Jackson Heart Study (JHS), to examine the association of SCT with HbA<sub>1c</sub>, controlling for fasting glucose or 2-hour glucose levels. Details regarding the design of each study have been published.<sup>13,14</sup> In brief, the CARDIA study enrolled, from March 25, 1985 to June 7, 1986, a stratified sample of 2637 black people and 2478 white people (n = 5115) from Minneapolis, Minnesota; Chicago, Illinois; Birmingham, Alabama; and Oakland, California. After their initial visit, participants were followed up approximately 2, 5, 7, 10, 15, 20, and 25 years later (data collection, 1985-present). The Jackson Heart Study, a single-site study in Jackson, Mississippi, enrolled 5301 African Americans during the years 2000 through 2004. Participants returned for 2 follow-up examinations approximately 5 and 10 years after their initial visit (data collection, 2000–2013). The data used for these analyses were from years 20 and 25 from the CARDIA cohort and from baseline and years 5 and 10 from the JHS cohort. All participants included in analyses provided written informed consent for genetic studies. Institutional review board approval was obtained separately from each participating institution.

## Covariate Assessment

Details regarding data collection procedures for CARDIA<sup>15,16</sup> and JHS<sup>17</sup> have been published. Data on participants' sex, self-reported race, date of birth, diet, physical activity, smoking status, medical history, and medication use were collected at each visit by trained interviewers. Physical activity was classified as poor (0), intermediate (>0-<150), or ideal (150) using minutes per week of moderate to vigorous physical activity. Diet was classified as poor (0–1), intermediate (2–3), or ideal (4–5) using the number of components achieved from the following list: 4.5 or more cups of fruits and vegetables daily; 198 g or more of fish weekly; less than 1500 mg of sodium daily; less than 450 calories each week of sugar-sweetened beverages; and 3 or more servings daily of whole grains. Smoking was classified as poor (current smoker), intermediate (quit <12 months ago) or ideal (never smoked or quit 12 months ago). Height and weight were measured by certified study personnel and used to calculate body mass index (BMI), weight in kilograms divided by height in meters squared. Estimated glomerular filtration rate (eGFR) was calculated at years 20 and 25 in CARDIA and at baseline and year 10 in JHS using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.<sup>18</sup> Serum ferritin was measured at year 20 in CARDIA and at baseline in JHS. Previous diabetes diagnosis was defined as self-report of a physician's diagnosis. Current use of diabetes medications was defined as use of diabetes medications in the 2 weeks prior to the examination.

## SCT Status

In CARDIA, SCT status was determined with available DNA samples from the 10-year follow-up and afterwards using single-gene, single-nucleotide polymorphism (SNP) genotyping with TaqMan SNP Genotyping Assays (Life Technologies). In JHS, genotype data for rs334 encoding the sickle hemoglobin mutation (*HBB p.Glu7Val*) was obtained through whole-exome sequencing using data from baseline. Sickle cell trait was defined as the presence of 1 abnormal allele for HbS.

## Plasma Glucose Measures

Plasma glucose was measured using the hexokinase method at all visits in both studies except at baseline in JHS, at which time the glucose oxidase method was used. Previous research has shown these 2 methods of glucose measurement to be highly correlated.<sup>19,20</sup> Additionally, 2-hour glucose levels were measured in CARDIA and obtained during a standard oral glucose tolerance test, using 75 g of glucose solution. The coefficient of variation for glucose measures ranged from 1.6% to 3.8% (eTable 1 in the Supplement).

## HbA<sub>1c</sub> Measures

Two NGSP-certified assays were used to measure HbA<sub>1c</sub>, both using high-performance liquid chromatography. In JHS, a Tosoh 2.2 was used at baseline and a Tosoh G7 (variant mode) was used at the 5- and 10-year follow-ups. In CARDIA, a Tosoh G7 (variant mode) was used at the 20- and 25-year follow-up. According to the NGSP, neither Tosoh 2.2 nor Tosoh G7 (variant mode) has experienced clinically significant interference in those with SCT.<sup>6</sup> The coefficient of variation for HbA<sub>1c</sub> assays ranged from 1.2% to 1.9% (eTable 1 in the Supplement).

## Main Outcome Measure

The main outcome measure, HbA<sub>1c</sub>, was assessed at multiple time points and pooled cross-sectionally to examine the association between HbA<sub>1c</sub>, modeled as a continuous variable, and SCT, adjusting for fasting or 2-hour glucose measures. Prespecified secondary outcomes include prediabetes, diabetes, and combined prediabetes or diabetes, which were defined using the following measures based on cutpoints established by the American Diabetes Association<sup>21</sup>: (1) fasting glucose levels (prediabetes, 100-<126 mg/dL; diabetes, ≥126 mg/dL; and combined prediabetes or diabetes, ≥100 mg/dL), 2-hour glucose levels (prediabetes, 140-<200 mg/dL; diabetes, ≥200 mg/dL; and combined prediabetes or diabetes, ≥140 mg/dL), and HbA<sub>1c</sub> levels (prediabetes, 5.7%-<6.5%; diabetes, ≥6.5%; combined prediabetes or diabetes, ≥5.7%). (To convert glucose from mg/dL to mmol/L, multiply by 0.0555.)

## Statistical Methods

Baseline characteristics of participants with and without SCT were compared using  $\chi^2$  tests and analysis of variance for discrete and continuous variables, respectively. All visits with concurrent measurement of HbA<sub>1c</sub> and fasting glucose or HbA<sub>1c</sub> and 2-hour glucose levels were included in the analyses. Mean HbA<sub>1c</sub> values were calculated by SCT status across a range of glucose categories in 10-mg/dL increments for fasting glucose (<80- 150mg/dL) and in 20-mg/dL increments for 2-hour glucose levels (<80- 200mg/dL).

Generalized estimating equations (GEE) using random effects at the participant level and an exchangeable correlation matrix to account for correlation among repeated measures were used to assess the association of SCT with HbA<sub>1c</sub> controlling for fasting glucose levels.<sup>22</sup> A multistep approach was used to examine the robustness of findings to model specification. First, unadjusted GEE models were fit using HbA<sub>1c</sub> as the outcome, SCT as the exposure, and glucose as the primary covariate. Next, GEE analyses were adjusted for the following potential confounders that were identified a priori based on the literature: age, sex, BMI, ferritin levels, eGFR, physician-diagnosed diabetes, use of diabetes medications, and study cohort.<sup>23-25</sup> In addition, multiplicative SCT × glucose interaction was tested in unadjusted and adjusted models. Analyses were repeated using 2-hour glucose measures in lieu of fasting glucose measures as the main covariate. Model fit was compared using quasi-likelihood under the independence-model criterion.<sup>26</sup> Prespecified subgroup analyses were conducted among participants not taking diabetes medications and in groups of participants stratified by cohort. Interaction by cohort and HbA<sub>1c</sub> assay on the association between SCT and HbA<sub>1c</sub> was tested.

Next, among a subset of participants with no previous diabetes or current use of diabetes medications, GEE analyses with a Poisson distribution and an identity link function were used to estimate the unadjusted prevalence of prediabetes and diabetes by SCT status.<sup>27</sup>

In the same subset of participants, GEE analyses with a Poisson distribution and a log link function (sometimes called a modified Poisson model) were used to generate predictive probabilities that were then used in logistic regression models to compare the discriminative ability of HbA<sub>1c</sub> levels to identify the combined presence of prediabetes or diabetes.<sup>28</sup> A

combined outcome of prediabetes or diabetes was used due to consideration of sample size. Area under the receiver operating characteristic (AUROC) curves were calculated for HbA<sub>1c</sub> levels in those with and without SCT. Unpaired comparisons of the AUROC curves were conducted to assess the discriminatory power of HbA<sub>1c</sub> by SCT status.<sup>29,30</sup> Complete case analysis was performed for adjusted analyses because data were more than 98% complete, with the exception of ferritin (7% missing). A 2-sided *P* value of .05 was used for level of significance. Analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc).

## Results

### Baseline Characteristics

A total of 7938 participants were enrolled at baseline, of whom 2637 were in CARDIA and 5301 in JHS. One thousand sixty-five CARDIA and 2253 JHS participants were excluded. Of those excluded in CARDIA, 550 had no available SCT data; 3 had HbSS; 2, HbCC; 41, HbAC; and 469, no concurrent measurements of HbA<sub>1c</sub> or fasting or 2-hour glucose measurements. Of those excluded in JHS, 2079 had no available SCT data; 2, HbSS; 80, HbAC; and 92, no concurrent measurements of HbA<sub>1c</sub> and fasting or 2-hour glucose. A total of 4620 participants (58.2%) were included in these analyses—1572 in CARDIA and 3048 in JHS. Other than having a lower mean BMI, the 1019 CARDIA and 2171 JHS participants excluded from the analyses because of missing data had comparable baseline characteristics with those included in the analysis (BMI, 29.4 vs 29.8; *P* = .01; eTable 2 in the Supplement).

The 367 participants (7.9%) with SCT were older (53.9 vs 52.2 years, *P* = .007) and had lower eGFR (92.5 vs 97.5 mL/min/1.73 m<sup>2</sup>, *P* < .001), and lower HbA<sub>1c</sub> values (5.7% vs 5.9%, *P* = .001; Table 1) than did participants without SCT. Additionally, participants with SCT were more likely to report previously diagnosed diabetes (17.2% vs 14.7%, *P* = .20) and current use of diabetes medications (15.0% vs 12.5%, *P* = .19), although these findings did not reach statistical significance.

### Association of HbA<sub>1c</sub> With Glucose Measures

For all 4620 participants, each visit with concurrent HbA<sub>1c</sub> and fasting glucose or HbA<sub>1c</sub> and 2-hour glucose measures was included, resulting in 9062 concurrent measures of HbA<sub>1c</sub> and fasting glucose (2583 from CARDIA; 6479 from JHS) from 4620 unique participants and 2001 concurrent measures of HbA<sub>1c</sub> and 2-hour glucose measures (2001 from CARDIA) from 1323 unique participants (eFigure in the Supplement). The majority of participants (74.6%) had HbA<sub>1c</sub> and glucose measured at least twice. Using all available observations, the mean HbA<sub>1c</sub> was 5.7% in those with SCT vs 6.0% in those without SCT, despite similar mean fasting (103.0 vs 102.9 mg/dL; *P* = .88) and 2-hour glucose values (118.5 vs 113.0 mg/dL; *P* = .19) for those with SCT vs those without SCT, respectively. Across all categories of fasting and 2-hour glucose measures, mean HbA<sub>1c</sub> values were lower in those with vs without SCT (Table 2).

Unadjusted GEE analyses revealed that, at the same fasting glucose concentration, HbA<sub>1c</sub> values were statistically significantly lower in those with SCT (mean HbA<sub>1c</sub>, 5.72%) vs

those without SCT (mean HbA<sub>1c</sub>, 6.01%; mean HbA<sub>1c</sub> difference, -0.29%; 95% CI, -0.35% to -0.23%;  $P < .001$ ). In adjusted analyses, HbA<sub>1c</sub> values remained significantly lower in those with SCT (mean HbA<sub>1c</sub> difference, -0.32%; 95% CI, -0.38% to -0.26%;  $P < .001$ ). The difference in HbA<sub>1c</sub> levels by SCT status was greater at higher concentrations of fasting glucose ( $P = .02$  for interaction in unadjusted analyses, Figure 1A;  $P = .01$  in adjusted analyses, Figure 1B). Results were similar in analyses stratified by study cohort and when excluding 1302 observations from participants taking diabetes medications at the time of examination (eTable 3 in the Supplement). There was no evidence of interaction by HbA<sub>1c</sub> assay ( $P = .43$  for SCT  $\times$  fasting glucose  $\times$  HbA<sub>1c</sub> assay) or by study cohort ( $P = .63$  for SCT  $\times$  fasting glucose  $\times$  study cohort).

Results for 2-hour glucose measures revealed similar HbA<sub>1c</sub> differences by SCT status. For a given 2-hour glucose level, HbA<sub>1c</sub> values were statistically significantly lower in those with SCT (mean HbA<sub>1c</sub>, 5.35%) vs in those without SCT (mean HbA<sub>1c</sub>, 5.65%), for a mean HbA<sub>1c</sub> difference of -0.30% (95% CI, -0.39% to -0.21%;  $P < .001$ ). HemoglobinA<sub>1c</sub> levels remained significantly lower in those with SCT in adjusted analyses (mean difference in HbA<sub>1c</sub>, -0.38%; 95% CI, -0.49% to -0.28%;  $P < .001$ ). The difference in HbA<sub>1c</sub> levels by SCT status was greater at higher 2-hour glucose concentrations ( $P = .03$  for interaction in unadjusted analyses, Figure 1C;  $P = .03$  in adjusted analyses, Figure 1D).

### Prevalence of Prediabetes and Diabetes

Among a subset of participants with no prior diagnosis of diabetes or current use of diabetes medications (7449 observations for fasting glucose and HbA<sub>1c</sub>; 1869 observations for 2-hour glucose and HbA<sub>1c</sub>), the prevalence of prediabetes and diabetes was not significantly different among participants with vs without SCT when defined using fasting glucose (28.6% with vs 25.0% without SCT for prediabetes;  $P = .12$ ; 2.5% with vs 3.6% without SCT for diabetes;  $P = .25$ ) or 2-hour glucose values (15.9% with vs 12.9% without SCT for prediabetes,  $P = .45$ ; and 3.6% with vs 3.3% without SCT for diabetes;  $P > .89$ ; Figure 2). In contrast, the prevalence of prediabetes and diabetes was statistically significantly lower among participants with SCT when defined using HbA<sub>1c</sub> values (29.2% with vs 48.6% without SCT for prediabetes and 3.8% with vs 7.3% without SCT for diabetes;  $P < .001$  for all comparisons, Figure 2).

### Discriminative Ability of HbA<sub>1c</sub> to Identify Prediabetes or Diabetes

In the same subset of participants without diabetes or diabetes medication use, the discriminative ability of HbA<sub>1c</sub> to identify the presence of prediabetes or diabetes was statistically significantly lower among participants with SCT (AUROC, 0.70; 95% CI, 0.65–0.74) vs without SCT (AUROC, 0.77; 95% CI, 0.75–0.78; absolute difference, 0.07; 95% CI, 0.02–0.12) when using fasting glucose-defined prediabetes or diabetes ( $P < .01$ , Figure 3A). The same held true among participants with SCT (AUROC, 0.60; 95% CI, 0.47–0.72) vs those without SCT (AUROC, 0.74; 95% CI, 0.71–0.78; absolute difference, 0.15; 95% CI, 0.02–0.28) when using 2-hour glucose-defined prediabetes or diabetes measures ( $P = .02$ , Figure 3B).

## Discussion

In this retrospective cohort study of African Americans participating in 2 large US cohorts, we demonstrated that, at the same fasting or 2-hour glucose concentration, HbA<sub>1c</sub> is statistically significantly lower among participants with vs without SCT. Moreover, differences in HbA<sub>1c</sub> concentration by SCT status were greater at higher glucose concentrations. These differences are based on an HbA<sub>1c</sub> method reported to have no clinically significant interference in individuals with SCT.<sup>6,31</sup>

Our findings stand in contrast to 2 previous studies. Bleyer and colleagues<sup>32</sup> investigated the HbA<sub>1c</sub>-glucose association in 385 African American in patients, the majority of whom had diabetes and among whom there was an unusually high prevalence of SCT: 109 (28%) had SCT. Despite higher baseline HbA<sub>1c</sub> values, the authors did not find that SCT significantly altered the relationship between HbA<sub>1c</sub> and serum glucose. Sumner and colleagues<sup>33</sup> examined the sensitivity of HbA<sub>1c</sub> to detect impaired glucose tolerance in a cohort of 216 African immigrants without diabetes, 46(21%) of whom had either HbC trait or SCT. They found no significant difference in the sensitivity of HbA<sub>1c</sub> by variant hemoglobin status in the detection of prediabetes; however, this study combined participants with SCT and HbC trait, which may have affected findings. Additionally, both of these studies are potentially limited by their small sample size.

We consider 2 ways in which SCT could modify the ability of HbA<sub>1c</sub> to accurately reflect past glycemia. First, the lifespan of the red blood cells in persons with SCT may be shortened compared with those with normal hemoglobin, resulting in less time available for glycation. However, the evidence to support this hypothesis remains limited and conflicting.<sup>9-12</sup> Second, the presence of HbS can result in assay interference with common HbA<sub>1c</sub> measurement techniques. Current testing on HbA<sub>1c</sub> laboratory methods uses a relative bias of plus or minus 7.0% to classify clinically significant interference from hemoglobin variants.<sup>6</sup> Although the assays used in this study report no clinically significant interference in individuals with SCT, the possibility of minor interference that could potentially explain our findings cannot be ruled out.

Irrespective of the mechanism, our results suggest that currently accepted clinical measures of HbA<sub>1c</sub> do not reflect recent past glycemia in the same way in African Americans with and without SCT, as evidenced by significantly lower HbA<sub>1c</sub> values at the same glucose concentration in those with vs without SCT. These results could have clinically significant implications. As a screening tool, an HbA<sub>1c</sub> value that systematically underestimates long-term glucose levels may result in a missed opportunity for intervention. In the present study, using standard clinical HbA<sub>1c</sub> criteria to identify prediabetes and diabetes resulted in identifying 40% fewer cases of prediabetes and 48% fewer cases of diabetes among participants with SCT compared with those without SCT, while glucose-based methods resulted in a similar prevalence regardless of SCT status (Figure 2). The discriminative ability of HbA<sub>1c</sub> concentration to identify individuals with prediabetes or diabetes was significantly lower in those with vs those without SCT (Figure 3). These findings raise the possibility of benefit from incorporating information on hemoglobin variants into clinical guidelines for interpreting HbA<sub>1c</sub> values for screening and diagnosis of prediabetes and



diabetes. Because black people typically have a higher prevalence of diabetes and experience a number of diabetic complications at higher rates than white people, the cost of inaccurately assessing risk and treatment response is high.<sup>34–36</sup>

In our study, African Americans with and without SCT had relatively high HbA<sub>1c</sub> levels with mean values greater than 5%. This is possibly due to the higher values often found in black people than in white people.<sup>37,38</sup> Future studies that include biracial populations should further investigate HbA<sub>1c</sub> differences by race in relation to hemoglobinopathies. We also noted that individuals with SCT had a lower eGFR as was observed previously by Naik and colleagues.<sup>39</sup> Future studies should focus on whether a possible delay in the diagnosis and treatment of prediabetes and diabetes in those with SCT could explain their lower kidney function.

Strengths of our study include the availability of detailed information on demographics, medical history, and clinical measures as well as the reproducibility of findings across 2 different versions of the Tosoh HbA<sub>1c</sub> assay (2.2 and G7) and across 2 different measures of glucose concentration (fasting and 2-hour glucose).

This study has a number of limitations. Despite pooling data from 2 large cohorts, a relatively small number of participants had SCT (367 participants). Although, to our knowledge, this is the largest study to date examining the association between HbA<sub>1c</sub>, SCT, and other glucose measures, further studies including biracial populations and other hemoglobin variants are needed to confirm and complement our findings. Second, validation of these findings with other HbA<sub>1c</sub> assays would help explain the potential mechanisms of the disparate HbA<sub>1c</sub>-glycemia association between those with and without SCT. Third, even though multiple measures of glucose were available and findings were consistent with fasting and 2-hour glucose measures, these measures cannot fully represent average glycemia over the prior 2 to 3 months, which might lower the precision of our estimates. However, our findings were robust in analyses adjusted for potential confounding variables and in various sensitivity analyses suggesting that the likelihood of such bias is low. Fourth, a large number of participants were excluded from analyses due to missing data on SCT status, HbA<sub>1c</sub> measures, or glucose measures; however, participants excluded were comparable with those in the analytic sample with the exception of a lower BMI at baseline among those excluded. In addition, no clinical outcomes were assessed in this study. Whether the findings in this study have clinical implications is unclear.

## Conclusions

Among African Americans from 2 large, well-established cohorts, participants with SCT had lower levels of HbA<sub>1c</sub> at any given concentration of fasting or 2-hour glucose compared with participants without SCT. These findings suggest that HbA<sub>1c</sub> may systematically underestimate past glycemia in black patients with SCT and may require further evaluation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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### Key Points

**Question**

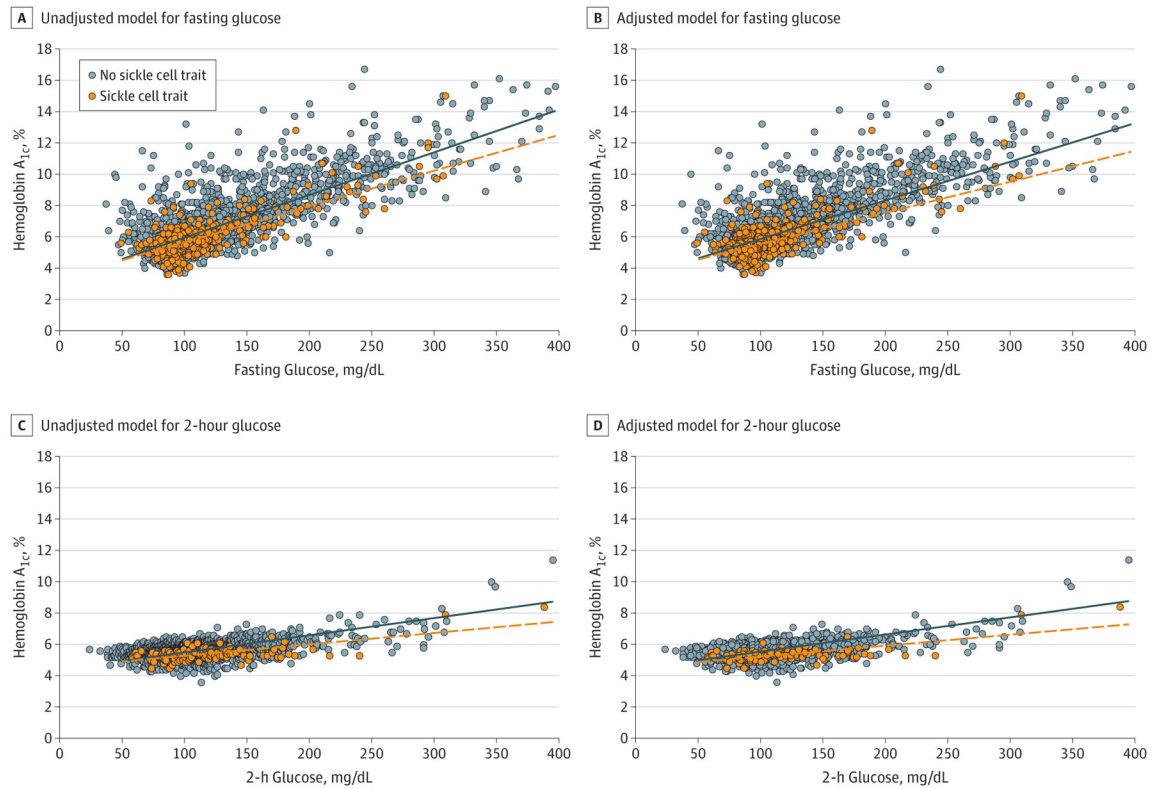
Does hemoglobin A<sub>1c</sub> reflect past glucose concentrations in a similar manner in African Americans with sickle cell trait as it does in those without sickle cell trait?

**Findings**

In this retrospective cohort study of 4620 African Americans, for any given fasting or 2-hour glucose concentration, individuals with sickle cell trait had significantly lower hemoglobin A<sub>1c</sub> values, 5.72% vs 6.01%, than those without sickle cell trait.

**Meaning**

Among African Americans with sickle cell trait, hemoglobin A<sub>1c</sub> concentration may systematically underestimate past glycemia and should be further evaluated.



**Figure 1. Scatterplot of Observed Data Model of Hemoglobin A<sub>1c</sub> vs Fasting and 2-Hour Glucose Measures in Participants With or Without Sickle Cell Trait**

Scatterplot of observed data points along side unadjusted and adjusted regression lines examining the association between sickle cell trait (SCT) and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), controlling for fasting or 2-hour glucose values was obtained using generalized estimating equations (GEE) with an exchangeable correlation matrix to account for correlation of repeated measures. All continuous covariates are centered at the population mean. The solid blue lines represent the regression line for those for who did not have SCT and the dashed orange lines for those who had SCT. BMI indicates body mass index; CARDIA, Coronary Artery Risk Development in Young Adults study. To convert glucose from mg/dL to mmol/L, multiply by 0.0555.

A, Included 9062 observations, 720 from participants with SCT and 8342 from participants without SCT. The regression equation: predicted HbA<sub>1c</sub> = 6.01 + (−0.28 × SCT) + (0.03 × fasting glucose) + (−0.004 × SCT × fasting glucose).

B, Included 8460 observations, 683 from participants with SCT and 7777 from participants without SCT. The regression equation: predicted HbA<sub>1c</sub> = 5.93 + (−0.32 × SCT) + (0.03 × fasting glucose) + (−0.005 × SCT × fasting glucose) + (0.04 × 1 if male) + (0.008 × age) + (0.01 × BMI) + (−0.0004 × ferritin) + (0.001 × estimated glomerular filtration rate) + (−0.08 × 1 if a CARDIA participant) + (0.46 × 1 if currently using diabetes medications) + (0.14 × 1 if previous diabetes diagnosis).

C, Included 2001 observations, 127 from participants with SCT and 1874 from participants without SCT. Regression equation: predicted HbA<sub>1c</sub> = 5.65 + (−0.28 × SCT) + (0.01 × 2-hour glucose) + (−0.004 × SCT × 2-hour glucose).

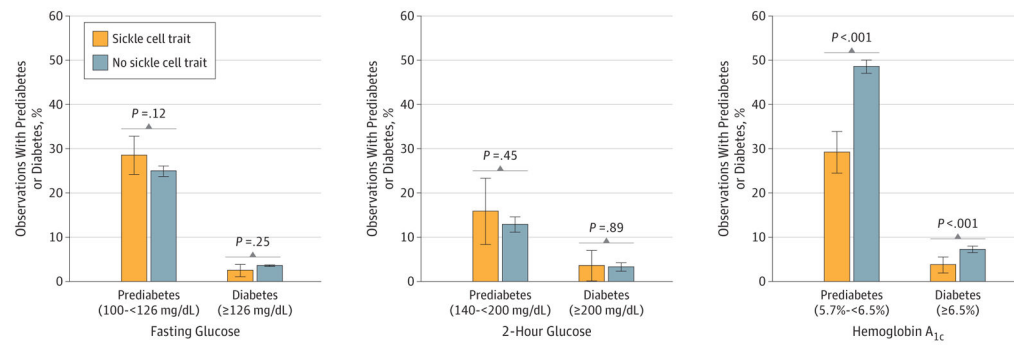
D, Included 1712 observations, 109 from participants with SCT and 1606 from participants without SCT. Regression equation: predicted  $HbA_{1c} = 5.66 + (-0.36 \times SCT) + (0.01 \times 2\text{-hour glucose}) \times (-0.004 \times SCT \times 2\text{-hour glucose}) + (0.24 \times 1 \text{ if male}) + (0.02 \times \text{age}) + (0.006 \times BMI) + (-0.0006 \times \text{ferritin}) + (0.0003 \times eGFR) + (0.07 \times 1 \text{ if previous diabetes diagnosis})$ .

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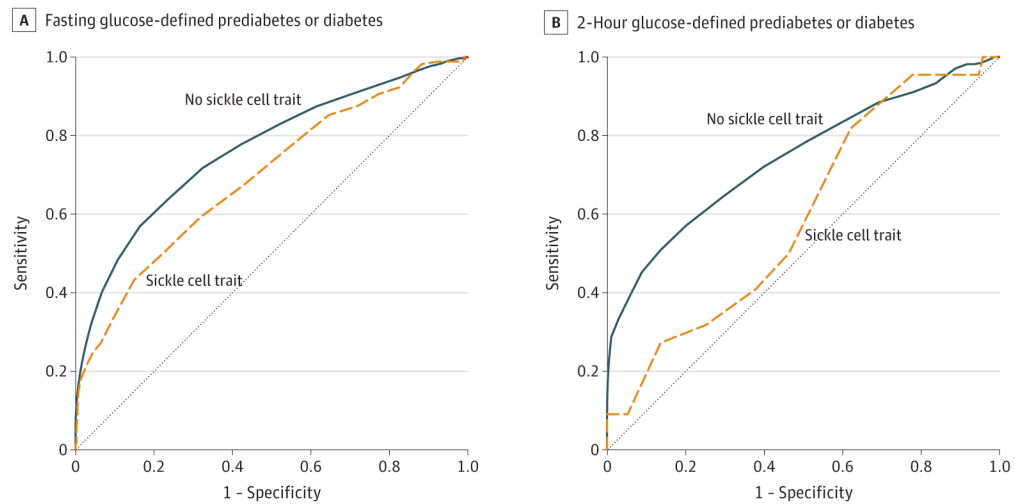
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**Figure 2. Prevalence of Prediabetes and Diabetes by Sickle Cell Trait Status Among Participants Not Taking Diabetes Medications and With No Prior Diagnosis of Diabetes**

Fasting glucose and hemoglobin A<sub>1c</sub> analyses included 7499 total observations (6877 observations from participants without sickle cell trait [SCT] and 572 from participants with it). Analyses for 2-hour glucose concentrations were only available from CARDIA participants and included 1869 total observations (1752 observations from participants without SCT and 117 from participants with SCT). For the definition of prediabetes and diabetes by glucose measures, see the Methods section. The prevalence of prediabetes and diabetes by fasting glucose and 2-hour glucose concentration was similar in those with and without SCT ( $P > .10$  for all comparisons). However, the prevalence of prediabetes and diabetes as defined by hemoglobin A<sub>1c</sub> was significantly higher among participants with vs without SCT ( $P < .001$  for both). Error bars indicate 95% CIs.





**Figure 3. Comparison of the Diagnostic Sensitivity of Hemoglobin A<sub>1c</sub> to Identify Combined Prediabetes or Diabetes by Sickle Cell Trait Status**

A, For fasting glucose of 100mg/dL or higher, the area under the receiver operating characteristic (AUROC) of hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) was 0.77 (95% CI, 0.75–0.78) among those without sickle cell trait (SCT) and 0.70 (95% CI, 0.65–0.74) among those with SCT. An unpaired comparison of the AUROC curves indicated that the diagnostic ability of HbA<sub>1c</sub> to identify fasting glucose–defined prediabetes or diabetes was significantly lower among those with SCT than among those without it ( $P = .007$ ).

B, For 2-hour glucose levels of 140mg/dL or higher, the AUROC of HbA<sub>1c</sub> was 0.74 (95% CI, 0.71–0.78) among those without SCT and 0.60 (95% CI, 0.47–0.72) among those with SCT. An unpaired comparison of the AUROC curves indicated that the diagnostic ability of HbA<sub>1c</sub> to identify 2-hour glucose-defined prediabetes or diabetes was significantly lower in those with SCT than in those without it ( $P = .03$ ). To convert glucose from mg/dL to mmol/L, multiply by 0.0555.

Table 1

Baseline Characteristics of Study Participants by Sickle Cell Trait Status<sup>a</sup>

Characteristic	CARDIA and JHS			CARDIA			JHS			
	Overall (n = 4620)	No SCT (n = 4253)	SCT (n = 367)	P Value	No SCT (n = 1467)	SCT (n = 105)	P Value	No SCT (n = 2786)	SCT (n = 262)	P Value
Men, No. (%)	1785 (38.6)	1634 (38.4)	151 (41.1)	.31	598 (40.8)	42 (40.0)	.88	1036 (37.2)	109 (41.6)	.16
Age, mean (SD), y	52.3 (11.81)	51.3 (11.8)	53.9 (12.2)	.007	45.7 (4.3)	46.1 (4.2)	.31	55.6 (13.0)	57.1 (12.9)	.08
BMI, mean (SD)	31.8 (7.4)	31.8 (7.5)	31.7 (7.5)	.82	31.5 (7.7)	31.8 (6.9)	.74	32.0 (7.6)	31.7 (7.8)	.57
Hemoglobin, mean (SD), mg/dL <sup>b</sup>	13.0 (1.5)	13.1 (1.5)	12.9 (1.4)	.14				13.1 (1.5)	12.9 (1.4)	.14
Ferritin, mean (SD), ng/mL <sup>c</sup>	155.9 (169.7)	156.3 (171.8)	151.4 (143.7)	.61	124.0 (148.0)	107.2 (98.7)	.32	169.7 (179.1)	165.0 (152.6)	.68
eGFR, mean (SD), mL/min/1.73 m <sup>2</sup>	97.1 (21.5)	97.5 (21.3)	92.5 (23.3)	<.001	103.0 (19.7)	101.6 (19.7)	.46	94.6 (21.5)	88.8 (23.6)	<.001
Fasting glucose, mean (SD), mg/dL	101.6 (33.2)	101.5 (33.2)	102.7 (34.2)	.49	101.1 (30.2)	106.0 (38.2)	.11	101.7 (34.6)	101.4 (32.4)	.91
HbA <sub>1c</sub> , mean (SD), %	5.9 (1.2)	5.9 (1.2)	5.7 (1.2)	.001	5.8 (1.0)	5.7 (1.1)	.44	6.0 (1.3)	5.7 (1.2)	<.001
2-h glucose, mean (SD), mg/dL <sup>d</sup>	113.9 (44.5)	113.8 (44.9)	116.1 (39.0)	.66	113.8 (44.9)	116.1 (39.0)	.66			
Diabetes, No. (%) <sup>e</sup>	685 (14.9)	622 (14.7)	63 (17.2)	.20	213 (14.5)	23 (21.9)	.04	409 (14.7)	40 (15.3)	.82
Diabetes medications, No. (%) <sup>f</sup>	577 (12.75)	523 (12.53)	54 (14.97)	.19	116 (7.9)	15 (14.43)	.02	407 (15.0)	39 (15.1)	.95
<b>Physical Activity, No. (%)<sup>g</sup></b>										
Poor health	1584 (34.4)	1445 (34.1)	139 (38.1)		71 (4.9)	3 (2.9)		1374 (49.4)	136 (51.9)	
Intermediate health	1481 (32.2)	1368 (32.3)	113 (31.0)	.29	494 (33.9)	35 (34.0)	.66	874 (31.4)	78 (29.8)	.82
Ideal health	1540 (33.4)	1427 (33.7)	113 (31.0)		892 (61.2)	65 (63.1)		535 (19.2)	48 (18.3)	

Characteristic	CARDIA and JHS		CARDIA		JHS					
	Overall (n = 4620)	No SCT (n = 4253)	SCT (n = 367)	P Value	No SCT (n = 1467)	SCT (n = 105)	P Value	No SCT (n = 2786)	SCT (n = 262)	P Value
<b>Diet, No. (%)<sup>h</sup></b>										
Poor health	2498 (58.6)	2292 (58.5)	206 (59.4)	.17	595 (52.7)	40 (47.1)	.18	1697 (60.9)	166 (63.4)	.73
Intermediate health	1710 (40.1)	1577 (40.3)	133 (38.3)		512 (45.4)	41 (48.2)		1065 (38.2)	92 (35.1)	
Ideal health	54 (1.3)	46 (1.2)	8 (2.3)		22 (2.0)	4 (4.7)		24 (0.9)	4 (1.5)	
<b>Smoking, No. (%)<sup>i</sup></b>										
Poor health	791 (17.4)	754 (17.5)	57 (15.8)	.69	367 (25.4)	20 (19.1)	.25	367 (13.4)	37 (14.5)	.75
Intermediate health	83 (1.8)	77 (1.8)	6 (1.7)		45 (3.1)	2 (1.9)		32 (1.2)	4 (1.6)	
Ideal health	3683 (80.8)	3385 (80.7)	298 (82.6)		1036 (71.6)	83 (79.1)		2349 (85.5)	215 (84.0)	

Abbreviations: HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CARDIA, Coronary Artery Risk Development in Young Adults study; eGFR, estimated glomerular filtration rate; JHS, Jackson Heart Study; SCT, sickle cell trait.

SI conversion factor: to convert glucose from mg/dL to mmol/L, multiply by 0.0555.

<sup>a</sup>Baseline for this study was the first visit at which a participant had HbA<sub>1c</sub> and fasting or 2-hour glucose measured concurrently. For CARDIA participants, this was either the year-20 or year-25 follow-up examination. For JHS participants, this was either examination 1, 2, or 3.

<sup>b</sup>Hemoglobin was only measured in 2976 participants, all of whom are from JHS (ie, 64% of the total analytic sample).

<sup>c</sup>Ferritin was only measured in 4278 participants (ie, 93% of the total analytic sample).

<sup>d</sup>Two-hour glucose was only measured in 1222 participants all of whom are from CARDIA and are not taking diabetes medications (ie, 26% of the total analytic sample).

<sup>e</sup>Diagnosed diabetes is defined as self-reported use of diabetes medications or self-reported physician diagnosis.

<sup>f</sup>Diabetes medications is defined as use of a medication for the treatment of diabetes taken in the 2 weeks prior to the study examination.

<sup>g</sup>For the definitions of poor, intermediate, or ideal physical activity and health, see the Methods section.

<sup>h</sup>For the definition of a poor, intermediate, or ideal diet, see the Methods section.

<sup>i</sup>For the definition of poor, intermediate, or ideal smoking status, see the Methods section.

Observed Hemoglobin A<sub>1c</sub> Value Across Categories of Fasting and 2-Hour Glucose, by SCT Status

Table 2

	SCT					
	No SCT			SCT		
	Total No. of Observations	No. of Unique Participants	HbA <sub>1c</sub> %, Mean (SD)	Total No. of Observations	No. of Unique Participants	HbA <sub>1c</sub> %, Mean (SD)
<b>Fasting Glucose, mg/dL</b>						
<80	482	429	5.6 (0.9)	46	40	5.4 (0.6)
80–89	2207	1683	5.5 (0.5)	167	130	5.3 (0.5)
90–99	2712	2073	5.7 (0.5)	243	183	5.5 (0.5)
100–109	1394	1154	6.0 (0.6)	120	105	5.6 (0.6)
110–119	513	460	6.3 (0.7)	58	53	5.9 (0.6)
120–129	268	241	6.8 (0.9)	22	20	6.4 (0.8)
130–139	165	154	7.0 (0.9)	9	9	6.6 (0.5)
140–149	128	124	7.4 (1.2)	11	11	6.9 (0.9)
150	473	379	9.3 (2.1)	44	33	8.5 (1.9)
Overall	8342	4253	6.0 (1.2)	720	367	5.7 (1.0)
<b>Two-Hour Glucose, mg/dL</b>						
<80	269	230	5.4 (0.4)	14	14	5.2 (0.3)
80–99	507	440	5.5 (0.4)	33	30	5.2 (0.3)
100–119	529	465	5.6 (0.4)	29	26	5.4 (0.3)
120–139	268	244	5.7 (0.5)	26	23	5.5 (0.2)
140–159	130	123	5.8 (0.5)	8	8	5.3 (0.3)
160–179	69	66	5.9 (0.5)	9	8	5.6 (0.4)

No SCT		SCT			
Total No. of Observations	No. of Unique Participants	HbA <sub>1c</sub> %, Mean (SD)	Total No. of Observations	No. of Unique Participants	HbA <sub>1c</sub> %, Mean (SD)
180–199	37	35 6.2 (0.5)	3	3	5.6 (0.5)
200	65	59 7.6 (2.4)	5	5	6.5 (1.5)
Overall	1874	1239 5.7 (0.7)	127	84	5.4 (0.5)

Abbreviations: HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; SCT, sickle cell trait.

SI conversion factor: to convert glucose from mg/dL to mmol/L, multiply by 0.0555.