Does Genetic Ancestry Explain Higher Values of Glycated Hemoglobin in African Americans?

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OBJECTIVE—Glycated hemoglobin (HbA1c) values are higher in African Americans than whites, raising the question of whether classification of diabetes status by HbA1c should differ for African Americans. We investigated the relative contribution of genetic ancestry and nongenetic factors to HbA1c values and the effect of genetic ancestry on diabetes classification by HbA1c in African Americans.

RESEARCH DESIGN AND METHODS—We performed a cross-sectional analysis of data from the community-based Atherosclerosis Risk in Communities (ARIC) Study. We estimated percentage of European genetic ancestry (PEA) for each of the 2,294 African Americans without known diabetes using 1,350 ancestry-informative markers. HbA1c was measured from whole-blood samples and categorized using American Diabetes Association diagnostic cut points (<5.7, 5.7–6.4, and ≥6.5%).

RESULTS—PEA was inversely correlated with HbA1c (adjusted \( r = -0.07; P < 0.001 \)) but explained <1% of its variance. Age and socioeconomic and metabolic factors, including fasting glucose, explained 13.8% of HbA1c variability. Eleven percent of participants were classified as having diabetes; adjustment for fasting glucose decreased this to 4.4%. Additional adjustment for PEA did not significantly reclassify diabetes status (net reclassification index = 0.034; \( P = 0.94 \)) nor did further adjustment for demographic, socioeconomic, and metabolic risk factors.

CONCLUSIONS—The relative contribution of demographic and metabolic factors far outweighs the contribution of genetic ancestry to HbA1c values in African Americans. Moreover, the impact of adjusting for genetic ancestry when classifying diabetes by HbA1c is minimal after taking into account fasting glucose levels, thus supporting the use of currently recommended HbA1c categories for diagnosis of diabetes in African Americans. Diabetes 60:2434–2438, 2011

Glycated hemoglobin (HbA1c) values are significantly higher in African Americans compared with whites even after adjustment for fasting blood glucose (1–4). Whether this racial difference in HbA1c reflects true differences in hyperglycemia or differences in biologic determinants of HbA1c unrelated to hyperglycemia is controversial (5–7), especially in the context of the American Diabetes Association recommendation to use HbA1c ≥6.5% for diagnosis of diabetes (8).

Self-reported African American race is associated with many socioeconomic factors that influence health (9), particularly diabetes risk (10). Genetically derived ancestry can be used to partially deconstruct race as it places each individual on a continuous spectrum of race as opposed to grouping all individuals into one racial group. Therefore, our main objective was to determine the contribution of genetic ancestry to HbA1c in self-reported African Americans. Genetic ancestry may be associated with HbA1c through direct biological effects unrelated to hyperglycemia or indirectly through social and demographic determinants of hyperglycemia (11,12). Because epidemiologic studies report higher HbA1c values in African Americans compared with whites independent of their fasting glucose (1–4), we examine the ancestral genetic contribution to HbA1c after accounting for fasting glucose levels. We hypothesized that 1) percentage of European ancestry (PEA) explains only a small proportion of the variability in HbA1c in African Americans; 2) PEA and HbA1c are associated with similar social and biologic factors; and 3) PEA does not significantly alter diabetes classification by HbA1c independent of fasting glucose levels.

RESEARCH DESIGN AND METHODS

Study population. We included 2,294 African American participants without known diabetes and with a complete set of covariates of interest presenting to visits 1 and 2 of the Atherosclerosis Risk in Communities (ARIC) Study, an ongoing prospective cohort study of adults from four U.S. communities who were 45–64 years of age at the baseline visit in 1987–1989 (13).

Estimation of percentage of European ancestry from ancestry-informative markers. We included single nucleotide polymorphisms (SNPs) whose frequencies differ significantly between Caucasian and African ancestral populations, ancestry-informative markers (AIMs), to estimate the PEA among African Americans, an admixed population (14). The race-specific frequency of each SNP in the AIM panel was estimated using West African and European samples to provide a Bayesian prior for ancestral allele frequencies (14).

Genotyping methods for estimating genetic ancestry in African Americans in the ARIC Study have been described previously (14). In brief, genotyping was performed on stored DNA from visit 1 using the Illumina BeadLab platform (15) at the Center for Inherited Disease Research (Johns Hopkins University). Evaluation of 218,461 blind duplicate genotypes yielded a mismatch rate of 0.1% (14). We used standard filters for quality control of individual SNP genotyping. Samples were excluded for duplicity, low call rate, lack of sex concordance, or excess heterozygosity. We used ANCESTRYMAP software to estimate PEA for each participant (14). Additional detail regarding study population and genotyping is provided in the Supplementary Data.
Measurement of glycated hemoglobin and other variables. HbA1c was measured from frozen, whole-blood samples from visit 2 using ion-exchange, high-performance liquid chromatography (Tosoh ALC 2.2 Plus Glycohemoglobin Analyzer in 2003–2004 and Tosoh G7 Instruments in 2005–2008; Tosoh Corp., San Francisco, CA). These methods are aligned to the Diabetes Control and Complications Trial assay (11). We classified participants according to guidelines from the American Diabetes Association for HbA1c: <5.7%, “lowest risk of diabetes (normoglycemia);” 5.7–6.4%, “increased risk for diabetes (pre-diabetes);” and ≥6.5%, “undiagnosed diabetes” (8).

Participants self-reported race, sex, education (<high school, high school, or >high school), combined family income (<$35,000, ≥$35,000, or unknown), employment (unemployed, employed, or retired), family history of diabetes, and physical activity (using the Baecke questionnaire [16]) at visit 1. Participants self-reported age, smoking status (current/former or never), and alcohol use (current or former/never) at visit 2.

Methods for measurement of glucose (11), lipids (17), BMI, waist-to-hip ratio (18), and blood pressure (19) at visit 2 were described previously. Hypertension was defined by current use of antihypertensive medication or mean of two blood pressure measurements ≥140/90 mmHg.

Statistical analysis. We evaluated for trends across quartiles of PEA using linear regression for means, Cuzick extension of Wilcoxon rank-sum (medians) (20), and Goodman and Kruskal γ for proportions (21). We used Spearman rank correlation coefficients to evaluate unadjusted linear relationships and partial τ (ranked partial correlation coefficient) to estimate adjusted correlations (22). We estimated variance in HbA1c explained by each variable from the square of these correlation coefficients.

For the analyses that examined the impact of covariates, including PEA and fasting glucose, on reclassification of diabetes status, we obtained the adjusted values of HbA1c, from several regression models. In Model 1, HbA1c was adjusted for fasting glucose, representing the variation in HbA1c in the population that is independent of hyperglycemia. Model 2 further adjusted for PEA (Model 1 + PEA); Model 3 further adjusted for demographic and socioeconomic factors (Model 2 + age, sex, site, education, income, and employment); and Model 4 included other metabolic risk factors (Model 3 + BMI, waist-to-hip ratio, hypertension status, LDL and HDL cholesterol, triglycerides, family history of diabetes, alcohol use, physical activity, and smoking status). Using the predicted (adjusted) HbA1c values from each model, we obtained the proportion of participants classified into the three HbA1c categories. The base, unadjusted model indicates the classification of diabetes status using measured HbA1c; Model 1 accounts for fasting glucose measured at the same visit; and Model 2 displays the effect of genetic ancestry (PEA) on diabetes status independent of fasting glucose. Recognizing that Model 1 is not directly relevant to clinical practice (as is often the case), as clinicians do not adjust for variables such as fasting glucose in the interpretation of other measures, we use Model 1 to estimate the proportion of variation in HbA1c that is independent of fasting glucose levels and to illustrate whether genetic ancestry can still contribute to HbA1c independent of fasting glucose levels.

We calculated the percentage of participants reclassified for each category as (Ni − N0)N0, where N0 is the number of participants in a given HbA1c category for fasting glucose-adjusted HbA1c (Model 1) and Ni is the number of participants in a given HbA1c category for the jth model (Models 2, 3, or 4). We then compared classification into and out of each of the three categories of diabetes status between the nested models. Models 2 (HbA1c adjusted for fasting glucose and PEA) and 1 (HbA1c adjusted for fasting glucose), with unadjusted (measured) HbA1c, as a reference (23): \[ r_j = \sum [n_{jk} + n_{kj} - n_{jk} - n_{kj}] \]

(\( i = \) number shifted into a given category, \( j = \) number shifted out of the category, \( k = \) number, \( N_0 = \) number in category from reference model, and \( l = \) HbA1cl category). We then calculated the overall net reclassification index: \[ P = \sum_{i,j} r_j \]

We used Stata version 11.1 (StataCorp LP, College Station, TX) for statistical analyses. Institutional review boards approved the study protocol at each study site, and written informed consent was obtained from each participant.

RESULTS

Population characteristics. PEA was right-skewed with a median (interquartile range [IQR]) of 14% (8–22) (Supplementary Fig. 1). Participants with lower PEA were more likely to have less than a high school education and were more likely to have an annual combined family income <$35,000 (Table 1). Median HbA1c and mean BMI were higher in lower quartiles of PEA, and the prevalence of hypertension was highest in the lowest quartile of PEA (Table 1). HbA1c was significantly and positively associated with age, family history of diabetes, prevalence of hypertension, BMI, glucose, LDL cholesterol, and triglycerides and inversely associated with education, income, HDL cholesterol, and current alcohol use (results not shown).

Contribution of PEA to HbA1c. PEA was significantly correlated with HbA1c but explained only 0.5% of the variance in HbA1c on adjusted analyses (Table 2). On the other hand, a single fasting glucose explained the largest fraction of variance in HbA1c (10%). Fasting glucose and PEA were not significantly correlated (\( r = 0.01; P = 0.63 \)). Contribution of PEA to classification of diabetes status by recommended HbA1c categories. Two hundred forty-four participants (11%) had diabetes defined by

TABLE 1

| Characteristics of African American participants without diabetes in the ARIC Study by quartile of percentage of European ancestry (N = 2,294) |
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Q1                      | Q2                      | Q3                      | Q4                      | P trend*                |
| Percentage of European ancestry | 5.2 (3.1–6.5) | 10.9 (9.4–12.3) | 17.4 (15.4–19.7) | 30.4 (25.9–38.1) | 0.001 |
| Age (years)             | 56 (6)                  | 56 (5)                  | 56 (6)                  | 57 (6)                  | 0.045 |
| Women                   | 380 (66)                | 365 (63)                | 363 (64)                | 362 (63)                | 0.385 |
| <High school education  | 418 (73)                | 404 (70)                | 385 (68)                | 288 (50)                | <0.001 |
| Unemployed              | 18 (3)                  | 19 (3)                  | 15 (3)                  | 19 (3)                  | 0.981 |
| Family income <$35,000  | 451 (78)                | 429 (74)                | 419 (74)                | 367 (64)                | <0.001 |
| Family history of diabetes | 137 (24)              | 153 (27)                | 146 (26)                | 131 (23)                | 0.654 |
| Hypertension            | 330 (57)                | 305 (53)                | 311 (55)                | 279 (49)                | 0.010 |
| BMI (kg/m²)             | 30.3 (6.6)              | 30.2 (6.3)              | 30.0 (6.3)              | 28.5 (5.6)              | <0.001 |
| Waist-to-hip ratio      | 0.91 (0.08)             | 0.91 (0.08)             | 0.91 (0.07)             | 0.91 (0.08)             | 0.320 |
| HbA1c (%)               | 5.8 (5.4–6.1)           | 5.8 (5.5–6.1)           | 5.7 (5.4–6.0)           | 5.6 (5.3–6.0)           | <0.001 |
| Fasting glucose (mmol/L)| 5.98 (1.07)             | 6.21 (1.87)             | 6.10 (1.49)             | 6.06 (1.49)             | 0.582 |
| LDL cholesterol (mmol/L)| 3.45 (0.98)             | 3.35 (0.88)             | 3.50 (0.98)             | 3.46 (0.98)             | 0.323 |
| HDL cholesterol (mmol/L)| 1.40 (0.43)             | 1.38 (0.44)             | 1.38 (0.42)             | 1.35 (0.42)             | 0.040 |
| Triglycerides (mmol/L)  | 1.15 (0.59)             | 1.16 (0.59)             | 1.18 (0.54)             | 1.24 (0.62)             | 0.011 |
| Current/former smoking | 280 (49)                | 331 (57)                | 303 (53)                | 338 (59)                | 0.003 |
| Current alcohol use     | 173 (30)                | 207 (36)                | 195 (34)                | 244 (43)                | <0.001 |

Characteristics presented as mean (SD) or median (IQR) for continuous variables and n (%) for categorical variables. *P trend across quartiles estimated using linear regression (means), Cuzick extension of Wilcoxon rank-sum (medians) (20), and Goodman and Kruskal γ (proportions) (21). †Income was unknown for n = 52, 60, 67, and 64 for quartiles 1, 2, 3, and 4, respectively.
HbA$_{1c}$ $\approx$ 6.5%. Accounting for fasting glucose (Model 1) shifted higher HbA$_{1c}$ values downward and lower HbA$_{1c}$ values upward. Consequently, diabetes prevalence decreased to 4.4%, and the prevalence of prediabetes and normal HbA$_{1c}$ increased (Table 3 and Supplementary Fig. 2). Further adjustment for PEA (Model 2) did not reclassify diabetes status substantially (Table 3 and Fig. 1). Normal HbA$_{1c}$ status and prediabetes status changed negligibly with net reclassification of $-$1% ($P$ = 0.21) and $-$4% ($P$ < 0.001), respectively, and there was no net reclassification of diabetes status. Taking these individual category-level changes into account, the overall classification of normal HbA$_{1c}$, prediabetes, and diabetes status did not change with adjustment of fasting glucose–adjusted HbA$_{1c}$ for PEA (net reclassification index 0.034; $P$ = 0.94). Additional adjustment for demographic and socioeconomic factors (Model 3) and traditional metabolic risk factors (Model 4) did not substantially affect reclassification (Table 3 and Fig. 1).

**DISCUSSION**

In our study, we show that there is not a substantial (<1%) contribution of genetic ancestry to HbA$_{1c}$ among African Americans; thus, ancestral genetic differences are unlikely to significantly explain the observed black–white difference in HbA$_{1c}$. Furthermore, a recent admixture scan failed to identify an HbA$_{1c}$ locus among African Americans (C.-Y.C., N.M.M., personal communication), suggesting the absence of a genetic variant that varies enough in frequency between whites and African Americans (i.e., a variant of African ancestral origin) to explain the observed racial disparity in HbA$_{1c}$ values.

The hypothesis that HbA$_{1c}$ values are higher among African Americans for reasons unrelated to hyperglycemia stems from evidence that HbA$_{1c}$ values are higher in African Americans when adjusted for fasting glucose and/or post-load glucose measurements (1–4). However, HbA$_{1c}$ reflects average glucose over 2–3 months (24) and may reflect racial disparities in socioeconomic and biologic factors. In our study, we show that hyperglycemia, as indicated by a fasting glucose value, accounts for the largest proportion of HbA$_{1c}$, and that adjustment for fasting glucose results in substantial reclassification of diabetes status. Moreover, after accounting for fasting glucose, additional adjustment for PEA does not significantly reclassify diabetes status.

**Strengths.** We used a large number of AIMs (1,350) to estimate PEA in an admixed population well described by AIMs, thus enhancing our ability to accurately assign percentage of genetic ancestry. Nonetheless, in this African American population, PEA was skewed toward lower values; the contribution of PEA to HbA$_{1c}$ might be further clarified in a population with a more uniform distribution of PEA.

**Limitations.** To evaluate the effect of PEA on classification of diabetes status by HbA$_{1c}$ independent of fasting glucose, we adjust HbA$_{1c}$ for fasting glucose. While not relevant to clinical practice, our approach directly addresses questions surrounding the interpretation of higher HbA$_{1c}$ values in African Americans as representing hyperglycemia because of observed racial differences in HbA$_{1c}$ even after glucose adjustment (6,7).

By estimating the global percentage of European ancestry for each individual, we may overlook local ancestry that could explain the observed racial differences in HbA$_{1c}$. A recent admixture scan to evaluate for specific regions that associate with HbA$_{1c}$ did not reveal a locus in African Americans (C.-Y.C., N.M.M., personal communication).

**Conclusions.** In this large community-based population of African Americans, PEA was associated with, but explained

**TABLE 2**

Percentage of variance in HbA$_{1c}$ explained by percentage of European ancestry, demographic, socioeconomic status, and traditional diabetes and cardiovascular disease risk factors

| Unadjusted (%) | Adjusted (%)* |
|----------------|---------------|
| Fasting glucose | 24.4 | 10 |
| BMI             | 6.6  | 1.0  |
| Triglycerides   | 5.0  | 0.9  |
| Age             | 1.8  | 0.6  |
| Percentage of European ancestry | 1.2† | 0.5‡ |
| Alcohol use§    | 0.9  | 0.4  |
| Education¶     | 1.7  | 0.3  |
| Hypertension‖   | 1.6  | 0.1  |
| Family history of diabetes | 0.2  | 0.0  |

*Adjusted percentage of variance is the square of the partial correlation coefficient obtained from a model including the other variables listed in table. †$r = -0.11$ ($P < 0.001$). ‡$r = -0.07$ ($P < 0.001$). §Alcohol use classified as current or former/never. ¶Education classified as < high school, high school, high school, ≥college education. ‖Measured blood pressure $\geq140/90$ mmHg or report of antihypertensive medication use.

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**TABLE 3**

Reclassification of diabetes status* upon adjustment for fasting glucose, percentage of European ancestry, demographic, socioeconomic status, and traditional diabetes and cardiovascular disease risk factors ($N$ = 2,294)

|                | Diabetes | Prediabetes | Normal | Adjustments                           |
|----------------|----------|-------------|--------|---------------------------------------|
| Measured HbA$_{1c}$ | 244 (10.6) | 824 (35.9)  | 1,226 (53.4) | None                   |
| Adjusted HbA$_{1c}$ |          |             |        |                                       |
| Model 1         | 102 (4.4)  | 883 (38.5)  | 1,309 (57.1) | Fasting glucose           |
| Model 2         | 104 (4.5)  | 940 (41.0)  | 1,250 (54.5) | Fasting glucose, PEA      |
| Model 3         | 113 (4.9)  | 917 (40.0)  | 1,264 (55.1) | Fasting glucose, PEA, age, sex, site, SES†, BMI, WHR, hypertension‡, LDL and HDL cholesterol, triglycerides, family history of diabetes, physical activity§, alcohol use||
| Model 4         | 115 (5.0)  | 955 (41.6)  | 1,224 (53.4) | Fasting glucose, PEA, age, sex, site, SES‡, BMI, WHR, hypertension§, LDL and HDL cholesterol, triglycerides, family history of diabetes, physical activity, alcohol use||

*SES, socioeconomic status; WHR, waist-to-hip ratio. †Diabetes, HbA$_{1c}$ $\approx$ 6.5% prediabetes, HbA$_{1c}$ 5.7–6.4% normal, HbA$_{1c}$ <5.7%. ‡Employment (unemployed, employed, or retired), income (combined family income <$35,000, ≥$35,000, or unknown), and education (<high school, high school, or ≥college education). §Measured blood pressure $\geq140/90$ mmHg or report of antihypertensive medication use. ¶Leisure sport activity assessed with the Baecke questionnaire (16). ‖Alcohol use classified as current or former/never. ‡Smoking classified as current/former or never.
FIG. 1. Percent reclassification of diabetes status relative to fasting glucose–adjusted HbA1c. Percentage of participants reclassified by HbA1c as having normal HbA1c (<5.7%), prediabetes (5.7–6.4%), or diabetes (≥6.5%). Model 1 is the reference model. Bars for Models 2, 3, and 4 represent percentages of participants reclassified into each diabetes category based on predicted HbA1c. Black bars, normal; white bars, prediabetes; hatch-marked bars, diabetes. Numbers above/below bars represent percentages of participants shifted into or out of a given category. Model 1, adjustment for fasting glucose; Model 2, additional adjustment for percentage of European ancestry; Model 3, additional adjustment for age, sex, site, employment (unemployed, employed, or retired), combined family income (< or ≥$35,000), and education (≤high school, high school, or college education); and Model 4, additional adjustment for BMI, waist-to-hip ratio, hypertension status (measured blood pressure ≥140/90 or report of antihypertensive medication use), LDL and HDL cholesterol, triglycerides, family history of diabetes, physical activity (assessed with the Baecke questionnaire [16]), alcohol use (current or former/never), and smoking (current/former or never).

Our results suggest that elevated HbA1c values in African Americans are likely not determined by ancestral genetic differences in the biology of HbA1c but instead may reflect a true disparity in glycemia likely mediated by socioeconomic and other downstream factors. These findings support the use of the currently recommended HbA1c categories for diagnosis of diabetes and classification of future diabetes risk [8] in African Americans. Consistent with this, previous studies have demonstrated that HbA1c is equally predictive of cardiovascular disease and all-cause mortality in African Americans and whites [11]. Future research should address the environmental reasons for disparities by PEA among African Americans and focus on methods to eliminate these disparities.

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N.M.M. refined the study design, analyzed data, and wrote the manuscript. W.H.L.K. refined the study design and reviewed and edited the manuscript. J.M.C. and F.L.B. reviewed and edited the manuscript. C.Y.C. analyzed data and reviewed the manuscript. J.S.P. reviewed and edited the manuscript. E.S. refined the study design and reviewed and edited the manuscript.

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