

Research Article

Blood Vitamin D Levels in Relation to Genetic Estimation of African Ancestry

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Abstract

Background: African-Americans generally have lower circulating levels of 25 hydroxyvitamin D [25(OH)D] than Whites, attributed to skin pigmentation and dietary habits. Little is known about the genetic determinants of 25(OH)D levels nor whether the degree of African ancestry associates with circulating 25(OH)D.

Methods: With the use of a panel of 276 ancestry informative genetic markers, we estimated African and European admixture for a sample of 758 African-American and non-Hispanic White Southern Community Cohort Study participants. For African-Americans, cut points of <85%, 85% to 95%, and ≥95% defined low, medium, and high African ancestry, respectively. We estimated the association between African ancestry and 25(OH)D and also explored whether vitamin D exposure (sunlight, diet) had varying effects on 25(OH)D levels dependent on ancestry level.

Results: The mean serum 25(OH)D levels among Whites and among African-Americans of low, medium, and high African ancestry were 27.2, 19.5, 18.3, and 16.5 ng/mL, respectively. Serum 25(OH)D was estimated to decrease by 1.0 to 1.1 ng/mL per 10% increase in African ancestry. The effect of high vitamin D exposure from sunlight and diet was 46% lower among African-Americans with high African ancestry than among those with low/medium ancestry.

Conclusions: We found novel evidence that the level of African ancestry may play a role in clinical vitamin D status.

Impact: This is the first study to describe how 25(OH)D levels vary in relation to genetic estimation of African ancestry. Further study is warranted to replicate these findings and uncover the potential pathways involved. *Cancer Epidemiol Biomarkers Prev*; 19(9); 2325–31. ©2010 AACR.

Introduction

It is well documented that circulating levels of 25 hydroxyvitamin D [25(OH)D, the established clinical marker of vitamin D status] are lower among African-Americans than Whites in the United States (1). This is mediated largely by skin color because melanin blocks the initial conversion of 7-dehydrocholesterol to cholecalciferol, the precursor of 25(OH)D, in the skin (1, 2). Other

possible contributors to the racial difference include diet because African-Americans tend to have diets lower in vitamin D and are less likely to take vitamin supplements (3). As vitamin D insufficiency is increasingly linked to a variety of chronic diseases, including cancer (1), this hormone is under scrutiny as a potential contributor to racial health disparities (3-5).

The extent to which racial differences in 25(OH)D levels are influenced by genetic variation tied to African ancestry is unknown. Evidence for a link between genetic markers of African ancestry and 25(OH)D levels might provide clues to investigate genetic determinants for vitamin D insufficiency, which could have implications for intervention strategies to ameliorate vitamin D insufficiency among African-Americans and possibly other groups. There is significant variation in the level of African ancestry among African-Americans, and this can now be estimated in fairly precise and quantitative terms (6-9). We therefore undertook a study to investigate the association between African ancestry and 25(OH)D levels within the Southern Community Cohort Study (SCCS), in which we have previously shown evidence of striking racial disparities in 25(OH)D levels based on self-reported race (4).

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Materials and Methods

Study population

The SCCS is a prospective cohort study of cancer risk disparities related to race, socioeconomic status, and other factors (10). Men and women ages 40 to 79 years were recruited in-person at community health centers and also by mail across 12 southeastern U.S. states between 2002 and 2009 (11). With ~86,000 participants enrolled, African-Americans comprise two thirds of the cohort. From SCCS participants who enrolled from March 2002 to October 2004 and donated a baseline blood sample ($N = 12,162$), 792 were randomly selected with the use of a $2 \times 2 \times 3 \times 3$ factorial design, with 22 individuals selected within each of the 36 strata defined by self-reported race (African-American/White), sex, smoking status (current/former/never), and body mass index (18-24.99 kg/m², 25-29.99 kg/m², 30-45 kg/m²). This design provided a balanced distribution across these factors in consideration of other blood biomarkers being measured in addition to vitamin D.

SCCS participants provided written informed consent, and protocols were approved by the Institutional Review Boards at Vanderbilt University and Meharry Medical College.

Baseline data and blood collection

Baseline information was collected with the use of a computer-assisted, in-person interview conducted at the time of enrollment. The interview covered demographics, health history, anthropometrics, and a wide range of potential cancer risk factors (questionnaire available at SCCS website; ref. 11). Dietary information was collected with the use of a validated food frequency questionnaire including foods, beverages, and nutritional supplements developed specifically for the SCCS (12). Race was self-reported by participants with use of a printed card and instructions to choose all racial/ethnic descriptors that applied. Venous blood samples (20 mL) were collected during the baseline interview within the community health center, kept refrigerated, and shipped cold overnight to Vanderbilt University, where they were centrifuged the next day and stored at -80°C to await analysis.

Measurement of 25(OH)D

Blinded serum 25(OH)D measurements were done in the laboratory of Dr. Bruce Hollis at the Medical University of South Carolina with the use of a radioimmunoassay method associated with high intra-assay reliability (13). One half of the samples was assayed in 2005 (median of 1.6 years after collection and previously thawed once) and the second half assayed in the same laboratory with the use of the same methods in 2009 (median of 5.5 years after collection and previously thawed once). Measured 25(OH)D is not known to be affected by storage times as long as 14 years nor by up to 10 freeze-thaw

cycles.⁷ A comparison of vitamin D levels from the first and second assay batches indicated no systematic differences that would prevent the data from the two groups being combined. The average 25(OH)D values for self-reported African-American subjects in batch 1 and batch 2 were 17.3 and 17.6 ng/mL, respectively, and were 27.2 and 27.2 ng/mL, respectively, for self-reported White subjects. A set of quintuplet identical samples was also included in each batch, 4 years apart, and their average measurement was the same in each batch: 13.2 ng/mL. The coefficients of variation on duplicate, blinded quality control samples in batches 1 and 2 were 6.7% and 7.4%, respectively.

Measures of vitamin D exposure

Dietary intake of vitamin D was estimated from the reported intake of the major dietary sources in the SCCS food frequency questionnaire: milk, cold cereal, tuna, eggs, multivitamins, and calcium supplements. Individual measures of sun exposure were not obtained. As a surrogate, we used ground UV radiation measurements from the National Oceanic and Atmospheric Administration UV station geographically closest to the subject's residence as an estimate of ambient UV radiation exposure (14). These UV radiation measurements are converted to an index that estimates the erythral intensity, with scores ranging from 0 (none) to 11+ (extreme). We used the average of the UV radiation scores recorded at the monitoring station during the 3-month period preceding each participant's enrollment in the study.

Genetic analysis and ancestry estimation

Genomic DNA was extracted from buffy coat with the use of Qiagen DNA Purification kits according to the manufacturer's instructions, and genotyping was carried out with the use of the Illumina GoldenGate genotyping platform (Illumina Inc.). Laboratory personnel were blinded to information about the status of the samples. Blinded quality control samples ($N = 29$) and another 171 pairs of duplicate samples were included, and the consistency rate was 99.9%.

We sought to construct a list of 300 ancestry informative markers (AIM) from two sources, the first being a list of 360 single nucleotide polymorphisms (SNP) we developed from comparing frequencies between individuals of European and African descent in HapMap with the use of χ^2 values to rank the markers, and the second being a list of 1,509 AIM SNPs from an Illumina-designed panel for ancestry estimation, giving a total of 1,865 potential AIMs (after excluding duplicates). Because initial genotyping efforts for this project were designed for a sample of females, AIMs on the Y chromosome as well as those with an Illumina-designed score ≤ 0.5 were excluded ($N = 1,826$ SNPs remaining). In addition, all potential AIMs

⁷ B. Hollis, personal communication.

within 40 candidate genes of interest (available upon request, and related to SCCS projects on obesity and cancer) or their 5-Mb flanking regions were excluded ($N = 635$ SNPs remaining). Potential AIMs were also excluded if they had a minor allele frequency of <0.05 in both the European and African populations in HapMap ($N = 367$ SNPs remaining). Finally, 300 of the remaining 367 potential AIMs were selected as the final set based on the highest allele frequency differences between the European and African populations in HapMap. Of these 300 AIMs, 292 passed the Illumina scoring algorithm and were sent for genotyping. Of the 292 AIMs, 276 were successfully genotyped with call rates $>95\%$, and were used to estimate African and European ancestry (see Supplementary Material for a list of the 276 SNPs).

Estimates of African and European ancestry were computed through a Bayesian clustering approach implemented with the use of STRUCTURE software version 2.2.3 (15, 16). STRUCTURE identifies groups of individuals with similar allele frequency profiles and estimates the shared ancestry of individuals based solely on their genotypes under an assumption of Hardy-Weinberg equilibrium and linkage equilibrium in ancestral populations. It identifies the number (K) of ancestry population clusters ($K = 2$ in this study) and assigns individuals admixture estimates for each, with the estimates summing to 1 across these clusters. An admixture estimate (from 0.00 to 1.00) for both African ancestry and European ancestry was thus generated for each participant.

Statistical methods

Of the 792 subjects selected for this study, 34 (4.3%) were excluded because either 25(OH)D or African/European ancestry could not be estimated, or because ancestry estimates were highly discordant with self-reported race, implying potential data entry errors. This left 758 subjects (379 African-Americans, 379 White) for analysis.

Ancestry estimates were used as continuous variables, and linear regression models were used to associate African ancestry (independent variable) with serum 25(OH)D levels (dependent variable). The distribution of serum 25(OH)D was approximately normal, so the values were included in the model untransformed. The ancestry variable was also categorized as White, and as low, medium, and high African ancestry with the use of predetermined arbitrary cut points of $<85\%$, 85% to 95% , and $\geq 95\%$ African ancestry, respectively. The use of alternate cut points (i.e., tertiles) resulted in the same overall findings. The linear regression models evaluating the association between ancestry and 25(OH)D were adjusted for vitamin D intake (IU from food and supplements, continuous), sunlight exposure (UV radiation score, continuous), body mass index (continuous), current cigarette smoking (yes/no), education (less than high school versus not), alcohol drinking (average number of drinks per day, continuous), and current employment (yes/no). Season of blood collection was not used as a

covariate because it was nearly interchangeable, and highly collinear, with UV radiation score, and we chose to use UV radiation score because it reflected both the time of year and the general geographical location of the participant.

To evaluate the influence of environmental exposures (sunlight and diet) on circulating 25(OH)D levels for African-Americans of varying admixture, we defined high exposure as having a UV radiation score above the median and a dietary intake >400 IU/d (current recommended daily intake), medium exposure as a UV radiation score above the median and a dietary intake ≤ 400 IU/d, and low exposure as those with a UV radiation score below the median. In this categorization, sunlight exposure was given dominance over dietary intake given its greater effect on circulating vitamin D. We also evaluated effect modification by ancestry with the use of regression models for African-Americans containing interaction terms for African ancestry \times UV radiation score and African ancestry \times dietary vitamin D intake, with the use of the covariates in their continuous form.

Results

African admixture in our self-reported White participants ranged from 0.001 to 0.171 (mean, 0.009), and in our self-reported African-American participants from 0.505 to 0.999 (mean, 0.929). Table 1 shows the distribution of the African-American participants across the defined African ancestry categories (16% were classified as low, 28% as medium, and 56% as high). SCCS methods of enrolling African-Americans and Whites from the same community health centers year-round resulted in only minor differences in residential UV radiation scores and season of enrollment by race. Among African-Americans, neither UV radiation score nor dietary vitamin D intake was significantly associated with ancestry level, diminishing their ability to confound the relationship between ancestry and circulating 25(OH)D. The mean UV radiation scores were 5.5, 5.2, and 5.2, and the mean vitamin D intake values were 208, 219, and 220 IU/d for African-Americans of low, medium, and high African admixture, respectively.

Average 25(OH)D levels decreased monotonically across categories of increasing African ancestry (Fig. 1). In adjusted models making use of the entire population as well as African-Americans only, we found a significant 1.0 to 1.1 ng/mL decrease in 25(OH)D per 10% increase in African admixture (Table 2). In the fully adjusted model making use of the entire population, the r^2 value increased from 0.16 to 0.35 with the addition of the ancestry variable, which would be expected given the ability of skin color differences between African-Americans and Whites to explain a good part of the variance in serum 25(OH)D. However, in models making use of African-Americans only, the r^2 value increased only slightly from 0.21 to 0.22 with the addition of the ancestry variable despite the significant effect of ancestry noted in the model. In Whites, the range of African admixture was too limited

Table 1. Ancestry estimation and other characteristics of 758 SCCS participants

Characteristic	African-American (N = 379)	White (N = 379)
No. of females/males	187/192	187/192
Median (IQR) percentage African ancestry	0.971 (0.887-0.997)	0.004 (0.003-0.009)
Median (IQR) percentage European ancestry	0.029 (0.003-0.113)	0.996 (0.991-0.997)
Ancestry categories		
White/European	0	379 (100%)
African - low (<85%)	60 (16%)	0
African - medium (85%-94.99%)	106 (28%)	0
African - high (≥95%)	213 (56%)	0
Mean (SD) serum 25(OH)D levels, ng/mL	17.5 (8.6)	27.2 (11.1)
Mean (SD) age, y	51.9 (9.0)	54.1 (9.5)
Mean (SD) body mass index,* kg/m ²	28.3 (5.6)	28.4 (5.8)
Mean (SD) daily dietary intake of vitamin D,† IU	218 (213)	269 (236)
Mean (SD) residential UV radiation score	5.2 (1.9)	5.2 (2.0)
Season of enrollment‡		
% In winter	17%	22%
% In spring	30%	27%
% In summer	25%	26%
% In fall	28%	25%
% Current smoker*	34%	34%
% Currently working	41%	34%
% With less than high school education	35%	27%

Abbreviations: IQR, interquartile range.

*Selection/matching factor.

†From food sources, and multivitamin and calcium supplement sources.

‡Winter: December to February; spring: March to May; summer: June to August; fall: September to November.

to reliably estimate the change in 25(OH)D per unit of African ancestry.

Among African-Americans, both diet and UV radiation score were significant predictors of 25(OH)D: 2.1 ng/mL increase per 200 IU of intake ($P < 0.001$) and 1.6 ng/mL increase per 1 UV radiation score ($P < 0.001$). Having defined high, medium, and low environmental exposure (sunlight and diet; see Materials and Methods) to vitamin D, linear regression models were used to examine the influence of environmental exposure on circulating 25(OH)D among African-Americans of varying admixture (Fig. 2). Those with low and medium African admixture were combined into one group because the results for the two groups were similar. For each defined ancestry group, we observed the expected overall effect of serum 25(OH)D increasing with increasing environmental exposure. However, the effect diminished as African ancestry increased. Whereas high vitamin D exposure was associated with a serum 25(OH)D increase of 10.5 ng/mL for participants with low/medium African ancestry, it was associated with an increase only about half as high (5.7 ng/mL) for those with high African ancestry. This interaction between environmental exposures and African ancestry, however, did not reach statistical significance ($P = 0.39$ in a likelihood ratio test to compare models with

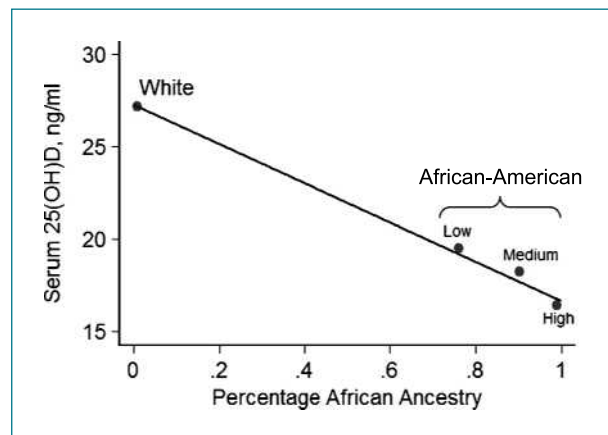


Figure 1. Plot of the average serum level of 25(OH)D (y-axis) in relation to genetic estimation of African ancestry (x-axis). Points represent the average African ancestry estimate and the average 25(OH)D level for each predetermined category of subjects (White, and low, medium, and high African ancestry). Superimposed is the predicted line from a univariate linear regression model with African admixture (continuous) as the independent variable and the 25(OH)D level (continuous) as the dependent variable. Mean (SE) 25(OH)D levels were 27.2 (0.6) ng/mL for Whites, and 19.5 (1.3), 18.3 (0.8), and 16.5 (0.6) ng/mL for African-Americans of low, medium, and high African ancestry, respectively.

Table 2. Linear regression–derived effect of African ancestry on circulating levels of 25(OH)D

African ancestry	Model including both African-Americans and Whites				Model including African-Americans only			
	Crude change in 25(OH)D		Adjusted change in 25(OH)D*		Crude change in 25(OH)D		Adjusted change in 25(OH)D*	
	β^\dagger	<i>P</i>	β^\dagger	<i>P</i>	β^\dagger	<i>P</i>	β^\dagger	<i>P</i>
Continuous measure of African ancestry (per 0.10 increase in African ancestry)	-1.1	<0.001	-1.1	<0.001	-1.5	0.002	-1.0	0.03

*From a linear regression model adjusted for age at enrollment (continuous), sex, average daily dietary intake of vitamin D (continuous), mean residential UV radiation score (continuous), body mass index (continuous), currently employed (yes/no), current smoker (yes/no), number of alcoholic drinks per day (continuous), and education (less than high school versus not).

†Parameter estimate from linear regression model, interpreted as the average change in serum 25(OH)D level (ng/mL) associated with a 10% increase in African admixture.

and without both interaction terms, $P = 0.19$ for the model containing only the UV radiation interaction term, and $P = 0.59$ for the model containing only the dietary interaction term).

Discussion

To our knowledge, this is the first study to describe how circulating 25(OH)D levels vary in relation to genetic estimation of African ancestry. We observed the expected difference in serum 25(OH)D between African-Americans and Whites. However, our findings also showed, within African-Americans, an inverse relationship between African ancestry and 25(OH)D. Furthermore, among African-Americans, vitamin D exposures had lesser effects on circulating 25(OH)D for those with higher African ancestry.

Little is known about the genetic determinants of 25(OH)D levels (17). For environmental determinants, previous studies consistently show factors related to sunlight (e.g., ambient UV radiation, season, time spent outdoors, latitude, leisure time physical activity), diet, and other subject characteristics (e.g., age, adiposity, self-reported race, smoking, alcohol drinking) to account for no more than ~20% to 40% of the variability in circulating 25(OH)D (4, 18-23). Whereas error in measuring these external factors decreases the ability to fully explain 25(OH)D variability, it is also reasonable to assume that genetic factors are at play. For example, a recent report by Fu et al. (21) found 34% of the variability in circulating 25(OH)D to be explained by a multivariate model including environmental and genetic factors, and a common vitamin D binding protein gene SNP was the second most explanatory factor, explaining 8.5% of the variance. This is among several studies that now show vitamin D binding protein SNPs (which have interethnic differences in

allele frequency) to be associated with 25(OH)D levels (20, 21, 23, 24). The mechanism for this genetic association is unclear but could involve changes to vitamin D binding protein levels or to the half-life of 25(OH)D (23). It has also been known for some time that there is

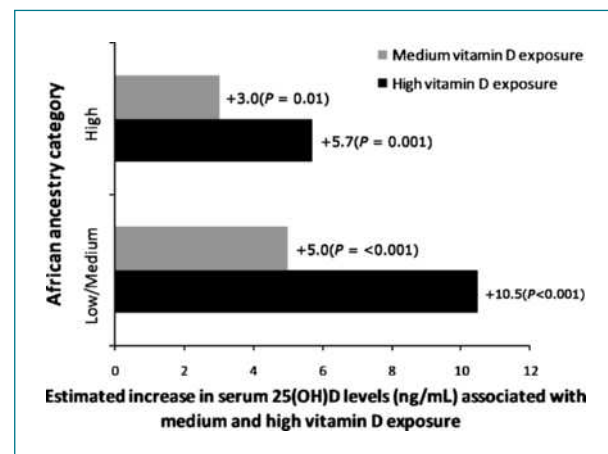


Figure 2. Effect of environmental vitamin D exposure (sunlight and diet) on serum 25(OH)D levels among African-Americans based on African ancestry category (grouped as low/medium and high). African ancestry of <85% was defined as low, 85% to 95% as medium, and $\geq 95\%$ as high. Increases were estimated from a linear regression model adjusted for age, gender, and body mass index, and are relative to low vitamin D exposure. High vitamin D exposure was defined as a UV radiation score above the median and dietary intake of >400 IU/d, medium exposure as a UV radiation score above the median and dietary intake of ≤ 400 IU/d, and low exposure as UV radiation score below the median. Among those with low/medium African ancestry, the mean UV radiation scores and dietary intakes for the reference, medium, and high exposure were 3.7 and 224, 6.9 and 93, and 6.9 and 526 IU, respectively. Among those with high African ancestry, the mean UV radiation scores and dietary intakes for the reference, medium, and high exposure were 3.5 and 226, 6.9 and 96, and 6.6 and 560 IU, respectively.

substantial ethnic variation in the vitamin D receptor gene (25), but the association between vitamin D receptor genotypes and circulating 25(OH)D levels is equivocal (20, 26). Further investigation of vitamin D pathway genes and their association with both African admixture and 25(OH)D levels may shed light on our findings.

It is unknown whether our findings reflect differences beyond skin color gradations along the spectrum of African ancestry because skin pigmentation was not measured during the SCCS baseline interview. Others have reported a correlation between African admixture and measured skin pigmentation among African-Americans (8, 27). Thus, it is possible that the observed association between African ancestry and vitamin D level is mediated through skin shade. However, with few exceptions (i.e., a newly identified candidate gene, *GNG2*; ref. 28), the AIM SNPs used in our analysis to assign African admixture were not on genes currently thought to affect skin pigmentation (8, 28, 29).

Limited research has addressed whether African-Americans and Whites may have inherently different capability to either synthesize (from UV radiation) or to absorb (from diet) vitamin D (30). Skin pigmentation has been an obvious focus of study, although the literature suggests that the interference of melanin in vitamin D synthesis is not insurmountable with sustained and controlled, and typically extended, UV radiation exposure (31-33). One small clinical study found similar serologic response to an oral challenge of ergocalciferol (vitamin D₂) in African-Americans and Whites (2). Still, in such studies, postintervention 25(OH)D levels remained substantially lower in African-Americans compared with Whites (2, 31).

We found that White SCCS participants had very little African admixture, and African-American SCCS participants had among the highest proportion of African ancestry reported from various U.S. studies (6-9, 34). A consequence of these participant characteristics is that we had limited data to describe the association between

African ancestry and 25(OH)D for a wide range of intermediate ancestry levels. Thus, the relationship between ancestry level and 25(OH)D may be more complex than what is shown in Fig. 2, which relies on points clustered near 0 and 1. Because of the generally high African admixture among African-American SCCS participants, we find it all the more intriguing that we detected significant variation in circulating 25(OH)D within this admixture range.

In summary, this study provides novel evidence that the level of African admixture, even among African-Americans, is associated with clinical vitamin D status. Further study is warranted to replicate these findings and uncover the potential pathways involved.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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