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RELATIONSHIP BETWEEN HBA1C AND CIRCULATING 25-HYDROXYVITAMIN D CONCENTRATION IN AFRICAN AMERICAN AND CAUCASIAN AMERICAN MEN

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Abstract

Objectives—To examine whether (1) serum 25-hydroxy-vitamin D level (25[OH]D) is a risk factor for hyperglycemia, as assessed by glycated hemoglobin (HbA1c), in African American men (AAM) and (2) 25(OH)D is a predictor of HbA1c in AAM and Caucasian American men (CAM).

Methods—We prospectively assessed 25(OH)D and HbA1c in 1,074 men, outpatients with and without diabetes, at an urban Veteran Administration Medical Center (66.8% AAM, 26.4% CAM, 6% Hispanic, 0.4% Asian, and 0.4% Native American men). Multivariate regression analyzed the determinants of HbA1c after accounting for potential confounders.

Results—We found high prevalence of low (< 30 ng/mL) 25(OH)D (81%) and elevated (≥ 5.7%) HbA1c (53.5%). The 25(OH)D was inversely associated with HbA1c in all men ($r = -0.12$, $P < .001$), in AAM ($r = -0.11$, $P = .003$), and in CAM ($r = -0.15$, $P = .01$). In the entire group the independent determinants of HbA1c included body mass index (BMI), age, 25(OH)D levels, systolic blood pressure (BP), triglycerides, high-density lipoprotein (HDL), and current alcohol use ($P < .0001$, .013, .009, .01, .008, .034, and .048, respectively) while glomerular filtration rate (GFR) and marital status showed borderline significance ($P = .08$ and .09, respectively). In AAM these determinants included BMI, 25(OH)D levels, systolic BP, and current alcohol use ($P < .0001$, .01, .02, and .03, respectively), while age had borderline significance ($P = .06$). In CAM, these included BMI, age, and triglycerides ($P = .01$, .03, and .004, respectively) but not 25(OH)D levels ($P = .50$).

Conclusion—Circulating low 25(OH)D is a risk factor for hyperglycemia, as assessed by HbA1c, in AAM. The 25(OH)D level is an independent determinant of HbA1c in AAM, but not in CAM, including men with and without diabetes.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

INTRODUCTION

There is a considerable body of literature on the relationship between vitamin D and various parameters of glucose metabolism, but there are little data on the relation between circulating vitamin D and hyperglycemia, as assessed by glycated hemoglobin (HbA1c), in the African American population (1,2). There are no data on this relationship in African American men (AAM) or on differences in this relation between AAM and Caucasian American men (CAM). Vitamin D status is defined by circulating 25-hydroxyvitamin D (25[OH]D) concentration (3–5). The vitamin D deficiency and insufficiency are most commonly defined as 25(OH)D <20 and 20 to 30 ng/mL, respectively, based on the relationship of 25(OH)D and bone health (3–5), while no data exist for the designation of healthy vitamin D levels for metabolic well-being. Moreover, no threshold has been suggested for the effect of vitamin D level on glucose metabolism. The HbA1c status is defined as normal HbA1c <5.7%, prediabetes HbA1c 5.7 to 6.4%, and type 2 diabetes mellitus (T2DM) HbA1c ≥6.5% (6,7).

Serum vitamin D levels have been linked to various parameters of glucose metabolism, where both 25(OH)D and HbA1c may contribute independently to the evolution of atherosclerosis and cardiovascular disease (CVD) morbidity and mortality, and both vary by gender and race (7–10). A predominantly negative association has been demonstrated between 25(OH)D and fasting plasma glucose (11–13) or incident T2DM (14–17). The data on the relationship of 25(OH)D and HbA1c in individuals with and without diabetes also vary with some (1,18,19) but not other (1,2,20) studies showing an association. However, there is a gap of knowledge on the relationship between HbA1c and vitamin D levels in AAM. The only studies that included a substantial number of AAM are the National Health and Nutrition Examination Surveys (NHANES) (1,2) but there was no analysis dedicated to AAM in these studies.

In the present study we examined whether serum 25(OH)D level (1) is a risk factor for hyperglycemia, as assessed by HbA1c, in AAM and (2) is a predictor of HbA1c in AAM and CAM.

PATIENTS AND METHODS

Study Subjects

Men receiving care at the outpatient clinics of an urban Veteran Administration Medical Center (VAMC) were recruited for an ongoing study of vitamin D. For this report we included men with available data on 25(OH)D and HbA1c levels who were recruited between December 2006 and December 2011. The inclusion criteria were as follows: men, age 25 years and older, willingness to participate in the study, and ability to provide informed consent. The exclusion criteria were as follows: known type 1 diabetes mellitus (T1DM), stage 5 chronic kidney disease, and inability to provide consent. The subjects could be taking calcium and vitamin D supplements. The institutional review board of the University of Illinois and Jesse Brown VAMC approved the studies and each subject signed an informed consent form. During the initial study visit, the subjects filled in the questionnaires concerning T2DM risk factors, dietary intake of calcium and vitamin D,

vitamin D supplements, and medications. The past medical history, height, weight, and blood pressure were also recorded. Serum derived from a single blood sample was collected for 25(OH)D and stored at -70°C . The medical records were reviewed to verify past medical history and medications and to collect data on serum levels of creatinine, random blood glucose, HbA1c, and lipid profile performed within three months of the initial study visit.

Study Procedures

The risk factors for hyperglycemia and T2DM were ascertained based on a questionnaire and review of medical records. The questionnaire included data on demographics, smoking (never, past, or current), alcohol use (never, past, or current defined as 14 drinks per week), exercising (yes/no, yes defined as 3 days per week for more than 30 minutes at a time), use of multiple vitamins (MVI) or other vitamin D supplements (yes/no), number of years of education, marital status (married or not married), work status (not working, including retirement, or working, including physically challenging work), health self-perception (good or fair/poor), medical history, and medications. Vitamin D supplements and the amount of vitamin D (IU) was as follows: MVI (200 IU daily), calcium plus D (200 IU daily), ergocalciferol (50,000 IU weekly), and calcitriol (doses not recorded). The dietary questionnaire to assess intake of vitamin D and calcium-rich food was a modified food frequency questionnaire that included questions related to calcium and vitamin D intake (e.g., intake of milk and dairy products, fish, eggs, fortified orange juice, and dark leafy vegetables). The total amount of dietary vitamin D and calcium intake was calculated based on the information provided by the U.S. Department of Agriculture (USDA) for vitamin D and calcium (5). Past medical history comprised relevant medical conditions, including T2DM, hypertension (HTN), hyperlipidemia (HL), cardiovascular disease (CVD; including CHD, peripheral vascular disease, cardiovascular accident, and congestive heart failure), chronic disease (including cancer, depression, and chronic obstructive pulmonary disease), and degenerative joint disease (DJD). The seasons for measuring 25(OH)D level were recorded as follows: Winter: December 21 to March 20; Spring: March 21 to June 20; Summer: June 21 to September 20; and Autumn September 21 to December 20 for each year. The ranges were approximately equally distributed. The number of subjects missing information for different risk factors varied from 96 to 223.

Serum 25(OH)D was measured by a direct, competitive-type chemiluminescence immunoassay (CLIA) original assay (Liaison, DiaSorin, Stillwater, MN, USA) (21,22). The intra- and inter-assay coefficients of variability (CVs) were 10.8% and 13.9%, respectively. The laboratory participated in the Vitamin D External Quality Assessment Scheme (DEQAS). Creatinine, blood glucose, HbA1c, and lipid profile, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were measured by automated standard laboratory methods at the VAMC laboratory, and estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation. The HbA1c was either measured in the laboratory ($n = 588$) or calculated for subjects with unavailable HbA1c. The HbA1c was calculated based on an estimated average (over three months within the initial study visit) blood glucose using the American Diabetes Association (ADA) recommended formula (6,7,23).

Statistical analysis

We generated descriptive statistics of our study population. The HbA1c, 25(OH)D, and lipid values were not normally distributed and therefore we used log transformed HbA1c for statistical modeling. For continuity, all continuous variables are reported as median (interquartile range [IR]). We combined all vitamin D supplement users for analysis, since preliminary analysis showed no significant contribution of each separate supplement or supplement dose.

We divided the study population into groups based on HbA1c levels and used the Kruskal-Wallis test for comparisons of the groups to account for nonlinear distribution of the variables. We initially examined the relationship between HbA1c and the risk factors using Spearman's correlation for continuous variables and the Kruskal-Wallis test for categorical variables. We checked for evidence of statistical interaction between 25(OH)D and variables known to be associated with 25(OH)D concentrations, including age, race, exercise, calcium, and vitamin D intake and supplements, the season of vitamin D measurement, diabetes status, and body mass index (BMI) category for HbA1c outcome. We performed a separate analysis of HbA1c blood levels or HbA1c blood levels in combination with calculated HbA1c, and since there was no substantial difference in the statistics, we used the combined HbA1c values for final analysis. To determine the simultaneous effect of potential risk factors on the relationship between HbA1c and 25(OH)D, we first performed an analysis of interactions between 25(OH)D and other T2DM risk factors and univariate analysis, and then performed a multiple linear regression analysis for determinants of HbA1c, including risk factors with $P \leq .10$ from the univariate model, including the interactions between 25(OH)D and other T2DM risk factors. We further checked the model selection procedure to evaluate whether different sets of covariates improved the model prediction of HbA1c. Statistical significance was set at $P < .05$. All analyses were performed using SAS 9.2 statistical software (SAS Institute, Inc., Cary, NC).

RESULTS

Subject Characteristics by HbA1c Status

In the entire study group ($N = 1,074$) the race distribution was 66.8% AAM, 26.4% CAM, 6% Hispanic, 0.4% Asian, and 0.4% Native American, which reflected the population seen at our VAMC (Table 1). The elevated HbA1c (prediabetes plus diabetes) was present in 53.5% of the overall population and in 54.5% of AAM and 47.5% of CAM. The majority of men were younger than 70 years (76%), retired (61%), considered themselves to be in good health (54.8%), and had low (<30 ng/mL) 25(OH)D levels (81%). Overall, 78.3% of men had higher than normal BMI (>25 kg/m²), with 35.2% being overweight and 43.1% being obese.

In the entire group, circulating 25(OH)D levels were similar between winter and spring (mean [SD]: 16.1 [8.7] and 18.9 [10.9], respectively; $P = .14$) and between summer and autumn (23 [10.6] and 21.4 [11.1], respectively; $P = .24$). The comparison of serum 25(OH)D levels during cold (winter and spring) and warm (summer and fall) seasons showed a significant difference ($P = .0002$).

Relationship of HbA1c with 25(OH)D and Other Diabetes Risk Factors

Correlation analysis showed a relatively weak but significant association between HbA1c and 25(OH)D levels that did not differ between AAM and CAM (Table 2). Race was associated with HbA1c status ($P = .015$), but comparison of AAM and CAM showed that the prevalence of prediabetes in AAM (23.2%) and CAM (26.3%) was similar, while 25(OH)D levels were lower in AAM compared to CAM [median (IR): 16.0 (11.5 to 21.2) versus 26.0 (18.1 to 32.3) ng/mL, respectively; $P < .001$] (Fig. 1).

Determinants of HbA1c

There were no significant correlations between serum 25(OH)D levels and other T2DM risk factors. In a multivariate regression analysis of the entire group, the independent determinants of HbA1c included BMI, age, 25(OH)D levels, systolic BP, current alcohol use, triglycerides, and HDL, while marital status and eGFR were of borderline significance (Table 3). In AAM, the independent determinants of HbA1c included BMI, 25(OH)D levels, systolic BP, and current alcohol use ($P < .0001$, .01, .02, .03, respectively; data not shown), while age was of borderline significance ($P = .06$); in CAM, these included BMI, age, and TG ($P = .01$, .03, and .004, respectively; data not shown) but not 25(OH)D levels ($P = .50$). Overall, the model predicted 18%, 18%, and 28% of HbA1c variability in the entire group, AAM, and CAM, respectively.

DISCUSSION

We confirmed our hypothesis that low serum 25(OH)D was a risk factor for hyperglycemia, as assessed by HbA1c, in AAM. Most importantly, the circulating 25(OH)D concentration was an independent determinant of HbA1c in our population of male veterans and in a subgroup of AAM. We also observed that the prevalence of prediabetes in AAM and CAM was similar, while serum 25(OH)D levels were lower in AAM compared to CAM, suggesting that the threshold of the vitamin D effect on HbA1c may be different between two races.

The major strengths of our study include the expansion of previous studies regarding the link between vitamin D and glucose metabolism to a population enriched in AAM and inclusion of serum 25(OH)D levels and psychosocial risks among determinants of HbA1c. We were able to engage a population that is commonly underrepresented in research studies (24, 25), yet has a high burden of health problems and requires an increased effort from health professionals (26, 27). However, our study has important limitations as well. We only obtained a single measurement of 25(OH)D, which fails to take into account the intraindividual seasonal variation. Our sample of CAM is relatively small, and we used calculated HbA1c in some cases. The cross-sectional design does not allow establishing causality between serum vitamin D level and hyperglycemia. We also cannot account for some possible confounders, such as dietary and diabetes medication variability. Therefore, residual confounding may still remain. Indeed, our model predicts a relatively modest 18 to 28% of HbA1c variability despite the inclusion of the most common T2DM risks, suggesting that future research of HbA1c determinants in a veteran population should

incorporate a wide variety of risk factors, including dietary assessment and diabetes treatment.

Our findings are consistent with the previous report on the relationship of 25(OH)D and HbA1c in U.S. adults from the National Health and Nutrition Examination Survey (NHANES) III, which showed that 25(OH)D level was inversely associated with HbA1c in subjects between the ages of 35 and 74 years as well as those without a history of diabetes (1). Similarly, a negative association of 25(OH) D and HbA1c was reported in NHANES 2003–2006 (2). Our data are also in agreement with the data from British (28,29), Scandinavian (30), and Arab American (31) populations. All previous studies, however, included predominantly non-African-derived populations, and none had a separate analysis of the AAM group. The only studies that included a substantial number of AAM were the NHANES (1,2), but the results of these studies are controversial, with one study showing a positive association between 25(OH) D and HbA1c in African Americans (1) and the other showing no significant correlation between 25(OH)D and race/ethnicity (2). Our study showed significant correlation between 25(OH)D levels and race and a negative correlation between 25(OH)D levels and HbA1c in AAM. To the best of our knowledge, this is the first study to perform a detailed analysis of the relationship between HbA1c and 25(OH)D levels that included psychosocial T2DM risk factors in men of a predominantly African American racial background.

Physiological mechanisms accounting for similarities and differences between our results and other studies include the possibility that interactions between 25(OH) D and glucose metabolism may be bidirectional. Obesity varies by gender and race, is a recognized risk factor for vitamin D deficiency (1–3,11–21), and may contribute to lower serum vitamin D levels by influencing vitamin D sequestration in subcutaneous and visceral fat (32,33). Obesity and fat intake may also influence 25(OH)D levels by changing vitamin D absorption and metabolism (33–35). On the other hand, vitamin D insufficiency may contribute to hyperglycemia and obesity by affecting muscle strength and physical activity (36). Similarly, vitamin D deficiency is an important contributor to insulin resistance, which is a pathogenic mechanism of T2DM (37,38). Conversely, higher vitamin D intake may increase diet-induced thermogenesis and fat oxidation as well as reduce spontaneous energy intake (39). Genetic factors related to polymorphisms of the vitamin D-binding protein (DBP) gene are also implicated in the contribution of vitamin D to human obesity (40). Thus, our study together with the previous studies suggest that there is a multifactorial and bidirectional (or possibly multidirectional) nature of the vitamin D/hyperglycemia connection. Bidirectional effects of this connection may help to explain complexity, gender, and race-related differences in the vitamin D/glucose homeostasis relationship and should be explored in future research.

CONCLUSION

Some limitations notwithstanding, to the best of our knowledge this report is the first detailed evaluation demonstrating that low circulating 25(OH)D levels represent a risk factor for hyperglycemia, as assessed by HbA1c, in AAM. Moreover, the 25(OH)D level is an independent determinant of HbA1c in AAM, but not in CAM, including men with and

without diabetes. Further detailed analysis of subgroups with variable risk factors and confounders would help to understand inconsistencies in the vitamin D/HbA1c relationship and to better define the role of vitamin D deficiency and/or insufficiency in glucose metabolism.

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Abbreviations

25(OH)D	25-hydroxyvitamin D
AAM	African American men
CAM	Caucasian American men
NHANES	National Health and Nutrition Examination Survey
VAMC	Veteran Administration Medical Center

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Fig. 1.

Serum 25-hydroxyvitamin D (25[OH]D) (ng/mL) levels in African American (AA) and Caucasian American (CA) men. Data are median (interquartile range). ■ AA men; □ CA men. $P < .05$ for all comparisons of 25(OH)D in AA versus CA with the same glycated hemoglobin (HbA1c). To convert to nmol/L, multiply by 2.5.

Table 1Characteristics of Men by HbA1c Status^a

Factor	Normal HbA1c <5.7%	Prediabetes HbA1c 5.7–6.4%	T2DM HbA1c ≥6.5%	P value
Number of men	499	289	286	
Age (y)	60 (51–69)	61 (55–67)	62 (58–70)	<.0001
Race:	64.7	60.8	70.3	.015
African	30.4	29.4	21.1	
Caucasian	4.5	9.0	7.2	
Hispanic	0.2	0	1.0	
Asian	0.2	0.8	0.4	
Native				
Smoking status:	24.5	29.0	22.2	.044
never	36.9	29.5	29.2	
current	38.6	41.5	48.6	
past				
Alcohol use:	43.6	50.7	43.2	<.0001
never	30.6	22.8	16.1	
current	25.8	26.5	40.7	
past				
Exercise	59.8	55.3	48.4	.017
Vitamin D supplements ^b	49.0	25.0	26.0	.581
Marital status:	31.8	36.6	43.2	.016
married	68.2	63.4	56.8	
not married				
Work status:	59.3	60.8	63.2	.621
not working	40.7	39.2	36.8	
working				
Health perception:	41.6	42.5	55.5	.002
fair/poor	58.4	57.5	44.5	
good				
Hypertension	64.2	74.9	88.4	<.0001
Hyperlipidemia	39.8	59.6	78.9	<.0001
CVD	17.6	25.5	31.4	<.0001
DJD	34.1	38.8	29.0	.171
Chronic disease ^c	40.8	48.6	35.8	.011
Dietary intake:	70 (31–129)	63 (29–121)	68 (31–120)	.519
vitamin D (IU/d)	310 (127–443)	303 (100–431)	287 (113–400)	.091
calcium (mg/d)				
Education (y)	14 (12–16)	12 (12–14)	12 (12–14)	.082
Weight (kg)	84.3 (73.6–96.6)	95.5 (82–111.1)	98.2 (85.5–112.1)	<.0001
Height (cm)	175 (170–180)	175 (170–180)	175 (170–180)	.598
BMI (kg/m ²)	26.9 (23.6–30.5)	30.4 (27.1–34.5)	31.2 (27.8–34.7)	<.0001
Systolic BP (mm Hg)	129 (119–140)	132 (120–140)	133 (122–144)	.013
Creatinine (mg/dL)	1.1 (1.0–1.3)	1.1 (1.0–1.3)	1.2 (1.0–1.4)	.002
GFR (mL/min/1.73 m ²)	80 (61–97)	75 (62–94)	71 (54–91)	.002
Random BG (mg/dL)	97 (89–105)	111 (100–124)	156 (123–195)	<.0001
HbA1c (%)	5.4 (5.2–5.5)	6.0 (5.9–6.2)	7.6 (6.9–8.9)	<.0001

Factor	Normal HbA1c <5.7%	Prediabetes HbA1c 5.7–6.4%	T2DM HbA1c ≥6.5%	P value
TC (mg/dL)	172 (143–198)	170 (142–200)	153 (129–182)	<.0001
Triglycerides (mg/dL)	98 (72–148)	117 (82–181)	117 (84–183)	.0001
LDL (mg/dL)	97 (76–123)	96 (73–123)	82 (65–110)	<.0001
HDL, mg/dl	45 (38–54)	44 (37–52)	39 (33–46)	<.0001
25(OH)D, ng/ml ^d	20.4 (14.1–28.7)	17.6 (12.2–25.9)	18.0 (11.3–25.3)	.0006

Abbreviations: BG = blood glucose; BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; DJD = degenerative joint disease; GFR = glomerular filtration rate; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MVI = multivitamin infusion; TG = triglycerides.

^a Data are median (interquartile range) or %.

^b Including MVI, calcium plus vitamin D, ergocalciferol, and calcitriol.

^c Including depression, cancer, and chronic obstructive pulmonary disease.

^d To convert to nmol/l multiply by 2.5.

Table 2

Associations Between HbA1c and Other Variables in Men^a

Characteristics	All men		AA men		CA men	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
Continuous						
Age	.11	.0004	.12	.0017	.14	.019
BMI	.36	<.0001	.37	<.0001	.36	<.0001
Systolic BP	.10	.0009	.09	.017	.12	<.0001
GFR	-.10	.001	-.10	.012	-.13	.026
TG	.17	<.0001	.15	<.0001	.22	.0002
HDL	-.23	<.0001	-.20	<.0001	-.32	<.0001
25(OH)D	-.12	<.0001	-.11	.003	-.15	.011
Dietary:						
calcium	-.06	.06	-.04	.32	-.08	.20
vitamin D	-.03	.39	-.00	.98	-.11	.10
Education	-.07	.06	-.07	.11	-.08	.22
Categorical	<i>H</i>	<i>P</i> value	<i>H</i>	<i>P</i> value	<i>H</i>	<i>P</i> value
Smoking	8.28	.01	6.43	.040	2.33	.31
Alcohol use	18.6	<.0001	14.8	.001	2.49	.29
Exercise	6.03	.01	2.04	.154	2.01	.15
Marital status	6.17	.01	8.80	.003	0.01	.94
Work status	.77	.38	.72	.397	0.62	.43
Health perception	9.99	.002	6.85	.009	3.78	.05

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; AA = African American; CA = Caucasian American; BMI = body mass index; BP = blood pressure; GFR = glomerular filtration rate; HDL = high-density lipoprotein; TG = triglycerides.

^a *r* is Spearman's Rho; *H* is from a Kruskal-Wallis test.

Table 3Predictors of HbA1c^a

Predictors	Coefficient estimate	SE	P value
Age	.0019	.0007	.013
BMI	.0084	.0014	<.0001
Systolic BP	.0012	.0004	.010
GFR	-.0004	.0002	.083
TG	.0002	.0001	.008
HDL	-.0015	.0007	.034
25(OH)D	-.0019	.0007	.009
Dietary calcium	-.00004	.00003	.199
Education	.0022	.0034	.518
Smoking	.0244	.0218	.262
Alcohol use	-.0395	.0199	.048
Exercise	-.0040	.0159	.803
Marital status	.0562	.0331	.090
Health perception	-.0195	.0159	.221

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; BMI = body mass index; BP = blood pressure; GFR = glomerular filtration rate; HDL = high-density lipoprotein; TG = triglycerides.

^a Coefficients represent change in HbA1c (%) for an increase in the value of the predictor variables shown. $R^2 = 0.18$ in multiple regression analysis.