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Association of 25-hydroxyvitamin D with Blood Pressure in Predominantly 25-hydroxyvitamin D Deficient Hispanic and African Americans

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Abstract

Background—Several observational studies have recently suggested an inverse association of circulating levels of vitamin D with blood pressure. These findings have been based mainly on Caucasian populations; whether this association also exists among Hispanic and African Americans has yet to be definitively determined. This study investigates the association of 25-hydroxyvitamin D (25[OH]D) with blood pressure in Hispanic and African Americans.

Methods—The data source for this study is the Insulin Resistance Atherosclerosis Family Study (IRASFS), which consists of Hispanic- and African-American families from three U.S. recruitment centers (n=1334). A variance components model was used to analyze the association of plasma 25[OH]D levels with blood pressure.

Results—An inverse association was found between 25[OH]D and both systolic (β for 10 ng/mL difference= −2.05; $p<0.01$) and diastolic (β for 10 ng/mL difference= −1.35; $p<0.001$) blood pressure in all populations combined, after adjusting for age, sex, ethnicity and season of blood draw. Further adjustment for body mass index (BMI) weakened this association (β for 10 ng/mL difference= −0.94; $p=0.14$ and β for 10 ng/mL difference = −0.64; $p=0.09$, respectively).

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Disclosure
The authors do not have any conflicts of interest to disclose.

Conclusions—25[OH]D levels are significantly inversely associated with blood pressure in Hispanic and African Americans from the IRASFS. However, this association was not significant after adjustment for BMI. Further research is needed to determine the role of BMI in this association. Large, well-designed prospective studies of the effect of vitamin D supplementation on blood pressure may be warranted.

Keywords

Vitamin D; 25-hydroxyvitamin D; blood pressure; hypertension; race; ethnic groups; Hispanic; African American

Introduction

Hypertension, or high blood pressure, is a major risk factor for heart disease, the leading cause of death in the U.S. Approximately 1 in 3 American adults has high blood pressure, but this condition is even more prevalent among African Americans.1 Despite its large health impact, primary prevention of hypertension is hampered partly due to a limited knowledge of risk factors for this condition. Recent observational evidence suggests that low levels of 25-hydroxyvitamin D (25[OH]D), the major circulating vitamin D metabolite, may be associated with elevated blood pressure.2–5 Additionally, small intervention studies have found that treatment of individuals with vitamin D supplementation, or ultraviolet-B (UV-B) radiation (to increase 25[OH]D), can lower blood pressure.6–8 A review of the complex relationship between vitamin D status, defined by levels of 25[OH]D, and cardiovascular risk in human and animal models has recently been conducted 9. However, it is uncertain whether this association between blood pressure and 25[OH]D, observed largely in Caucasian subjects, is also present in Hispanic and African Americans.3–5 When compared to Caucasians, Hispanic and African Americans typically have lower levels of 25[OH]D10 due to their darker skin pigmentation, which acts as a natural sunscreen by absorbing UV-B radiation from the sun, thereby decreasing the amount of UV-B radiation that penetrates the skin to ultimately produce 25[OH]D. Scragg and colleagues previously determined that an inverse association between blood pressure and 25[OH]D existed not only in Caucasians, but also in Hispanic and African Americans.4 However, Martins et al., using the same data source, concluded that 25[OH]D status was inversely associated with hypertension in whites and Hispanic females, but not in Hispanic males or African Americans of either sex (blood pressure was not analyzed as a continuous variable).3 Determining conclusively whether 25[OH]D status is related to blood pressure in Hispanic and African Americans may help to explain the mechanism behind observed differences in hypertension rates by ethnicity.

We investigated the association of 25[OH]D with blood pressure in rural and urban Hispanic-American families and urban African-American families from the Insulin Resistance Atherosclerosis (IRAS) Family Study (IRASFS).

Methods

Study Population

Details of the IRASFS design and recruitment11 and the vitamin D phenotyping12 have been previously published. Briefly, the IRASFS is a multi-center study designed to identify the genetic determinants of insulin resistance and adiposity in a multi-ethnic population. Participants in the IRASFS were recruited by clinical centers in Los Angeles, California (African Americans); San Luis Valley, Colorado (Hispanic-American); and San Antonio, Texas (Hispanic-American). Probands for the IRASFS were generally recruited from the original IRAS cohort 13. Additional probands were ascertained from the general population. Criteria for proband selection were based on large family size, not on disease status or

extreme phenotypes. Participants who reported taking anti-hypertensive medication (n= 196) were excluded from the analyses in this report. A total of 1334 participants with information on blood pressure and 25[OH]D levels were included in the analyses. This research has been approved by the Institutional Review Board at each institution and informed consent was obtained from all subjects.

Measurement of blood pressure

Resting seated blood pressure was measured three times at a single study visit using a mercury sphygmomanometer, after a 5-min rest by centrally trained technicians using identical equipment. Blood pressure technicians participated in monthly reproducibility studies within center and the inter-rater coefficient of variation (CV) for repeat diastolic and systolic blood pressure measures among 22 pairs of readings was 3% and 2%, respectively. The mean of the last two measurements was used to calculate blood pressure.

Measurement of 25[OH]D levels

Levels of 25[OH]D were measured by a 2-step process involving rapid extraction of 25[OH]D and other hydroxylated metabolites from plasma and radioimmunoassay with a 25[OH]D-specific antibody (DiaSorin, Stillwater, Minnesota) with interassay CVs <8%.

Measurement of covariates

For the purpose of the analysis, blood draws taken from December through May were categorized as winter/spring and all others as summer/fall samples. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Hispanic- or African-American ethnicity was self-reported. As previously reported12, physical activity was assessed by a 1-year recall using a modification of a validated instrument14 that incorporated activities common among IRAS Family Study participants, including ranching and homemaking activities. Total energy expended (in kcal/kg) per year was calculated by summing across all activity groups, plus the estimated energy expenditure (EEE) from sleep (metabolic equivalent [MET] value of 1.0), plus the EEE from light activities (e.g., sitting MET value of 1.5). Gender-specific quartiles of physical activity were calculated. Smoking status was self-reported as never (“Have you smoked at least 100 cigarettes in your lifetime” answered “No”), past (“Have you smoked at least 100 cigarettes in your lifetime” answered “Yes”, but participant does not currently smoke), or current.

Statistical analyses

The analyses were conducted using a generalized estimating equations (GEE) model via the GENMOD procedure in the SAS software version 9.1 (SAS Institute, Cary, NC, USA). Familial correlation was accounted for by using a sandwich estimator of the variance and exchangeable correlation. There was no significant interaction between study center and blood levels of 25[OH]D (*p* for interaction term = 0.31 for systolic and 0.99 for diastolic blood pressure) so all centers were combined for the analyses. The following variables were included in the initial model as potential covariates: gender, age, ethnicity, season of blood draw, body mass index (BMI), physical activity, and smoking status. A backwards stepwise regression was performed, starting with this initial model.

Results

A total of 1334 participants from 130 families (mean family size = 10.2; range = 1 to 42) were included in the analyses. The mean age of the participants was 38.5 (range = 18 to 81). The mean 25[OH]D for these Hispanic- and African-American participants was quite low (14.8 ng/mL, which is considered to be vitamin D deficient; discussed in further detail

previously 12). Unadjusted mean 25[OH]D levels varied between categories of demographic and lifestyle variables (Table 1). 25[OH]D was lower in women, African Americans, participants with a winter/spring season of blood draw, overweight and obese participants, and participants in the least active quartile of leisure-time physical activity. 25[OH]D levels did not vary significantly by smoking status or categories of systolic and diastolic blood pressure. 25[OH]D levels showed a trend towards being lower in both the youngest and oldest age categories.

A difference of 10 units in 25[OH]D (measured in ng/mL) was associated with statistically significant differences of −2.05 and −1.35 mm Hg in systolic and diastolic blood pressure, respectively after adjusting for age, sex, ethnicity, and season of blood draw (Table 2, Model 1). However, the effect of 25[OH]D was attenuated and only marginally significant after further adjustment for BMI (Table 2, Model 2). An interaction term between ethnicity and 25[OH]D levels was not statistically significant in predicting blood pressure (*p* for interaction term = 0.31 for systolic and 0.99 for diastolic blood pressure), indicating that the association between 25[OH]D levels and blood pressure is similar in the Hispanic- and African-American populations in this study, which was confirmed by race-stratified analyses (data not shown).

Discussion

Our results suggest that circulating 25[OH]D concentrations are inversely associated with systolic and diastolic blood pressure in Hispanic and African Americans, but the effect is weakened after adjusting for BMI. This finding supports those from a nationally representative study including Hispanic and African Americans.4

If the inverse association between 25[OH]D and blood pressure could be replicated using an observational longitudinal study design or a randomized clinical trial, it could have public health significance, as the potential influence of raising 25[OH]D levels to sufficiency could substantially lower blood pressure. For example, raising 25[OH]D levels of individuals in the lowest quintile of 25[OH]D in this study (~8 ng/mL) to levels of the highest quintile (~32 ng/mL, a sufficient level of vitamin D) could potentially lower systolic blood pressure by 2.3 mmHg and diastolic blood pressure by 1.5 mmHg (estimates based on models including BMI). As noted by Scragg et al.,4 a decrease in systolic blood pressure of this magnitude would be estimated to produce an approximate 10–15% decline in cardiovascular mortality. However, as stated above, additional studies with a longitudinal study design are needed to confirm the causative effect of 25[OH]D levels on blood pressure. Only one large prospective randomized study has looked at the effect of vitamin D supplementation on blood pressure thus far.15 No effect was detected in that study, possibly due to several factors previously described,16 including the possibility of unequal proportions of participants in the treatment and placebo groups on anti-hypertensive medication during follow-up and the dosage level of vitamin D being too low to have an effect on blood pressure. Additionally, the effect of vitamin D supplementation on 25[OH]D levels was not reported.

The interpretation of the association between 25[OH]D levels and blood pressure depends on whether it is appropriate to adjust for BMI. Scragg and colleagues described evidence suggesting that BMI may be an intermediate step in the vitamin D-blood pressure causal pathway and therefore it should not be adjusted for.4 The lower levels of 25[OH]D typically seen in individuals with high BMI17, 18 is thought to be due to the sequestering of vitamin D within fatty tissue.19 However, there is evidence suggesting that lower vitamin D levels could lead to higher BMI, which in turn could increase blood pressure. Low vitamin D levels may promote weight gain through the action of excess parathyroid hormone, which

causes an influx of calcium into adipocytes.20 Furthermore, several small studies have shown that administration of α-calcidol (synthetic analogue of 1,25-dihydroxyvitamin D_2 [$1,25(OH)_2D$], the more biologically active vitamin D metabolite) have resulted not only in lowered blood pressure, but also moderate weight loss.21⁻23

The exclusion of participants on anti-hypertensive medication could have introduced a bias in our results. However, results from analyses investigating an association of 25[OH]D levels with baseline hypertension (defined as having either systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or currently taking anti-hypertensive medication) supported the inverse directionality of the association of 25[OH]D with blood pressure, although the association was not significant ($p>0.05$, data not shown). An additional limitation is that a relatively small proportion of the participants included in the analyses had high blood pressure (72 out of 1334 [5%] had a systolic blood pressure ≥140 mmHg and 93 [7%] had a systolic blood pressure ≥90 mmHg). Consequently, even though there was a trend toward a lower mean 25[OH]D as systolic blood pressure increased (Table 1), the results were not significant for the group with systolic blood pressure ≥140 mmHg, which could be due to a small sample size in this group.

This study shows an inverse association between vitamin D status, measured by 25[OH]D, and blood pressure in Hispanic and African-American populations, after adjustment for several potentially confounding variables, although this association was not significant after adjustment for BMI. This finding could potentially have important public health implications, as increased vitamin D levels can be easily attained by vitamin D supplementation, or modest sun exposure. However, this type of intervention should be supported by the results of large, well conducted, randomized intervention trials of vitamin D supplementation.

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Table 1

Unadjusted mean 25[OH]D levels in the study participants†

Variable	Number	25[OH]D mean (SD) ng/mL	*P* value
Overall	1334	14.8 (7.2)	
Gender			
Male	569	16.0 (6.8)	*
Female	763	13.9 (7.4)	<.001
Age (y)			
<30	369	13.7 (6.8)	*
30–39	406	15.5 (7.6)	<.01
40–49	335	15.0 (7.4)	.056
50–59	137	15.5 (6.5)	<.05
≥60	85	14.6 (6.8)	.97
Race/ethnicity			
Hispanic American	920	16.5 (7.3)	*
African American	412	11.2 (5.4)	<.001
Season of blood draw			
Summer/fall	550	17.8 (7.6)	*
Winter/spring	774	12.8 (6.1)	<.001
Body mass index (kg/m^2)			
underweight (<18.5)	27	13.8 (9.1)	.28
normal weight (18.5–24.9)	407	16.6 (7.9)	*
overweight (25.0–29.9)	440	15.6 (7.1)	<.05
obese (≥30)	458	12.6 (5.9)	<.001
Physical activity			
4th quartile (most active)	368	15.8 (7.6)	*
3rd quartile	347	15.5 (7.2)	.71
2nd quartile	319	14.9 (6.8)	.73
1st quartile (least active)	288	12.8 (6.8)	<.001
Smoking status			
Never	765	14.6 (7.2)	*
Past	243	15.3 (6.9)	.30
Current	324	15.0 (7.4)	.73
Systolic blood pressure (mm Hg)			
<120	924	15.1 (7.3)	*
120–139	336	14.3 (6.9)	.053
≥140	72	13.8 (6.7)	.31
Diastolic blood pressure (mm Hg)			
<80	942	14.8 (7.5)	*
80–89	297	15.1 (6.7)	.44
≥90	93	14.5 (6.3)	.84

*Reference category for *P* value.

Table 2

Effect on systolic and diastolic blood pressure for each 10 unit difference in 25[OH]D

	Dependent variable: Systolic Blood Pressure (mmHg)	**Dependent variable: Diastolic Blood Pressure (mmHg)**
Independent variable: 25[OH]D (ng/mL)	**β† (95% CI)**	**β† (95% CI)**
Unadjusted	−0.72 (−1.97, 0.52)	0.01 (−0.70, 0.71)
	p=0.25	*p*=0.99
Model 1*	−2.05 (−3.33, −0.76)	−1.35 (−2.10, −0.59)
	p<0.01	*p*<0.001
Model 2: Model 1 also	−0.94 (−2.19, 0.32)	−0.64 (−1.38, 0.10)
adjusted for BMI	*p*=0.14	*p*=0.09

*Model 1= adjusted for age, sex, ethnicity and season of blood draw

†β represents difference in blood pressure per 10 ng/mL difference in 25[OH]D