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Serum 25-hydroxyvitamin D and risk of venous thromboembolism: The Atherosclerosis Risk in Communities (ARIC) Study

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Summary

Background—Some evidence suggests that an inadequate vitamin D level may increase the risk atherosclerotic cardiovascular disease. Whether low vitamin D has a role in venous thromboembolism (VTE), i.e., venous thrombosis and pulmonary embolism, is largely unexplored.

Objectives—We tested prospectively in the Atherosclerosis Risk in Communities (ARIC) cohort whether the serum concentration of 25-hydroxyvitamin D (25(OH)D) is inversely associated with VTE incidence and whether it partly explains the African American excess of VTE in ARIC.

Patients and Methods—We measured 25(OH)D using mass spectroscopy in stored samples of 12,752 ARIC study participants and followed them over a median of 19.7 years (1990-92 through 2011) for incidence of VTE (n = 537).

Results—The seasonally-adjusted 25(OH)D concentration was not associated with VTE incidence. In a model adjusted for age, race, sex, hormone replacement therapy, and body mass

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Addendum

A. R. Folsom, M. Cushman, and P. L. Lutsey designed the research. W.D. Rosamond, S.R. Heckbert, M. Cushman, and P. L. Lutsey conducted research. N. S. Roetker, S. Basu, and P. L. Lutsey analyzed data or performed statistical analysis. A. R. Folsom wrote the paper. A. R. Folsom had primary responsibility for final content. N. S. Roetker, W. D. Rosamond, S. R. Heckbert, S. Basu, M. Cushman, and P. L. Lutsey made critical comments on the paper. All authors read and approved the final manuscript.

Disclosure of Conflicts of Interest

None of the authors declared a conflict of interest.

index, the hazard ratios of VTE across 25(OH)D quintiles 5 (high) to 1 (low) were: 1 (Ref.), 0.84 (0.65, 1.08), 0.88 (0.68, 1.13), 1.04 (0.78, 1.38), and 0.90 (0.64, 1.27). The lowest 25(OH)D quintile comprised 59% African Americans, whereas the highest quintile comprised 7% African Americans. Yet, lower 25(OH)D concentrations explained little of the 63% greater VTE risk of African Americans over whites in this cohort.

Conclusions—Low 25(OH)D was not a risk factor for VTE in this prospective study. Yet, the totality of literature (three studies) suggests that low 25(OH)D might modestly increase VTE risk in whites, but this needs further confirmation.

Keywords

Prospective studies; pulmonary embolism; risk factors; venous thrombosis; vitamin D

There is considerable interest in the role of vitamin D in human health. The best marker of vitamin D status is serum 25-hydroxyvitamin D [25(OH)D] [1]. An area that needs clarification is whether a low level of 25(OH)D may predispose to venous thromboembolism (VTE), as it may do for atherothrombotic diseases. Lindqvist et al suggested this possibility by showing in a cohort of Swedish women that sunbathers (with, presumably, extra sun-induced vitamin D had a 30% reduced VTE risk, and that population VTE risk was 50% lower in summer than winter (when vitamin D levels decrease) [2]. A large prospective study from Copenhagen reported an inverse association of seasonally-adjusted plasma 25(OH)D with VTE, with a relative risk of 1.28 (95% CI = 1.06, 1.53) for the lowest versus highest tertile of 25(OH)D [3]. However, the Tromsø Study found no association of serum 25(OH)D with VTE, but was underpowered for low versus high 25(OH)D quartiles (relative risk 1.32, 95% CI = 0.78, 2.22) [4]. Administration of calcitriol, the active hormone form of vitamin D, was shown to reduce VTE occurrence in chronic kidney disease [5] and cancer patients [6]. Vitamin D receptor −/− mice, who display vitamin D deficiency, have increased thrombogenic activity [7].

25(OH)D levels are seemingly deficient in 38% of black women, 18% of black men, 5% of white women, and 1% of white men, and they are optimal in only 2%, 4%, 29%, and 26%, respectively [8]. Grant speculated that a link between low vitamin D and VTE might explain an African American excess of VTE, compared with whites [9]. However, along with lower mean levels of 25(OH)D, recent evidence suggests that African Americans also have lower levels of vitamin D-binding protein and hence mean levels of bioavailable vitamin D similar to those in whites [10].

We tested prospectively in the Atherosclerosis Risk in Communities (ARIC) cohort whether 25(OH)D is inversely associated with VTE incidence and partly explains the African American excess of VTE in our sample [11].

Methods

Study population

The ARIC Study [12] and its methods for identification and classification of VTE have been described in detail elsewhere [11, 13]. In brief, in 1987-89, 15,792 men and women aged 45

to 64 years from four U.S. communities (Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; Washington County, MD; ranging in latitude from 32.3° N to 45.0° N) enrolled in the ARIC Study. The cohort underwent four subsequent examinations and annual telephone contact. The present analysis used ARIC visit 2 (1990-92) as its start point for VTE follow-up through 2011. The institutional review committees at each study center approved the methods, and staff obtained informed participant consent.

Measurement of 25(OH)D and VTE risk factors

All risk factors were measured at the 1990-92 ARIC visit 2, except for the sports physical activity score, factor VIII, and activated partial thromboplastin time (APTT), which were available from the previous 1987-89 ARIC visit [14, 15]. Participants were asked to fast for 12 hours before their morning visit 2 appointments, and serum and plasma samples were obtained and stored at −80 °C. Soon after the visit, central laboratories measured serum creatinine by the Jaffe method and glucose by a hexokinase assay. In 2012-13, a number of analytes, including vitamin D, were measured on a previously unthawed visit 2 serum aliquot. 25(OH)D [sum of 25(OH)D_2 and 25(OH)D_3] was measured using liquid chromatography-tandem high-sensitivity mass spectrometry (Waters Alliance e2795, Milford, Massachusetts). Using duplicate samples collected at visit 2 and stored, we calculated the 25(OH)D coefficient of variation (CV) as 10.9%. This CV encompasses variability related to both sample processing and laboratory methods. Calcium and phosphorous were measured using colorimetric methods on a Roche Modular P Chemistry Analyzer with reagents from Roche Diagnostics Corporation (Indianapolis, IN). The CVs were 2.4% for calcium and 3% for phosphorous. Intact parathyroid hormone (PTH) was measured on a Roche Elecsys 2010 Analyzer using a sandwich immunoassay method (CV, 9.7%). High sensitivity C-reactive protein (CRP) was assayed using a latex-particle enhanced immunoturbidimetric assay kit (Roche Diagnostics) and read on the Roche Modular P Chemistry analyzer (CV, 7%). Cystatin C was measured using Gentian Cystatin C reagent on the Roche Modular P Chemistry analyzer (CV, 3%).

Cigarette smoking, education level attained, and history of cancer were obtained by self-report. Sports physical activity was assessed by the Baecke questionnaire [16] and yielded a score from 1 (low) to 5 (high). Current hormone replacement therapy was queried in women and medication bottles were inspected to verify ARIC visit 2 use. Diabetes was defined as a fasting blood glucose of 126 mg/dl or higher, non-fasting blood glucose of 200 mg/dl or higher, a self-reported physician diagnosis of diabetes, or use of antidiabetic medication in the past 2 weeks. Glomerular filtration rate (eGFR) was estimated from cystatin C and creatinine using the Chronic Kidney Disease Collaboration algorithm [17]. Height to the nearest centimeter and weight to the nearest pound were measured with participants in scrub suits and without shoes. Body mass index was calculated as weight (kg)/height $(m)^2$.

VTE occurrence

ARIC participants are contacted annually by phone and asked about all hospitalizations in the previous year. Hospital records with discharge diagnoses for possible VTE events [12] were obtained from baseline through 2011. To validate the VTE events, two physicians (ARF, MC) reviewed the records using standardized criteria [12]. A diagnosis of deep vein

thrombosis (DVT) or pulmonary embolism (PE) required positive imaging tests. We restricted DVTs for this analysis to those in the lower extremity or vena cava. Cases were classified by the reviewers as unprovoked (no obvious cause) or provoked (associated with recent hospitalization cancer, major trauma, surgery, marked immobility).

Statistical analysis

Of the 14,348 participants at ARIC visit 2, we excluded those who did not have 25(OH)D measurements (n = 1,198), had a prior VTE (n = 264), were taking anticoagulants (n = 93), were not white or African American (n = 38), or had no follow-up (n = 3). This left 12,752 participants (n = 9,618 whites and 3,134 African Americans) for the present analyses relating 25(OH)D to incident VTE. Time at risk was computed from the date of visit 2 to the earliest of the following: date of hospital discharge with incident VTE, date of death, date of last follow-up contact, or end of follow-up (December 31, 2011).

Our main hypothesis was that 25(OH)D levels would be associated inversely with VTE incidence. Since serum 25(OH)D levels vary greatly by sun exposure, which is seasonal, we accounted for seasonal variation by computing the residuals from race-specific linear regression models with 25(OH)D as the dependent variable and month of blood draw as the independent variable. The grand mean was added to the 25(OH)D residuals to create a new variable, “25(OH)D adjusted for month of blood draw,” which was used as the main exposure variable. 25(OH)D was modeled either as a continuous variable or categorized into percentiles of the overall distribution: 75-100 (reference), 50-74, 25-49, 10-24, and 0-9%.

Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals of incident VTE. We verified the proportional hazards assumption of the Cox models by inspection of ln(-ln) survival curves for 25(OH)D categories. We selected possible confounding variables for regression models based on our previous prospective findings [13-15]. We subsequently examined and ruled out a few additional possible confounders suggested by reviewers of this report (i.e., smoking, physical activity, education level, and cancer history). Final Model 1 adjusted for age (continuous), sex, and race (African American, white), and also verified that there was no significant sex or race by 25(OH)D interaction. Model 2 adjusted for age, race, sex/hormone replacement therapy (male, women using hormone replacement therapy (HRT), women not using HRT) and body mass index (continuous). Adding smoking status, sports activity score, education, and cancer history to Model 2 had no impact, and so these covariates were dropped. Model 3 added diabetes status (yes or no) and CRP (continuous). Model 4 added eGFR, PTH, calcium, and phosphorous (all continuous). Model 5 added Factor VIII and aPTT (both continuous) from ARIC visit 1. Whether 25(OH)D explains the African American excess of VTE was tested by comparing the race coefficient with and without 25(OH)D in Model 2. Ultimately, we did not show Models 3 in Table 1 and 5 in any tables, because results for Models 2 through 5 were similar.

Results

At baseline the mean (SD) serum 25(OH)D concentration was 24.3 (8.5) ng/mL (18.9 mg/mL in African Americans and 26.1 mg/mL in whites), and the median was 23.8 ng/mL.

As expected, lower 25(OH)D percentiles had a greater proportion of African Americans (Table 1), and most other characteristics varied by percentile.

During a median of 19.7 years of follow-up, 537 incident VTEs were identified (*n* = 349 in whites and 188 in African Americans; 336 provoked and 201 unprovoked). The Supplemental Table shows crude incidence rates of VTE according to levels of participant characteristics.

Adjusted for age, sex, and race (Model 1), there was no apparent association between 25(OH)D and VTE whether categorized on the basis of percentiles or analyzed per SD increment of 25(OH)D (Table 2). In the percentile model, the association was similar for men and women (i.e., sex by 25(OH)D interaction term p-value = 0.49) but appeared non-significantly stronger in whites than African Americans (race by 25(OH)D interaction term p-value = 0.10). When stratified by race (not shown in Table 2), the Model 1 hazard ratios (95% CI) across the five descending percentile groupings were 1 (ref), 0.96 (0.73, 1.26), 0.87 (0.64, 1.16), 1.32 (0.94, 1.86), and 1.44 (0.91, 2.26) in whites, whereas in African Americans the hazard ratios were 1 (ref), 0.63 (0.33, 1.18), 0.97 (0.56, 1.66), 0.94 (0.54, 1.64), and 0.82 (0.46, 1.47).

In the more fully adjusted models (Table 2), there was no evidence in the overall ARIC sample of an association of 25(OH)D with VTE. This was also true when we looked separately at provoked and unprovoked VTE (data not shown). There was also no evidence for association between 25(OH)D and VTE (*n* = 152 VTEs) when limited to the first 10 years of follow-up (and thus closer to the vitamin D measurement).

Since the previous two studies of 25(OH)D included only whites, we excluded African Americans calculated VTE hazard ratios for whites in ARIC (Table 3). When participants in the lowest quartile of 25(H)D were pooled and compared to the highest quartile, the Model 1 hazard ratio (1.36; 95% CI = 1.00, 1.83) was slightly elevated (p=0.05). However, there was no evidence of a dose-response, and adjustment for body mass index and hormone replacement therapy eliminated the association for quartile four versus one (Table 3, Model 2).

The hazard ratio of VTE for African Americans relative to whites was 1.63 (95% CI = 1.36, 1.97), adjusted for age, sex/HRT, and body mass index (BMI). When 25(OH)D percentiles were added to this model, the hazard ratio for race changed only to 1.62 (95% CI = 1.33, 1.98), suggesting that racial differences in 25(OH)D concentration explain little of the greater VTE risk of African Americans over whites in this cohort.

Discussion

This prospective population-based cohort study found no significant association between serum 25(OH)D levels and incidence of VTE over two decades of follow-up. Not surprisingly, therefore, racial differences in 25(OH)D did not explain why African Americans had a 63% higher VTE risk than did whites in this cohort.

Our results showing no association are consistent with the Tromsø Study, with *n* = 201 VTEs [4]. It is less consistent with the Copenhagen Study (*n* = 950 VTEs) which reported a weak inverse association between 25(OH)D and VTE [3]. All three studies appear to be of high quality, with 25(OH)D measured on blood samples stored more than a decade. The Copenhagen Study had the greatest statistical power among these three epidemiologic studies, but our study also had a large number of VTEs (n = 537). The two European studies included only whites, and our findings for whites alone hinted at a nonsignificant association between 25(OH)D and VTE, but none at all in African Americans. Interestingly, another study suggested low 25(OH)D is a stronger risk factor for arterial cardiovascular events in whites than African Americans [18]. In all three VTE studies, the 25(OH)D association (in whites) tended to be for low versus high 25(OH)D and not apparent across the entire 25(OH)D range. Meta-analyzing the hazard ratios of 1.28, 1.32, and 1.14 for the highest versus lowest 25(OH)D categories in the Copenhagen, Tromsø, and ARIC (whites) studies yields a pooled hazard ratio estimate of 1.25 (95% CI = 1.07, 1.45) with no evidence of between-study heterogeneity. Thus, the totality of evidence suggests that low 25(OH)D is associated with a modestly increased VTE risk.

Given that 25(OH)D was not associated overall with VTE incidence in ARIC, it was not surprising that lower levels of 25(OH)D did not explain the higher VTE risk of African Americans than whites. If African Americans and whites have similar levels of bioavailable vitamin D, as has been suggested [10], then that would also argue against differences in vitamin D levels contributing importantly to racial differences in VTE.

Some methodologic aspects of this study warrant consideration. Firstly, 25(OH)D in ARIC was measured on serum samples stored at −80 °C for two decades. Evidence exists that 25(OH)D is stable over at least four years [19] and is unaffected by multiple freeze-thaw cycles [20, 21]. Any sample deterioration, if uniform across the 25(OH)D distribution, should not have biased our results. Secondly, we had only a single measurement of 25(OH)D, and over the long follow-up participants 25(OH)D levels may have fluctuated. The Copenhagen Study reported a two decade 25(OH)D reliability coefficient of r = 0.45 [3], similar to the long-term reliability of other nutritional biomarkers. Thus, misclassification of 25(OH)D is substantial and would tend to weaken observed associations with VTE. Seasonal variation in 25(OH)D is another potential source of misclassification, but we and the two other cohort studies controlled for seasonal variation. Thirdly, we captured hospitalized VTEs only, but several pilot studies in ARIC have suggested that the vast majority of initial VTEs are hospitalized.

Conclusions

We did not find low 25(OH)D to be a risk factor for VTE in this prospective study. Yet, the totality of literature (three studies) suggests that low 25(OH)D might modestly increase VTE risk in whites. Possible future research might include more observational studies, including nonwhites; basic studies of 25(OH)D and thrombus generation; and examining VTE as an outcome in ongoing vitamin D supplementation trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of participants [mean standard deviation or %] in relation to categories of serum 25-hydroxyvitamin D [25(OH)D], Atherosclerosis Risk in Communities Study, 1990-1992

Characteristic	25(OH)D* Percentiles (High to Low)				
	75-100	50-74	25-49	10-24	<10
25(OH)D range, ng/mL	≥29.6	23.8-29.6	18.3-23.8	13.9-18.3	<13.9
Number of participants†	3,188	3,188	3,188	1,912	1,276
Age, years	57.4 (5.7)	57.1 (5.7)	56.9 (5.7)	56.4 (5.7)	55.8 (5.6)
African Americans, %	7.1	14.4	26.8	44.4	58.5
Men, %	51.1	51.0	42.9	33.3	24.4
Hormone replacement use in women, %	40.0	25.6	21.2	18.7	18.8
Body mass index, kg/m^2	26.3 (4.2)	27.6 (4.8)	28.3 (5.2)	29.4 (6.2)	30.1 (6.8)
Current smoking, %	19.2	19.3	21.9	25.9	30.0
Sports activity score ≥3, %	41.5	31.1	24.7	19.1	14.6
Greater than high school degree, %	45.7	45.6	46.6	43.4	45.8
History of cancer, %	7.3	6.6	6.9	5.7	4.9
Diabetes, %	9.0	12.0	16.5	21.0	21.1
C-reactive protein, mg/L	3.7 (6.7)	3.9 (6.4)	4.3 (7.1)	4.9 (6.4)	6.3 (10.5)
eGFR, mL/min/1.73m^2	93.2 (15.7)	94.4 (15.8)	96.4 (17.0)	96.8 (18.0)	98.4 (20.0)
Calcium, mg/dL	9.3 (0.4)	9.4 (0.4)	9.3 (0.4)	9.4 (0.4)	9.4 (0.5)
Phosphorous, mg/dL	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.6 (0.5)	3.6 (0.5)
Parathyroid hormone, pg/mL	36.8 (12.5)	40.4 (17.5)	43.1 (29.2)	47.1 (27.5)	53.6 (32.7)
Factor VIII, %‡	124.8 (33.3)	126.7 (35.8)	130.5 (38.2)	136.1 (41.8)	140.2 (45.4)
aPTT, seconds‡	29.1 (2.9)	29.1 (2.9)	29.1 (3.0)	29.0 (3.1)	29.2 (3.5)

aPTT, activated partial thromboplastin time; eGFR, estimated glomerular filtration rate; 25(OH)D, 25-hydroxyvitamin D.

*25(OH)D values adjusted for season separately by race.

†N = 12,518 to 12,752 for various characteristics.

‡Value from 1987-89.

Table 2

Hazard ratio (95% confidence interval) of venous thromboembolism (VTE) incidence in relation to either percentiles or 1 standard deviation decrement of serum 25-hydroxyvitamin D [25(OH)D], Atherosclerosis Risk in Communities Study, 1990-2011

		25(OH)D* Percentile (High to Low)					Per 1-SD Decrement of 25(OH)D†
		75-100 (≥29.6 ng/mL)	50-74 (23.8-29.6 ng/mL)	25-49 (18.3-23.8 ng/mL)	10-24 (13.9-18.3 ng/mL)	<10 (<13.9 ng/mL)	
Incidence rate per 1,000 py (95% CI)		2.2 (1.9, 2.7)	2.1 (1.7, 2.5)	2.3 (2.0, 2.8)	3.0 (2.5, 3.7)	2.8 (2.2, 3.6)	--
Model 1	N events	128	117	132	100	60	--
	Person-years	57154	56631	56415	32923	21303	--
	HR (95% CI)	1 (Ref.)	0.89 (0.69, 1.15)	0.96 (0.75, 1.24)	1.20 (0.90, 1.58)	1.09 (0.78, 1.52)	1.02 (0.92, 1.10)
Model 2	N events	128	117	132	100	60	--
	Person-years	57112	56601	56322	32847	21281	--
	HR (95% CI)	1 (Ref.)	0.84 (0.65, 1.08)	0.88 (0.68, 1.13)	1.04 (0.78, 1.38)	0.90 (0.64, 1.27)	0.96 (0.87, 1.05)
Model 4	N events	119	113	126	96	54	--
	Person-years	56176	55756	55007	31996	20475	--
	HR (95% CI)	1 (Ref.)	0.88 (0.68, 1.14)	0.92 (0.71, 1.19)	1.07 (0.80, 1.44)	0.89 (0.62, 1.28)	0.98 (0.88, 1.08)

Model 1: Adjusted for age, race, and sex.

Model 2: Adjusted for age, race, sex/hormone replacement therapy, body mass index.

Model 4: Adjusted for age, race, sex/hormone replacement therapy, body mass index, diabetes, C-reactive protein, estimated glomerular filtration rate, parathyroid hormone, calcium, and phosphorous.

CI, confidence interval; HR, hazard ratio; 25(OH)D, 25-hydroxyvitamin D.

*25(OH)D values adjusted for season separately by race.

†Standard deviation of 25(OH)D is 8.52 ng/mL.

Table 3

Hazard ratio (95% confidence interval) in white participants only of venous thromboembolism (VTE) incidence in relation to either percentiles or 1 standard deviation decrement of serum 25-hydroxyvitamin D [25(OH)D], Atherosclerosis Risk in Communities Study, 1990-2011

		25(OH)D* Percentile (High to Low)				Per 1-SD Decrement of 25(OH)D†
		75-100 (≥29.6 ng/mL)	50-74 (23.8-29.6 ng/mL)	25-49 (18.3-23.8 ng/mL)	<25 (<18.3 ng/mL)	
Model 1	N events	111	95	73	70	--
	Person-years	53433	48712	41863	27179	--
	HR (95% CI)	1 (Ref.)	0.96 (0.73, 1.26)	0.87 (0.64, 1.16)	1.36 (1.00, 1.83)	1.01 (0.91, 1.14)
Model 2	N events	111	95	73	70	--
	Person-years	53391	48712	41800	27144	--
	HR (95% CI)	1 (Ref.)	0.89 (0.68, 1.17)	0.78 (0.57, 1.05)	1.14 (0.83, 1.56)	0.95 (0.85, 1.06)
Model 3	N events	103	94	71	65	--
	Person-years	53166	48484	41414	26923	--
	HR (95% CI)	1 (Ref.)	0.95 (0.72, 1.26)	0.81 (0.60, 1.11)	1.13 (0.82, 1.57)	0.96 (0.86, 1.08)
Model 4	N events	103	94	71	64	--
	Person-years	52900	48354	41282	26858	--
	HR (95% CI)	1 (Ref.)	0.96 (0.72, 1.28)	0.82 (0.60, 1.12)	1.12 (0.80, 1.56)	0.96 (0.86, 1.09)

Model 1: Adjusted for age, race, and sex.

Model 2: Adjusted for age, race, sex/hormone replacement therapy, body mass index.

Model 3: Adjusted for age, race, sex/hormone replacement therapy, body mass index, diabetes, C-reactive protein

Model 4: Adjusted for age, race, sex/hormone replacement therapy, body mass index, diabetes, C-reactive protein, estimated glomerular filtration rate, parathyroid hormone, calcium, and phosphorous.

CI, confidence interval; HR, hazard ratio; 25(OH)D, 25-hydroxyvitamin D.

*25(OH)D values adjusted for season separately by race.

†Standard deviation of 25(OH)D is 8.52 ng/mL.