

Association of Vitamin D Level and Subclinical Coronary Artery Disease

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Abstract

Background: The role of vitamin D level in subclinical atherosclerosis remains controversial. We aimed to investigate the relationship between vitamin D level and coronary artery calcium score (CACS).

Patients methods: We investigated 303 consecutive patients referred to an outpatient clinic for CACS. The 25-hydroxy vitamin D [25(OH) D] levels were checked within three months of CACS evaluation. Vitamin D levels of <30 and <20 ng/mL were used as thresholds of vitamin D insufficiency and deficiency, respectively. The correlation between CACS and vitamin D was assessed. Unadjusted and covariate-adjusted logistic regression analyses were used to predict positive CACS.

Results: The mean age in this study is 61.8 ± 11.8 years (39.9% female). The majority of patients enrolled were Caucasian (87.4%). Median (interquartile range) serum 25(OH) D concentration was 30.0 (23.0, 39.0) ng/ml. Vitamin D was insufficient (<30 ng/ml) in 47.2% and deficient (<20 ng/mL) in 14.9% of the sample. Positive CACS (CACS>0) was prevalent in 206 (68%) participants. In the unadjusted model, the 25 (OH) D levels were not associated with the prevalence of CACS among all cases or among patients with positive CACS. Logistic regression models, after controlling for risk factors, did not change the results. In addition, among the 206 participants with prevalent CACS, 25 (OH) D levels were not associated with CACS severity.

Conclusions: Our single centre retrospective study in a population with low prevalence of vitamin D deficiency failed to find a significant relation between 25(OH) D level and CACS even when adjusted for risk factors.

Keywords: Vitamin D deficiency and insufficiency; Cardiac computed tomography; Coronary artery calcium score; Atherosclerosis

Introduction

There is a growing interest in the various health effects of vitamin D. Vitamin D levels are inadequate in about 50% of the world population [1]. Although vitamin D has traditionally been related to bone health, it is also linked to other chronic conditions, such as cardiovascular disease (CVD). Individuals may receive vitamin D from sun exposure, dietary intake, or supplements. Vitamin D₂ is synthesized by the ultraviolet irradiation of 7-dehydrocholesterol. Vitamin D is metabolized in the liver to 25-hydroxy vitamin D [25(OH) D], which is metabolized in the kidneys through the enzyme 25-hydroxy vitamin D-1 α -hydroxylase to 1, 25-dihydroxyvitamin D (the biologically active form). The renal production of 1, 25-dihydroxy vitamin D is regulated by the parathyroid hormone, serum calcium, and phosphorus levels [2].

There is no consensus on the optimal serum levels of vitamin D; classifications are mainly based on bone-related studies since available data are still not enough to give recommendations related to CVD [3]. The Endocrine Society Guideline suggests that individuals with vitamin D levels <30 ng/mL are insufficient and <20 ng/mL are deficient [3]. Some studies used a threshold of <15 ng/mL of vitamin D to define vitamin D deficiency that was associated with an increased risk for incident cardiovascular events [4-6].

There are conflicting results from the sparse studies that evaluated the effect of vitamin D level and vitamin D supplementation on CVD. Although several studies found no association between low vitamin D and CVD [7-11], there are studies reporting an association [4,5,12-14]. Vitamin D is essential for calcium homeostasis. Shen et al. identified common genotyped single-nucleotide polymorphisms in CYP24A1, a major enzyme responsible for the catabolism of vitamin D, that are

associated with the quantity of coronary artery calcium [15]. We aimed to investigate the role of low serum vitamin D levels in individuals living in "sunny Southern California" on coronary artery calcium score (CACS), a measurement of subclinical coronary atherosclerosis [16].

Patients Methods

Patient population

We retrospectively enrolled 7980 patients (39.9% female) who visited an outpatient cardiology clinic and had their vitamin D evaluated, in the period from 2005 to 2012, at the Cardiovascular Medical Group of Southern California (Beverly Hills, California). Out of those, we included 303 patients who underwent CACS scanning within three months of the date of serum vitamin collection. Exclusion criteria were prior coronary interventions (coronary stents or coronary artery bypass grafts). Average age was 61.8 ± 11.8 years. All patients had clinical demographics, cardiac risk factors (including hypertension, diabetes, dyslipidemia, current smoking, and family history of CVD), medication history, laboratory values, and CACS reports obtained

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from the clinic's patient chart. This study was conducted in compliance with human studies guidelines.

Vitamin D measurements

A blood sample was obtained from all patients under standardized conditions. Blood samples were sent to ARUP Laboratories, at 500 Chipeta Way, Salt Lake City, UT (www.aruplab.com). The 25(OH) D concentrations were measured using quantitative chemiluminescent immunoassays. According to the lab reference for 25 (OH) D levels, optimum level: 30-80 ng/mL, insufficiency: 20-29 ng/mL, deficiency: <20 ng/mL, and possible toxicity: >150 ng/mL.

Non-contrast CT acquisition

Images were acquired by a 64-slice multi-detector computed tomography scanner (General Electric Healthcare, Milwaukee - Wisconsin). The settings were 120 kVp, 430 mA, and 350 ms per rotation, with 227 ms in temporal resolution, 2.5 mm in slice thickness, and 75% trigger.

Coronary artery calcium score measurements

All CACS were evaluated by experienced readers. Coronary calcium was measured by the method of Agatston score [17] using GE SmartScore™ software. A calcified lesion was defined as at least three contiguous pixels with a density >130 Hounsfield units (HU). The lesion score was calculated by multiplying the lesion area by a density factor derived from the maximal HU. A total CACS was determined from summing individual lesion scores from each of the coronary artery segments.

Statistical analysis

25(OH) D concentration was evaluated as a continuous variable, scaled to 10 ng/mL, and was categorized using a threshold of 20 and 30 ng/mL. The Kolmogorov-Smirnov test was used to evaluate the normality of continuous variables. Continuous variables were presented as mean ± SD or median (interquartile range) because of the violation of normality. Student's t-test and the Mann-Whitney U test were performed to compare the risk distributions between vitamin D deficiency and normal groups. Categorical variables were presented as frequencies (percentage), and the chi-square test of proportion was performed to assess risk factors. Prevalent CACS was defined as an Agatston score > zero. A Poisson regression model was used to calculate the relative risk in the relationship between vitamin D levels (10 ng/mL scaled), deficiency (<20 ng/mL), insufficiency (<30 ng/mL), and prevalent CACS. Further adjustments were performed: covariates age, gender, race/ethnicity, body mass index, creatinine, vitamin D medication, cigarette smoking, hypertension, diabetes, hyperlipidaemia, and family history of coronary heart disease were entered into the model based on their potential roles as confounders. CACS severity was examined simply among patients with Agatston scores > zero. The Agatston score was assessed as a log-transformed continuous outcome. The relationship between vitamin D levels (10 ng/mL scaled), deficiency, and insufficiency and CACS severity were examined using linear regression, likewise, with adjusted models previously described. CACS were divided into groups according to CACS severity: CACS=0, 0<CACS ≤ 100, and 100<CACS ≤ 400 [18]. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC), and statistical significance levels of all the analyses were set at p=0.05 (2-sided).

Results

The mean age in this study is 61.8 ± 11.8 years (39.9% female). The majority of patients enrolled were Caucasian (87.4%), followed by African-American (5.0%). Only 10 patients had abnormally high creatinine levels >1.3 mg/dL (3.3%). The median (interquartile range) of serum 25(OH) D concentration was 30.0 (23.0, 39.0) ng/mL. Vitamin D was insufficient (<30 ng/mL) in 47.2% and was deficient (<20 ng/mL) in 14.9% of the participants. Positive CACS (CACS>0) was present in 206 (68%) participants. Table 1 demonstrates demographics and risk factor distributions among all participants and participants with vitamin D levels ≥ 20 ng/mL and <20 ng/mL. In the unadjusted model, the 25 (OH) D levels were not associated with the prevalence of CACS neither among all cases nor among patients with positive CACS.

Logistic regression models, after controlling for age and gender, did not show a significant association between serum 25(OH) D level (<30 ng/mL or <20 ng/mL) and all patients (Table 2) or patients with positive CACS (Table 3). Further adjustment for body mass index, creatinine, vitamin D supplement use, cigarette smoking, hypertension, diabetes, hyperlipidaemia, and family history of coronary heart disease

	Total (n=303, 100%)	≥ 20 ng/ml (n= 258, 85.1%)	< 20 ng/ml (n= 45, 14.9%)	P-value
Age, years	61.8 ± 11.8	61.6 ± 11.8	63.0 ± 11.2	0.478
Female, n (%)	121 (39.9)	99 (38.4)	22 (48.9)	0.184
Race, n (%) [†]				0.042 [‡]
White, Caucasian	229 (87.4)	202 (89.4)	27 (75.0)	
Black, African-American	13 (5.0)	9 (4.0)	4 (11.1)	
Hispanic	7 (2.7)	6 (2.7)	1 (2.8)	
Asian	7 (2.7)	4 (1.8)	3 (8.3)	
Other	6 (2.3)	5 (2.2)	1 (2.8)	
Body mass index, kg/m ² [‡]	27.1 (23.7, 30.3)	27.1 (23.7, 30.3)	28.0 (23.8, 30.9)	0.575
Vitamin D 25 Hydroxy, ng/ml [‡]	30.0 (23.0, 39.0)	33.0 (26.0, 41.0)	15.0 (12.0, 16.0)	<0.001 [†]
Vitamin D < 30 ng/ml, n(%)	143 (47.2)	98 (38.0)	45 (100.0)	<0.001 [†]
Vitamin D Medication, n(%)	79 (28.4)	69 (29.5)	10 (22.7)	0.362
CACS [‡]	41.0 (0.0, 340.0)	42.0 (0.0, 309.0)	30.0 (0.0, 629.0)	0.837
Prevalence of CACS (CACS>0), n(%)	206 (68.0)	175 (67.8)	31 (68.9)	0.888
CACS groups, n(%)				0.136
CACS = 0	97 (32.0)	83 (32.2)	14 (31.1)	
0 < CACS ≤ 100	84 (27.7)	69 (26.7)	15 (33.3)	
100 < CACS ≤ 400	55 (18.2)	52 (20.2)	3 (6.7)	
CACS > 400	67 (22.1)	54 (20.9)	13 (28.9)	
Creatinine, mg/dl	1.0 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	0.431
Active Smoker, n(%)	21 (7.2)	16 (6.4)	5 (11.4)	0.242
Hypertension, n(%)	136 (45.3)	111 (43.5)	25 (55.6)	0.135
Diabetes Mellitus, n(%)	25 (8.4)	18 (7.1)	7 (15.6)	0.059
Hyperlipidemia, n(%)	210 (70.2)	178 (70.1)	32 (71.1)	0.889
CHD Family History, n(%)	122 (44.7)	105 (45.1)	17 (42.5)	0.763

[†]p<0.05, [‡]p<0.01, [‡]p<0.001

[‡]Data presented by median (interquartile), and p-value was calculated by Mann-Whitney U test.

[†]P-value was presented by fisher's exact test.

Abbreviation: CACS: Coronary Artery Calcium Score; CHD: Coronary Heart Disease

Table 1: Demographics and characteristics by vitamin D concentration.

RR (95 CI)	Vitamin D				
	≥ 30 ng/ml	< 30 ng/ml	≥ 20 ng/ml	< 20 ng/ml	Per 10 ng/ml Lower Concentration
Total					
n(n of CACS>0)	160 (109)	143 (97)	258 (175)	45 (31)	303 (206)
Unadjusted model	1 (reference)	1.00 (0.85, 1.16)	1 (reference)	1.02 (0.82, 1.26)	0.99 (0.96, 1.01)
Adjusted model 1	1 (reference)	0.99 (0.86, 1.14)	1 (reference)	1.02 (0.83, 1.25)	0.99 (0.96, 1.01)
Adjusted model 2	1 (reference)	1.08 (0.78, 1.48)	1 (reference)	0.97 (0.56, 1.68)	0.97 (0.83, 1.13)

*p<0.05, **p<0.01, ***p<0.001 compared to reference group; CACS = coronary artery calcium score.

Adjusted model 1 adjusted for age, gender.

Adjusted model 2 adjusted for age, gender, ethnicity, body mass index, creatinine, vitamin D medication, cigarette smoking, hypertension, diabetes, hyperlipidemia, and family history of coronary heart disease.

Table 2: Associations of vitamin D concentration with prevalent coronary artery calcium score.

	Unadjusted model	Adjusted model 1	Adjusted model 2
Per 10ng/ml Lower Concentration	-0.14* (0.07)	-0.10 (0.05)	0.02 (0.21)
Vitamin D, ng/ml ≥ 30 <30	Referent -0.57* (0.26)	Referent -0.41 (0.22)	Referent -0.31 (0.42)
Vitamin D, ng/ml ≥ 20 <20	Referent -0.06 (0.37)	Referent -0.09 (0.30)	Referent 0.16 (0.65)

Abbreviations: CACS: Coronary Artery Calcium Score.

*p<0.05, **p<0.01, ***p<0.001 compared to reference group;

*p<0.05, **p<0.01, ***p<0.001; the calcium scores were logarithmic transformed.

Adjusted model 1 adjusted for age, gender

Adjusted model 2 adjusted for age, gender, ethnicity, body mass index, creatinine, vitamin D medication, cigarette smoking, hypertension, diabetes, hyperlipidemia, and family history of coronary heart disease.

Table 3: Associations of vitamin D concentration with coronary artery calcium score for patients with positive coronary artery calcium score (more than zero).

did not change the results. In addition, among the 206 participants with prevalent CACS, 25 (OH) D levels were not associated with the severity of CACS.

Discussion

In this study of the predominantly Caucasian individuals with low prevalence of vitamin D deficiency we did not observe an association between low serum 25(OH) D and subclinical CVD as measured by CACS. Vitamin D was deficient only in 14.9% (<20 ng/mL) of the individuals enrolled in our study. In contrast, previous studies in the US reported that more than 40% of the population has vitamin D deficiency [2]. The high prevalence of sufficient vitamin D levels in the current study may in part be due to the abundance of year-round sun exposure of the southern California climate, which would be expected to reduce vitamin D deficiency.

Low vitamin D levels have been associated with the cardiovascular risk factors hypertension, diabetes, obesity, and high triglyceride levels in the Third National Health and Nutrition Examination Survey [19]. Despite this finding, the association of low vitamin D and CVD is widely debated in the literature. Systemic reviews of the available research have been inconclusive and conclude that there is insufficient evidence to support vitamin D supplements to reduce the risk of CVD and improve cardiac outcomes [20,21]. Further, low vitamin D level

was linked to increased cardiovascular events in patients scheduled for coronary angiography procedure [12] and patients with kidney disease [22,23].

In contrast, there was no association between vitamin D level and cardiovascular events in healthy postmenopausal women [9], patients with stable coronary heart disease [24], in the MIDSPAN Family Study from the West of Scotland (populations with generally low sunlight exposure) [7], and the Rancho Bernardo Study [8]. In the Rancho Bernardo study, similar to our study, the median serum 25 (OH) D concentrations was 30.0 ng/mL and 28.4% of participants were on vitamin D supplements.

Unlike our study, two studies evaluated the incidence of new calcified lesions. The Multi-Ethnic Study of Atherosclerosis assessed the relation between vitamin D level (<15 ng/mL) and the incidence of new coronary calcium. In this study, there was no association between low 25(OH) D and the incidence of new coronary calcium lesions when vitamin D was treated as binary. However, considering vitamin D as a continuous variable, the incidence of new coronary calcium lesions was higher for low vitamin levels. The association was stronger among patients with chronic kidney disease [4]. Young et al. prospectively studied 374 non-Hispanic white individuals with type 1 diabetes and observed that 25(OH) D deficiency (<20 ng/mL) was associated with the presence of CACS at the 3-year visit (OR=3.3) [25]. In patients free of CACS at the 3-year visit, 25(OH) D deficiency predicted the development of CACS in those with the vitamin D receptor M1T CC genotype (OR=6.5, P=0.04), rather than in those with the CT or TT genotype (OR=1.6, P=0.57) [25]. However, that study only adjusted for age, sex, and hours of daylight [25].

Similar to our results, a number of studies evaluated the prevalence of CACS and reported no association between low circulating 25(OH) D levels and the prevalence of positive CACS (CACS >0). No associations were found among the 1370 patients without pre-existing clinical CVD in the Multi-Ethnic Study of Atherosclerosis, after adjusting for traditional risk factors, seasonal variation, and kidney function [4]. Among the 723 patients in the Multi-Ethnic Study of Atherosclerosis with coronary calcium lesions, the 25 (OH) D levels were not associated with the severity or progression of CACS [4]. Similarly, no association was found between vitamin D level and CACS among the 650 participants of the Amish Family Calcification Study [10], 1193 participants with type 1 diabetes [26], or 80 chronic kidney failure patients [27]. Freedman et al. assessed the association between vascular calcification and serum vitamin D level in 340 African-Americans with type 2 diabetes and observed a negative association between lower 25(OH) D levels with visceral, carotid, and aortal, but not coronary artery, calcified lesions evaluated by computed tomography [11].

In accordance with our study, a recent systemic review included ten studies (three longitudinal and seven cross-sectional in design) found insufficient evidence to support a consistent association between low vitamin D levels and CACS [28].

Our study is limited by its retrospective design and is from a single centre. The discordant findings between our result and studies in the literature may be due several reasons. Different studies have considered various confounding factors that may affect vitamin D level, for example cardiac risk factors, physical exercise, kidney function, and seasonal variation. In our study, we have adjusted for all traditional risk factors, kidney disease, and vitamin D medication history. It is also possible that an additional confounding influence was not considered. Despite studies observing a low 25(OH) D level and association CACS,

this does not demonstrate causality. Furthermore, vitamin D level fluctuates and a one-time 25(OH) D measurement may not reflect lifetime status; similarly, coronary calcium calcification develops over many years and we did not study the development of new calcium lesions [29].

Accordingly, our study of primarily Caucasian individuals with low prevalence of vitamin D deficiency and living in sunny southern California did not observe an association between low serum 25(OH) D and CACS.

Conflict of Interest

Dr. Budoff is a consultant for General Electric; the other authors have no conflict of interest.

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