

# Association of Low Vitamin D Levels With Noninfectious Anterior Uveitis

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**IMPORTANCE** Vitamin D plays an important role in both the innate and adaptive immune systems. It has been shown to contribute to the etiology of T-cell-mediated autoimmune diseases through the upregulation of type 2 anti-inflammatory T helper cells and the suppression of type 1 T helper cells. Noninfectious uveitis is postulated to be caused by immune dysfunction.

**OBJECTIVE** To determine whether there is an association between vitamin D levels and noninfectious anterior uveitis.

**DESIGN, SETTING, AND PARTICIPANTS** This was a case-control study. We identified patients with and without noninfectious uveitis using the Massachusetts Eye and Ear Infirmary Ocular Inflammation Database and electronic medical records from March 1, 2008, to December 12, 2015, at the Massachusetts Eye and Ear Infirmary Uveitis and Comprehensive Ophthalmology Clinics. One hundred patients with noninfectious anterior uveitis and 100 patients without uveitis were recruited. Patients with noninfectious uveitis were diagnosed by fellowship-trained uveitis specialists after exclusion of infectious causes and neoplastic masquerades of uveitis. All patients included had a total 25-hydroxyvitamin D level recorded. Multivariate regression models were constructed to determine the association between vitamin D levels and the presence of uveitis.

**MAIN OUTCOME AND MEASURE** Presence of noninfectious anterior uveitis.

**RESULTS** We identified 100 patients (64 white, 8 African American, 25 Asian, and 3 Hispanic) with a mean (SD) age of 51.8 (15.9) years (26 men) and 100 control individuals (58 white, 23 African American, 8 Asian, and 11 Hispanic) with a mean (SD) age of 53.6 (16.2) years (27 men). Hypovitaminosis D was associated with noninfectious uveitis in the univariate analysis (odds ratio, 2.53; 95% CI, 1.42-4.51;  $P = .002$ ). The association in multivariate regression after adjusting for age, sex, and race/ethnicity was 2.96 (95% CI, 1.60-5.50;  $P = .001$ ). The odds of developing uveitis were 4% lower for every 1-ng/mL increase in vitamin D level (odds ratio, 0.96; 95% CI, 0.93-0.99;  $P = .01$ ) in the main multivariate analysis.

**CONCLUSIONS AND RELEVANCE** In this retrospective study, lower vitamin D levels were associated with an increased risk of noninfectious anterior uveitis. However, this does not confirm a causal effect.

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Beyond its known effects on bone and calcium homeostasis, vitamin D acts as an immune modulator in the innate and adaptive immune systems.<sup>1,2</sup> It is hypothesized to be a key environmental factor in the etiology of T-cell-mediated autoimmune diseases by inhibiting Th1 and Th17 cell development. Vitamin D deficiency is present in patients with various autoimmune disorders including multiple sclerosis, rheumatoid arthritis, and Behçet disease.<sup>3-6</sup> Tian et al<sup>6</sup> suggested that the inhibitory effect of vitamin D on the Th17 and Th1 response was mediated via both T cells and dendritic cells.<sup>6</sup> The underlying pathophysiology in noninfectious uveitis is thought to be caused by uveal antigen-specific T lymphocytes.<sup>2</sup> Oral calcitriol (1,25 dihydroxyvitamin D<sub>3</sub>) has been shown to prevent and partially reverse experimental autoimmune uveitis in mice through Th17 T-cell inhibition.<sup>7</sup> There have been previous small studies examining vitamin D levels in patients with uveitis.<sup>8-10</sup> Because uveitis is driven by immune dysfunction, our purpose was to determine whether low vitamin D levels were associated with the presence of noninfectious anterior uveitis in a larger case-control study.

## Methods

This case-control study was approved by the institutional review board of the Massachusetts Eye and Ear Infirmary and conformed to the tenets of the Declaration of Helsinki and Health Insurance Portability and Accountability Act regulations. A waiver of informed consent was approved by the Massachusetts Eye and Ear Infirmary institutional review board because this study was retrospective and presented minimal risk to the patients involved. Case participants were patients with noninfectious anterior uveitis from the Massachusetts Eye and Ear Infirmary uveitis clinics with recorded 25-hydroxy vitamin D levels, measuring the serum concentration by mass spectroscopy or immunoassay from March 1, 2008, to December 12, 2015. Control participants were patients without any history of eye inflammation who had recorded 25-hydroxyvitamin D levels and a normal ophthalmologic examination apart from mild cataracts and/or refractive error. The type of uveitis examined was idiopathic noninfectious anterior uveitis to examine a homogenous population as well as to allow for a well-powered study. We excluded patients with conditions that affect vitamin D levels: age younger than 18 years, parathyroid dysfunction, sarcoidosis, renal failure, gastric bypass, systemic autoimmune diseases such as rheumatoid arthritis or inflammatory bowel disease, and medications that interfere with vitamin D metabolism including phenytoin, phenobarbital, high-dose oral prednisone, orlistat, and cholestyramine.

In the primary analysis, vitamin D was assessed as a dichotomous variable: vitamin D level lower than the laboratory normal range vs vitamin D level within the laboratory normal range. In the secondary analysis, the vitamin D level was analyzed as a continuous variable for maximal power (Figure). To obtain evidence that would support a causal role of low vitamin D in the onset of noninfectious anterior uveitis, we also performed subanalyses that took into account when vitamin

## Key Points

**Question** What are the associations between vitamin D levels and noninfectious anterior uveitis?

**Findings** In this case-control study, hypovitaminosis D was associated with noninfectious uveitis in the univariate analysis, and the odds of developing uveitis were 4% lower for every 1-ng/mL increase in vitamin D level.

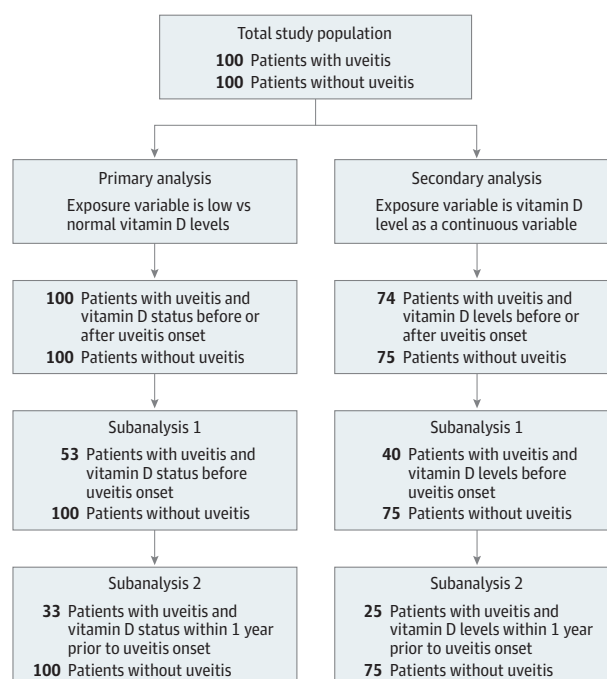
**Meaning** Lower vitamin D levels are associated with an increased risk of noninfectious anterior uveitis.

D levels were measured in relation to uveitis onset. The covariates recorded were age, sex, race/ethnicity, smoking status, vitamin D blood draw date, and history of vitamin D supplementation. For the analyses, the vitamin D draw date was dichotomized into whether it was within the Daylight Saving Time. The main outcome in all analyses was presence vs absence of uveitis. We used univariate and **multivariate logistic regression** using Stata/IC, version 12.1 (StataCorp). Age, sex, and race/ethnicity were included in all multivariate models. Other covariates with a *P* value of less than .10 in the univariate analyses were included in the multivariate models.

## Results

We identified 100 patients with noninfectious uveitis (64% white, 8% African American, 25% Asian, and 3% Hispanic) with

**Figure. Flowchart Showing the Number of Patients Included in the Primary and Secondary Analyses**



All patients had vitamin D levels from the same laboratory (Massachusetts General Hospital laboratory, normal range of 30-100 ng/mL; to convert to nanomoles per liter, multiply by 2.596).

Table 1. Clinical Characteristics of Participants With and Without Uveitis

Variables	Patients		P Value
	With Uveitis	Without Uveitis	
Total participants, No.	100	100	NA
Age, mean (SD), y	51.8 (16.2)	53.6 (15.9)	.42
Male sex, No.	26	27	.83
Race/ethnicity, No.			
White	64	58	.07
African American	8	23	
Asian	25	8	
Hispanic	3	11	
Smoking, No.	14	15	.79
History of vitamin D supplementation, No.	42	47	.44
Blood draw in low sun exposure months, No.	35	39	.50
Presence of low vitamin D, No.	67	44	.001

Abbreviation: NA, not applicable.

Table 2. Logistic Regression Results Examining the Association Between Hypovitaminosis D and Noninfectious Anterior Uveitis

	No.		Univariate		Multivariate <sup>a</sup>		Vitamin D Levels, Mean (SD), ng/mL	
Time of Vitamin D Drawn	Patients With Uveitis	Control Participants	OR (95% CI)	P Value	OR (95% CI)	P Value	Patients With Uveitis	Control Participants
Before or after uveitis onset								
Vitamin D as a dichotomous variable (low vitamin D vs normal vitamin D)	100	100	2.53 (1.42-4.51)	.002	2.96 (1.60-5.50)	.001	26.3 (11.9)	31.2 (12.7)
Vitamin D as a continuous variable <sup>b</sup>	74	75	0.97 (0.94-0.99)	.02	0.96 (0.93-0.99)	.011		
Before uveitis onset								
Vitamin D as a dichotomous variable (low vitamin D vs normal vitamin D)	53	100	2.90 (1.42-5.86)	.003	3.25 (1.52-6.95)	.002	25.2 (12.3)	31.2 (12.7)
Vitamin D as a continuous variable <sup>b</sup>	40	75	0.96 (0.91-0.98)	.019	0.95 (0.91-0.98)	.010		
Within 1 y prior to uveitis onset								
Vitamin D as a dichotomous variable (low vitamin D vs normal vitamin D)	33	100	3.90 (1.60-9.50)	.003	3.91 (1.52-10.10)	.005	22.8 (10.4)	31.2 (12.7)
Vitamin D as a continuous variable <sup>b</sup>	25	75	0.93 (0.89-0.97)	.005	0.92 (0.87-0.97)	.004		

Abbreviation: OR, odds ratio.

SI conversion factor: to convert vitamin D to nanomoles per liter, multiply by 2.496.

<sup>a</sup> Adjusted for age, sex, and race/ethnicity.<sup>b</sup> For patients who had vitamin D levels analyzed at the same laboratory (Massachusetts General Hospital laboratory, normal range of 30-100 ng/mL).

a mean (SD) age of 51.8 (15.9) years (26 men) and 100 control individuals (58 white, 23 African American, 8 Asian, and 11 Hispanic) without uveitis with a mean (SD) age of 53.6 (16.2) years (27 men). **Table 1** summarizes the clinical characteristics of patients. **Table 2** shows the results of univariate and multivariate analyses of noninfectious anterior uveitis and vitamin D as both a dichotomous and continuous variable. The odds of having uveitis were 2.5 times higher for patients with low vitamin D status where the vitamin level was obtained at any time before or after uveitis onset (odds ratio [OR], 2.53; 95% CI, 1.42-4.51;  $P = .002$ ). This association remained when the analysis was limited to patients who had vitamin D drawn at any time prior to uveitis onset (OR, 2.90; 95% CI, 1.42-5.86;  $P = .003$ ) and within 1 year prior to uveitis onset (OR, 3.90; 95% CI, 1.60-

9.50;  $P = .003$ ). The association also persisted in multivariate regression after adjusting for age, sex, and race/ethnicity at any time before or after uveitis onset (OR, 2.96; 95% CI, 1.60-5.50;  $P = .001$ ), any time prior to uveitis onset (OR, 3.25; 95% CI, 1.52-6.95;  $P = .002$ ), and within 1 year prior to uveitis onset (OR, 3.91; 95% CI, 1.51-10.10;  $P = .005$ ). This association strengthened when the analyses were limited to patients who had vitamin D drawn prior to uveitis onset.

There were 74 patients with uveitis and 75 control participants with vitamin D levels analyzed by the same laboratory (Massachusetts General Hospital laboratory, normal range, 30-100 ng/mL [to convert to nanomoles per liter, multiply by 2.596]). Mean (SD) vitamin D levels were 26.3 (11.9) ng/mL (range, 6-64 ng/mL) and 31.3 (12.7) ng/mL (range, 10-80 ng/

mL) in case participants and control participants, respectively. The associations in univariate analyses revealed OR, 0.97; 95% CI, 0.94-0.99;  $P = .02$  at any time before or after uveitis onset; OR, 0.96; 95% CI, 0.91-0.98;  $P = .02$  at prior to uveitis onset (25.1 ng/mL in case participants vs 31.2 ng/mL in control participants); and OR, 0.93; 95% CI, 0.89-0.97;  $P = .005$  within 1 year prior to uveitis onset (22.8 ng/mL in case participants vs 31.2 ng/mL in control participants). The associations in multivariate regression after adjusting for age, sex, and race/ethnicity demonstrated OR, 0.96; 95% CI, 0.93-0.99;  $P = .01$  at any time point before or after uveitis onset; OR, 0.95; 95% CI, 0.91-0.98;  $P = .01$  before uveitis onset; and OR, 0.92; 95% CI, 0.87-0.97;  $P = .004$  within 1 year prior to uveitis onset.

## Discussion

In this study, patients with noninfectious anterior uveitis with vitamin D levels drawn before or after uveitis onset had significantly lower vitamin D levels compared with controls. The association was stronger when the analyses were limited to patients whose levels were checked prior to the onset of uveitis, providing supportive evidence for the potential causal role of hypovitaminosis D. These data add to the increasing body of literature showing that vitamin D may play a role in autoimmune disease.<sup>1,3-6,8,11</sup> The benefits of vitamin D supplementation in those with autoimmune dis-

ease are being elucidated with vitamin D treatment trials underway for various autoimmune conditions including multiple sclerosis.

## Strengths and Limitations

There are several strengths to this study. Sun exposure, diet supplementation, skin pigmentation, medications, and certain systemic diseases can all affect vitamin D levels. Our study accounted for these variables by excluding patients with pertinent conditions and examining the remaining factors as covariates. This study was larger than what is, to our knowledge, the only previous investigation of vitamin D levels and uveitis.<sup>8</sup> The limitation of this study is that the cross-sectional design does not allow us to establish causal relationships of the associations we found.

## Conclusions

To our knowledge, this is the largest study to establish a relationship between low vitamin D levels and noninfectious anterior uveitis that does not confirm a causal effect. The association strengthens when the analysis is limited to patients with vitamin D levels prior to uveitis onset. A longitudinal, prospective study is needed to confirm the findings and to determine whether vitamin D supplementation is able to prevent or alter the course of uveitis.

## ARTICLE INFORMATION

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**Concept and design:** Grotting, Davoudi, Sobrin.  
**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Grotting, Davoudi, Sobrin.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Grotting, Davoudi, Sobrin.  
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**Supervision:** Sobrin.

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