A pilot study assessing the role of 25 hydroxy vitamin D levels in patients with vitiligo vulgaris

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Background: Very low vitamin D levels have been noted in patients with a variety of autoimmune diseases.

Objective: To determine whether low vitamin D levels are associated with autoimmunity in the setting of vitiligo vulgaris.

Methods: A prospective cohort study was conducted on 45 consecutive patients with vitiligo vulgaris. 25-Hydroxyvitamin D levels were determined from sera collected at the time of study enrollment. Logistic regression analysis of the relationship of 25-hydroxyvitamin D levels to disease state was performed, including surface area, recent-onset vitiligo, Fitzpatrick skin type and ethnicity, dairy intake, and both personal and family history of autoimmunity. Multiple univariate and multivariate logistic regression models were developed to assess the interrelationship of these parameters.

Results: 25-Hydroxyvitamin D levels were divided into 3 groups: 31.1% were normal (>30 ng/mL), 55.6% were insufficient (<30 ng/mL), and 13.3% were very low (<15 ng/mL). Insufficient 25-hydroxyvitamin D levels were associated with increasing Fitzpatrick phototypes (odds ratio [OR] = 1.76, 95% confidence interval [CI] = 1.12-2.77). Very low 25-hydroxyvitamin D levels were associated with comorbid autoimmune illness (OR = 10.00, 95% CI = 1.06-94.7), but not with age, gender, race/ethnicity, family history of vitiligo or autoimmune disease, new-onset disease, or body surface area affected. None of the surveyed patients reported daily vitamin D intake of greater than 200 IU.

Limitations: This study consists of a small cohort that assesses point prevalence without assessing seasonal variation in vitamin D levels.

Conclusions: Very low 25-hydroxyvitamin D levels (<15 ng/mL) appear to be a reasonable screening tool for the presence of comorbid autoimmunity. Furthermore, we demonstrate that Fitzpatrick phototype, rather than ethnicity, is specifically associated with 25-hydroxyvitamin D levels that are insufficient (<30 ng/mL). (J Am Acad Dermatol 2010;62:937-41.)

Key words: autoimmunity; hypopigmentation; 25 (OH) vitamin D; vitiligo vulgaris.

INTRODUCTION

Vitiligo vulgaris (VV) is an autoimmune depigmentation disorder that affects up to 1% of the population in the United States.[1] Vitiligo is commonly associated with systemic autoimmune conditions, including hypothyroidism and hyperthyroidism,[2] diabetes

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mellitus,[3] and Sjögren's syndrome.[4] Many autoimmune conditions have been associated with reduced vitamin D levels, including rheumatoid arthritis, diabetes mellitus, and multiple sclerosis.[5] However, little is known about the association of VV and reduced vitamin D levels.

Vitamin D is a secosteroid that has multiple effects on innate and adaptive immune responses through its varied effects on T and B lymphocytes, macrophages, and dendritic cells, all of which express vitamin D receptors.[5] Vitamin D analogues are effective topical therapies for cutaneous autoimmune conditions, including psoriasis and VV. In particular, pediatric patients with VV have been reported to respond to topical calcipotriene in combination with corticosteroids, even when prior response to the same topical corticosteroid was lacking.[6] Anecdotal reports of tacalcitol reversing pigmentary deficits in VV have appeared in the literature.[6,7] Given the effectiveness of topical vitamin D compounds on repigmenting vitiligo and the association of low vitamin D levels with autoimmunity, we sought to determine whether VV (ie, autoimmune pigmentary loss[8]) is associated with low vitamin D levels.

CAPSULE SUMMARY

- 25(OH) Vitamin D insufficiency and deficiency both in childhood and in adulthood have been associated with a variety of autoimmune diatheses.
- In this article the authors identify a subset of patients with vitiligo vulgaris with 25(OH) vitamin D deficiency who were at higher risk for secondary forms of autoimmunity.
- The data suggest that monitoring vitamin D levels in patients with vitiligo vulgaris may identify individuals at greater risk for secondary autoimmune diatheses.

METHODS

Subjects

Patients with VV from a dermatology clinic in New York City were selected to participate in the study based on a clinical diagnosis of VV by one of the investigators (N.B.S.) between the years 2007 and 2008. Exclusion from analysis was based upon refusal to have laboratory testing, loss to follow-up, oral vitamin D supplementation, dairy allergy, and incomplete documentation. The study was approved by the hospital's institutional review board review committee.

Vitamin D levels

Forty-five of 50 consecutive patients had sera drawn to determine 25-hydroxyvitamin D (25[OH]D) levels. Vitamin D levels and patient information were gathered between the months of February and November 2008. Laboratory testing was performed at the laboratories of Continuum Health Partners (St. Luke's- Roosevelt Hospital Center and Beth Israel Medical Centers, New York, NY).

Dietary intake of vitamin D

The patients were asked for the amount of dairy products eaten per day and supplements taken. No individual was taking a vitamin D supplement. Fifteen patients indicated intake of two dairy products per day, approximately 200 IU vitamin D, and 30 patients reported 100 IU (single vitamin D) or less of intake. Patient dietary intake of vitamin D was not a significant predictor of serum vitamin D levels or comorbid autoimmune illness.

Clinical parameters

Patient demographics, including ethnicity (Caucasian, black, Hispanic, Indian/East Asian, or Mediterranean/Arabic), history of vitiligo onset, dietary intake of vitamin D, as well as personal and family history of comorbid autoimmune disease were acquired from patient interviews in the clinic. Sunscreen usage patterns were not obtained. Fitzpatrick skin phototype and affected body surface area were assessed on clinical history and physical examination by an attending dermatologist (N. S.), based on clinical parameters and history of patient response to sun exposure.

Statistical analysis

Multiple univariate and multivariate logistic regression models were performed to examine relationships between insufficient 25(OH)-D levels (<30 ng/mL), as a dependent variable, as well as age, gender, race/ethnicity, Fitzpatrick skin type, the season in which 25(OH)D was tested, new-onset disease, positive history of comorbid autoimmune history, positive family history of autoimmune disease, and body surface area, as independent variables. Similar models looked at the association between very low 25(OH)D levels (<15 ng/mL) or positive history of comorbid autoimmune illness, as dependent variables, and the aforementioned variables. Regression models, and estimated odds ratios and 95% confidence intervals were calculated by using SPSS 17.0 Software (SPSS Inc., Chicago, IL).

Abbreviations used:

25(OH)D: 25 hydroxy vitamin D
BSA: body surface area
CI: confidence interval
OR: odds ratio
VV: vitiligo vulgaris

Two-sided *P* value less than .05 was taken to indicate statistical significance for all estimates.

RESULTS

Subject demographics

The study assessed 45 subjects, 2 to 71 years of age (mean = 22.6 years; standard deviation = 18.5 years); the demographic characteristics of the 45 subjects are listed in Table I. Subjects were distributed across all Fitzpatrick skin phototypes.

Vitiligo characteristics

The disease characteristics of the study subjects are presented in Table II. Approximately half (53%) of the subjects were newly diagnosed with VV less than 3 months prior to vitamin D level testing, defined as recent-onset VV (see Table II). Subjects predominantly had generalized disease (95.6%) as determined by the presence of bilateral depigmented lesions symmetrically distributed in characteristic locations, including periorificial areas, extensor surfaces of the extremities, and overlying joints. Body surface area (BSA) of depigmentation was divided into 3 groups: 1%-5 % BSA, 6%-19 % BSA, >20% BSA (57.8%, 20.0%, and 22.2%, respectively). One third (n = 15) of the subjects had one or more comorbid autoimmune diseases, including systemic autoimmune thyroiditis and systemic lupus erythematosus. Family history of autoimmune illnesses was reported in 51% of subjects.

Distribution of 25(OH)D levels

Sixty-two percent of the vitamin D levels were tested during the summer months of June through September. Serum concentrations of 25(OH)D spread from 7 to 52 ng/mL (mean ± standard deviation: 23.5 ± 9.0 ng/mL) and appeared to have a bimodal distribution. The first peak was centered on a peak value of 18 ng/mL, whereas the second peak was centered on a peak value of 31 ng/mL. Serum 25(OH)D concentrations were divided into 3 groups: 31.1% were normal (>30 ng/mL), 55.6% were insufficient (<30 ng/mL), and 13.3% were very low (<15 ng/mL). There were no significant differences in 25(OH)D concentrations between months (analysis of variance, $P = .60$); thus the 4 seasons were combined for logistic regression into summertime (June to September, inclusive) and the rest of the year (October through May, inclusive).

Table I. Demographics of study subjects

Demographic data	Number of subjects	%
Age, yr		
1-9	14	31.1
10-19	12	26.7
≥ 20	19	42.2
Sex		
Male	24	53.3
Female	21	46.7
Race/ethnicity		
Caucasian	16	35.6
African American	11	24.4
Hispanic	10	22.2
Indian/East Asian	7	15.5
Mediterranean/Arabic	1	2.2
Fitzpatrick skin type		
I	7	15.6
Caucasian	7	
II	9	20.0
Caucasian	8	
Hispanic/Latino	1	
III	6	13.3
Caucasian	1	
Hispanic/Latino	3	
Indian/East Asian	2	
IV	9	20.0
African American	1	
Hispanic/Latino	6	
Indian/East Asian	1	
Mediterranean/Arabi	1	
V	7	15.6
Indian/East Asian	3	
African American	4	
VI	7	15.6
African American	6	
Indian/East Asian	1	
Season tested		
Summer	28	62.2
Other	17	37.8

Logistic regression modeling of 25(OH)D levels

In the univariate logistic regression models, two distinct cut-off points for 25(OH)D were used for dependent variable encoding: 30 ng/mL (insufficiency) and 15 ng/mL (very low). By using a 30-ng/mL cut-off point, insufficient 25(OH)D levels were associated with Fitzpatrick skin phototype (OR = 1.76, 95% CI = 1.12-2.77), but were not associated with age, gender, race/ethnicity, season of testing, comorbid autoimmune illnesses, family history of vitiligo or autoimmune disease, new-onset disease, or body surface area affected . This implies that for every

Table II. Characteristics of vitiligo and comorbid autoimmune illness

Vitiligo	Frequency	%
Type		
Segmental	2	4.4
Generalized	43	95.6
Onset		
Old	21	46.7
New	24	53.3
Surface area		
1%-5%	26	57.8
6%-19%	9	20.0
≥ 20%	10	22.2
Comorbid autoimmune illness		
Negative	30	66.7
Positive	15	33.3
Systemic lupus erythematosus	2	4.4
Sjögren's syndrome	1	2.2
Hashimoto thyroiditis	8	17.8
Graves' disease	2	4.4
Alopecia areata	1	2.2
Inflammatory bowel disease	1	2.2
Family autoimmune history		
Negative	22	48.9
Positive	23	51.1

unit increase of the Fitzpatrick skin type, there is a 1.76-fold increased risk of 25(OH)D insufficiency. By using a 15-ng/mL cut-off point, very low 25(OH)D levels were associated with comorbid autoimmune illness (OR = 10.00, 95%CI = 1.06-94.7), but were not associated with Fitzpatrick skin type, age, gender, race/ethnicity, season of testing, family history of vitiligo or autoimmune disease, new-onset disease, or body surface area affected. The data suggest that patients with comorbid autoimmune disease may be identified by presence of very low 25(OH)D levels (15 ng/mL or lower).

A logistic regression model for comorbid autoimmune illness was then created by using one or more comorbid autoimmune illnesses for the dependent variable encoding. Comorbid autoimmune illness was associated with very low 25(OH)D levels (15 ng/mL) (OR = 10.00, 95% CI = 1.06-94.68) and inversely associated with younger age (OR = 0.04, 95% CI = 0.00-0.45), but not with insufficient 25(OH)D levels (30 ng/mL. With the use of a multivariable logistic regression model in which the independent variables are simultaneously adjusted for the other variables in the model, association with very low 25(OH)D levels and inverse association with younger age (1-9 and 10-19 years) remained statistically significant (OR = 20.04, 95%CI = 1.03-388.55, and OR = 0.06 [ages 1-9 years], 0.08, 95%CI = 0.004-0.684, 0.007-0.984, respectively [ages 10-19 years]). In our data set, the younger the patient, the less likely they were to have comorbid autoimmune disease. Moreover, patients with very low 25(OH)D levels have an increased risk of comorbid autoimmune disease. However, as interpreted above, since the 95%CI is wide, it is difficult to determine the precise OR.

DISCUSSION

We found that 25(OH)D levels in patients with VV have a bimodal distribution of 25(OH)D levels. There is a distinct population of patients with normal 25(OH)D levels and those with insufficient and deficient levels. Although prior studies have demonstrated ethnic variations in 25(OH)D levels, with black patients having lower levels than Hispanic patients, to our knowledge this is the first study to demonstrate stepwise incremental reduction in 25(OH)D levels with increasing Fitzpatrick skin type (IV to VI). This result is not very surprising given that past studies have shown black patients have greater insufficiency of 25(OH)D than white patients. Willis et al[9] demonstrated prepubescent white girls have higher 25(OH)D levels than black girls in the United States. Authors have previously postulated that lower vitamin D levels in patients of color may explain increased peripheral vascular disease and greater rates of invasive breast cancer.[10-12] Vitamin D receptor polymorphisms have been associated with breast cancer cases in Caucasian females, but not in African American females, suggesting that chronic low levels of vitamin D are more at fault.[13] Advancement of age was also associated with lower 25(OH)D levels, as has been previously demonstrated in larger assessments of pediatric and adolescent vitamin D blood levels.[14] In a Canadian sampling, children demonstrated insufficient vitamin D levels (there defined as 27.5 nmol/L or lower) in 2% to 13% of 9- to 16-year-old patients.[14] In our patient sample, low 25(OH)D levels were noted in patients 3 years of age and older and continue to decrease with advancement over the ensuing decades. The fact that low vitamin D levels are so common has recently prompted multiple health agencies, including the American Academy of Pediatrics and the American Academy of Dermatology to recommend higher levels of intake and supplementation with calcium and vitamin D.

The increase in lower vitamin D levels with age may also be contributory to the development of secondary autoimmunity. We found patients with comorbid autoimmune illness to be more likely to have very low 25(OH)D levels. In previous studies, low vitamin D levels have been associated with autoimmune diseases, including systemic lupus,[5,15-17] diabetes

mellitus,[18] rheumatoid arthritis,[18] and multiple sclerosis.[19,20] In multiple sclerosis patients, low vitamin D levels have been associated both with greater risk of disease and with greater disease activity.[19,20] The mechanism by which vitamin D affects autoimmunity is unknown, but there is a clear regulation of immune cells by vitamin D in vitro.[5,21] The association of low vitamin D levels needs to be further evaluated as it relates to vitiligo and multiple forms of autoimmunity. Either low 25(OH)D levels confer greater risk of developing secondary autoimmunity or the autoimmune inflammatory processes consume excess vitamin D, resulting in drops of 25(OH)D levels. In either event, 25(OH)D screening may be a worthwhile screen for deciding whether to test for secondary autoimmune illnesses in patients with VV.

Future studies need to be performed to assess the relationship of vitamin D receptor polymorphisms to disease activity in vitiligo; the role of vitamin D intake in prevention of disease onset in susceptible family members of patients with vitiligo; and whether vitamin D supplementation will help control long-term disease activity in VV.

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