Serum 25-hydroxyvitamin D concentration does not correlate with atopic dermatitis severity

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Background: An inverse correlation between serum 25-hydroxyvitamin D concentration and atopic dermatitis (AD) severity has been suggested.

Objective: To determine if a statistically significant relationship exists between serum 25-hydroxyvitamin D concentration and AD severity.

Methods: A cross-sectional study was conducted of patients with AD who were 1 to 18 years of age. An objective Severity Scoring of Atopic Dermatitis (SCORAD) and a serum 25-hydroxyvitamin D concentration were measured for each subject. Statistical analysis was performed using appropriate univariate tests and multivariable models.

Results: Ninety-four of 97 enrolled subjects were included in the analysis. Vitamin D deficiency (25-hydroxyvitamin D <20 ng/mL) was present in 37 subjects (39%), insufficiency (25-hydroxyvitamin D 21-29 ng/mL) in 33 (35%), and sufficiency (25-hydroxyvitamin D ≥ 30 ng/mL) in 24 (26%). The correlation between 25-hydroxyvitamin D concentration and SCORAD was not significant ($r = -0.001$; $P = .99$). A multivariate model showed that a lower serum 25-hydroxyvitamin D concentration was significantly associated with age 3 years or older ($P < .0001$), black race ($P < .0001$), and winter season ($P = .0084$).

Limitations: Limitations of this study include the inability to control for natural sunlight exposure, vitamin D intake, and AD treatment; in addition, only a single time point was captured.

Conclusions: Serum 25-hydroxyvitamin D concentration is not significantly correlated with AD severity in our pediatric population. (J Am Acad Dermatol 2013;69:40-6.)

Key words: asthma; atopic dermatitis; atopy; eczema; 25-hydroxyvitamin D; vitamin D.

INTRODUCTION

Vitamin D is a fat-soluble vitamin primarily made in the skin but also derived from dietary sources and supplements. Ultraviolet light exposure triggers the initial steps of synthesis of vitamin D. Subsequently, vitamin D is hydroxylated in the liver into 25-hydroxyvitamin D (25(OH)D), the major circulating

Abbreviations used:

1,25(OH)2D:	1,25-dihydroxyvitamin D
25(OH)D:	25-hydroxyvitamin D
AD:	atopic dermatitis
SCORAD:	Severity Scoring of Atopic Dermatitis

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form, and serum concentrations of this metabolite are considered the primary indicator of vitamin D status. A second hydroxylation step in the kidney, as well as in other target tissues, generates the active metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D). 1,25(OH)2D binds the vitamin D receptor and exerts its effects on cells by binding to vitamin D–responsive elements on DNA. In addition to regulation of calcium and phosphorus homeostasis, vitamin D plays a role in other physiologic processes and the vitamin D receptor is found on many target cells, including keratinocytes and almost all immune cells.[1]

Vitamin D plays a crucial role in normal cutaneous physiology and the immune response. It promotes cornified envelope formation and synthesis of the lipid permeability barrier.[2] Vitamin D also stimulates the production of human cathelicidin, an antimicrobial peptide that is deficient in atopic dermatitis (AD).[3,4] As the pathogenesis of AD involves a complex interplay of epidermal barrier dysfunction and dysregulated immune response, and vitamin D is involved in both processes, it is reasonable to expect that vitamin D status could be associated with AD risk or severity.

The results from prior studies offer conflicting information for practicing clinicians. Both increased and decreased vitamin D concentrations have been implicated as risk factors for the development of AD, while one study found an inverse correlation between serum 25(OH)D and AD severity.[5-7] Improvement of AD after oral supplementation with vitamin D has also been reported.[8-10] We sought to clarify the relationship between serum 25(OH)D and AD severity in our urban pediatric AD population.

CAPSULE SUMMARY

- Low serum vitamin D concentration has been associated with atopic dermatitis (AD) severity and risk.
- In a cross-sectional study of 94 children with AD, we found high rates of vitamin D deficiency but no correlation between serum vitamin D concentration and AD severity.
- Further studies are needed before vitamin D supplementation can be recommended as a treatment option for AD.

METHODS

Study population

Subjects were enrolled from the Children's Hospital of Wisconsin dermatology clinic in Milwaukee. Inclusion criteria included diagnosis of AD by a pediatric dermatologist and age 1 to 18 years old. Only children with a primary residence in Milwaukee County were enrolled in order to capture a high-risk urban population and minimize the confounding variable of increased sunlight exposure in rural children.[11] Exclusion criteria were as follows: chronic systemic disease other than asthma or environmental allergies, hyperimmunoglobulin E syndrome, ichthyosis disorder other than ichthyosis vulgaris, prior systemic therapy or phototherapy for AD, ongoing or prior treatment for known vitamin D deficiency, and chronic systemic corticosteroid therapy for asthma.

Study design

Institutional review board approval was obtained. Written informed consent was obtained from the parent or legal guardian, and subjects signed written assent when appropriate. AD disease severity was graded by the Severity Scoring of Atopic Dermatitis (SCORAD) index. The objective SCORAD has a range of 0 to 83 with an additional 20 points given for subjective symptoms of pruritus and sleep loss. An objective SCORAD score of <15 was classified as mild, 15-40 as moderate, and >40 as severe.[12] Patient variables of age, height, weight, race, Fitzpatrick skin type, and asthma diagnosis were documented. Subject enrollment was categorized by season: winter (January 1 to March 31), spring (April 1 to June 30), summer (July 1 to September 30), and fall (October 1 to December 31).

Serum concentration of 25(OH)D was obtained for each patient on the day of enrollment. The serum concentration of 25(OH)D was determined by using liquid chromatography tandem mass spectrometry (Quest Diagnostics Nichols Institute, San Juan Capistrano, CA). A serum 25(OH)D concentration was categorized as deficient if less than or equal to 20 ng/ml, insufficient if 21-29 ng/ml, and sufficient if equal to or greater than 30 ng/mL.[13] Subjects with deficient or insufficient serum 25(OH)D concentrations were treated with vitamin D supplementation as medically appropriate.

Statistical analysis

All statistical analyses were performed by means of SAS version 9.2 (SAS Institute, Cary, NC). Correlation between vitamin D and objective SCORAD was measured by Pearson correlation. The association of serum 25(OH)D concentration with categorical variables was assessed by one-way analysis of variance (ANOVA) and by nonparametric Wilcoxon rank sum test or Kruskal-Wallis test. A multiple linear regression model was used to

Table I. Vitamin D and atopic dermatitis: Demographic and clinical characteristics of subjects

Age (years); median (min-max)	3 (1-16)
Sex, No. (%)	
Male	40 (43.0)
Female	54 (57.0)
Race/Ethnicity, No. (%)	
White	8 (8.5)
Black	70 (74.5)
Latino	8 (8.5)
Asian	0
Native American	0
Other	8 (8.5)
Season of enrollment, No. (%)	
Winter	37 (39.4)
Spring	12 (12.8)
Summer	18 (19.1)
Fall	27 (28.7)
Mean serum 25-hydroxyvitamin D (ng/mL; min-max)	24.84 (6-58)
Vitamin D status, No. (%)	
Deficient ($\leq$20 ng/mL)	37 (39.4)
Insufficient (21-29 ng/mL)	33 (35.1)
Sufficient ($\geq$30 ng/mL)	24 (25.5)
Mean objective SCORAD (min-max)	31.48 (3.77-73.89)
Atopic dermatitis severity, No. (%)	
Mild (SCORAD <15)	14 (15.1)
Moderate (SCORAD 15-40)	58 (62.4)
Severe (SCORAD >40)	21 (22.6)

SCORAD, Severity scoring of atopic dermatitis.

examine relationships between serum 25(OH)D concentration and objective SCORAD while controlling for other variables. A stepwise selection procedure was used to determine the significant variables among race, age, gender, body mass index, season, and Fitzpatrick skin type, using a 5% significance level for entering the model. A nonparametric Friedman rank test was also used to test for association between serum 25(OH)D concentration and objective SCORAD while controlling for race, age, and season.

RESULTS

Subject characteristics

Ninety-seven patients were enrolled between November 2010 and February 2012. Serum 25(OH)D concentration was unavailable for 3 subjects; 94 subjects were included in the analysis (Table I). Forty subjects (43%) were male, and 54 (57%) were female. Patient ages ranged between 1 and 16 years (mean, 5.0 years; median, 3 years). Seventy (74.5%) were black, 8 (8.5%) were white, 8 (8.5%) were Latino, and 8 (8.5%) self-identified as other race or ethnicity; there were no Asian or Native American subjects. Fourteen children (15.1%) had mild AD, 58 (62.4%) had moderate AD, and 21 (22.6%) had severe AD; the SCORAD evaluation was incomplete for one patient. Vitamin D deficiency was present in 32 children (34.0%), insufficiency in 38 children (40.4%), and sufficiency in 24 (25.5%). In the 70 subjects of black race, vitamin D deficiency was present in 34 (48.6%), insufficiency in 22 (31.4%), and sufficiency in 14 (20.0%). Thirty-seven subjects (39.4%) were enrolled in the winter, 12 subjects (12.8%) in the spring, 18 subjects (19.1%) in the summer, and 27 subjects (28.7%) in the fall.

Vitamin D associations

On univariate analysis, lower serum 25(OH)D concentration was associated with age 3 years or older ($P < .0001$), female sex ($P = .0088$), black race ($P = .0019$), Fitzpatrick skin type VI ($P = .038$), diagnosis of asthma ($P = .030$), and winter season ($P = .042$) (Fig 1). There was a trend toward an association of lower serum 25(OH)D concentration with a body mass index of 25 ($P = .13$). On multivariate analysis, lower serum 25(OH)D concentration was significantly associated with age of 3 years or older ($P < .0001$), black race ($P < .0001$), and winter season ($P = .0084$) (Table II).

The Pearson correlation coefficient between serum 25(OH)D concentration and objective SCORAD was $r = -0.001$ ($P = .99$) (Fig 2), and total SCORAD was $r = -0.02$ ($P = .86$). The serum 25(OH)D concentration was lower in mild AD (mean, 23.0 ng/mL) compared with moderate AD (mean, 25.1 ng/mL) and severe AD (mean, 25.5 ng/mL; $P = .74$). When comparing 25(OH)D concentration between AD severity classes while controlling for race, age, and season, the Friedman rank test P value was .61.

DISCUSSION

There are multiple studies showing an association between vitamin D deficiency and adverse outcomes beyond its well-known role in bone health. Although these relationships have been the focus of intense research, the full implications of vitamin D deficiency remain controversial and many claims remain unproven. Controversy even exists as to the optimal serum concentration of 25(OH)D and recommended dietary intake of vitamin D, especially in children. The American Academy of Pediatrics recommends a daily intake of 400 IU of vitamin D for infants and children, whereas the Institute of Medicine and The Endocrine Society recommend 400 IU daily for infants and 600 IU daily for children 1 to 18 years old.[14-16] The American Academy of Pediatrics and The Endocrine Society use serum 25(OH)D concentrations of 20 ng/mL as the cut off for deficiency, but

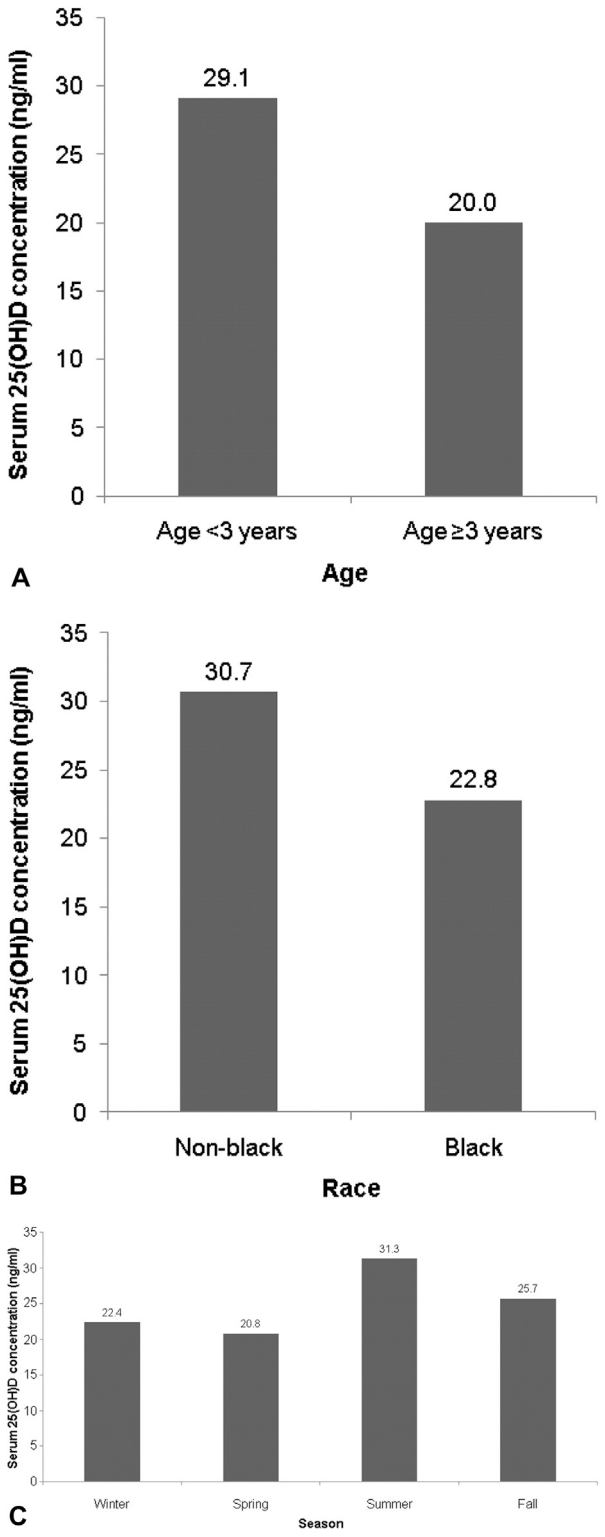

Fig 1. Mean serum 25-hydroxyvitamin D (25(OH)D) concentrations in pediatric atopic dermatitis subjects. **A**, Lower concentration in older subjects. **B**, Lower concentration in black subjects. **C**, Lowest concentration in winter and spring (25(OH)D concentrations were lowest in the spring on univariate analysis but lowest in the winter on multivariate analysis).

the Institute of Medicine proposes that 16 ng/mL is the appropriate cut-off level.[14-16] The Endocrine Society recommends the additional classification of 21 to 29 ng/mL as vitamin D insufficiency.[16] At the time of study conception, we used the existing Endocrine Society recommendations for categorizing serum 25(OH)D concentrations.

As reported by other authors, our study confirmed an association between serum 25(OH)D concentration and season, race, and age.[17-24] Since ultraviolet light exposure is necessary for vitamin D synthesis, it is not surprising that race and season have a significant impact on vitamin D status. The reason for the inverse relationship between serum 25(OH)D concentration and age is unclear, though some authors have theorized that older children may have decreased oral supplementation or spend less time playing outdoors.[21,24]

Female sex has been associated with lower serum 25(OH)D in some studies, but this relationship was seen only on univariate analysis in our study.[17,19] Body mass index has been inversely correlated with serum 25(OH)D, although this association did not reach statistical significance in our study.[17,18,20,21] In our population, a diagnosis of asthma was associated with significantly lower serum 25(OH)D concentrations than in patients without asthma, though the difference did not achieve statistical significance on multivariate analysis. Multiple studies have associated vitamin D deficiency and lower 25(OH)D with higher asthma risk.[25-29] Serum 25(OH)D concentration has also been inversely correlated with asthma severity.[30-33] Our study was not specifically designed and powered to address these other correlations, perhaps explaining the lack of a statistically significant association on multivariate analysis.

Nearly 40% of our subjects were vitamin D deficient, a higher rate than found in a National Health and Nutrition Examination Survey in which an estimated 18% of children ages 1 to 11 years had serum 25(OH)D concentrations less than 20 ng/mL.[34] Our study population had a high proportion of black subjects, nearly 75%, of whom 48.6% had a serum 25(OH)D concentration of less than or equal to 20 ng/mL, again higher than the national rate of 34%.[34] These numbers are in contrast to a study of Japanese schoolchildren that found children with AD had serum 25(OH)D concentrations comparable to their peers.[26] Further studies are necessary to determine whether vitamin D deficiency is more prevalent in children with AD, or if other factors, such as race or geography, contributed to the high rates seen in our population.

The evidence linking vitamin D to atopy and AD has been conflicting. One study suggested that

Table II. Multivariate analysis of factors associated with serum 25-hydroxyvitamin D concentration in 94 children with atopic dermatitis

Variables	Mean* serum 25(OH)D concentration	*P* value
Objective SCORAD (overall)		.60 (*df* = 2)
Objective SCORAD (mild)	25.55	.32
Objective SCORAD (moderate)	26.86	.49
Objective SCORAD (severe)	28.31†	
Age <3 years	31.07	<.0001
Age ≥3 years	22.74†	
Non-black race	31.13	<.0001
Black race	22.68†	
Season (overall)		.0084 (*df* = 3)
Winter	23.89	.04
Spring	24.12	.15
Summer	31.38	.22
Fall	28.24†	

df, Degrees of freedom; *SCORAD*, Severity Scoring of Atopic Dermatitis.
*Least squares mean.
†Reference value.

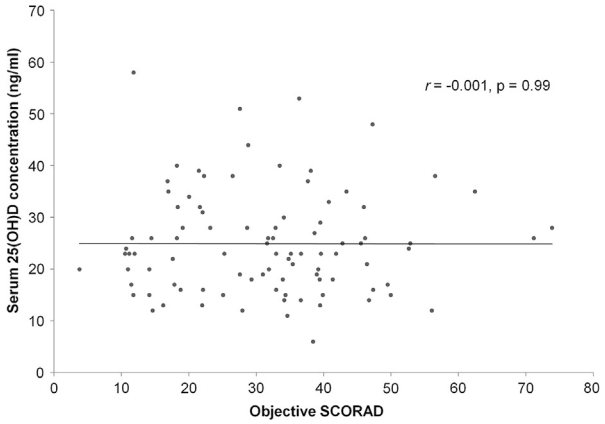

Fig 2. Correlation between 25-hydroxyvitamin D (25(OH)D) concentration and objective Severity Scoring of Atopic Dermatitis (SCORAD) in 94 children with atopic dermatitis.

increased vitamin D intake during infancy predisposed to the development of AD in later childhood.[6] Miyake et al[35] found higher levels of maternal vitamin D intake to be protective against the development of AD, while there was no effect of maternal vitamin D intake on AD risk in a study by Camargo et al.[36] In contrast, a study in obese adults found that those who were vitamin D deficient were 5 times more likely to have AD than those who were vitamin D replete.[5]

Vitamin D has also been suggested as a treatment for AD. A small randomized controlled trial of 11 children found that oral ergocalciferol 1000 IU daily reduced AD severity more than placebo, though the results were not statistically significant.[8] Vitamin D treatment resulted in statistically significant decreases in the SCORAD index in adult AD patients in two additional randomized, placebo-controlled, double-blinded trials.[9,10] Larger studies are needed before vitamin D can be recommended as a treatment option for AD.

Although an association between serum 25(OH)D concentration and AD severity has been reported in other studies, we were unable to replicate the findings in our urban population. Peroni et al[7] employed a similar cross-sectional study design with 37 children with AD and found a negative correlation between serum 25(OH)D concentration and total SCORAD ($r = -0.49$, $P = .002$). Vitamin D deficiency was present in 21%, lower than the 34% in our cohort. In their study, serum 25(OH)D concentration was also significantly lower in children with severe AD (20.5 ± 5.9 ng/mL) compared with those with moderate (27.5 ± 8.3 ng/mL) and mild AD (36.9 ± 15.7 ng/mL). Interestingly, our subjects with mild AD had decreased mean serum 25(OH)D concentrations compared with the moderate and severe AD groups, although these differences were not found to be statistically significant. The study by Peroni et al excluded children who had used topical corticosteroids within the past 4 weeks and topical calcineurin inhibitors within 2 weeks prior to study enrollment, which may have improved the accuracy of the SCORAD in determining AD severity. Additionally, environmental differences such as natural sunlight exposure and population differences such as race may explain the differences in serum 25(OH)D concentration and rates of vitamin D deficiency.

The main limitation of this study is that we were unable to control for AD treatments as most patients evaluated, even new patients, had been prescribed topical therapies. Compliance with topical corticosteroid use is poor, and controlling for self-reported steroid use may not have been accurate.[33] The fact that most subjects had moderate to severe AD suggested under-treatment or non-adherence to the prescribed therapy, and we believe the SCORAD accurately reflected AD severity at the time of evaluation. Confounding variables of sunlight exposure and dietary vitamin D intake were not assessed because reliable quantitative measures were not thought to be feasible.

A cross-sectional study design was chosen to best correlate serum 25(OH)D concentration with AD severity across a study population of AD patients. As a result of the cross-sectional nature, only a single time point was captured. Other study designs could explore the relationship between vitamin D and AD

and answer the correlation question more definitively. A cohort study would better assess correlation between SCORAD and serum 25(OH)D concentration over time for a given individual. A case-control study could evaluate the correlation between 25(OH)D and SCORAD while controlling for confounding variables, although recruitment for such a study would be difficult.

In conclusion, although further studies may elucidate whether a relationship exists between AD and vitamin D, we found no statistically significant correlation between vitamin D status and AD severity, as measured by serum 25(OH)D and SCORAD, respectively, in our urban pediatric AD population. There were statistically significant associations between serum 25(OH)D concentration and age, race, and season. Vitamin D deficiency and insufficiency were prevalent in children with AD, but whether this represents a higher prevalence rate than in the general population is unclear.

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