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Serum vitamin D levels in a cohort of adult and pediatric patients with eosinophilic esophagitis

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Abstract

Background—Vitamin D deficiency has been associated with increased risk for severe asthma, challenge-proven food allergy, and severe atopic dermatitis. Vitamin D levels have not been reported in patients with eosinophilic esophagitis (EoE).

Objective—To determine levels of 25-hydroxyvitamin D in a cohort of patients with EoE.

Methods—Total serum 25-hydroxyvitamin D was measured using liquid chromatography with tandem mass spectroscopy in adults ($n = 35$) and children ($n = 34$) with EoE. Results were compared with patient demographics, EoE-specific disease parameters, markers of sensitization, and features of severity using multivariable logistic regression.

Results—The median vitamin D level was 28.9 ng/mL. Patients with insufficient vitamin D (<30 ng/mL) were older (median 25.5 vs 16.2 years) and had a higher body mass index (median 25.2 vs 19.8 kg/m²). Peak median esophageal eosinophil counts were not significantly different for vitamin D insufficient and sufficient patient groups; however, higher vitamin D levels correlated with higher histologic eosinophil counts ($R = 0.61$, $P = .03$). Although there were no statistical differences in total IgE or levels of specific IgE between patients with vitamin D insufficiency and those with sufficiency, a positive skin prick test reaction to peanut was more common in patients who had vitamin D insufficiency (adjusted odds ratio 7.57, $P = .009$). Vitamin D insufficiency was not associated with surrogate markers of severity (dilation in adults or hospitalization or emergency visits in children).

Conclusion—In these patients with EoE, vitamin D levels were low overall (median <30 ng/mL). The only marker of sensitization associated with insufficient vitamin D in these patients with EoE was a positive skin prick test reaction to peanut.

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Introduction

Eosinophilic esophagitis (EoE) is a chronic disease defined by the histopathologic finding of at least 15 eosinophils per high-power field (hpf) in an esophageal biopsy specimen from a patient with concurrent upper gastrointestinal symptoms after treatment with a proton pump inhibitor.¹ Recognition of EoE has increased dramatically during the past 10 to 15 years.^{2–4} The current prevalence is estimated to be similar to that of inflammatory bowel disease.^{3,4} The reason for the increase is unclear. Based on an association with other atopic diseases and the frequent finding of specific sensitization to food and environmental allergens, EoE is generally believed to be an allergic disease.

An association between vitamin D and allergic diseases was first proposed when Litonjua and Weiss⁵ suggested that an increased risk for asthma could be related to vitamin D deficiency. Evaluation of vitamin D status in adults and children in Costa Rica and children enrolled in the Childhood Asthma Management Program (CAMP) study showed that lower vitamin D level (<30 ng/mL) is relatively common in patients with moderate to severe asthma.^{6,7} Studies have suggested that there also is an association between vitamin D and other atopic diseases. An inverse correlation between vitamin D level and severity of atopic dermatitis has been observed.⁸ A relation between food allergy and vitamin D status has been supported by studies demonstrating a higher incidence of epinephrine auto-injector prescriptions and emergency department visits for allergic reaction in the northern United States and increased challenge-proven peanut and egg allergies in infants with insufficient levels of vitamin D.^{9,10}

Vitamin D deficiency has become an epidemic in the United States such that approximately 42% of adults and 15% of children are deficient in vitamin D depending on the defining value.^{11,12} The Institute of Medicine classifies vitamin D status based on the level of total 25-hydroxyvitamin D: deficiency is defined as a level lower than 20 ng/mL, insufficiency as a level from 20 to 30 ng/mL, and sufficiency as a level of at least 30 ng/mL.¹³ To date, no studies have addressed vitamin D status in patients with EoE. The objective of this study was to evaluate relationships between serum total 25-hydroxyvitamin D levels and demographics, EoE-specific disease parameters, markers of sensitization, and features suggestive of disease severity in adult and pediatric patients with EoE.

Methods

Study Patients

Patients diagnosed with EoE were recruited from September 2010 through April 2014 from the allergy clinics at The Ohio State University Wexner Medical Center and Nationwide Children's Hospital (Columbus, Ohio) for a prospective, cross-sectional study of skin prick allergy testing and serologic IgE assays. The study was independently approved by the institutional review boards of Nationwide Children's Hospital and The Ohio State University. Thirty-five adult and 34 pediatric patients who had given consent for additional testing and had sufficient serum were included in the present study.

Additional information that had been collected for the original study was included in the present analysis. Questionnaire responses were used to establish symptoms and allergic history. Medical charts were reviewed to obtain endoscopy findings, pathology reports, hospitalizations, and emergency department visits. Results of skin prick testing and serum IgE measurements were used as a marker of allergic status. These tests were performed using Greer Pick (adult subjects) or Sharp-Test Applicators (pediatric subjects) to apply commercially available extracts (Greer Laboratories, Inc, Lenoir, North Carolina). Skin prick testing to foods included egg, milk, wheat, soy, peanut, and tree nuts. Environmental allergens tested included dust mite, cat, dog, *Alternaria* species, *Cladosporium* species, *Penicillium* mix, *Aspergillus* mix, ragweed, and a variety of locally relevant tree pollens, grass pollens, and weed pollens. Skin prick test responses with a wheal at least 3 mm larger than the negative control were considered positive. Total IgE and specific IgE antibody to chicken egg, cow's milk, wheat, soy, peanut, cashew, *Dermatophagoides pteronyssinus*, cat, dog, mold mix, birch, rye grass, weed mix, and ragweed were measured using the ImmunoCAP System (ThermoFisher Scientific/Phadia, Uppsala, Sweden). Specific IgE antibody values of at least 0.35 IU/mL were considered positive.

Serum 25-Hydroxyvitamin D

Serum samples were stored at -80 C until analysis was performed. Total 25-hydroxyvitamin D was measured by the Analytical Chemistry and Small Molecules Core at the Research Institute at Nationwide Children's Hospital using a modified previously published method.¹⁴ Samples were analyzed using liquid chromatography and tandem mass spectroscopy on an AB SCIEX 4000 QTRAP (AB SCIex, Framingham, Massachusetts) coupled with a Shimadzu 20 Series high-pressure liquid chromatography system (Columbia, Maryland). Analysis was performed using multiple reaction monitoring. Accuracy and precision were evaluated with an internal standard of 50 ng/mL of vitamin D. Serum 25-hydroxyvitamin D₂ and D₃ levels were measured in duplicate for each sample. Total 25-hydroxyvitamin D was the sum of the D₂ and D₃ fractions. The mean of the 2 assays was used for analysis.

Statistical Analysis

Patient demographics and clinical characteristics were summarized across vitamin D sufficiency levels, where sufficiency was defined as at least 30 ng/mL and insufficiency as lower than 30 ng/mL for 25-hydroxyvitamin D. Categorical variables are presented as frequencies and percentages and continuous variables are presented as medians. Logistic regression was used to determine whether vitamin D levels were associated with binary clinical outcomes and linear regression was used to determine whether there was an association with continuous outcomes and vitamin D levels. All these continuous outcomes, except peak esophageal eosinophil counts, were first natural log transformed to normalize the distribution and stabilize the variance across groups. Seven of the 69 subjects were missing body mass index (BMI) information. Thus, multiple imputation (M = 20) was used to impute these missing values using a linear regression in which the patient's age, sex, race, serum vitamin D levels (continuous variable), rhinitis status, and asthma status were used as predictors. All analyses were run using STATA 13.1 (StataCorp, College Station, Texas).

Results

The EoE cohort was similar to other groups that have been reported. Most patients were male, and there was a high prevalence of other allergic diagnoses (Table 1). The finding of positive skin prick test reactions to food and/or environmental allergen was common (Table 1). Vitamin D levels in patients with EoE ranged from 9.63 to 83.9 ng/mL (median 28.9 ng/mL; Fig 1). In this cohort, 14 patients (20%) were deficient in vitamin D (<20 ng/mL) and an additional 22 patients (32%) were considered to have insufficient levels (20–30 ng/mL; Fig 1). The sample included patients from 23 of 88 counties in Ohio; the county with the largest number of patients ($n = 26$) was Franklin, which is centrally located in the state (latitude 40°N; Fig 2). In addition, 1 patient was from northern Kentucky and another was from central West Virginia (these patients are not shown in Fig 2). The southernmost location from which patients were included in the study was 38.12°N. Median vitamin D levels varied but were not significantly different based on the season during which the serum was collected ($P = .3$; Fig 3).

Potential relationships between patient demographics and clinical characteristics and vitamin D level were explored by comparing patients with vitamin D sufficiency and those with insufficiency (Table 2). Sex and race were similar regardless of vitamin D level. However, patients with insufficient vitamin D levels were older (median 25.5 years, range 4.8–64 years) than those who had sufficient levels (median 16.2 years, range 1.4–59 years, $P = .02$). Median BMI was higher in patients who had insufficient vitamin D levels (25.2 kg/m², range 14–48 kg/m²) than in patients who had sufficient levels (19.8 kg/m², range 13–36 kg/m², $P < .001$). In most cases, the proportion of patients reporting each symptom and associated allergic diagnosis was similar between the groups with insufficient and sufficient vitamin D levels. However, the proportion of patients having food impaction was larger in the group with an insufficient vitamin D level (86.1%) compared with a sufficient level (60.6%, $P = .03$). After adjusting for age and BMI, the relationship between food impaction and vitamin D insufficiency was not significant ($P = .3$).

Differences in measurements of eosinophils also were analyzed based on vitamin D status. Median peripheral blood eosinophil counts were not significantly different in patients with vitamin D insufficiency (330/mm³, range 100–1,400/mm³). The median for patients with sufficient vitamin D was 400/mm³ (range 120–1,100/mm³). Similarly, peak esophageal eosinophil counts did not differ in patients with insufficient vitamin D (median 35/hpf, range 15–70/hpf) and patients with sufficient vitamin D (median 45/hpf, range 15–130/hpf). However, there was a moderate positive correlation between esophageal eosinophil count and vitamin D level such that a *greater* number of eosinophils per hpf or high power field was associated with a *higher* vitamin D level ($R = 0.61$, $P = .03$; Fig 4).

Multivariable analysis of continuous measurements of sensitization for patients with insufficient and sufficient vitamin D levels showed no differences in total IgE or levels of serum specific IgE. However, logistic regression of the categorical skin prick test results showed that a positive skin prick test reaction to peanut was more common in patients who had vitamin D insufficiency (Table 3). The proportion of patients with a positive skin prick test reaction to peanut who had vitamin D insufficiency was 38.4% compared with 9.4% in

those who had sufficient levels. This result remained significant when adjusted for age and BMI ($P = .009$). There was no significant association between sensitization to other food allergens or environmental allergens and vitamin D level.

Although this study sample was small, the relationship between potential markers of EoE severity and vitamin D levels was investigated. For adults, esophageal dilation was used as a marker of severity. Dilation was performed in 6 adults (30%) with an insufficient vitamin D level and 6 (40%) with a sufficient vitamin D level. In children, severity was evaluated based on emergency department visit or hospitalization. A larger proportion of patients with an insufficient vitamin D level had a hospitalization or an emergency department visit (7, 44%) compared with those with a sufficient vitamin D level (3, 17%, $P = .1$).

Discussion

Eosinophilic esophagitis is an increasingly recognized allergic condition for adult and pediatric patients. Low levels of serum vitamin D have been proposed as one explanation for the increased prevalence of atopic disease in Westernized countries, regions farthest from the equator, inner city populations, and obese individuals.⁵ The emerging epidemiologic patterns of EoE share some of these features. First, the patient burden of EoE has been reported to be significantly greater in the northeast.¹⁵ Second, African-American patients with EoE who lived in 1 inner city were found to have a more severe phenotype.¹⁶ Third, gastroesophageal reflux, a disease that might have some overlap with EoE, is associated with increased BMI such that these patients have more severe and more frequent symptoms. Thus, it seemed possible that low vitamin D levels were related to the increased prevalence of EoE. In the present group of adult and pediatric patients with EoE, vitamin D levels were low overall and a positive skin prick test reaction to peanut was associated with “insufficient” levels.

Historically, clinical manifestations of vitamin D deficiency were associated with hypocalcemia, hypophosphatemia, and decreased alkaline phosphatase and manifested as bone disease and rickets.^{17,18} During the 1970s and 1980s, concern for the increased frequency of insufficient vitamin D levels in the general population emerged, and the cause was presumed to be the shift to an indoor lifestyle and/or a change in diet.^{19,20} Interestingly, the first links between vitamin D deficiency and allergy were presented from the viewpoint of recommended nutritional changes resulting from allergic disease (to food) causing vitamin D deficiency.²¹ In the present patients, no association was found between vitamin D levels and dietary elimination of cow's milk. Before study recruitment, 11 of 69 patients (15.9%) were avoiding cow's milk. Eight of these patients were children, 6 of whom had sufficient vitamin D. This result is not surprising given that a separate comparison of patients ingesting cow's milk with those taking a cow's milk substitute showed that vitamin D intake was similar in the 2 groups.²²

It is somewhat difficult to compare results among studies because for many years, and on a continued basis, the required level of vitamin D has not generally been agreed upon and levels can vary depending on the assay used. Based on cutoffs used in publications from the past decade, vitamin D insufficiency did appear to be common in the present patients with EoE, with 20% having levels below 20 ng/mL.^{11,23,24} However, these results appear to be

similar to levels reported from an analysis of data from the Third National Health and Nutrition Evaluation Survey.²⁵ In that population-based sample, 24.3% of boys of all races (12–19 years old) were found to have serum vitamin D below the threshold of 50 nmol/L (equivalent to 20 ng/mL). Vitamin D levels were lower in girls. Older age, obese BMI, protection from the sun, and no or rare intake of foods rich in vitamin D also were associated with having lower levels of vitamin D.²⁵ A larger proportion of the present patients with EoE (52%) had vitamin D insufficiency (<30 ng/mL) compared with children who participated in the CAMP study (35% had insufficient levels).⁷

Low levels of vitamin D could be related to EoE in several ways. First, vitamin D has been shown to have a direct influence on immune function by inhibiting human dendritic cells and inducing T-regulatory cells, resulting in overall downregulation of T-effector cells.²⁶ Second, vitamin D receptor knockout mice have exhibited disruption in epithelial junctions, suggesting that vitamin D also plays a role in maintaining the intestinal mucosal barrier.²⁷ This could suggest an indirect influence on gastrointestinal tolerance and exposure to allergens. Third, vitamin D has been shown to alter gene expression in smooth muscle cells in the airway, affecting pathways for cell recruitment, growth, and survival, which could contribute to tissue remodeling.²⁸ A similar process could occur in the smooth muscle of the esophagus in EoE. From a clinical standpoint, some patients with EoE have been noted to have seasonal symptoms, and fluctuations in diagnosis based on the time of year have been observed.²⁹

Given the overall low levels of vitamin D in the present patients with EoE, it was surprising that peak esophageal eosinophil counts increased with *higher* vitamin D levels. As proposed by other investigators one possible explanation for this finding would be that the quantity of esophageal eosinophils is not a good marker for severity of EoE.³⁰ The absence of a correlation between esophageal symptoms and histologic findings is generally recognized and has made endoscopy with esophageal biopsy an essential part of diagnosis and management.^{1,31}

Interestingly, in contrast with other food allergens, having an insufficient vitamin D level was strongly associated with a positive skin prick test reaction to peanut in the present patients (odds ratio 7.57, $P = .009$). In the United Kingdom, the United States, and Australia, the prevalence of peanut allergy has increased since 1990.^{32–34} The present results support the possibility that decreased vitamin D levels are associated with the increase in peanut allergy.¹⁰ Interestingly in the present study, peanut was the only food to which patients with vitamin D insufficiency and EoE had an increased prevalence of positive skin prick test reactions. Thus, the second question to consider is why the results for peanut are different from other foods because patients with EoE are known to often have sensitization to multiple foods (and environmental allergens).¹ The mechanism of developing sensitization might not be the same for all foods. Some researchers have proposed that sensitization to peanut can occur by an epicutaneous route.³⁵ The link between the immune response to allergen exposure and vitamin D level is not clear. However, studies in animal models have suggested that interleukin-6 is a mediator of sensitization in the airways and through the skin.³⁶ Goleva et al³⁷ studied the effect of different levels of vitamin D on peripheral blood mononuclear cells in vitro.³⁷ The cells exposed to a level lower than 30 ng/mL of vitamin D

produced high levels of interleukin-6. Thus, in the absence of adequate vitamin D, molecular signaling promoted inflammation.

For patients with EoE, having food impaction is sometimes believed to be a symptom associated with more severe disease because it leads to acute visits to the emergency department and sometimes hospital admission. In the present study, food impaction was more common in patients with vitamin D insufficiency. The effect seemed to interact with BMI. Patients with EoE sometimes have low weight, presumably because of the problems they encounter when eating. The present patients who had food impaction had a higher BMI than those who did not have food impaction. In fact, many had a BMI higher than 25 kg/m², suggesting that they are overweight. These results could suggest evidence for different phenotypes of patients with EoE. Those who have food impaction might have more severe episodes. Thus, they might be taking more (or higher doses) of medications. Alternatively, their symptoms might be intermittent in nature, allowing them to have a normal appetite between episodes. Further study of this unique group of patients will be important to identify the cause of their BMI and symptom differences.

The present study is limited by having only 1 vitamin D measurement from each patient. As a result, it was not possible to evaluate seasonal changes in vitamin D levels. This deficiency was addressed by analyzing the relationship between vitamin D and season for the entire group. It did not seem that grouped vitamin D levels correlated with the time of the year. This seems to be consistent with the results from other investigators who have studied patients who live in areas of the world with abundant sunshine.³⁸ Vitamin D deficiency remains a significant problem despite adequate sun exposure, likely owing to a combination of behavioral and intrinsic factors. An additional limitation of the present study is the small sample. It was not powered to study all the observed clinical differences. Larger studies will be the next step to determine whether these differences remain consistent.

In conclusion, similar to other chronic allergic diseases, vitamin D levels were low in patients with EoE. There did not appear to be a direct link between low vitamin D levels and increased eosinophils. The link between low vitamin D level and EoE could be related to T-helper cell type 2-specific immune alterations as evidenced by the association between vitamin D insufficiency and an increased odds of having a positive skin prick test reaction to peanut.

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Figure 1.

Distribution of serum vitamin D levels in the study population. The height of each bar represents the total number of patients having a vitamin D level within each range. Children (*black bars*) and adults (*gray bars*) are shown separately.

Figure 2.

For each patient, vitamin D status as insufficient or sufficient is represented and each patient's home location is shown by ZIP code.

Figure 3.

Box-and-whisker plots show levels of serum vitamin D based on season of recruitment. A *line* represents the median vitamin D level. Values between the 25th and 75th percentiles are contained within the *box*, and *whiskers* extend to the maximum and minimum levels. Outliers are represented by individual *dots*.

Figure 4.

Correlation between serum vitamin D level and esophageal eosinophil counts. The *solid line* depicts the *R* value. The *dashed line* at 30 ng/mL divides vitamin D insufficient levels from sufficient levels.

Table 1

General characteristics of entire study population (N = 69)

Age (y), median (range)	19.9 (1.4–64)
Male patients, n (%)	42 (61)
White race, n (%)	44 (98) ^a
BMI (kg/m ²), median (range)	22.7 (13.0–48.4)
Physician diagnosis of asthma, n (%)	25 (36)
Patient report of rhinitis, n (%)	52 (75)
Patient report of food allergy, n (%)	28 (42) ^b
Dysphagia, n (%)	48 (70)
Abdominal pain, n (%)	31 (45)
Vomiting, n (%)	24 (35)
Food impaction, n (%)	51 (74)
Positive skin prick test reaction to food, n (%)	37 (54)
Positive skin prick test reaction to inhalant allergen, n (%)	53 (77)

Abbreviation: BMI, body mass index.

^aData available for 45 patients.^bData available for 67 patients.

Table 2

Patient demographics and baseline clinical characteristics based on having insufficient or sufficient vitamin D levels

	Insufficient (n = 36)	Sufficient (n = 33)	P value
Age (y), median (range)	26 (4.8–64)	16 (1.4–59)	.02
Male patients, n (%)	22 (61)	20 (61)	>.9
White race	23 (64)	21 (64)	>.9
BMI (kg/m ²), median (range)	25 (14–48)	20 (13–36)	<.001
Physician diagnosis of asthma, n (%)	14 (39)	11 (33)	.6
Patient report of rhinitis, n (%)	28 (78)	24 (73)	.6
Patient report of food allergy, n (%)	13 (36)	15 (45)	.4
Dysphagia, n (%)	26 (72)	22 (67)	.6
Abdominal pain, n (%)	18 (50)	13 (39)	.4
Vomiting, n (%)	10 (28)	14 (42)	.2
Food impaction, n (%)	31 (86)	20 (61)	.03

Abbreviation: BMI, body mass index.

Table 3
Logistic regression for allergic sensitization to food related to vitamin D insufficient vs sufficient levels

Variable	Unadjusted logistic regression			Adjusted logistic regression ^a		
	OR ^b	95% CI	P value	OR	95% CI	P value
SPT reaction to egg	0.59	0.09–3.75	.6	0.56	0.07–4.49	.6
SPT reaction to milk	1.12	0.31–4.09	.9	1.48	0.35–6.27	.6
SPT reaction to wheat	1.88	0.16–21.8	.6	0.85	0.06–12.2	.9
SPT reaction to soy	2.00	0.46–8.77	.4	2.76	0.52–14.6	.2
SPT reaction to peanut	5.98	1.51–23.7	.01	7.57	1.66–34.6	.009
SPT reaction to tree nut	1.33	0.40–4.43	.6	1.52	0.40–5.86	.5

Abbreviations: CI, confidence interval; OR, odds ratio; SPT, skin prick test.

^aLogistic regression adjusted for body mass index and age.

^bOdds ratio based on unadjusted logistic regression.