

Vitamin D Level in Children Is Correlated with Severity of Atopic Dermatitis but Only in Patients with Allergic Sensitizations

Aysegul Akan, M.D.,* Dilek Azkur, M.D.,* Tayfur Ginis, M.D.,* Muge Toyran, M.D.,* Aysenur Kaya, M.D.,* Emine Vezir, M.D.,* Celal Özcan, M.D.,* Zeynep Ginis, M.D.,† and Can Naci Kocabas, M.D.*

*Department of Pediatric Allergy and Immunology, Ankara Children's Hematology Oncology Education and Research Hospital, Ankara, Turkey, †Department of Biochemistry, Diskapi Yildirim Beyazit Teaching and Research Hospital, Ankara, Turkey

Abstract: Vitamin D is believed to affect the progression and severity of atopic dermatitis (AD). Allergic sensitization may cause this effect to vary. Individuals who fulfilled the Hanifin and Rajka criteria for AD underwent epidermal prick tests and blood tests for specific immunoglobulin E (IgE), serum total IgE, 25-hydroxy vitamin D, and peripheral blood eosinophil count and percentage. Disease severity was determined according to the Scoring Atopic Dermatitis (SCORAD) index. Patients were grouped according to allergic sensitization. Seventy-three children with AD (median age 33.0 mos, interquartile range 19.0–61.5 mos) were enrolled in the study; 33 (45.2%) were found to have allergic sensitization. In this group there was a negative correlation between SCORAD score and serum vitamin D level ($p = 0.047$, correlation coefficient $[r] = -0.349$), whereas there was no correlation in the group without sensitization ($p = 0.30$, $r = -0.168$). Vitamin D was not correlated with total IgE and eosinophil percentage in either AD group ($p = 0.77$, $r = 0.054$ and $p = 0.73$, $r = -0.062$, respectively). Vitamin D may affect the severity of AD, especially in children with allergic sensitization.

In addition to its effect on calcium homeostasis, vitamin D has major effects on innate and adaptive immunity (1), which makes the association between vitamin D and allergic diseases a field of interest.

Although there are conflicting results, a considerable body of evidence suggests that vitamin D has an important influence on the progression of allergic diseases (2–4). Epidemiologic studies have indicated that atopic diseases are more common in individuals

Address correspondence to Can Naci Kocabas, M.D., Ankara Children's Hematology Oncology Education and Research Hospital, Department of Pediatric Allergy and Immunology, Altındağ/Ankara 06100 Turkey, or e-mail: cankocabas@yahoo.com.

with vitamin D deficiency (2–4). Atopic dermatitis (AD) is one of the most studied forms of these allergic diseases. Cross-sectional studies have demonstrated that the risk of AD in children born in autumn and winter is higher than in those born in spring and summer. Furthermore, children whose mothers had lower vitamin D levels during pregnancy were reported to have AD more frequently (5).

Vitamin D may also influence the severity of AD. In a recent study of a small group of children with AD, a negative correlation between the Scoring Atopic Dermatitis (SCORAD) index score and vitamin D was reported (6). Moreover, improvement in the SCORAD score with vitamin D supplementation has been found (7–9).

Although there are studies investigating the effect of vitamin D on the severity of AD, they have been conducted in small groups, and the influence of atopic sensitization has not been evaluated (6–9). Patients with and without sensitization may have different pathophysiologic mechanisms under similar clinical presentations (10–13). Having a role in allergic sensitization and inflammation (12), vitamin D may affect disease severity in individuals with and without allergic sensitization differently.

This study was planned to investigate the effect of vitamin D on disease severity in children with AD who had or did not have allergic sensitization.

METHODS

Patients

Between February and March 2012, children with AD who were consecutively seen in the Pediatric Allergy Department of our tertiary hospital were enrolled in the study. All fulfilled the Hanifin and Rajka criteria (14) for the diagnosis of AD. Patients who had used systematic steroid treatment in the last month and had vitamin supplementation in the last 6 months were not included. Patients using local steroids were excluded from the study because current treatment with local steroids influences the severity of eczema and the SCORAD score.

Clinical and Laboratory Investigations

The severity of AD was determined according to the SCORAD index (15). Patients with a SCORAD score less than 25 were classified as having mild AD, those with a score of 25–50 with moderate AD, and those with a score greater than 50 with severe AD, as previously defined (15). After detailed physical

examination and determination of disease severity according to the SCORAD index, skin prick tests were performed on the volar aspect of the forearm for foods (cow's milk, egg white, wheat, peanut, soy, and fish) and common aeroallergens (house dust mites, cockroaches, animal dander, mold, and mixed grass pollen). The reaction was read 15 minutes later. The test was considered positive if the diameter of the wheal was at least 3 mm greater than that of the negative control (16).

The count and percentage of peripheral blood eosinophils were determined, and serum immunoglobulin E (IgE) was measured in all patients using the nephelometric method (Siemens Healthcare Diagnostics Products, Marburg, Germany). Specific serum immunoglobulin E (IgE) levels of the positive allergens on the skin prick test or suspected allergens according to the reports of caregivers were measured using a commercially available fluorescence enzyme immunoassay (UniCAP, Phadia, Uppsala, Sweden). For patients with negative results on the skin prick test, mixed food (fx5) and mixed inhalant-specific IgE tests were performed as a screening tool to identify IgE-mediated allergic sensitization. If mixed food or inhalant-specific IgE tests were positive, specific IgE tests were performed to identify IgE-mediated allergic sensitization. For specific IgE tests, the results above the detection limit (≥ 0.35 kU/L) were defined as IgE-mediated sensitization. 25-hydroxy vitamin D levels were measured from all participants using the chemiluminescence method (Architect i2000, Abbott Laboratories, Abbot Park, IL).

Patients positive for at least one skin prick test or specific IgE positivity were defined as sensitized, and those who did not have any positive result were defined as not sensitized.

Ethical Concerns

The ethics committee of our hospital approved the study. The ethical procedures for the study protocol included informed consent of all patients and their caregivers for scientific reporting of research findings based on the study protocol.

Statistical Analysis

The distribution of the continuous variables was skewed from the standard Gaussian distribution, so nonparametric methods were used to test statistical significance. To compare the characteristics of the subgroups, the Mann–Whitney *U* test, Kruskal–Wallis test, and chi-square test were used. Correlation

analyses were performed using Spearman rank correlation. Comparisons were two-tailed, and $p < 0.05$ was considered to be statistically significant. Statistical analysis was performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL).

RESULTS

One hundred twenty-three children with AD were screened for this study; 50 were excluded because they had used oral or topical steroids in the past month or vitamin D supplementation in the last 6 months, leaving 73 participants; 40 (54.8%) were boys. The median age of the study group was 33 months (range 5.5–204 mos). The median SCORAD score was 35 (range 7.3–101).

Thirty-three (45.2%) patients had allergic sensitization with respect to skin prick tests or specific IgE levels and 40 (54.8%) had no allergic sensitization. There was no difference between these two groups in terms of age, sex, SCORAD score, or vitamin D level (Table 1).

Vitamin D levels of participants with moderate and severe AD were significantly lower than those with mild disease ($p = 0.01$). In the group with sensitization, vitamin D levels of participants with moderate and severe disease were also significantly lower than those of participants with mild eczema ($p = 0.01$), although vitamin D levels did not differ between nonsensitized participants with mild, moderate, and severe disease ($p = 0.47$) (Fig. 1).

Vitamin D and SCORAD score were correlated negatively in the whole study group ($p = 0.02$, correlation coefficient [r] = -0.271). When the groups were analyzed separately, the same relationship was present in patients from the sensitized group ($p = 0.047$, $r = -0.349$), but there was no correlation in the nonsensitized group ($p = 0.30$, $r = -0.168$) (Fig. 2).

There was no correlation between vitamin D and total IgE ($p = 0.60$, $r = -0.063$) and percentage of

eosinophils in the whole study group ($p = 0.53$, $r = -0.076$). No correlation was found between vitamin D and total IgE ($p = 0.90$, $r = -0.153$) or eosinophil percentage ($p = 0.20$, $r = 0.153$) when the sensitized and nonsensitized groups were evaluated separately.

DISCUSSION

The relationship between serum vitamin D level and severity of AD and the effect of allergic sensitization on this relationship were investigated in a group of children with AD. The SCORAD score was inversely correlated with vitamin D levels in participants with allergic sensitization but not in nonsensitized participants.

According to the results of epidemiologic studies, vitamin D affects the development of allergic sensitization. In cohort studies, the risk of wheezing and eczema was lower in infants whose mothers had taken high-dose vitamin D during pregnancy (5). In another study on children and adolescents, vitamin D deficiency was found to be associated with the level of IgE-mediated sensitizations (17). Several studies support the hypothesis that vitamin D deficiency might cause atopic diseases (18–20).

Reports have also suggested that vitamin D affects the severity of atopic diseases (18,21). Other studies have found a beneficial effect of vitamin D supplementation on allergic diseases (5,7,9). In a recent study in children with AD, a negative correlation was detected between vitamin D and SCORAD score (6). In accordance with this study, vitamin D was found to be correlated negatively with SCORAD score in our study population.

The hypotheses suggested to explain the effect of vitamin D on the severity of atopic diseases are as follows: effect on the immune system, the reduction of inflammation, the prevention of infections, and the elimination of steroid resistance (18,22).

Vitamin D inhibits T cell proliferation (25) and contributes to the conversion of CD4⁺ T cells to T

TABLE 1. Clinical Characteristics of the Participants with Sensitized and Nonsensitized Atopic Dermatitis

Variable	Sensitized ($n = 33$)	Nonsensitized ($n = 41$)	p
Age, months, median (IQR)	33.0 (20.0–70.5)	32.0 (19.0–59.0)	0.54
Male, n (%)	20 (60.6)	20 (48.8)	0.31
Total immunoglobulin E, IU/mL, median (IQR)	125 (49–407)	30 (16–156)	0.001
Peripheral blood eosinophil percentage, median (IQR)	3.4 (1.7–5.4)	2.3 (1.5–4.4)	0.55
Vitamin D, ng/mL, median (IQR)	11.2 (6.8–16.0)	12.3 (10.2–21.8)	0.07
SCORAD score, median (IQR)	36.8 (20.3–55.5)	32.7 (17.8–52.6)	0.41
Disease severity (SCORAD), n (%)			0.75
Mild	9 (27.3)	14 (35.0)	
Moderate	13 (39.4)	15 (37.5)	
Severe	11 (33.3)	11 (27.5)	

IQR, interquartile range; SCORAD, Scoring Atopic Dermatitis.

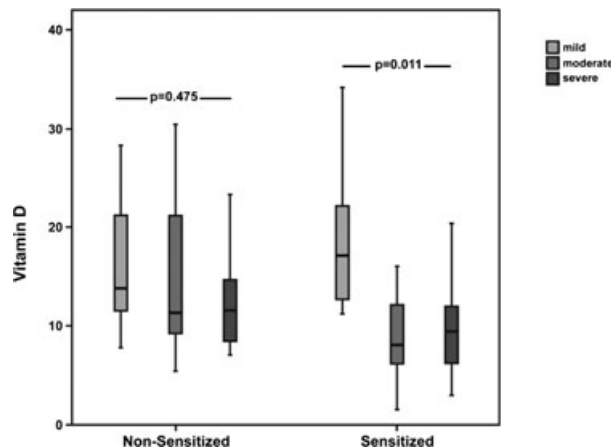


Figure 1. Vitamin D levels of sensitized and non-sensitized patients according to atopic dermatitis severity.

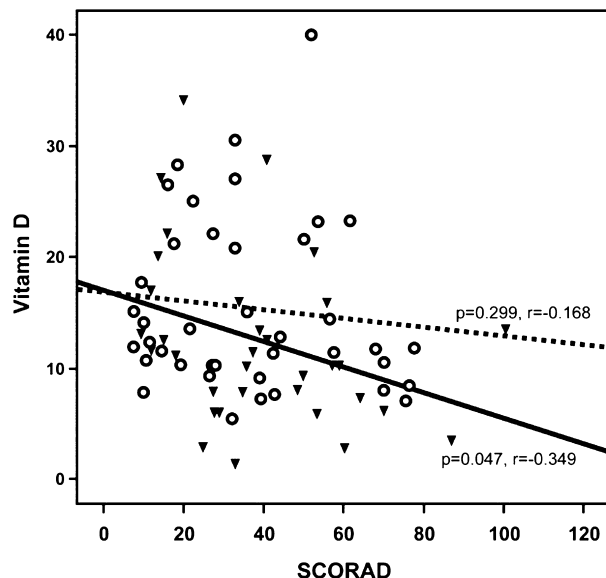


Figure 2. Correlation of vitamin D levels and SCORAD index of sensitized and nonsensitized patients.

regulatory cells, which have been shown to suppress proallergic mechanisms (25,26).

Patients with AD are at higher risk of cutaneous infections. Defects in the production of broad-spectrum antimicrobial peptides such as cathelicidin may account for this increase in infection. The active form of vitamin D is essential for induction of cathelicidin (27). Recent studies have demonstrated that vitamin D supplementation induces the expression of cathelicidin and reduces antigen expression of cutaneous lymphocytes selectively (23–25).

Although clinical features are the same, individuals with AD with and without sensitization have differ-

ences in pathogenesis. Those with allergic sensitization have an immune response characterized by T helper type 2 cells and high interleukin (IL)-4, IL-5, and IL-13 levels, eosinophil counts, eosinophilic cationic protein levels, and total IgE levels. Participants with the nonatopic form of AD had total IgE and eosinophil counts in normal ranges. These patients had allergen-specific IgG in their sera instead of allergen-specific IgE (11,12,22,26).

To our knowledge, our study is the first to investigate the relationship between vitamin D and AD severity according to sensitization status. Although disease severity was related to vitamin D levels in the sensitized group, this relationship was not found when nonsensitized patients were analyzed separately. This indicates that vitamin D may have different immunomodulating effects on the different inflammatory profiles of AD patients with and without allergen sensitization. In their study, Heine et al (27) reported that previously stimulated B cells showed markedly lower IL-4 mediated production of IgE after the administration of vitamin D. Another study supported this finding, revealing that calcitriol and vitamin D receptor antagonists led to suppressed IgE production by cultured human B cells and in an allergy mouse model (28). Because IgE-mediated inflammation is the mainstay of allergy-mediated AD but not of the nonallergic form, this effect may be related to the different effect of vitamin D on the disease severity of sensitized and nonsensitized patients.

Although there are studies reporting a negative correlation between vitamin D and serum IgE (4), this needs further clarification. In our study, vitamin D was not correlated with serum IgE and peripheral blood eosinophil percentage in the whole study population or in the atopic and nonatopic forms of AD, in accordance with other studies (6,11,19).

In conclusion, the lower the vitamin D level, the more severe the degree of eczema of individuals with AD with allergic sensitization. Large-scale prospective studies are needed to clarify this correlation and to investigate whether vitamin D supplementation reduces the severity of AD in individuals with vitamin D deficiency. Investigations in this area may be beneficial in the management and prevention of AD.

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