



Relationship between serum 25-hydroxyvitamin D and interleukin-31 levels, and the severity of atopic dermatitis in children

Bo Ram Cheon, MD, Jeong Eun Shin, MD, Yun Ji Kim, MD, Jae Won Shim, MD, PhD, Deok Soo Kim, MD, PhD, Hye Lim Jung, MD, PhD, Moon Soo Park, MD, PhD, Jung Yeon Shim, MD, PhD

Department of Pediatrics, Kangbuk Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Purpose: Atopic dermatitis (AD) is a chronic inflammatory relapsing skin disorder. Vitamin D plays a pivotal role in the development of AD, and interleukin (IL) 31 is known to be related to pruritus in AD. The aim of our study was to determine whether 25-hydroxyvitamin D (25(OH)D) levels are related to IL-31 levels or to the severity of AD.

Methods: We enrolled 91 children with AD and 32 control subjects without history or symptoms of allergic diseases. Blood was drawn to evaluate complete blood cell count, total eosinophil count (TEC), and total IgE, specific IgE to common allergens, 25(OH)D, and IL-31 levels. Serum 25(OH)D and IL-31 levels were measured using high-performance liquid chromatography and enzyme-linked immunosorbent assay, respectively. The scoring atopic dermatitis (SCORAD) index was used to evaluate the severity of AD.

Results: The mean 25(OH)D level was significantly lower in the AD group than in the control group; 25(OH)D decreased greatly in the moderate and severe AD groups compared with the mild AD group. Children with atopic sensitization showed significantly lower 25(OH)D levels than nonatopic children. However, serum IL-31 levels were not related to AD group, SCORAD index, or 25(OH)D levels. The SCORAD index was inversely correlated with serum 25(OH)D level and positively correlated with TECs and total IgE levels. Children with moderate and severe AD had significantly higher TECs than children with mild AD.

Conclusion: Vitamin D is related to the severity of AD independently of IL-31.

Key words: Atopic dermatitis, 25-hydroxyvitamin D, Atopic sensitization, Interleukin-31, Child

Corresponding author: Jung Yeon Shim, MD, PhD
Division of Pediatric Allergy & Pulmonology, Department of Pediatrics, Kangbuk Samsung Medical Center, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 110-746, Korea

Tel: +82-2-2001-2484

Fax: +82-2-2001-2199

E-mail: jy7.shim@samsung.com

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Introduction

Atopic dermatitis (AD), a common chronic inflammatory skin disease, is characterized by pruritus and eczematous plaques. Prevalence of AD in children varies worldwide from approximately 10% to 20%, and AD may persist into adolescence or adult life in up to 10% of patients^{1,2}. In recent decades, the prevalence of AD has been steadily increasing. A number of hypotheses have been put forward to explain this trend, including diet, air pollution, and the hygiene hypothesis. New insights into the genetics and pathophysiology of AD indicate the important role of structural abnormalities in the epidermis, as well as immune dysregulation, in the pathogenesis of the disease³.

Recently, in addition to its classical role in calcium homeostasis, vitamin D has been shown to influence immunomodulation and cellular differentiation, by altering local calcium balance and binding nuclear vitamin receptors, which regulate gene transcription⁴.

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Vitamin D regulates the activity of various immune cells such as monocytes, dendritic cells, and lymphocytes, as well as regulating the function of epithelial cells, which are important in allergic inflammation⁵.

Previous studies have investigated the relationship between vitamin D and allergic diseases. However, the results were controversial with regard to prevalence and severity of allergic diseases. The severity of allergic disease, specifically AD, tends to increase in patients who have lower levels of vitamin D, or have a lower vitamin D dietary intake⁶⁻⁸. In addition, recent clinical trials suggest a therapeutic role for vitamin D supplementation in the treatment of AD^{9,10}. Despite the positive association between low levels of vitamin D and increased prevalence or severity of AD, several studies have also reported conflicting results^{11,12}.

Interleukin (IL) 31 is a T helper type 2 (Th2) effector cytokine mainly produced by activated Th2 cells¹³. IL-31 is believed to play an important role in the pathogenesis of AD, especially in pruritus¹⁴. IL-31 expression is not only elevated¹⁵ but also positively correlated with disease activity in AD¹⁶. Since vitamin D status is related to the severity of AD which is well known as a Th2-polarized disease and IL-31 is a Th2-associated cytokine, we hypothesized that there might be a potential interaction between vitamin D and IL-31. However, quite a few data are available on the relationship between vitamin D and IL-31 in AD¹⁷.

In this study, we investigated whether 25-hydroxyvitamin D (25(OH)D) and IL-31 serum levels were elevated in children with AD, and also the relationship between 25(OH)D, IL-31, and the severity of AD.

Materials and methods

1. Study subjects and design

We enrolled 91 children with AD, and 32 children with no symptoms or signs of allergic diseases as controls, who visited outpatient clinic of the Department of Pediatrics, Kangbuk Samsung Medical Center, from June to August 2011. All the AD patients fulfilled the Hanifin and Rajka criteria¹⁸. Severity of AD was assessed in all the children by the same physician using the scoring atopic dermatitis (SCORAD) index: mild AD (<15), moderate AD (15-40), and severe AD (>40).

2. Laboratory tests

Venous bloods were drawn and sera were stored at -20°C after centrifugation, until testing. All assays were carried out at the same time. The levels of 25(OH)D were assayed using high-performance liquid chromatography (Neodin, Seoul, Korea). The levels of IL-31 were measured using an ELISA (enzyme-linked immunosorbent assay) kit (R&D systems, Minneapolis, MN, USA).

Serum total IgE, and specific IgE antibodies to *Dermatophagoides farinae*, cat, dog, alternaria, weed mixture, tree mixture, egg white, soy bean, and milk were assayed using immune CAP (Pharmacia Diagnostics, Uppsala, Sweden). Atopic sensitization was defined as a level of 0.35 IU/mL of at least one specific IgE.

3. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA). Differences between two groups were analyzed using *t*-test or chi-square test. Depending on the characteristics of variables, differences between three groups were compared using one-way analysis of variance, followed by the Bonferroni *post hoc* test for multiple comparisons.

Quantitative variables are expressed as means±standard deviations, or median values with interquartile range. The analysis was conducted by transforming the data to a logarithmic scale (log) when data had skewed distributions. The correlation analyses were performed using Pearson correlation test. A *P* value of <0.05 was considered statistically significant.

Results

The clinical and laboratory characteristics of the study subjects are shown in Table 1. The median ages of both the AD group and controls were 6 years, and there were no differences in age and sex between the two groups. The mean value of logarithmic transformation of blood total eosinophil counts (logTEC) was significantly elevated in the AD group (5.96/mm³) compared to controls (4.83/mm³). The mean value of logarithmic transformation of serum total IgE (logIgE) in the AD group (4.78 IU/mL) was significantly higher than in the control group (3.96 IU/mL). The prevalence of asthma and allergic rhinitis in the AD group was 8.7% and 12.6%, respectively. The prevalence of atopic sensitization was 64.1% in the AD group.

Table 1. Clinical and laboratory characteristics of the study subjects

Characteristic	AD (n=91)	Control (n=32)
Age (yr), median (IQR)	6 (4-9)	6 (2-10)
Male sex (%)	49	50
LogTEC (/mm ³), mean±SD	5.96±0.69*	4.83±1.17
LogIgE (IU/mL), mean±SD	4.78±1.46*	3.96±1.43
Asthma (%)	8.7	0
Allergic rhinitis (%)	12.6	0
Atopic sensitization (%)	64.1	0

AD, atopic dermatitis; IQR, interquartile range; logTEC, logarithmic transformation of blood total eosinophil counts; SD, standard deviation; logIgE, logarithmic transformation of serum total IgE.

**P*<0.05.

The levels of 25(OH)D and logIL-31 were compared between the AD and the control groups (Fig. 1). Children with AD showed significantly lower levels of 25(OH)D (23.1±1.7 ng/mL) than controls (35.9±2.9 ng/mL). However, there were no differences in serum levels of IL-31 between the two groups.

We categorized the AD group into mild, moderate, and severe AD groups, based on the SCORAD index, and compared 25(OH)D, IL-31, and other allergic parameters between the three groups (Table 2). The logTEC value was higher in the moderate and severe AD group than in the mild AD group. However, there was no significant difference in logIgE values. The 25(OH)D values were significantly decreased in the moderate and severe AD groups compared to the mild AD group. The IL-31 levels showed no significant difference among the three groups. The prevalence of atopic sensitization was significantly higher in the severe AD group compared to the mild AD group.

We compared 25(OH)D, IL-31 levels, and allergic parameters

between atopic and nonatopic AD groups (Table 3). The atopic AD group comprised children with both AD and atopic sensitization. Children with atopic AD had higher logTEC and logIgE values, and lower 25(OH)D levels, than children with nonatopic AD. However, there were no significant differences in IL-31 level and the SCORAD index between the two groups.

We analyzed the relationship between 25(OH)D, IL-31, total IgE, blood eosinophils, and SCORAD index (Fig. 2). Serum 25(OH)D levels showed weak but significant inverse correlations with SCORAD index and serum total IgE level, however it did not correlate with serum IL-31 levels. Serum IL-31 levels also showed no correlation with SCORAD index. The SCORAD index showed a weak correlation with serum total IgE concentration and a strong positive correlation with blood eosinophil counts.

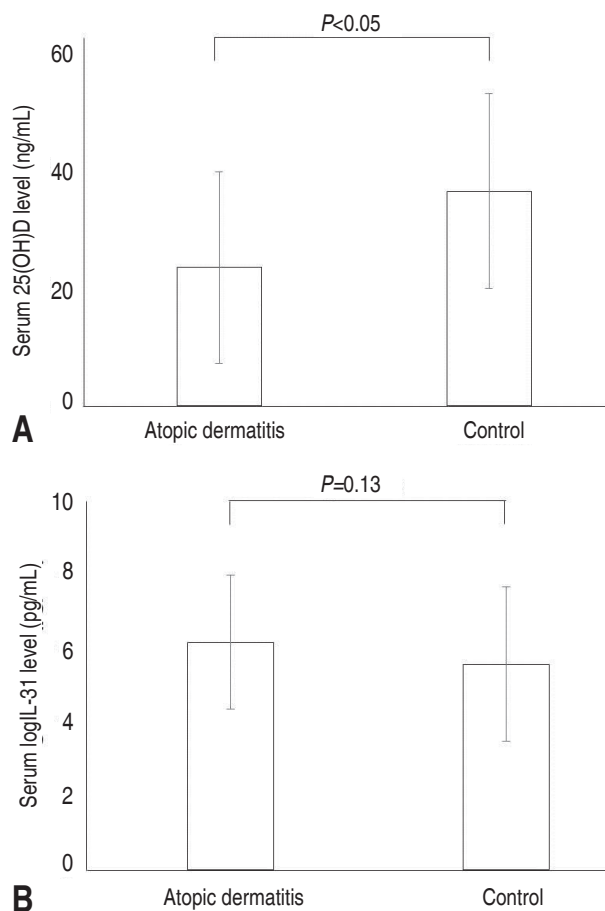


Fig. 1. Mean 25(OH)D and IL-31 levels in the atopic dermatitis (AD) group compared with those in controls. (A) The mean level of 25(OH)D was significantly lower in the AD group than that in controls. (B) However, serum IL-31 levels did not differ significantly between the AD group and controls. 25-hydroxyvitamin D; IL, interleukin.

Table 2. Comparison of 25(OH)D levels, IL-31 levels, and allergic parameters according to the severity of AD

Parameter	Mild AD (n=22)	Moderate AD (n=39)	Severe AD (n=30)
Age (yr), median (IQR)	5 (3–7)	5 (2–8)	6 (3–9)
Male sex (%)	55	54	40
LogTEC (/mm ³)	5.29±0.73	5.80±0.59*	6.23±0.71*
LogIgE (IU/mL)	4.55±1.50	4.46±1.24	4.87±1.58
25(OH)D (ng/mL)	32.7±3.1	21.4±3.3*	23.2±2.5*
LogIL-31 (pg/mL)	5.90±1.87	6.01±1.48	6.18±2.06
Atopic sensitization (%)	37.0	58.9	76.7*

Values are presented as mean±standard deviation unless otherwise indicated. 25(OH)D, 25-hydroxyvitamin D; IL, interleukin; AD, atopic dermatitis; IQR, interquartile range; logTEC, logarithmic transformation of blood total eosinophil counts; logIgE, logarithmic transformation of serum total IgE; logIL-31, logarithmic transformation of interleukin 31. *P<0.05 vs. mild AD.

Table 3. Comparison of 25(OH)D levels, IL-31 levels, and allergic parameters between nonatopic AD and atopic AD groups

Parameter	Nonatopic AD (n=31)	Atopic AD (n=60)
Age (yr), median (IQR)	5 (3–7)	4 (2–8)
Male sex (%)	45	51
LogTEC (/mm ³)	5.63±0.79	6.13±0.58*
LogIgE (IU/mL)	3.91±1.44	5.23±1.27*
25(OH)D (ng/mL)	26.5±3.2	21.3±1.9*
LogIL-31 (pg/mL)	6.47±1.42	6.01±1.96
SCORAD index	32.44±2.63	27.70±3.26

Values are presented as mean±standard deviation unless otherwise indicated. 25(OH)D, 25-hydroxyvitamin D; IL, interleukin; AD, atopic dermatitis; IQR, interquartile range; logTEC, logarithmic transformation of blood total eosinophil counts; logIgE, logarithmic transformation of serum total IgE; logIL-31, logarithmic transformation of interleukin 31; SCORAD index, scoring atopic dermatitis index. *P<0.05.

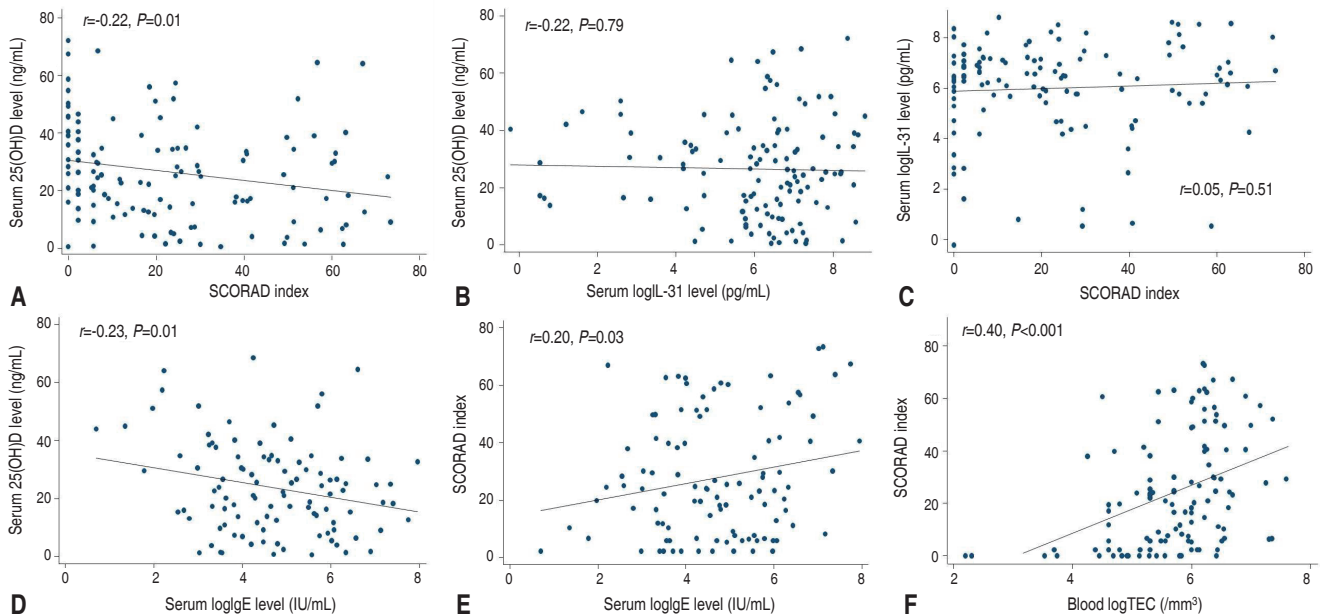


Fig. 2. Correlation between the SCORAD index; serum levels of 25(OH)D, IL-31, and total IgE; and blood eosinophil counts. (A) The 25(OH)D level inversely correlated with the SCORAD index. There was no correlation between 25(OH)D level and IL-31 level (B), or between IL-31 level and the SCORAD index (C). (D) 25(OH)D levels were inversely correlated with total IgE concentrations. The SCORAD index showed a positive correlation with serum total IgE concentration (E) and blood eosinophil count (F). SCORAD index, scoring atopic dermatitis index; 25(OH)D, 25-hydroxyvitamin D; IL, interleukin.

Discussion

The aim of our study was to determine whether 25(OH)D levels were elevated in children with AD, and whether 25(OH)D was related to the severity of childhood AD. In addition, we investigated the relationship between IL-31, 25(OH)D, and the severity of AD. In this study, 25(OH)D level was lower in the AD group compared to the control group, and considerably decreased in the moderate and severe AD groups compared to the mild AD group. We found a weak inverse correlation between 25(OH)D level and the severity of AD. This is in agreement with other reported studies on the relationship between vitamin D and AD^{6,7}. Vitamin D deficiency was found to increase the risk of AD among obese individuals, and serum levels of 25(OH)D were higher in patients with mild AD compared to those with moderate or severe cases⁶. In addition, vitamin D may have protective role in the development of AD. In a prospective study using mother-child pairs, children whose mothers had higher consumption of vitamin D during pregnancy, showed a reduced risk of wheeze and eczema at 16–24 months of age¹⁹.

Vitamin D may play a crucial role in the pathogenesis of AD through enhancing the integrity of the permeability barrier²⁰ and antimicrobial peptide (AMP) expression²¹, and suppressing inflammatory responses²². It is well known that the skin plays an important role in host defense against microbial invasion and allergen penetration. Patients with AD display skin barrier defects

involved in permeability and antimicrobial function. Permeability of the epidermis is determined by interactions of differentiated keratinocytes and structural proteins, such as filaggrin, regulatory enzymes, and lipids²³. Vitamin D has been demonstrated to have a beneficial effect in maintaining the permeability barrier in the epidermis. In a study using a null mouse model for the expression of 25(OH)D 1 α -hydroxylase, which produces the active form of vitamin D, the null mice showed lower levels of filaggrin in the epidermis, and delayed recovery of normal barrier function, compared to wild-type mice²⁰.

AMPs play a critical role in the antimicrobial barrier on the surface of the skin. An essential part of the innate immune response to injury is the capacity to recognize microbial invasion and stimulate production of AMPs²¹. Patients with AD express fewer AMPs, especially cathelicidin, in inflamed skin, so they are more susceptible to infections²⁴. The release of AMPs is triggered by Toll-like receptors (TLRs). Vitamin D has been shown to have a significant role in cathelicidin expression in the skin by inducing the transcription of genes coding for the microbial pattern recognition receptors, CD14 and TLR2²¹. Vitamin D is also known to increase the synthesis of platelet-derived growth factor, promoting wound healing²⁵. Furthermore, decreased synthesis of IL-1 α , IL-6, and RANTES (regulated upon activation, normal T cell expressed and secreted) associated with vitamin D, has resulted in decreased inflammatory response in epidermal keratinocytes²⁶⁻²⁸.

Supplementation with vitamin D might be a possible treatment to improve AD. In a randomized controlled trial of 11 winter-related AD children, four of the five children who received 1,000 IU of vitamin D for one month showed improvement, while only one of the six children in the placebo group improved⁹. Another randomized, double-blind, placebo-controlled trial demonstrated that the vitamin D group (receiving 1,600 IU/day for 2 months) showed a significant improvement in the SCORAD index compared to the placebo group¹⁰. Conversely, other studies have reported that an increased intake of vitamin D during childhood correlated with an increased risk of AD at 6 years of age¹², and that increased maternal serum levels of vitamin D predisposed infants to AD at 9 months old¹¹.

Our data showed a correlation between 25(OH)D levels and the severity of AD. Levels of 25(OH)D were lower in AD patients with atopic sensitization than in patients with no sensitization. This is supported by other study²⁹ and can be explained by the findings of Hartmann's study that reports that vitamin D inhibits IgE synthesis in B cells³⁰. However, studies on the relationship of vitamin D with Th2 cytokines have shown inconsistent results; both increased and decreased IL-4 synthesis in cultured T cells has been reported^{31,32}. In our study, vitamin D showed an inverse correlation with serum total IgE levels. This may be due to suppression of IgE in B cells by vitamin D.

IL-31 is a novel Th2-cell-derived cytokine that induces severe pruritus and dermatitis, and is increased in AD skin lesions¹⁴. In several studies, IL-31 serum levels in AD correlate with disease severity^{16,33}. Vitamin D and IL-31 play an important role in the pathogenesis of AD. However, there have been quite a few studies on the relationship between IL-31 and vitamin D in allergic diseases. In one study, patients with atopic asthma and allergic rhinitis demonstrated decreased vitamin D and increased IL-31 serum levels compared to healthy controls, however vitamin D did not correlate with IL-31³⁴. On the contrary, another study showed vitamin D which was decreased in patients with AD promoted IL-31 production from stimulated T cells of patients with AD¹⁷. In our study, vitamin D level was lower in children with AD, however, IL-31 levels showed no differences between children with AD and control subjects. Furthermore, there was no statistically significant correlation between IL-31 and 25(OH)D levels, or between IL-31 level and the severity of AD. It might be because AD has diverse pathogenesis besides Th2 inflammation and vitamin D might be related to AD independently of IL-31.

Strong points of our study include the use of high-performance liquid chromatography, which is the most sensitive means of measuring 25(OH)D levels, and assaying 25(OH)D levels from all the study subjects during the same season. The synthesis of vitamin D is influenced by the amount of ultraviolet exposure. Therefore, seasonal variation should always be taken into account when measuring vitamin D. In addition, we investigated the

relationship between 25(OH)D and IL-31.

A limitation of our study was not taking into account clinical factors, such as individual physical activity and dietary habits that can affect vitamin D homeostasis³⁵. In addition, as we only measured the vitamin D level at one time-point, we could not examine changes in levels at different time-points, or following treatment.

In conclusion, this study showed that the 25(OH)D level was an important factor related to the severity of AD. No relationship was found between IL-31 and 25(OH)D levels. Large-scale, randomized, controlled trials are needed to clarify the relationship between vitamin D, IL-31, and AD.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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