



ORIGINAL ARTICLE

House Dust Mite Sensitization Is Inversely Associated with Plasma 25-Hydroxyvitamin D3 Levels in Patients with Severe Atopic Dermatitis

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Background: The relationship between atopic dermatitis (AD) and low vitamin D levels has been studied. Emerging evidence has implicated vitamin D as a critical regulator of immunity, playing a role in both the innate and cell-mediated immune systems. However, the effect of vitamin D on house dust mite (HDM) sensitization in patients with AD has not been established. **Objective:** We investigated the association between vitamin D levels and HDM sensitization according to AD severity. **Methods:** In total, 80 patients (43 men and 37 women) with AD were included. We classified AD severity using Rajka and Langeland scores. Laboratory tests included serum 25-hydroxyvitamin D3, total immunoglobulin E (IgE), and specific IgE antibody titer against *Dermatophagoides farinae* and *D. pteronyssinus*. **Results:** There were no differences in vitamin D levels between the mild or moderate AD and severe AD groups. In the severe AD group, high HDM sensitization group had lower serum vitamin D levels compared to low HDM sensitization group with statistical significance. In addition, a significant neg-

ative correlation was found between vitamin D levels and HDM sensitization in the severe AD group. **Conclusion:** Our results demonstrate that low vitamin D levels may link to high HDM sensitization in patients with the severe AD. Further elucidation of the role of vitamin D in HDM sensitization may hold profound implications for the prevention and treatment of AD. (*Ann Dermatol* 29(4) 400~406, 2017)

-Keywords-

Atopic dermatitis, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, Sensitization, Vitamin D

INTRODUCTION

Recently, several reports about the relationship between vitamin D and many allergic diseases, including atopic dermatitis (AD), have appeared^{1,2}. Some studies have indicated that vitamin D has influenced the course of immune-mediated disorders, including AD and asthma³. However, data surrounding the effect of vitamin D on the development of allergic skin diseases are conflicting. In addition, there are several debates surround the relationship between vitamin D and AD severity. Some studies demonstrated an inverse association between vitamin D levels and AD severity⁴⁻⁷. Other studies showed no significant correlation between vitamin D levels and AD severity⁸⁻¹⁰. The exact role of vitamin D in the pathogenesis of AD also has not been fully addressed.

Vitamin D, as a critical regulator of immunity, plays a role in both the innate and adaptive immune systems³. Antimicrobial defense mechanisms and epidermal barrier integrity are impaired by defective immune systems. There-

Received July 18, 2016, Accepted for publication August 31, 2016

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fore, vitamin D deficiency might exacerbate AD via disturbed epidermal barrier function and immunologic dysregulation, with subsequent impaired defense against common allergens such as house dust mite (HDM) and infections¹¹. Considering the functions of vitamin D, there is a possibility that vitamin D relates to HDM sensitization in AD. The effect of vitamin D on HDM sensitization in AD patients with different severity has not been established. The aim of this study was to evaluate the correlation between serum vitamin D levels and HDM sensitization according to AD severity.

MATERIALS AND METHODS

Subjects

Data were collected from a retrospective case series of 80 patients with AD at the Department of Dermatology, Kyungpook National University Hospital, Korea, between January 2013 and September 2014. The study protocol was approved by the institutional review board of Kyungpook National University Hospital (KNUH 2015-01-002-001).

Evaluation of AD severity

Two dermatologists evaluated AD severity in all patients by means of the Rajka and Langeland score¹². Grading, which may be carried out on the basis of one single consultation, permits distinction between mild, moderate, and severe AD by means of a score summation using the following parameters (each parameter had a score from 1 to 3): (1) extent (by "rule of nine"); (2) course (via history); and (3) intensity (disturbance of nightly sleep by itching)¹². We classified the AD patients into two groups, either the mild to moderate group (0~7.5) or the severe group (≥ 8).

Laboratory determination

The *Dermatophagoides farinae* and *D. pteronyssinus* specific immunoglobulin E (IgE) levels were assayed by the immunoblot analysis (Advansure Allostation[®]; LG Life Sciences, Seoul, Korea) and total IgE levels were assayed by the fluorescent enzyme immunoassay (UniCAP[®]; Pharmacia, Stockholm, Sweden). The total IgE levels were measured up to 5,000, therefore we regarded over 5,000 as 5,000. The each HDM-specific IgE level was classified into seven quantitative classes by the following criteria: class 0, below 0.35 IU/ml; class 1, 0.35 to 0.69 IU/ml; class 2, 0.7 to 3.49 IU/ml; class 3, 3.5 to 17.49 IU/ml; class 4, 17.5 to 49.99 IU/ml; class 5, 50 to 99.99 IU/ml; and class 6, above 100 IU/ml. The patients were divided into two groups, the low sensitization group, composed of HDM-specific IgE classes 0~2, and the high sensitization group, composed of classes 3~6¹³. Serum 25-hydroxyvitamin D3

levels were measured by an electrochemiluminescence immunoassay (Elecsys[®] 2010; Roche Diagnostics, Mannheim, Germany).

Assessment

To study the association between AD severity, HDM sensitization for *D. farinae* and *D. pteronyssinus* and vitamin D levels, we carried out a comparative study with the following five subsections: (1) differences in vitamin D and total IgE levels according to AD severity; (2) comparison of both HDM-specific IgE levels according to AD severity; (3) differences in vitamin D levels according to HDM sensitization; (4) relationship between vitamin D levels and HDM sensitization; and (5) relationship between vitamin D and total IgE levels.

Statistical analysis

The difference of serum vitamin D levels and serum IgE levels according to AD severity was assessed with the Mann-Whitney U-test respectively. The difference of serum vitamin D levels according to HDM sensitization was also analyzed with the Mann-Whitney U-test. Spearman's rank correlation coefficient was used to assess the relationship between vitamin D levels and HDM sensitization according to AD severity. The relationship between serum vitamin D and log transformed total IgE levels was evaluated with regression analysis and Spearman's rank correlation coefficient. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics ver. 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

In total, 43 men and 37 women, mean age 19.0 ± 11.0 years, were included in the study. We classified 35 (43.8%) and 45 (56.2%) patients into the mild to moderate AD and severe AD groups, respectively.

Differences in vitamin D and total IgE levels according to AD severity

The mean serum vitamin D level was 19.29 ± 8.03 ng/ml. There was no significant difference between serum vitamin D levels between patients with severe AD (19.46 ± 8.10 ng/ml) and mild to moderate AD (18.98 ± 7.97 ng/ml, $p=0.72$; Fig. 1A). On the other hand, the mean total serum IgE level in patients with severe AD ($2,011.96 \pm 993.89$ kU/L) was significantly higher than that in patients with mild to moderate AD (260.88 ± 431.54 kU/L, $p < 0.05$; Fig. 1B).

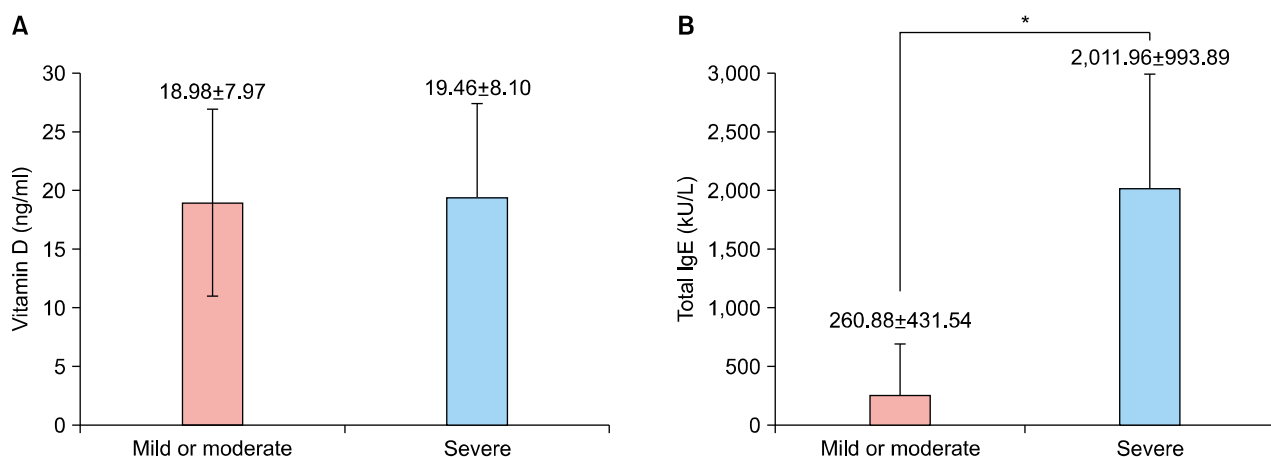


Fig. 1. Differences in vitamin D and total immunoglobulin E (IgE) levels according to atopic dermatitis (AD) severity. (A) There was no difference in mean vitamin D levels between the mild to moderate AD and severe AD groups ($p=0.72$). (B) A significant difference of total IgE levels was found according to AD severity ($*p<0.05$).

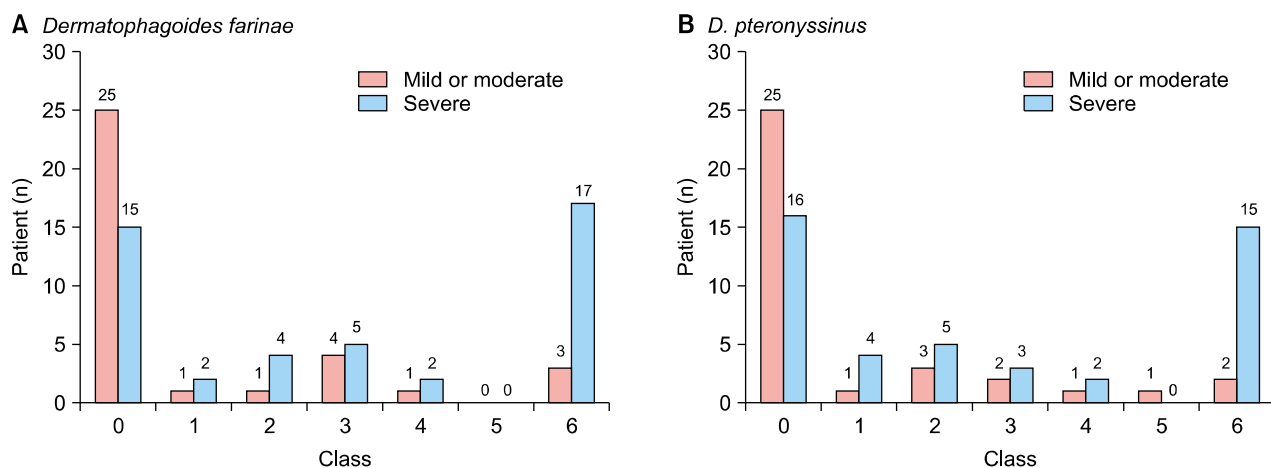


Fig. 2. Comparison of both house dust mite (HDM)-specific IgE levels according to atopic dermatitis (AD) severity. More patients with class 6 both HDM sensitization were found in the severe AD group.

Comparison of HDM-specific IgE levels according to AD severity

In our study, there was no significant relevance between both HDM sensitization and AD severity. However, more patients with class 6 both HDM sensitizations were found in the severe AD group (Fig. 2).

Differences in vitamin D levels according to HDM sensitization

In the severe AD group, significantly lower serum vitamin D levels were found in AD patients with high *D. farinae* sensitization ($p<0.05$). However, in AD patients with mild to moderate severity, serum vitamin D levels showed no significant difference between the low and high *D. farinae* sensitization groups ($p=0.77$, Fig. 3A).

Results of *D. pteronyssinus* showed a similar tendency with those of *D. farinae*. In the severe AD group, high *D. pteronyssinus* sensitization group had lower serum vitamin D levels with statistical significance ($p<0.05$). However, there is no significant difference of vitamin D levels between the low and high *D. pteronyssinus* sensitization groups in mild or moderate AD patients ($p=0.51$, Fig. 3B).

Relationship between vitamin D levels and HDM sensitization

In total AD patients, vitamin D levels showed a negative correlation with *D. farinae* sensitization ($r_s = -0.283$, $p<0.05$). In addition, there was a negative correlation between vitamin D levels and *D. farinae* sensitization in severe AD patients with statistical significance ($r_s = -0.515$, $p<0.05$). However, no correlation was found between *D. farinae*

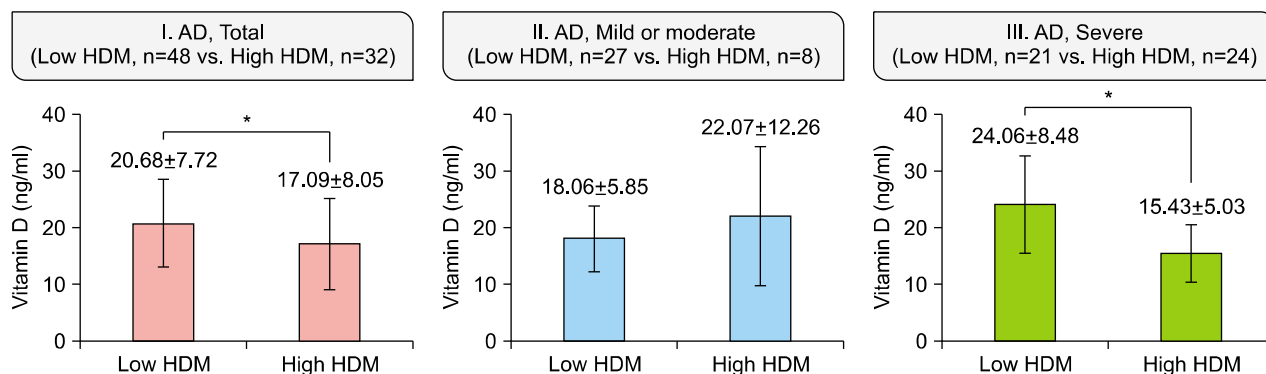
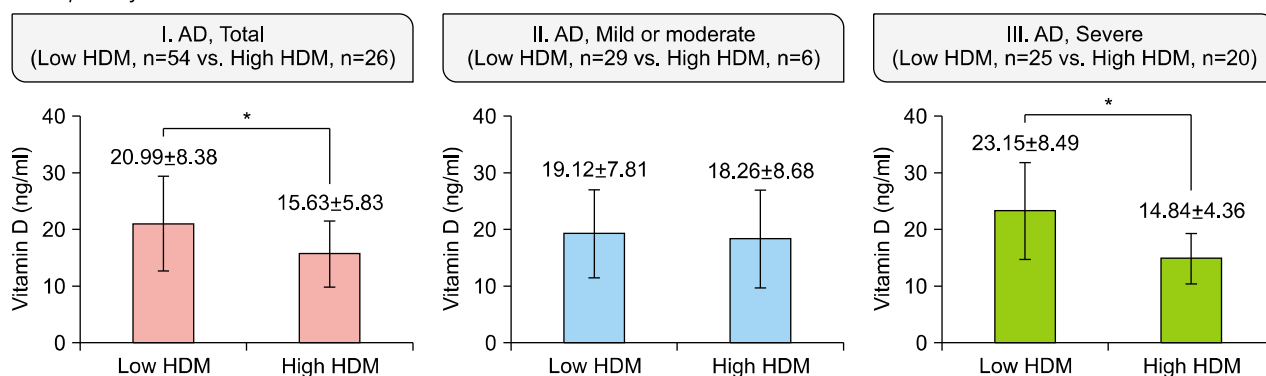
A *D. farinae***B** *D. pteronyssinus*

Fig. 3. Differences in vitamin D levels according to house dust mite (HDM) sensitization (* $p < 0.05$). (A) In the severe atopic dermatitis (AD) group, significantly lower vitamin D levels were found in AD patients with high *Dermatophagoides farinae* sensitization ($p < 0.05$). However, vitamin D levels showed no significant difference between the low and high *D. farinae* sensitization groups in patients with the mild or moderate AD severity ($p = 0.77$). (B) In the severe AD group, high *D. pteronyssinus* sensitization group had significantly lower serum vitamin D levels with statistical significance ($p < 0.05$). However, in mild or moderate AD group, there is no significant difference of vitamin D levels between the low and high *D. pteronyssinus* sensitization groups ($p = 0.51$).

sensitization and serum vitamin D levels in AD patients with mild or moderate severity ($r_s = -0.081$, $p = 0.64$; Fig. 4A).

Results of *D. pteronyssinus* showed the similar findings. Vitamin D levels showed a negative correlation with *D. pteronyssinus* sensitization with statistical significance in total AD patients ($r_s = -0.254$, $p < 0.05$). In severe AD patients, serum vitamin D levels showed significantly negative correlation with *D. pteronyssinus* sensitization ($r_s = -0.484$, $p < 0.05$). However, there was no correlation between serum vitamin D levels and *D. pteronyssinus* sensitization in mild or moderate AD patients group ($r_s = -0.002$, $p = 0.99$; Fig. 4B).

Relationship between vitamin D and total IgE levels

There was a negative relationship between log transformed total IgE levels and serum vitamin D levels in total AD patients ($R^2 = 0.119$, $p < 0.05$). In addition, a negative correlation between log transformed total IgE levels and

serum vitamin D levels was found in the severe AD group ($R^2 = 0.234$, $p < 0.05$). However, an association between log transformed total IgE and serum vitamin D levels was not found in AD patients with mild or moderate severity ($R^2 = 0.107$, $p = 0.06$; Fig. 5).

DISCUSSION

There are many controversies about the association between serum vitamin D levels and AD severity¹⁴. Overall, it seems that a predominance of reports points to a negative association between serum vitamin D levels and AD severity^{4,10,15}. However, in our study, serum vitamin D levels were not correlated with AD severity. Most AD patients have increased serum IgE levels, which correlate with disease severity¹⁶. Our results also showed a positive correlation between serum IgE levels and AD severity. Several previous studies reported a positive association between AD severity and HDM sensitization¹⁷⁻¹⁹. Howev-

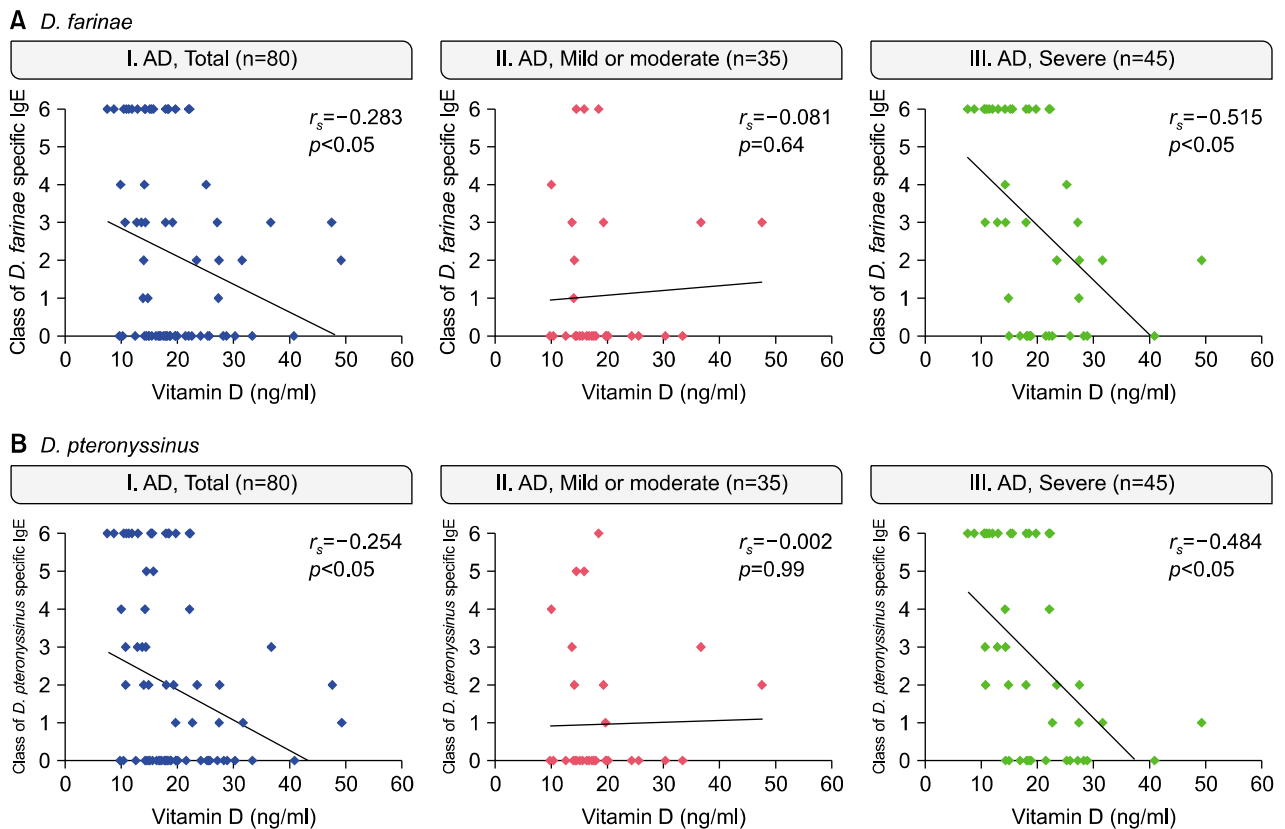


Fig. 4. Relationship between vitamin D levels and house dust mite (HDM) sensitization. (A) *Dermatophagoides farinae* sensitization showed a negative correlation with vitamin D levels with statistical significance in severe atopic dermatitis (AD) patients ($r_s = -0.515$, $p < 0.05$). (B) There was a negative correlation between serum vitamin D levels and *D. pteronyssinus* sensitization in severe AD group ($r_s = -0.484$, $p < 0.05$).

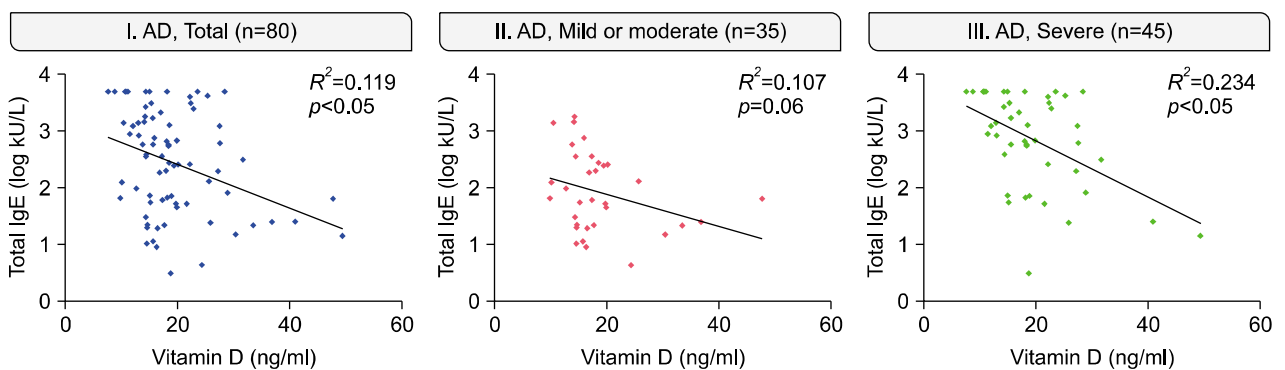


Fig. 5. Relationship between vitamin D and total immunoglobulin E (IgE) levels. There was a negative correlation between log transformed total IgE levels and vitamin D levels with statistical significance in total ($R^2 = 0.119$, $p < 0.05$) and severe atopic dermatitis (AD) group ($R^2 = 0.234$, $p < 0.05$).

er, we were unable to replicate these findings in our study. We only found more patients with class 6 HDM sensitization in the severe AD group than in the mild or moderate groups.

A few studies examined the relationship between serum vitamin D levels and AD severity according to allergen

sensitization. Akan et al.²⁰ showed a negative correlation between AD severity and serum vitamin D levels in the group with allergic sensitization but no correlation in the group without sensitization. This study suggested that vitamin D levels in children are correlated with AD severity but only in patients with allergic sensitizations¹⁶. However,

they investigated the sensitization status according to common food and aeroallergens, not specific sensitization to HDM¹⁶. Another study suggested that vitamin D deficiency increases the risk of sensitization to food allergens and that AD may be more severe in infants with vitamin D deficiency²¹. In our study, significantly lower vitamin D levels were found in severe AD patients with the high HDM sensitization. We thought that these results demonstrated that low serum vitamin D levels may be linked to high HDM sensitization in patients with severe AD. These results did not depend on the type of HDM, *D. farinae* or *D. pteronyssinus*.

On a molecular basis, vitamin D in the skin affects the three domains of AD pathogenesis, including the immune system, antimicrobial defense mechanisms, and epidermal barrier integrity¹⁰. Specifically, regarding its immunomodulatory effects, vitamin D influences both the innate and adaptive immune system. Vitamin D has antimicrobial effects related to macrophages and monocytes, enhancing chemotaxis and the phagocytic capabilities of innate immune cells²². In adaptive immunity, vitamin D functions in the differentiation and proliferation of T- and B-cells, leading to a shift from a proinflammatory to a more tolerogenic immune status²³. Defected immune systems can influence antimicrobial defense systems and epidermal barrier integrity. Therefore, in consideration of the function of vitamin D, there is a possibility that serum vitamin D levels are associated with HDM sensitization and exaggerated immune response to HDM. Our hypothesis is that low serum vitamin D levels lead to disturbed epidermal barrier function, immunologic dysregulation, and impaired cutaneous defense mechanism in patients with an atopic background. Patients with low serum vitamin D levels have an increased risk of HDM sensitization by increased penetration of HDM through broken skin barrier. Then, high HDM sensitization may induce the aggravation of immunologic dysregulation and the development of severe AD. Findings of this study suggest that vitamin D level may affect HDM sensitization.

Regarding the relationship between serum total IgE and vitamin D levels, a previous study suggested that lower serum vitamin D levels were associated with elevated serum IgE levels^{6,24}. Our study also showed that serum vitamin D levels were negatively correlated with total IgE levels in the severe AD group.

The main limitation of this study is that we did not account for clinical factors associated with serum vitamin D levels, such as individual outdoor activity and dietary habits that can affect vitamin D homeostasis. Seasonal variations in vitamin D levels were not considered. In addition, we used the Rajka and Langeland score to evaluate AD se-

verity instead of time consuming but, more reliable scoring methods (e.g., SCORAD or EASI)²⁵. However, recent report reintroduced the Rajka and Langeland score as a simple, useful and sensitive eczema scoring system²⁶.

In conclusion, our results demonstrate that low vitamin D levels may be relevant to high HDM sensitization in severe AD patients. Further investigation regarding the effect of vitamin D in HDM sensitization can give new strategies for the prevention and treatment of AD. We also need the refinement and modification of large-scale studies to determine the relationship between serum vitamin D levels and HDM sensitization in AD.

ACKNOWLEDGMENT

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (NRF-2015R1D1A3A01016229 and 2014R1A5A2009242).

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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