

The association between hypovitaminosis D and pediatric allergic diseases: A Korean nationwide population-based study

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ABSTRACT

Background: There is still considerable disagreement regarding the role of vitamin D in the development or exacerbation of allergic diseases.

Objective: To investigate the association between serum vitamin D levels and recent symptoms of allergic diseases in elementary schoolchildren.

Methods: A nationwide cross-sectional survey was conducted in children ages 6–7 years from 45 randomly selected elementary schools. The presence of atopic dermatitis (AD) or asthma was defined as medical treatment of children for AD or asthma within 12 months of the survey. The presence of allergic rhinitis (AR) was defined as medical treatment for AR during the past 12 months and a positive skin test response. Current AD was defined as confirmed eczema on physical examination. Serum 25-hydroxyvitamin D (25[OH]D) was measured by chemiluminescent immunoassay.

Results: Questionnaire data and blood samples were collected from 3720 children. The overall prevalence rates of vitamin D insufficiency (20–29 ng/mL) and deficiency (<20 ng/mL) were 64.0% and 18.4%, respectively. For a 1 ng/mL decrease in 25(OH)D, the adjusted odds ratio (aOR) for AR was 1.020 (95% confidence interval [CI], 1.002–1.040) and the aOR for current AD was 1.027 (95% CI, 1.006–1.047). For each 1 ng/mL decrease in 25(OH)D, the aOR for positive skin-prick test reactivity was 1.013 (95% CI, 1.000–1.027). No significant association between vitamin D level and the prevalence of asthma was observed.

Conclusions: A high prevalence of vitamin D deficiency and insufficiency was found in Korean elementary schoolchildren, and low vitamin D levels were associated with recent symptoms of AD and AR.

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Atopic dermatitis (AD), allergic rhinitis (AR), and asthma are the most common chronic diseases among children. A chronic course and recurrent exacerbation of allergic diseases both have a negative im-

pact on the quality of life of children and their parents. The development and aggravation of allergic diseases are caused by complex mechanisms that involve both genetic and environmental factors.¹ According to the previous International Study of Asthma and Allergies in Childhood, the lifetime prevalence of physician-diagnosed AD, AR, and asthma in Korean elementary schoolchildren increased between 2000 and 2010.² Several dietary and environmental factors are considered possible causes for the increased prevalence of allergic diseases.¹

Vitamin D is synthesized from dietary sources and through endogenous production after exposure to sunlight, hence, it is sometimes called the sunshine vitamin.³ Hepatic 25-hydroxylation of vitamin D₃ leads to the generation of serum 25(OH)D₃, which is a good indicator of the level of vitamin D intake.³ Recent studies demonstrated that the activated form of vitamin D plays an important role in innate and adaptive immune systems, and might affect immune-mediated disorders, including AD, AR, asthma, and atopic sensitization.^{4–11} However, there is still considerable disagreement regarding the role of vitamin D in the de-

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velopment or exacerbation of allergic diseases. For example, recent studies reported that vitamin D deficiency increased the lifetime prevalence of asthma and AR, and was a significant risk factor for wheezing episodes.^{12–14} On the contrary, some previous studies showed that vitamin D levels were not associated with the prevalence of AD and asthma.^{15,16} There have even been reports that vitamin D supplementation during infancy was related to an increased risk for atopy, asthma, and food allergy later in childhood.^{17,18}

These conflicting results have caused confusion regarding the role of vitamin D in children's health. Understanding the effect of vitamin D on allergic diseases through a population-based study could contribute to the generation of evidence-based health policy. Therefore, we performed a nationwide population-based study to investigate the vitamin D status in Korean elementary schoolchildren and to determine the association between vitamin D deficiency and allergic diseases such as AD, AR, and asthma.

METHODS

Study Design and Population

A nationwide cross-sectional survey was conducted in children ages 6–7 years between October and November 2010. To obtain a representative population, the survey was performed in first-grade students from 45 elementary schools in Korea. The participants were randomly selected by using a stratified two-stage cluster sampling design according to the method described in our previous study.¹⁹ The present study was approved by the institutional review board of Dankook University in Cheonan and Samsung Medical Center, and written informed consent was obtained from all the parents before their children's participation in this study.

Definition of AD, AR, and Asthma

Parents of all the students were given the Korean version of the International Study of Asthma and Allergies in Childhood questionnaires to be completed.^{20,21} They were also asked to respond to a questionnaire regarding demographic information and a parental history of allergic diseases, such as AD, AR, or asthma. Recent symptoms of AD or asthma in children were defined as the parents responding "yes" to the question "In the last 12 months, has your child been treated by a physician for eczema or asthma?" Recent symptoms of AR were defined as medical treatment for AR within 12 months of the survey and a positive skin test response to at least 1 of the 18 allergens. In addition, each subject was examined by pediatricians to determine the presence of eczema on the neck and the flexural areas of both arms. Current AD was defined as

confirmed eczema on physical examination and satisfaction of the diagnostic criteria of Hanifin and Rajka.²²

Skin-Prick Tests

Skin-prick tests were performed on the volar aspects of the forearms by using the following 18 inhalant allergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Tyrophagus putrescentiae*, cockroach, cat, dog, alder, birch, oak, Japanese cedar (Lofarma, Milan, Italy), Bermuda grass, orchard grass, timothy, mugwort, ragweed, Japanese hop, *Alternaria*, and *Aspergillus fumigatus*. Histamine was used as a positive control, and normal saline solution was as a negative control. Unless otherwise stated, the allergens were provided by Allergopharma (Reinbek, Germany). A test was regarded as positive if the wheal diameter was ≥ 3 mm and controls showed adequate reactions.

Blood Tests

On the day of the survey, blood samples were taken to measure serum levels of total immunoglobulin E (IgE) and 25(OH)D. Total IgE levels were determined by using the Immuno-CAP system (Thermo Fisher Scientific, Waltham, MA), and 25(OH)D levels were measured by using a Centaur XP chemiluminescent immunoassay (Siemens Health care Diagnostics Inc., Tarrytown, NY). Vitamin D deficiency was defined as a serum concentration of 25(OH)D of <20 ng/mL, and vitamin D insufficiency was defined as a serum concentration of 25(OH)D between 20 and 29 ng/mL.⁵

Statistical Analysis

Data were analyzed by using SPSS for Windows (version 23.0; SPSS, Chicago, IL). The χ^2 test was applied to determine differences in the proportions. Univariable and multivariable logistic regression analyses were applied to determine the effect of serum 25(OH)D concentrations on the prevalence of symptoms of AD, AR, or asthma. Variables for adjustment included sex, parental history of allergic diseases, maternal education level, dampness or mold at home, remodeling of the home in which the child resided at the time, and residence in a new house built in the past 2 years. In addition, bivariate associations between two continuous variables, such as log-transformed total IgE and 25(OH)D concentrations, were assessed with Pearson correlations. A p value of <0.05 was considered significant.

RESULTS

Questionnaire data and blood samples were collected from 3720 children (1878 boys and 1842 girls), which represented 85.6% of the subjects who participated in this survey. Among the participants who completed the study, 1208 mothers (32.5%) and 1178 fa-

Table 1 Characteristics of the participants
(N = 3720)

Variable	No. (%)
Sex	
Boys	1878 (50.5)
Girls	1842 (49.5)
Family history of allergic diseases	
Mother	1208 (32.5)
Father	1178 (31.6)
Maternal education level	
College degree	1578 (43.4)
High school diploma or less	2054 (56.6)
Dampness or mold at home	
Yes	1059 (26.7)
No	2903 (73.3)
Remodeling of the current home	
Yes	617 (16.0)
No	3248 (84.0)
Residence in a new house in the past	
2 years	
Yes	152 (4.1)
No	3535 (95.9)
Serum 25(OH)D concentrations	
≥30.0 ng/mL	653 (17.6)
20.0–29.9 ng/mL	2384 (64.0)
<20.0 ng/mL	683 (18.4)

25(OH)D = 25-hydroxyvitamin D.

thers (31.6%) had allergic diseases, including AD, AR, or asthma (Table 1). The mean concentration of serum 25(OH)D was 24.7 ng/mL. The overall prevalence rates of vitamin D insufficiency and deficiency were 64.0% (2384/3720) and 18.4% (683/3720) (Table 1). Of 3649 children who underwent skin-prick testing, a positive response to at least 1 of the 18 allergens was observed in 1508 (41.3%). The presence of recent symptoms during the past 12 months was reported in 15.3% (571/3720), 3.7% (140/3720), and 15.6% (567/3645) of the subjects for AD, asthma, and AR, respectively. On physical examination on the day of the survey, current AD was found in 437 children (11.7%).

Univariable analysis showed no significant relationship between serum 25(OH)D levels and the recent symptoms of AD, asthma, or AR. In a multivariable analysis, however, a lower concentration of serum 25(OH)D was associated with a higher prevalence of AR. For a 1 ng/mL decrease in 25(OH)D level, the adjusted odds ratio (aOR) for AR was 1.020 (95% confidence interval [CI], 1.002–1.040) (Table 2). No significant effects of the vitamin D level were observed on the prevalence of AD (aOR 0.991 [95% CI, 0.974–1.009]) or asthma (aOR 0.989 [95% CI, 0.956–1.022]) in a multivariable analysis. A lower level of serum 25(OH)D

Table 2 Multivariable analysis of factors that influenced recent symptoms of atopic dermatitis, asthma, and allergic rhinitis

Variables	Atopic Dermatitis, aOR (95% CI)	Current Atopic Dermatitis, aOR (95% CI)	Asthma, aOR (95% CI)	Allergic Rhinitis, aOR (95% CI)
Serum 25(OH)D, 1 ng/mL decrease	0.991 (0.974–1.009)	1.027 (1.006–1.047)	0.989 (0.956–1.022)	1.020 (1.002–1.040)
Boys	0.723 (0.591–0.884)	0.914 (0.733–1.139)	1.844 (1.246–2.728)	1.908 (1.549–2.351)
Paternal allergic diseases, yes	1.197 (0.967–1.482)	0.968 (0.759–1.235)	1.707 (1.165–2.502)	2.139 (1.739–2.631)
Maternal allergic diseases, yes	1.440 (1.172–1.769)	1.055 (0.835–1.333)	1.971 (1.351–2.876)	2.510 (2.046–3.079)
Maternal education levels, college degree	1.115 (0.907–1.371)	0.967 (0.772–1.211)	1.174 (0.793–1.738)	1.160 (0.939–1.433)
Residence in a new house, yes	0.999 (0.589–1.695)	1.026 (0.579–1.817)	1.808 (0.848–3.851)	1.012 (0.598–1.713)
Dampness or mold at home, yes	1.169 (0.935–1.460)	1.081 (0.843–1.385)	0.964 (0.627–1.483)	1.027 (0.816–1.292)
Remodeling of home, yes	1.170 (0.896–1.526)	1.044 (0.773–1.411)	0.914 (0.544–1.536)	0.962 (0.729–1.269)

aOR = adjusted odds ratio; CI = confidence interval; 25(OH)D = 25-hydroxyvitamin D.

*Children diagnosed by pediatricians on examination of the neck and flexural areas of both arms on the day of the survey according to criteria of Hanifin and Rajka (Ref. 22).

Table 3 Relationship between allergic sensitization and risk factors

Variable	Allergic Sensitization, aOR (95% CI)
Serum 25(OH)D, 1 ng/mL decrease	1.013 (1.000–1.027)
Boys	1.427 (1.233–1.652)
Paternal allergic diseases, yes	1.344 (1.147–1.575)
Maternal allergic diseases, yes	1.325 (1.136–1.545)
Maternal education level, college degree	1.038 (0.894–1.205)
Residence in a new house, yes	0.895 (0.605–1.322)
Dampness or mold at home, yes	1.068 (0.906–1.260)
Remodeling of the home, yes	1.113 (0.911–1.361)

aOR = adjusted odds ratio; *CI* = confidence interval; 25(OH)D = 25-hydroxyvitamin D.

was associated with an increased risk for current AD in univariate and multivariate analyses. For a 1 ng/mL decrease in the serum 25(OH)D level, the aOR for the presence of AD on the day of the survey was 1.027 (95% CI, 1.006–1.047). Furthermore, a lower concentration of serum 25(OH)D was associated with a higher prevalence of allergic sensitization in multivariable analysis, although no significant differences were observed in the univariable analysis. For each 1 ng/mL decrease in the 25(OH)D value, the aOR for positive skin-prick test reactivity was 1.013 (95% CI, 1.000–1.027) (Table 3). However, no relationship was found between log-transformed total IgE levels and serum 25(OH)D concentrations ($p = 0.223$).

DISCUSSION

Recently, there has been an increase in the number of studies that investigated the relationship between vitamin D levels and allergic diseases, such as AD, AR, or asthma. In the present study, we investigated the association between serum vitamin D and current symptoms of allergic diseases and atopic sensitization, and found that lower levels of 25(OH)D increased the risk of AD, AR, and atopic sensitization. These results were in agreement with previous studies that showed that the serum vitamin D concentration was lower in patients with allergic diseases than in normal controls.^{12,23,24} To our knowledge, this is the first Korean study to show a significant relationship between vitamin D and atopy in the general pediatric population.

Vitamin D plays an important role in T-helper type 1 and type 2 balance as a modulator of the innate and adaptive immune systems.^{4,5} The active form of vitamin D₃, 1,25(OH)₂D₃, prevents the differentiation and maturation of dendritic cells, which leads to impaired

activation of T cells.²⁵ Furthermore, 1,25(OH)₂D₃ is reported to promote the induction of regulatory T cells.^{26–28} Therefore, it has been presumed that vitamin D modulates immune-mediated inflammatory reactions and is linked to allergic sensitization. In support of this, a number of studies reported that vitamin D deficiency was associated with the high production of total IgE or allergen-specific IgE.^{7,23,29} A Taiwanese birth cohort study showed that lower maternal 25(OH)D levels were related to a higher prevalence of allergen sensitization during infancy as well as eczema and asthma at the age of 4 years.⁷ A U.S. nationwide study also demonstrated that children with lower 25(OH)D levels had a higher risk of sensitization to food or inhalant allergens.²⁹ In accordance with previous studies, an association was observed between low 25(OH)D levels and a high prevalence of atopic sensitization and AR in our study. A Korean nationwide study of adults also showed that lower 25(OH)D levels were associated with a higher prevalence of AR.³⁰ The relationship between vitamin D and allergic sensitization might explain the association of vitamin D with the prevalence of AR because AR is a representative disease caused by immune-mediated mechanisms through allergen exposure and sensitization.

The relationship between low 25(OH)D levels and a high prevalence of current eczema reaffirms similar results in previous studies. Vitamin D deficiency and insufficiency were found to be common in Hong Kong, and vitamin D deficiency was more frequently observed in children with AD than in normal controls.²³ Moreover, serum 25(OH)D levels were inversely correlated with AD severity in that study. In another study, adults with vitamin D insufficiency had an increased risk of AD, which indicates that vitamin D has a protective effect against AD in adults as well as in children.²⁴ Vitamin D also plays an important role in the induction of cathelicidin expression in keratinocytes and the upregulation of antimicrobial peptides, which thus strengthens the innate defense in the skin barrier.^{3,31,32}

However, there has been considerable controversy regarding the relationship between vitamin D levels and asthma. Several studies reported an inverse association of vitamin D levels with current wheeze and asthma severity, whereas another case-control study of 263 subjects, ages 2–19 years, did not identify any differences in 25(OH)D levels between patients with asthma and controls.^{16,33–35} Similarly, our study did not find any relationship between 25(OH)D level and recent symptoms of asthma. Although the exact mechanism is not yet clear, there is accumulating evidence that indicates that vitamin D deficiency is related to dysfunction of the pulmonary defense mechanism against respiratory tract infection and might contribute to the aggravation of asthma triggered by viral infec-

tion.^{5,36} For example, low serum 25(OH)D levels were inversely correlated with the risk of respiratory syncytial virus or rhinovirus infection in children with acute severe wheezing that necessitated hospitalization.^{36–39} A second explanation for the link is a role for vitamin D in lung development.^{5,40} Lower vitamin D levels were associated with decrements in lung function in a cohort study of children⁴⁰ as well as an animal study.⁴¹ Unfortunately, we did not evaluate virus-induced wheezing, lung function test, or the degree of asthma control in the present study. Further studies, therefore, are needed to determine a causal relationship and its mechanism.

In the present study, vitamin D sufficiency, defined as serum concentrations of ≥ 30 ng/mL, was observed in only 17.6% of our subjects. This result is consistent with that of Lee *et al.*,⁴² who studied vitamin D levels in 2880 children ages 10–18 years by using data from the Korean National Health and Nutrition Examination Survey. They reported that 75% of subjects showed 25(OH)D levels of < 20.86 ng/mL, which indicated a high prevalence of hypovitaminosis D in Korean schoolchildren. Recent Turkish⁴³ and Taiwanese⁴⁴ studies also showed that only 5.7% and 10.6% of healthy schoolchildren had serum 25(OH)D levels ≥ 30 ng/mL in the autumn season. Results of these studies indicated that vitamin D deficiency is prevalent worldwide. Vitamin D deficiency in children might be a major public health concern because vitamin D influences cardiovascular, endocrine, and immune systems as well as the regulation of calcium, phosphorus, and bone metabolism.⁵

The seasonal variation of vitamin D concentrations should be taken into account because vitamin D levels vary by season.³ Our present study was conducted only during the autumn season to estimate interindividual differences of vitamin D levels in one season. However, it might have led to lower levels of vitamin D and a higher prevalence of hypovitaminosis D in our study. Further studies are needed to assess the cost-effectiveness of vitamin D monitoring and supplementation, to determine cutoff limits for vitamin D in children with allergies, and to find out the coexistence of other risk factors for low vitamin D levels.

CONCLUSION

A high prevalence of vitamin D deficiency and insufficiency was found in Korean elementary schoolchildren, and low vitamin D levels were associated with an increased risk of AD, AR, and atopic sensitization. Our results supported the role of vitamin D in allergic diseases and provided a rationale for monitoring vitamin D levels in children.

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