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TITLE: An evaluation of vitamin D levels in children with seasonal allergic rhinitis during pollen season

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An evaluation of vitamin D levels in children with seasonal allergic rhinitis during pollen season

Pediatr Allergy Immunol

Abstract

Background: Serum vitamin D levels have not been studied in children with seasonal allergic rhinitis (SAR). The aim of this study was to evaluate the vitamin D levels of children with SAR and to compare them to levels in healthy children during pollen season.

Methods: This study was conducted in 100 children with SAR and 100 healthy controls. Clinical and laboratory evaluations and vitamin D analyses of all the participants were performed between the months of April and July. Pollen sensitization was detected in the patient group using a skin prick test. 25(OH)D₃ levels were compared between the patient and

control groups. Associations among the patient 25(OH)D₃ levels and their demographic, clinical, and laboratory characteristics were analyzed.

Results: Overall, 72% of the patients were male, the median age was 12.35 years (range: 6–17.8 years), and the median body mass index value was 19.15 (range: 13.6–27.8). There were no differences between the patients and healthy controls in terms of gender, age, or body mass index. The mean levels of 25(OH)D₃ (20.78 ± 6) in patients were higher than those of the controls (17.92 ± 4). In the patient group, no associations were found among 25(OH)D₃ levels, demographic characteristics, atopy test results, atopy history, severity of rhinitis, and the total four-symptoms score (all $p > 0.05$).

Conclusions: During pollen season, children with SAR may have higher vitamin D levels than healthy controls. The presence of asthma and/or atopic dermatitis in addition to SAR did not change this result.

Keywords allergic rhinitis, children, seasonal allergic rhinitis, pollen allergy, pollen season, vitamin D

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Introduction

Over the past 50 years, the prevalence of allergic diseases has been on the rise, and a similar increase in prevalence has been observed for allergic rhinitis (AR) (1, 2). There are approximately 500 million AR patients worldwide, and the precise reason for this increased prevalence is unknown (3). The frequency of AR, however, does change with age among

children. It occurs most frequently between the ages of 13 and 14, and 14.6% of individuals in this age range have this condition (4). The prevalence of seasonal AR (SAR) is reportedly 9.1% (3). Although AR and SAR are frequently occurring diseases, they are not life-threatening; nonetheless, they are noteworthy, as they are globally prevalent and can adversely affect patient quality of life (3, 4).

Given the increase in the prevalence of allergic diseases, attention has been paid to environmental factors such as diet, climate, and lifestyle (5). Vitamin D affects the human body not only through diet but also via climate and lifestyle. Therefore, vitamin D is considered to be an important environmental factor (5). Wjst et al. suggest that the prevalence of allergic diseases increased worldwide after vitamin D supplementation was offered to the general population (6). Following this suggestion, studies on the association between allergic diseases and vitamin D increased. In the last decade, vitamin D has been found to be associated with allergic diseases, especially in research investigating the immunological effects of vitamin D (5). It is believed that this association is based on the regulation of the adaptive and innate immune systems by vitamin D (5, 7).

Studies conducted to explain the relationship between vitamin D and allergic diseases have usually focused on asthma or atopic dermatitis (AD) (5, 8). However, AR can serve as a more suitable disease in examining this association, as it has a less-complicated pathogenesis than does asthma or AD (4). Few studies on vitamin D have focused solely on AR, despite there being a high prevalence of this disease within the general population (3, 4). Additionally, prospective studies on vitamin D levels in children with AR have tended to feature very small patient samples. There has been no study of vitamin D levels in children with SAR. The aim of the current study is to compare the vitamin D levels of children with SAR to those of healthy children during pollen season.

Material and methods

The patients examined in this study were selected from among children admitted to the Department of Pediatric Allergy and Immunology at Ondokuz Mayıs University between April and July 2016 with a complaint of AR (i.e., sneezing, rhinorrhea, nasal obstruction, and nasal itching) that had been recurrent for at least two years. In the city in which this hospital is located, pollen exposure usually occurs in May and June of each year. The city is on the seaside, and 4 m above sea level. It is located at a latitude of 41° and a longitude of 36°. The temperature change between April and July is 11–26°C, the moisture change is between 64% and 73%, and the amount of rainfall is between 30 and 95 kg/m².

AR diagnoses were made in line with the Allergic Rhinitis and Its Impact on Asthma (ARIA) 2008 criteria (3). AR symptoms were assessed using the total four-symptoms score (T4SS). In all, 136 children aged 6–18 years, all of whom had AR symptoms between April and July for the previous two years and who had tested positive for pollen sensitivity via a skin prick test, were examined for this study. ARIA 2008 criteria were also used to diagnose SAR (3). Exclusion criteria included weight, height, or body mass index (BMI) values that were not normal for the age of the patient; immunotherapy; perennial rhinitis symptoms; infectious rhinitis; any chronic illnesses that influence calcium and vitamin D metabolism; and any food allergy. In addition, patients who had taken any of the following drugs within the previous month were also excluded: a multi-vitamin drug or food supplement, nasal or systemic steroid, or drugs that can influence calcium and vitamin D metabolism (e.g., antidepressants, antacids, anticonvulsants, ketoconazole, etc.). Ultimately, 100 children with SAR who also satisfied these criteria were included in the study.

The patients' demographic information, BMI, presence of asthma or AD, and family history of atopy (recorded as a history of parents and siblings) were recorded. Patients with comorbidity of asthma or AD were assigned to the SAR+AA group, whereas those with no

comorbidity of asthma or AD were assigned to the *SAR only* group. The severity of AR was classified as either *mild* or *moderate/severe*, in line with ARIA criteria (3).

The control group comprised children aged 6–18 years who had been admitted to the pediatric clinic between April and July 2016 and who, upon examination, were deemed healthy. We excluded from the study any children with ear–nose–throat symptoms upon admission, those who had respiratory system or dermatological symptoms or signs, those with an atopic disease in their clinical history, and those who satisfied any exclusion criterion relevant to the patients. Ultimately, 100 healthy children who satisfied these criteria were included in this study as controls. The demographic characteristics and BMI values of the children within the control group were recorded, and their serum vitamin D levels were measured between April and July 2016. Written informed consent was obtained from the children's caregivers, and the study protocols were approved by the Ondokuz Mayıs University Faculty of Medicine Ethics Committee.

Laboratory measurements

Pollen sensitization was determined through a skin prick test. Histamine was used as a positive control, while normal saline was used as a negative control. The test was considered positive if the mean diameter of the wheal was at least 3 mm greater than the negative control test after 15–20 minutes. The following allergens were used in the skin prick test: grass mix (*Anthoxanth odoratum*, *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*), tree mix (*Castanea vulgaris*, *Quercus robur*, *Fagus sylvatica* ACE), weeds (*Chenopodium album*, *Amaranthus retroflexus*), *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternata*, *Aspergillus mix*, *Blattella germanica*, and cat feathers (Stallergenes SA, Antony, France). Patients who were found through the skin prick test to be sensitive to at least one of weeds, grass mix, or tree mix were considered *pollen-sensitive* patients. The patients were divided into two groups, according to the skin

prick test results. Patients sensitized to pollen and other aeroallergens were assigned to the *pollen+* group. Patients with no aeroallergen sensitization aside from pollen were assigned to the *pollen only* group. IgE levels were recorded only for the patient group, and eosinophil counts were recorded for both the patient and the control groups.

To determine the serum vitamin D levels, we measured serum 25-hydroxyvitamin D₃ (25(OH)D₃) levels (9). In this study, vitamin D and 25(OH)D₃ are used interchangeably. Fasting peripheral venous blood samples were obtained from all subjects, and blood samples were centrifuged. The blood-derived serums were stored at –80 °C until analysis to allow 25(OH)D₃ levels to be measured concurrently. Serum 25(OH)D₃ levels were measured via liquid chromatography–tandem mass spectrometry (LC–MS/MS) (Thermo TSQ lc-ms, serial no. TQU 04154, San Jose California, USA). The LC–MS method was undertaken using Recipe-Clin Mass kits (Clin Mass lc-ms/ms complete kit, Munich, Germany). D₃–D₆ deuterium was used as an internal standard. Serum 25(OH)D₃ levels were classified as follows: ≤5 ng/mL, severely vitamin D-deficient; 5–15 ng/mL, vitamin D-deficient; 15–20 ng/mL, vitamin D-insufficient; 20–100 ng/mL, optimal vitamin D level; and ≥100 ng/mL, potential vitamin D toxicity (10).

Statistical analysis

The normality of continuous variables was analyzed by using a Kolmogorov–Smirnov test. A student *t*-test was used to analyze differences between two groups that were normally distributed, and a Mann–Whitney *U* test was used to analyze differences between groups not normally distributed. A one-way ANOVA test and a post-hoc Bonferroni test were used to analyze differences among more than two groups that were normally distributed, while a Kruskal–Wallis test and a Bonferroni corrected Mann–Whitney *U* test were used to analyze differences among more than two groups that were not normally distributed. A Pearson chi-

square test and a Fisher exact test were used to analyze the distributions of the nominal variables among groups, if necessary.

Results

There were no statistically significant differences between the patient groups and control groups with regards to age, gender, or BMI (Table 1). The mean 25(OH)D₃ level of the patient group was found to be significantly higher than that of the control group ($p = 0.002$) (Figure 1). The frequency of normal 25(OH)D₃ levels was higher in the patient group than in the healthy control group ($p = 0.002$), and the vitamin D deficiency of the former was higher ($p = 0.005$). The data are shown in Table 1.

Patient characteristics are shown in Table 2. The mean 25(OH)D₃ level of the *SAR only* group was 20.33 ± 6.53 ng/mL, whereas that of the *SAR+AA* group was 21.24 ± 6.46 ng/mL. No significant difference was found between the two groups in terms of 25(OH)D₃ levels ($p = 0.486$). No differences were found between the *SAR only* group and the control group ($n = 100$) in terms of gender, age, or BMI ($p = 0.498$, $p = 0.175$, and $p = 0.257$, respectively), but 25(OH)D₃ levels in the *SAR only* group were found to be significantly higher than those of the controls ($p = 0.033$). The 25(OH)D₃ level of the *SAR+AA* group was compared to that of the control group ($n = 100$); the 25(OH)D₃ level of the *SAR+AA* group was found to be significantly higher ($p = 0.004$). The *SAR only*, *SAR+AA*, and control groups ($n = 100$) were compared by one-way ANOVA. The 25(OH)D₃ levels of the *SAR only* group were not significantly different from those of the *SAR+AA* or control groups ($p = 0.764$, $p = 0.081$, respectively). However, the level of 25(OH)D₃ in the *SAR+AA* group was found to be higher than that of the control group ($p = 0.010$).

The patients were divided into three groups according to atopic family history (Table 2). No significant differences were found among these three groups in terms of 25(OH)D₃

levels ($p = 0.420$). No significant difference was found between the mild rhinitis and moderate–severe rhinitis group in terms of 25(OH)D₃ levels in either all patients or the *SAR only* group ($p = 0.914$, $p = 0.256$, respectively). No correlation was found between the serum 25(OH)D₃ levels and T4SS values in either all patients or the *SAR only* group (Table 3).

There were no differences between the *pollen only* group and the *pollen+* group in terms of gender or BMI. However, patient age was higher in the second group ($p = 0.027$). When the 25(OH)D₃ levels of both groups were compared via independent-samples *t*-test, no significant difference was found ($p = 0.854$). The frequency of moderate–severe rhinitis was higher ($p = 0.007$), the T4SS was higher ($p = 0.008$), and the mean IgE level was higher ($p = 0.009$) in the *pollen only* group than in the *pollen+* group. No significant correlation was found between the serum 25(OH)D₃ levels and the median IgE levels and median eosinophil counts both in either all patients or the *SAR only* group (Table 3).

Although a negative correlation was found between vitamin D levels and age in the healthy control group, no correlation was found between the vitamin D levels and age in the patient group (Table 3). A negative correlation was found between the vitamin D levels and age in the healthy controls. However, among patients, there was no such correlation. In the healthy control group, the vitamin D levels of male subjects were found to be significantly higher than those of female subjects, as expected ($p = 0.002$). Patient vitamin D levels were analyzed according to gender. In the patient group, no differences were found in 25(OH)D₃ level in terms of gender ($p = 0.504$). Associations in the healthy control group between mean vitamin D levels and BMI values were analyzed, and a negative correlation was found (Table 3). In the patient group, no correlation was found between vitamin D levels and BMI.

Discussion

This is the first study to investigate vitamin D levels in children who have SAR during pollen season. This case-control study is the first to determine that the mean vitamin D levels of

children with AR are higher than those of healthy controls. Among children with SAR who have not used a systemic steroid in the previous month, in cases of SAR and asthma and/or AD comorbidity, mean vitamin D levels were higher than those of healthy controls.

To date, the association between AR and vitamin D levels has been investigated generally in birth-cohort or population-based studies, with a focus specifically on subjects with allergic disease (11). In the general population, age, gender, BMI, the use of certain drugs, multivitamin intake, comorbid diseases, and the season can affect serum vitamin D levels (9, 12). Factors that affect vitamin D levels in a healthy population should be considered, especially in case-control studies. Kim et al. analyzed studies that measured vitamin D levels in AR patients and reported that prevalence and incidence studies generally found no association between AR and vitamin D. Additionally, in case-control studies, vitamin D levels have been found to be lower in children with AR than in healthy controls (11). Our results are not consistent with the results of this meta-analysis. However, the case-control studies within the meta-analysis included fewer patients than our study or they included retrospective data (11). The strength of the current case-control study lies in the fact that it includes a larger number of patients and that it was conducted in the season when the intensity of the responsible antigen is high. In the meta-analysis, the low vitamin D levels in children with AR were hypothesized to occur due to the steroid effect of comorbid allergic diseases or low external environment activity. An inverse relationship has been reported between serum vitamin D levels and the use of an inhaler or a systemic steroid (13, 14, 15). We analyzed vitamin D levels in children within the *SAR only* group and without asthma or AD, to remove the systemic and inhaler steroid effect. Similarly, we found higher vitamin D levels in the patients than in the healthy controls. A case-control study recently conducted on vitamin D in children with AR reported results different from ours. In that study, vitamin D levels in children with AR were found to be lower than those of control subjects (16). The

weaknesses of that study in comparison to our own are that it examined a smaller number of children with AR and was conducted over multiple seasons.

Among retrospective population-based and cohort studies, there have been reports that an inverse relationship between vitamin D level and frequency of AR (17), no association (12, 18, 19), or a positive association (20, 21) exists. These conflicting results indicate that the relationship between vitamin D and allergic diseases is not clear. Most studies that found an inverse relationship between the frequency of allergic diseases and vitamin D level focus on asthma and AD patients (22, 23). However, in some studies that included children with asthma, no inverse relationship was found (14, 24). One-half of our patients who did not receive a systemic or inhaler steroid in the previous month were comorbid with asthma and/or AD. Unexpectedly, the mean vitamin D levels of these patients were found to be higher than those of the healthy controls. Steroid use, age, BMI, gender, and season are major confounding factors in investigating the association between allergic diseases and vitamin D levels. These factors can produce different results among studies that examine vitamin D levels (8). For this reason, in the current study, we took these factors into due consideration.

Recently, vitamin D supplementation studies have been conducted for some allergic diseases (26). Our results do not support the assertion that children with AR should receive vitamin D supplementation. Although maternal supplemental vitamin D intake has been reported not to change AR frequency in children (27), maternal food-based vitamin D intake reportedly changes AR frequency in children (19, 28). Interestingly, maternal food-based vitamin D intake has been reported not to increase vitamin D levels in cord blood (22). These studies indicate that the association between vitamin D serum levels and its function is unclear (22, 19).

As with the current study, recent studies found there to be no association between the severity of rhinitis and vitamin D levels in children with AR (16, 29). In our study, although

the *pollen only sensitized* group presented higher rhinitis severity and a higher IgE level than polysensitized patients, there was no significant difference between the two patient groups in terms of vitamin D levels. In line with the literature, we generally found there to be no association between vitamin D levels and atopy tests (19, 16, 20). In agreement with our results, it has been generally reported in the literature that for children with allergic diseases, there is no association between serum vitamin D levels and family atopy (21, 23).

As in the general population, with the control group in our study, we found there to be a negative correlation between vitamin D levels and age and BMI (9, 10, 12, 30). All patients had ages and BMI values similar to those of the controls, and we found there to be no correlation between vitamin D levels and either age or BMI in children with SAR. These results do not agree with those in the literature, which have reported an inverse correlation between vitamin D levels and BMI and age in children with asthma (14, 23), and sensitized children (17). As in the general population, the mean vitamin D levels of the male subjects in our control group were found to be higher than those of the female subjects (12, 30). Although children with SAR had a gender distribution similar to that of our control group, we found no correlation between gender and vitamin D levels in these patients. Similarly, no studies in the literature have found there to be any association between gender and vitamin D levels in children with AR. In retrospective studies that included asthma or sensitized children, the vitamin D levels of male subjects were reportedly higher than those of female subjects (17, 23). Given these results, we can say that the association we uncovered between the vitamin D levels of our patients and their demographic data do not agree with the findings in the literature. Finally, we measured vitamin D in the same pollen season in all participants. For this reason, our results may differ from those of population-based or cross-sectional studies.

Accepted Article

In our study, we did not question subjects about their nutritional history or sun exposure (a natural source of vitamin D). Additionally, in our country, dairy products are not fortified with vitamin D. We did not measure outdoor activity in either group. Since this study was conducted during pollen season, pollen-sensitized SAR patients may not be expected to be partaking in outdoor activities for long periods of time. Our study was conducted during the active period of SAR patients. The higher vitamin D levels in our patients compared to the controls may be associated with the regulatory mechanism of vitamin D. Vitamin D also has regulatory and suppressor effects on T-helper-2-cell responses (5). We do not know whether this difference in vitamin D levels is temporary. As such, our lack of questions regarding the sun exposure and diet history of the subjects both in infancy and upon admission, as well as our lack of 25(OH)D₃ measurements outside the pollen season and when there were no clinical symptoms, can be considered study limitations. We also did not measure mediators of the T-helper-2-cell pathway. To help explain the immunological mechanism of vitamin D on allergic diseases, prospective studies should be conducted in active periods of allergic disease and under conditions featuring the responsible antigen.

Conclusions

In conclusion, during pollen season, the serum vitamin D levels of children with SAR were higher than those of healthy controls. The vitamin D levels of children with SAR were not associated with their demographic features, clinical severity, or atopy. This study does not support the evaluation of children with AR in terms of vitamin D deficiency, even in cases of exposure to the responsible allergen.

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Conflict of interest

None of the authors have any conflict of interest to disclose.

References

1. Asher MI, Montefort S, Bjorkston B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; **368**: 733–43.
2. Duksal F, Akcay A, Becerir T, Ergin A, Becerir C, Guler N. Rising trend of allergic rhinitis prevalence among Turkish schoolchildren. *Int J Pediatr Otorhinolaryngol* 2013; **77**: 1434–9.
3. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update. *Allergy* 2008; **63**: 8–160.
4. Corren J, Baroody FM, Pawankar R. Allergic and nonallergic rhinitis. In: Adkinson NF, Bochner BS, Burks AW, eds. *Middleton's Allergy: Principles and Practice*. Philadelphia: Saunders 2014: 664–85.
5. Mirzakhani H, Al-Garawi A, Weiss ST, Litonjua AA. Vitamin D and the development of allergic disease: how important is it? *Clin Exp Allergy* 2015; **45**: 114–25.
6. Wjst M, Dold S. Genes, factor X, and allergens: what causes allergic diseases? *Allergy* 1999; **54**: 757–9.
7. Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. *Nat Clin Pract Endocrinol Metab* 2008; **4**: 80–90.
8. Reinholz M, Ruzicka T, Schaubert J. Vitamin D and its role in allergic disease. *Clin Exp Allergy* 2012; **42**: 817–26.

9. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; **96**: 1911-30.
10. Misra M, Pacaud D, Petryk A, Collet-Solberg PF, Kappy M; Drug and therapeutics committee of the lawson wilkins pediatric endocrine society. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics* 2008; **122**: 398-417.
11. Kim YH, Kim KW, Kim MJ, et al. Vitamin D levels in allergic rhinitis: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2016; **27**: 580-90.
12. Yao TC, Tu YL, Chang SW, et al. Suboptimal vitamin D status in a population-based study of Asian children: prevalence and relation to allergic diseases and atopy. *PLoS One* 2014; **9**: e99105.
13. Goleva E, Searing DA, Jackson LP, Richers BN, Leung DY. Steroid requirements and immune associations with vitamin D are stronger in children than adults with asthma. *J Allergy Clin Immunol* 2012; **129**: 1243-51.
14. Searing DA, Zhang Y, Murphy J, et al. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. *J Allergy Clin Immunol* 2010; **125**: 995–1000.
15. Skversky AL, Kumar J, Abramowitz MK, Kaskel FJ, Melamed ML. Association of glucocorticoid use and low 25-hydroxyvitamin D levels: results from the National Health and Nutrition Examination Survey (NHANES): 2001-2006. *J Clin Endocrinol Metab* 2011; **96**: 3838–45.
16. Dogru M, Suleyman A. Serum 25-hydroxyvitamin D3 levels in children with allergic or nonallergic rhinitis. *Int J Pediatr Otorhinolaryngol* 2016; **80**: 39-42.

17. Sharief S, Jariwala S, Kumar J, Muntner P, Melamed ML. Vitamin D levels and food and environmental allergies in the United States: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 2011; **127**: 1195–1202.
18. Baumann LM, Romero KM, Robinson CL, et al. Prevalence and risk factors for allergic rhinitis in two resource-limited settings in Peru with disparate degrees of urbanization. *Clin Exp Allergy* 2015; **45**: 192–9.
19. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, et al. Prenatal, perinatal, and childhood vitamin D exposure and their association with childhood allergic rhinitis and allergic sensitization. *J Allergy Clin Immunol* 2016; **137**: 1063–70.
20. Wjst M, Hyponen E. Vitamin D serum levels and allergic rhinitis. *Allergy* 2007; **62**: 1085–86.
21. Rothers J, Wright AL, Stern DA, Halonen M, Camargo CA Jr. Cord blood 25-hydroxyvitamin D levels are associated with aeroallergen sensitization in children from Tucson, Arizona. *J Allergy Clin Immunol* 2011; **128**: 1093–99.
22. Jones AP, Palmer D, Zhang G, Prescott SL. Cord blood 25-hydroxyvitamin D3 and allergic disease during infancy. *Pediatrics* 2012; **130**: e1128–35.
23. Brehm JM, Celedon JC, Soto-Quiros ME et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med* 2009; **179**: 765–71.
24. Dogru M, Kirmizibekmez H, Yesiltepe Mutlu RG, Aktas A, Ozturkmen S. Clinical Effects of Vitamin D in Children with Asthma. *Int Arch Allergy Immunol* 2014; **164**: 319–25.
25. Skversky AL, Kumar J, Abramowitz MK, Kaskel FJ, Melamed ML. Association of glucocorticoid use and low 25-hydroxyvitamin D levels: results from the National

- Health and Nutrition Examination Survey (NHANES): 2001-2006. *J Clin Endocrinol Metab* 2011; **96**: 3838–45.
26. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. *J Allergy Clin Immunol* 2011; **127**: 1294–96.
27. Maslova E, Hansen S, Jensen CB, Thorne-Lyman AL, Strøm M, Olsen SF. Vitamin D intake in mid-pregnancy and child allergic disease—a prospective study in 44,825 Danish mother-child pairs. *BMC Pregnancy Childbirth* 2013; **13**: 199.
28. Erkkola M, Kaila M, Nwaru BI, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy* 2009; **39**: 875–82.
29. Yoon SH, Kim YH, Park YA, et al. Correlation Between Serum 25-Hydroxyvitamin D Levels and Allergic Rhinitis in Children and Adolescents in Korea. *J Allergy Clin Immunol* 2015; **135**: AB270.
30. Mithal A, Wahl DA, Bonjour JP, et al. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int* 2009; **20**: 1807–20.

Figure 1 25-hydroxyvitamin D₃ levels of the patients and controls

Table 1 Sociodemographic features and 25(OH)D₃ levels of the patients and controls

	Patient group (<i>n</i> = 100)	Healthy Controls (<i>n</i> = 100)	p-value
Gender, n			
male/female	72/28	72/28	1
Age, years			
Median (min-max)	12.35 (6-17.8)	11.50 (6-17.8)	0.402
BMI (kg/m ²)			
Median (min-max)	19.15 (13.6-27.8)	19.15(14-26.6)	0.420
25(OH)D ₃ (ng/mL)			
Mean ± SS	20.78 ± 6.48	17.92 ± 6.48	0.002
Vitamin D status, n			
Normal	60	37	0.002
Insufficiency	34	28	0.445
Deficiency	16	34	0.005
Severe deficiency	0	1	1.000

25(OH)D₃, 25-hydroxyvitamin D₃; BMI, body mass index.

Table 2 Clinical and laboratory characteristics of the patients

Clinical and laboratory characteristics	Patients <i>n</i> = 100
Comorbid allergic disease	
No (<i>SAR only</i> group*)	51
Yes (<i>SAR-AA</i> group†)	49
Atopic family member	
No	27
One person	40
Two or more person	33
Severity of rhinitis	
Mild	43
Moderate/Severe	57
Skin prick test result	
<i>Pollen only</i> group‡	25
<i>Pollen+</i> group§	75
T4SS [median (min–max)]	8 (2–12)
Eosinophils (/mm ³) [median (min–max)]	335 (8–1520)
Total IgE (IU/mL) [median (min–max)]	264.5 (5–1920)

SAR, seasonal allergic rhinitis; T4SS, total four symptoms score; IgE, immunoglobulin E.

**SAR only* group is a subgroup of SAR patients who did not have asthma or atopic dermatitis.

†*SAR-AA* is a subgroup of SAR patients who had asthma and/or atopic dermatitis.

‡*Pollen only* group is *pollen-sensitive* SAR patients who did not present aeroallergen sensitization aside from pollen.

§ *Pollen+* group is *pollen-sensitive* SAR patients who presented aeroallergen sensitization in addition to pollen.

Table 3 The correlations between 25(OH)D₃ levels and patient and control characteristics

		Patient group	<i>SAR only</i> group*	Healthy controls
		<i>n</i> = 100	<i>n</i> = 51	<i>n</i> = 100
Age	r	-0.076†	-0.242†	-0.214‡
	p	0.452	0.087	0.033
BMI	r	0.006†	-0.046†	-0.265‡
	p	0.957	0.750	0.008
T4SS	r	-0.021‡	0.031†	
	p	0.837	0.828	
IgE	r	0.270‡	-0.051†	
	p	0.789	0.720	
Eosinophil	r	0.151‡	0.096‡	
	p	0.133	0.504	

25(OH)D₃, 25-hydroxyvitamin D₃; SAR, seasonal allergic rhinitis; BMI, body mass index; T4SS, total four symptoms score; IgE, immunoglobulin E; r, correlation coefficient.

**SAR only* group is a subgroup of SAR patients who did not have asthma or atopic dermatitis.

†Pearson korelasyon was used.

‡Spearman's rho was used.

