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25(OH)D3 levels in children with allergic rhinoconjunctivitis

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Abstract

Objective: In this prospective study, we investigated the serum vitamin D levels [serum 25(OH)D3 levels] in children with allergic rhinoconjunctivitis (ARC).

Methods: Sixty-one children with allergic rhinoconjunctivitis (study group) and 61 healthy children (control group) were included into the study. The children in the study group had an allergy against at least one active agent at skin-prick test; a total of 5 Symptoms Score (T5SS) was obtained for vitamin D [25(OH)D3] levels. Total eosinophil counts and total IgE measurement were performed.

Results: In ARC group, median of T5SS scores was 1.00 for each of the rhinorrhea, sneezing, nasal congestion and nasal pruritis items. In ARC group, total eosinophil count and total IgE values were also higher than the control group. In ARC group, familial atopy was higher, and sunlight exposure was lower than the control group. Serum 25(OH)D3 levels of the ARC group (median: 15.80 ng/ml) were significantly lower than the control group (18.40 ng/ml). Considering the vitamin D levels being as sufficient/or deficient; it was deficient in 80.3% of the children in the study group and in 57.4% of the children in the control group. In the study group, sunlight exposure was insufficient; and familial atopy was present. In children with sufficient sunlight exposure, serum 25(OH)D3 levels were detected as higher. In children with familial atopy, total IgE and total eosinophil counts also increased.

Conclusion: We concluded that vitamin D levels were lower in children with ARC. We recommend children to expose sunlight sufficiently to increase vitamin D levels; and therefore reduce the risk of allergic rhinoconjunctivitis.

Keywords: 25(OH)D3, allergic rhinoconjunctivitis, total IgE, total eosinophil count, familial atopy.

Özet: Alerjik rinokonjonktivitli çocuklarda 25(OH)D3 düzeyleri

Amaç: Bu prospektif çalışmada alerjik rinokonjonktivitli (ARK) çocuklarda serum D vitamini [serum 25(OH)D3 düzeyleri] düzeylerini araştırdık.

Yöntem: Alerjik rinokonjonktivitli 61 çocuk (çalışma grubu) ve 61 sağlıklı çocuk (kontrol grubu) çalışmaya dahil edildi. Çalışma grubu, deri iğneleme testinde en azından bir aktif etkene karşı alerjikti. D vitamini [25(OH)D3] düzeyleri için Toplam 5 Semptom Skoru (T5SS) elde edildi, total eozinofil sayımları ve total IgE ölçümleri yapıldı.

Bulgular: Alerjik rinokonjonktivit grubunda rinore, aksırma, nazal konjesyon ve nazal kaşıntı semptomlarının her biri için ortanca T5SS skoru 1.00 idi. ARK grubunda total eozinofil sayısı ve total IgE değerleri de kontrol grubuna göre daha yüksekti. Kontrol grubuna göre ARK grubunda ailevi atopi daha yüksek ve güneşe maruziyet daha düşüktü. ARK grubunda serum 25(OH)D3 düzeyleri (ortanca: 15.80 ng/ml) kontrol grubuna göre anlamlı derece daha düşüktü (18.40 ng/ml). D vitamini düzeylerinin yeterli veya yetersiz olma durumu ele alındığında kontrol grubundaki çocukların %57.4'ü ve çalışma grubundaki çocukların ise %80.3'ünde D vitamini eksikliği mevcuttu. Çalışma grubunda güneş ışığına maruziyet yeterli değildi ve ailevi atopi mevcuttu. Yeterince güneş ışığı alan çocuklarda serum 25(OH)D3 düzeylerinin daha yüksek olduğu saptandı. Ailevi atopisi olan çocuklarda total IgE ve total eozinofil sayıları da artmıştı.

Sonuç: Alerjik rinokonjonktivitli çocuklarda D vitamini düzeylerinin daha düşük olduğu sonucuna vardık. D vitamini düzeylerini yükseltmek ve böylece ARK riskini azaltmak çin çocukların yeterince güneş ışığı almasını öneriyoruz.

Anahtar sözcükler: 25(OH)D3, alerjik rinokonjonktivit, total IgE, total eozinofil sayısı, ailevi atopi.

Allergic rhinoconjunctivitis (ARC) is a common chronic disorder in children, especially in developed countries. It does not only cause nasal symptoms (such as congestion and sneezing) but may also cause general complaints such as fatigue and cough.[1–3] The prevalence of allergic rhinoconjunctivitis has approximately doubled over the past 20 years.[4]

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The prevalence of symptoms of rhinitis in children varies between countries, from 0.8% to 14.9% in 6–7 year olds and from 1.4% to 39.7% in 13–14 year olds. Environmental factors are probably responsible for these differences.[5]

Bener et al. reported that the proportion of severe vitamin D deficiency was significantly higher in children with wheezing (23.4%), allergic rhinitis (18.5%), and asthma (17%) than in healthy children (10.5%).[6] Exposure to the sun was significantly less in vitamin D deficient children with asthma (60.3%), allergic rhinitis (62.5%) and wheezing (64.4%) than in controls (47.1%) (P=0.008).

Vitamin D has been shown to have an immunomodulatory effect with a significant impact on immune function. Specifically, vitamin D regulates the mechanisms which suppress the inflammatory response and direct the differentiation fate of immune cells.[7] Vitamin D plays an integral role in the induction of cell differentiation, inhibition of cell growth, immunomodulation, and regulation of other hormonal systems.[8]

In the present study, we investigated the serum vitamin D levels [serum 25(OH)D3 levels] in children with ARC. Additionally, Total 5 Symptoms Score (T5SS)[9,10] for ARC group was obtained. Total eosinophil count and total IgE measurements were also performed.

Materials and Methods

This prospective study was conducted in Pediatric Immunology and Allergy and ENT Departments of Eskişehir State Hospital between November 2014 and April 2015 in accordance with the principles of the Helsinki Declaration. Approval from Ethics Committee of Eskişehir State Hospital was taken. Written informed consent was obtained from each child and his/her parents.

Sixty-one children with allergic rhinoconjunctivitis who attended to Pediatric Immunology and Allergy; and ENT Departments of Eskişehir State Hospital between November 2014 and April 2015 were included into the study group (Group 1). The patients in Group 1 had allergic rhinitis symptoms and active allergic conjunctivitis (conjunctival hyperaemia, itching, tearing, chemosis or lid edema); and identified to have an allergy against at least one active agent at skin-prick test. Their mean age was 8.37±2.34 (range: 4 to 12) years. The control group was consisted of 61 healthy children who attended to the Pediatrics Polyclinic of the Eskişehir State Hospital. Their mean age was 7.72±2.91 (range: 1 to 12) years.

Criteria for excluding subjects from this study were as follows: presence of a disorder with the potential to interfere with the blood vitamin D levels (rickets, osteoporosis, etc.); immune system disease potentially modifying blood cytokine levels; usage of steroids in the last one month and antihistamines in the last 15 days; upper respiratory tract infection; acute airway disease like non-allergic eosinophilic rhinitis or drug-induced rhinitis; drug intake with the potential to interfere with the vitamin D levels (anticonvulsants, antacids, ketoconazole, etc.); asthma; and presence of unilateral, isolated polyp.

Skin prick test

The allergy test kit consisted of eight different aeroallergens (Allergpharma, Reinberg Germany): *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, Mould mix I *(Alterneria tenius*, *Botrytis cinerea*, *Cladosporium herbarun*, *Curvularia lunata*, *Fusarium moniliforme*, *Helminthosporium halodes)*, Catepithelium, Weed mix *(Artemisia vulgaris*, *Urticia dioica*, *Toraxacum vulgare*, *Plantago Lanceolata)*, Grass mix *(Holcus lanatus*, *Dactylis glomerata*, *Lolium perenne*, *Pheleum pratense*, *Poa pratensis*, *Festuca pratensis)*, Trees mix (alder, hazel, poplar, elm, willow), *Olea europeae* along with positive and negative controls. A histamine solution in 10 mg of distilled water was used as the positive control, while a phyglycerol buffered physiological saline solution was used as the negative control. The skin tests were carried out on the volar surface of the forearm using prick lancets. The skin reactions triggered by the application of each allergen were compared with the reactions triggered by the positive and negative controls. Indurations with a diameter equal to or greater than 3 mm were considered as positive reactions.[11]

Outcome parameters

- Age, gender, parental allergic diseases (asthma, allergic rhino conjunctivitis and atopic dermatitis), and sunlight exposure (at least 10 minutes between 10 and 15 hours) were recorded.[12]
- **Total 5 Symptoms Score (T5SS):** Total 5 Symptoms Score (T5SS) of the subjects with AR is consisted of the sum of rhinorrhea, sneezing, nasal congestion, and nasal and ocular pruritus. Each symptom was scored on 0 to 3 scale; and T5SS score was between 0 and 15.[9,10]
- **Peripheral venous blood samples** were obtained to measure serum vitamin D, Immunoglobuline E (IgE) levels, and peripheral blood eosinophil was counted on the same day. 25(OH)D3 was studied by ECLIA (Electrochemiluminescence immunoassay; Cobas E601 Immunoassay System; Roche Diagnostics, Indianapolis, IN, USA), in the hormone laboratory. The values for

vitamin D levels >20 ng/ml were considered as sufficient and lower than 20 ng/ml as deficient.[13] Eosinophil counts were recorded from a complete blood count device (Cell Dyne 3700 Analyzer; Abbott Diagnostics, Lake Forest, IL, USA). Total IgE measurements were performed by chemiluminescence immunometric method (IMMULITE 2000 Immunoassay System, Siemens Healthcare, Malvern, PA, USA) in the biochemistry laboratory. Total IgE values were detected as IU/mL.

Statistical analysis

SPSS software (Version 16.0; SPSS Inc., Chicago, IL, USA) was used for statistical calculations. Mann–Whitney U test was used. A p value of <0.05 was considered to reflect statistical significance.

Results

In the study group, there were 34 males (55.7%) and 27 females (44.3%). In the control group, there were 31 males (50.8%) and 30 females (49.2%). There was no significant difference between gender distributions of the groups (p>0.05) (Table 1).

Skin prick test results

In the study group, positive results for skin prick tests were obtained for:

- *Dermatophagoides pteronyssinus:* 38 patients (62.3%)
- *Dermatophagoides farina:* 39 patients (63.9%)
- Mould mix I *(Alterneria tenius*, *Botrytis cinerea*, *Cladosporium herbarun*, *Curvularia lunata*, *Fusarium moniliforme*, *Helminthosporium halodes):* 11 patients (18.3%)
- Catepithelium: 3 patients (4.9%)
- Weed mix *(Artemisia vulgaris*, *Urticia dioica*, *Toraxacum vulgare*, *Plantago Lanceolata):* 12 patients (19.7%)
- Grass mix *(Holcus lanatus*, *Dactylis glomerata*, *Lolium perenne*, *Pheleum pratense*, *Poa pratensis*, *Festuca pratensis):* 17 patients (27.9%)
- Trees mix (alder, hazel, poplar, elm, willow): 7 patients (11.5%)
- *Olea europeae:* 3 patients (5.0%)

Familial atopy in the parents was present in 57.4% in the study group and in 32.8% in the control group. The difference was significant (p=0.006, χ^2=7.449) (Table 1).

Sufficient **sunlight exposure** was detected as 31.1% in the study group and 54.1% in the control group. The dif-

Table 1. Age, gender, 25(OH)D3, eosinophil, IgE, atopy in the family and sun exposure level of the groups.

	Study (n=61)			Control (n=61)			P*
	Mean	Median	Std. Dev.	Mean	Median	Std. Dev.	
Age	8.37	9.00	2.34	7.72	7.00	2.91	0.216
25(OH)D3 ng/ml	16.71	15.80	6.35	20.63	18.40	9.084	0.011
Total eosinophil count	326.86	250.00	276.82	296.67	200.00	375.51	0.322
Total IgE	248.40	61.10	361.38	47.45	19.30	73.52	0.000

		Study (n=61)		Control (n=61)		P**
		n	%	n	%	
Gender	Male	34	55.7	31	50.8	P=0.586
	Female	27	44.3	30	49.2	χ^2=0.296
Atopy in the family	Present	35	57.4	20	32.8	P=0.006
	Absent	26	42.6	41	67.2	χ^2=7.449
Sun-light exposure	Sufficient	19	31.1	33	54.1	P=0.010
	Deficient	42	68.9	28	45.9	χ^2=6.569
25(OH)D3 level	Deficient	49	80.3	35	57.4	P=0.006
	Sufficient	12	19.7	26	42.6	χ^2=7.491

*p value shows the results of Mann-Whitney U test.

**p value shows the results of the chi-square test.

ference was statistically significant (p=0.010, χ^2=6.569) (Table 1).

Total 5 Symptoms Score (T5SS): In the study group, T5SS values were detected as median 1.00 for each of the rhinorrhea, sneezing, nasal congestion and nasal pruritis items. For ocular pruritis, median value was 0.00, mean±standard deviation value was 0.73±0.87. T5SS value was 5.00 (median); and 5.49±2.75 (mean±standard deviation) (Table 2).

Vitamin D levels: Vitamin D level was 15.80 ng/ml (median) for the study group and 18.40 ng/ml (median) for the control group. The difference was significant (p=0.011) (Table 1). When considering the vitamin D levels as sufficient/or deficient; it was deficient in 80.3% of the children in the study group and in 57.4% of the children in the control group. The difference was significant (p=0.006, χ^2=7.491) (Table 1).

Total eosinophil count was 250 (median) and 200 (median) in the study and control groups respectively (p>0.05) (Table 1).

Total IgE value of the study group was 61.10 (median) in the study group and 19.30 (median) in the control group. The difference was found as significant (p=0.000).

Spearman's correlation rho efficient test results

In the study group, vitamin D levels were lower and total IgE values were higher than the control group. In the study group, sunlight exposure was insufficient; and familial atopy was present (p<0.05).

In children with sufficient sunlight exposure, vitamin D levels were detected as higher (p<0.05).

In children with familial atopy, total IgE and total eosinophil counts increased (p<0.05).

Discussion

In the present study, we investigated the relationship between vitamin D [serum 25(OH)D3 levels] and allergic rhinoconjunctivitis (ARC) in children. In the study group, skin prick test showed positive results for mainly *Dermatophagoides farina* (63.9%) and *Dermatophagoides pteronyssinus* (62.3%). In ARC group, median of T5SS scores was 1.00 for each of the rhinorrhea, sneezing, nasal congestion and nasal pruritis items. T5SS value was 5.00 (median). In ARC group, total eosinophil count and total IgE values were also higher than the control group.

In ARC group, familial atopy was higher; and sunlight exposure was lower than the control group. Serum 25(OH)D3 levels of the ARC group (median: 15.80 ng/ml) were significantly lower than the control group (18.40 ng/ml). When considering the vitamin D levels as sufficient/or deficient; it was deficient in 80.3% of the children in the study group and in 57.4% of the children in the control group

Goksugur et al.[14] investigated 25-hydroxycholecalciferol levels in tear and serum in young allergic rhinoconjunctivitis patients. 22 children with allergic rhinoconjunctivitis and 31 healthy control subjects underwent serum total IgE and 25-hydroxycholecalciferol measurements. Their results showed that the mean serum total IgE level in the ARC group (143.6±132.8 IU/ml) was significantly higher than that in the control group (54.8±44.1IU/ml; p=0.03). Serum 25(OH)D3 levels were significantly higher in the ARC group (34.1±12.7 ng/ml) than in the healthy controls (21.8±11.3ng/ml; p=0.001). They concluded that higher levels of serum 25-hydroxycholecalciferol in children with allergic rhinoconjunctivitis may indicate a possible aetiopathogenic mechanism in the development of allergic rhinoconjunctivitis.

Table 2. T5SS Scores of the study group.

T5SS subscores	Median	Mean	Std. Dev.	Min.	Max.
Rhinorrhea	1.00	0.98	0.80	0.00	3.00
Sneezing	1.00	1.37	0.89	0.00	3.00
Nasal congestion	1.00	1.26	0.96	0.00	3.00
Nasal pruritis	1.00	1.11	0.89	0.00	3.00
Ocular pruritis	0.00	0.73	0.87	0.00	3.00
TOTAL T5SS SCORE	5.00	5.49	2.75	0.00	14.00

Our results were not similar to the study of Goksugur et al.[14] In our study, serum 25(OH)D3 levels were lower in the ARC group, whereas in the study of Goksugur et al., 25(OH)D3 levels were higher in the ARC group. As similar to our study, Bener et al.[9] reported that vitamin D deficiency was significantly correlated for asthma (odds ratio [OR] =2.31; P<0.001), allergic rhinitis (OR=1.59; P<0.001) and wheezing (relative risk = 1.29; P=0.05).

Correlation tests showed that, in the study group, serum 25(OH)D3 levels were lower and total IgE values were higher than the control group. In the study group, sunlight exposure was insufficient; and familial atopy was present. In children with sufficient sunlight exposure, serum 25(OH)D3 levels were detected as higher. In children with familial atopy, total IgE and total eosinophil counts also increased.

It was reported that there are significant positive relationships between vitamin D intake or vitamin D supplementation in infancy and all of the allergic disorders examined.[15,16] In a cohort study carried out in Finland, subjects who had received vitamin D supplementation regularly during the first year compared to those who had received it irregularly or not at all had a significantly increased risk of allergic rhinitis and had a marginally significantly increased risk of asthma at 31 years of age.[16]

Higher maternal vitamin D intake during pregnancy was associated with reduced odds of wheeze: the pooled OR was 0.56 (95%CI 0.42–0.73).[17] This suggests that the effects of vitamin D intake before birth on allergic disorders might be beneficial, whereas postnatal effects might be detrimental.[18]

Mulligan et al.[19] reported an inverse relationship between vitamin D and the levels of various immune cells was established in CRS patients. In patients with chronic rhinosinusitis with nasal polyposis or allergic fungal rhinosinusitis, lower levels of vitamin D correlated to elevated levels of dendritic cells as compared with controls. Dendritic cells play an important role in directing the differentiation of T-helper cells into Th1 or Th2 subtypes – without vitamin D, the inflammatory response is skewed towards a Th1 subtype promoting a chronic local inflammatory response. Plasma levels of prostaglandin E2 and granulocyte monocyte-colony stimulating factor were upregulated in patients with CRS, and that these chemokine levels were inversely associated with serum vitamin D levels.[19]

Most of the natural sources of vitamin D are animal-based, including fish and fish oils, egg yolks, cheese, fortified milk, and beef liver. Therefore, these foods should be eaten for dietary vitamin D intake. Sunlight exposure is also important. In subjects with dark skin, melanin reduces the skin's ability to make vitamin D in response to sunlight exposure. These subjects may be candidate for high risk of vitamin D deficiency.[20]

In our study, we found that vitamin D levels were lower in children with ARC. We recommend children to expose sunlight sufficiently to increase vitamin D levels; and therefore reduce the risk of allergic rhino-conjunctivitis.

Conflict of Interest: No conflicts declared.

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