

Clinical Effects of Vitamin D in Children with Asthma

Mahmut Dogru Heves Kirmizibekmez Rahime Gul Yesiltepe Mutlu
Alev Aktas Seda Ozturkmen

Department of Pediatrics, Zeynep Kamil Maternity and Children's Disease Training and Research Hospital,
Istanbul, Turkey

Key Words

Asthma · Vitamin D · Child · Severity

Abstract

Objective: Both asthma and vitamin D deficiency are common among children. The results from studies examining the relationship between them are contradictory. The aim of this study is to determine the relationship between the clinical parameters of asthma and vitamin D status in children. **Methods:** One hundred and twenty children diagnosed with asthma and followed-up in our hospital were included in the study. The control group included 74 children with no evidence of allergic disease. The eosinophil counts, IgE levels and serum 25 OH cholecalciferol [25(OH)D] levels were measured. **Results:** The patient group consisted of 73 (60.8%) males and 47 (39.2%) females with a mean age of 4.4 ± 1.2 years. There was no significant difference between the patient and control groups with respect to gender and age. The mean 25(OH)D level was 21.49 ± 7.74 ng/ml in the study group and 23.94 ± 8.97 ng/ml in the control group, and this difference was not significant ($p = 0.094$). The patients with asthma were grouped according to their vitamin D status as 'deficient' (group 1), 'insufficient' (group 2) and 'normal' (group 3). The sociodemographic features, duration of illness, number of hospitalizations, number of sensitivities to

allergens, eosinophil count and serum IgE levels were not found to be different between the groups. However, the total number of exacerbations, asthma severity and systemic glucocorticoid need in the previous year were significantly higher in the deficiency group ($p < 0.05$). **Conclusion:** Vitamin D levels were not significantly different in patients with asthma. Vitamin D deficiency was common in the study group as well as in the control group. The clinical severity of disease, the number of exacerbations and the systemic glucocorticoid need were related to vitamin D level.

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Introduction

Asthma is a chronic lung disease characterized by recurrent attacks of cough, wheezing and dyspnea. It is a common health problem affecting 300 million people all over the world. The prevalence of the disease is higher in developed countries. Asthma is thought to be increasing due to dietary and behavioral changes over the last few decades [1]. The increase in the prevalence of vitamin D deficiency, as well as asthma, has mostly been attributed to lifestyle changes. Human beings obtain approximately 80% of their vitamin D need via exposure to the ultraviolet B components of sunlight. Western lifestyle favors

more indoor activities, thus leading to inadequate sunlight exposure. The relationship between asthma and vitamin D deficiency is suspected to be due to the increased prevalence of both conditions, especially in Western populations [2, 3].

Recent studies showed that vitamin D acts as a hormone and, in addition to its function in bone, takes a role in the function of many organs. Vitamin D supports the antimicrobial actions of the immune system but reduces the capacity of the adaptive immune response and inflammation. The antimicrobial activity against airway pathogens is improved with replacement of vitamin D due to the regulation of antimicrobial cationic peptides, β -defensin 2 and 4. Proliferation of Th1 and Th2, and production of interferon (IFN)- γ , interleukin (IL)-2 and IL-5 were found to be decreased by 1,25-dihydroxyvitamin D, while IL-4 production was increased [2, 4]. Results of studies investigating the vitamin D levels of patients with asthma are controversial [5–12]. Although some studies revealed low vitamin D levels in asthma [5–8], others did not confirm this finding [9–12]. Furthermore, results discussing the effects of vitamin D deficiency on the severity of symptoms, duration of hospitalization and glucocorticoid need are also controversial. While some studies confirm a relationship [6, 8, 12–15], some do not [7, 9, 16]. Only a few studies are from Turkey [6]. This study aimed to investigate the relationship between vitamin D status and the clinical parameters of asthma.

Methods

One hundred and twenty children with asthma, followed-up in the Pediatric Allergy and Immunology Department of a public hospital of obstetrics and pediatrics, were included in the study. In order to exclude the seasonal differences, patients were evaluated between September 2012 and February 2013. The control group consisted of seventy-four children with no evidence of allergic disease (i.e. asthma, allergic rhinitis, eczema). Patients with the clinical findings of rachitis (genu varum/valgum), patients receiving multivitamin support or any systemic glucocorticoid therapy, and patients with any other systemic disease were excluded. A detailed allergic history, including the age, parental consanguinity, familial atopy history and exposure to cigarette smoke, was recorded. Familial atopy history in first-degree relatives (parents and siblings) was considered as an allergic disease. The severity and diagnosis of asthma were evaluated according to the GINA guidelines [1]. Milk consumption was not evaluated because milk is not fortified with vitamin D in our country. Skin prick tests were performed using the same antigens for all patients. Eosinophil counts, IgE and serum 25 OH cholecalciferol [25(OH)D] levels were measured. Consent from the parents of each patient and the local ethical committee was obtained.

Table 1. Comparison of sociodemographic characteristics and vitamin D status between the patient and control groups

	Study group (n = 120)	Control group (n = 74)	p
Gender, n			0.126 ^a
Male/female	73/47	38/36	
Age, years			0.274 ^b
Mean $\pm$ SD	4.4 $\pm$ 1.2	4.6 $\pm$ 1.5	
Min–max	3–8.5	3–8	
Vitamin D level, ng/ml			0.094 ^b
Mean $\pm$ SD	21.49 $\pm$ 7.74	23.94 $\pm$ 8.97	
Min–max	7.6–53	6–59	
Vitamin D status, %			0.302 ^a
Deficient	43.3	32.4	
Insufficient	47.5	58.1	
Normal	9.2	9.5	

^a χ^2 test. ^b t test.

Skin Prick Tests

Skin prick tests were applied on the anterior forearm. Patients were considered eligible for the skin test if they had not received antihistamines for at least 1 week. Histamine (10 mg/ml) and physiological saline were used as positive and negative references, respectively. Skin reactions were evaluated at 20 min after the application, and indurations ≥ 3 mm were considered as a positive reaction. Skin prick tests for common aeroallergens (*Dermatophagoides pteronyssinus*, *D. farinea*), a mixture of grass pollens (*Lolium perenne*, *Dactylis glomerata*, *Phleum pratense*, *Anthoxanthum odoratum*, *Poa pratensis*, *Festuca elatior*, *Agrostis vulgaris*, *Holcus lanatus*, *Cynodon dactylon*, *Avena sativa*, *Avena fatua*, *Lotus corniculatus*), a mixture of grain pollens (oats, wheat, barley, corn), a mixture of tree pollens (*Acer pseudoplatanus*, *Aesculus hippocastanum*, *Robinia pseudoacacia*, *Tilia platyphyllos*, *Platanus vulgaris*), weed-mix pollens (*Medicago sativa*, *Trifolium pratense*, *Brassica nigra*, *Urtica dioica*, *Rumex acetosa*), fungus (*Alternaria alternaria*), cockroaches (*Blattella germanica*) and cat and dog dander (Stallerpoint (Stallergenes SA), Antony, France) were performed using Stallerpoint (Stallergenes SA). Patients with a positive history of food reactions underwent skin prick tests with the suspected food.

Vitamin D Levels

Peripheral venous blood samples were obtained from all patients and serum 25(OH)D₃ levels were measured using liquid chromatography-tandem mass spectrometry in Waters Quattro Premier XE™ (Waters Corp. Milford, Conn., USA). Serum 25(OH)D₃ levels ≤ 20 ng/ml were considered as vitamin D deficiency, while levels between 20 and 30 ng/ml were viewed as vitamin D insufficiency. Levels between 30 and 80 ng/ml were regarded as the optimal vitamin D level and ≥ 80 ng/ml as potential vitamin D toxicity.

Table 2. Comparison of sociodemographic features of the patient groups

	Group I (n = 52)	Group II (n = 57)	Group III (n = 11)	p
Male/female	28/24	36/21	9/2	0.199 ^a
Age, years	4.6 ± 1.3 (4.25)	4.3 ± 1.2 (4.1)	4.2 ± 1.3 (4)	0.317 ^b
Parental consanguinity	16 (30.8)	8 (14)	3 (27.3)	0.104 ^a
Familial atopy	22 (42.3)	20 (35.1)	6 (54.5)	0.436 ^a
Exposure to smoke	28 (53.8)	28 (49.1)	5 (45.5)	0.826 ^a

Data are either mean ± SD with median in parentheses, or n with percentages in parentheses.

^a χ^2 test. ^b Kruskal-Wallis test.

Statistical Analyses

Data was analyzed using the Statistical Package for Social Sciences for Windows 15.0 (SPSS, Chicago, Ill., USA) program. Results were given as either mean ± standard deviation (SD) or as mean ± standard deviation (median) according to the distribution. The Student t test, ANOVA and Kruskal-Wallis test were used for the comparison of normally distributed variables. The χ^2 and Mann-Whitney U tests were used for not normally distributed variables. Pearson's correlation test was used for the correlation analyses of continuous variables. $p < 0.05$ was considered as significant.

Results

This study consisted of 73 (60.8%) male and 47 (39.2%) female patients with a mean age of 4.4 ± 1.2 years (range 3–8.5) as the patient group, and 38 (51.4%) male and 36 (48.6%) female patients with a mean age of 4.6 ± 1.5 years (range 3–8) as the control group. There were no statistically significant differences between the asthma and the control group in terms of age and gender (table 1). Skin prick test sensitivity (atopy) was revealed in 60 (50%) patients.

The mean 25(OH)D₃ level was 21.49 ± 7.74 ng/ml (range 7.6–53) in the study group and 23.94 ± 8.97 ng/ml (range 6–59) in the control group. The difference was not statistically significant ($p = 0.094$). Vitamin D status was determined as being deficient in 52 (43.3%), insufficient in 57 (47.5%) and normal in 11 (9.2%) patients of the study group, while it was deficient in 24 (32.4%), insufficient in 43 (58.1%) and normal in 7 (9.5%) members of the control group. Vitamin D status was not found to be different between groups ($p = 0.302$; table 1).

The mean 25(OH)D₃ level was 20.94 ± 6.63 ng/ml (range 10–35) in children with atopic asthma and 21.8 ± 8.79 ng/ml (range 7.6–53) in children with nonatopic

asthma. The difference was not statistically significant ($p = 0.550$). Vitamin D status was not found to be different between children with atopic asthma and children with nonatopic asthma ($p = 0.947$).

The patients with asthma were grouped according to their vitamin D status as 'deficient' (group 1), 'insufficient' (group 2) and 'normal' (group 3). No statistically significant difference was present between the groups in terms of gender, age, parental consanguinity, familial atopy and exposure to smoke ($p > 0.05$; table 2).

The duration of illness, number of hospitalizations, number of positive sensitivities, sensitivity to allergens, eosinophil count and serum IgE levels were not found to be different between the groups. However, the total number of exacerbations, severity of asthma, number of exacerbations and systemic glucocorticoid need in the previous year were significantly different ($p < 0.05$; table 3).

The mean serum 25(OH)D level was negatively correlated with the severity of asthma ($r = -0.310$; $p = 0.001$), duration of wheezing ($r = -0.297$; $p = 0.001$), total number of exacerbations ($r = -0.441$; $p = 0.000$), number of exacerbations in the previous year ($r = -0.307$; $p = 0.001$) and systemic glucocorticoid need in the previous year ($r = -0.347$; $p = 0.000$).

Discussion

This study revealed that the mean serum 25(OH)D level of preschool children with asthma was not different from that of the healthy controls. Results of studies investigating the relationship between asthma and vitamin D are controversial [5–12]. Gergen et al. [9] reported that the vitamin D status of children with asthma was not different from the general population mentioned in the NHANES (National Health and Nutrition Examination Survey)

Table 3. Comparison of the clinical and laboratory findings of the patient groups

	Group I (n = 52)	Group II (n = 57)	Group III (n = 11)	p
Duration of disease, months	23.8±12.2	20.6±10.24	18.8±7.2	0.129 ^c
Min-max	2–54	4–46	12–30	
Serum 25(OH)D level, ng/ml	15.08±3.67 (16.2)	24.18±3.65 (24)	36.58±8.24 (34)	0.000 ^b
Total number of exacerbations	8±4.9 (6)	5.4±3.2 (4)	3.7±1 (3)	0.006 ^b
Severity of asthma				0.007 ^a
Mild intermittent	12 (30)	24 (60)	4 (10)	
Mild persistent	20 (40)	23 (46)	7 (14)	
Moderate persistent	12 (54.5)	10 (45.5)	0	
Severe persistent	8 (100)	0	0	
Number of hospitalizations	0.44±0.8 (0)	0.2±0.4 (0)	0.3±0.4 (0)	0.469 ^b
Number of systemic glucocorticoid need in the previous year	1.4±1.1 (1)	0.6±0.8 (0)	0.4±0.5 (0)	0.010 ^b
Number of exacerbations in the previous year	4.1±2.6 (3)	2.8±1.6 (3)	2.6±0.5 (3)	0.012 ^b
Eosinophil count, cell/mm ³	3.3±3.2 (2)	4.1±2.7 (3.7)	2.9±2.2 (2)	0.082 ^b
IgE level, IU/ml	322±438 (108)	217±392 (59)	251±399 (106)	0.202 ^b
Sensitivities in skin prick test (atopy)	26 (50)	29 (50.9)	5 (45.5)	0.947 ^a
Number of positive sensitivities	1.1±1.2 (0)	1.2±1.5 (1)	0.8±0.9 (0)	0.793 ^b
Sensitivity to				
House dust mite	22 (42.3)	27 (47.4)	4 (36.4)	0.748 ^a
Pollens	10 (19.2)	8 (14)	1 (9.1)	0.618 ^a
Dander	0	6 (10.4)	0	0.0 ^a
<i>A. alternata</i>	0	0	0	n.a.
Cockroach	4 (7.7)	2 (3.5)	0	0.441 ^a
Egg white	2 (4.3)	0	0	n.a.

Data are presented as means ± SD with medians in parentheses, or n with percentages in parentheses. n.a. indicates that statistical analyses could not be performed, since the variable was not adequate for calculation.

^a χ^2 test. ^b Kruskal-Wallis test. ^c ANOVA test.

study. The Asthma Control Evaluation (ACE) working group investigating children with asthma also declared no difference. Cheng et al. [10], investigating 15,212 adults from Korea, like Mai et al. [11] and Korn et al. [12], reported no relationship between asthma and vitamin D in adults. However, some studies of asthma and vitamin D deficiency have supported the relationship [5–8]. Uysalol et al. [6] investigated 85 patients with asthma and 85 controls from Turkey and found that the vitamin D levels were significantly lower in the asthma group. The study included 2- to 14-year-old patients being followed up for asthma, while our study investigated 3- to 8-year-old newly diagnosed patients. The time period was also different since we performed measurements in autumn and winter, while Uysalol et al. [6] conducted their study between September and May. The study design, cutoff levels for vitamin D deficiency, seasonal, geographical and climatic conditions might have been the reason for the difference.

Serum 25(OH)D is considered the most accurate marker for vitamin D status. While the Endocrine Society

advocates that levels below 20 ng/ml (50 nmol/l) should define deficiency, levels ranging from 20 to 29.9 ng/ml (52–72 nmol/l) should define insufficiency and levels above 30 ng/ml (75 nmol/l) should define sufficiency. The Institute of Medicine (IOM) considers levels >20 ng/ml to be sufficient for the majority of the general population [17, 18]. This latter classification is based largely on vitamin D's effects on bone and mineral homeostasis. The optimal 25(OH)D serum level regarding other aspects of human health is still under debate. For immune-mediated diseases, experts suggest that even higher serum 25(OH)D levels may be needed to lead to positive effects [19]. Thus, in the present study, the 25(OH)D cutoff level of 30 ng/ml was used to define vitamin D sufficiency.

Vitamin D plays a role in immune system functions as well as in bone health. Vitamin D deficiency predisposes to infections by effecting the production of antimicrobial peptides. 1,25 hydroxylation of 25(OH)D₃ was found to be related to an antimicrobial peptide called cathelicidin [20]. Cathelicidin acts as a chemoattractant for neu-

Table 4. Results of some studies investigating the relationship between vitamin D status and morbidity of asthma

Study	Cases/ controls Age group	Significant difference in respect to vitamin D status between case and control group	25(OH)D cutoff level for insuffi- ciency/ deficiency, ng/ml	Prevalence of vitamin D insufficiency/ deficiency, %	Relation between			Markers of atopy
					Asthma severity and vitamin D status	Asthma exacerbations/ hospitalization and vitamin D status	Emergency admissions/ Systemic steroid use and vitamin D status	
Bener et al. [5]	483/483 Child	Yes	<20/20–29	A: 68.1/18.4 C: 36.1/46.6	Unavailable	Unavailable	Unavailable	Asthmatics had significantly elevated serum IgE compared to controls
Uysalol et al. [6]	85/85 Child (2–14 years)	Yes	<20/20–29	A: 67/29.4 C: 35.3/23.5	Negative correlation	Negative correlation	Negative correlati- on between emer- gency admissions and 25(OH)D Systemic steroid use was not evalu- ated	The mean plasma eosinophil level and serum IgE levels were significantly higher in asthmatic patients than in healthy controls
Alyasin et al. [7]	50/50 Child (6–18 years)	Yes	<20/20–29	A: 12/4 C: 2/2	Unavailable	No association	No association between emergen- cy admissions and 25(OH)D Systemic steroid use was not evalu- ated	No association between eosinophil count and vitamin D status
Brehm et al. [8]	287/273 Child (6–14 years)	Yes	–/30	A: 44/– C: 47/–	Unavailable	Negative correlation	Unavailable	There was no significant association between vitamin D insufficiency and having at least one positive specific IgE to allergens No association between total IgE and vitamin D status
Gergen et al. [9]	NHANES: 6,485/– ACE: 226/332 (12–20 years)	No	–/20	Unavailable	No association	No association	No association	There was a negative correlation between 25(OH)D and total IgE among non-African Americans No association between skin prick tests and vitamin D status
Cheng et al. [10]	14,737/475 Adult	No	<12/12–20	Unavailable	Unavailable	Unavailable	Unavailable	No association between total or allergen-specific serum IgE levels and vitamin D status
Mai et al. [11]	584/1,958 Adult	No	–/50 ^a	F: 45/37 M: 47/41	Unavailable	Unavailable	Unavailable	Unavailable
Korn et al. [12]	280/40 Adult	No	20/20–30	A: 32.9/31.8	Negative correlation	Unavailable	Negative correlati- on between use of oral steroid and vitamin D status	No association between allergy, total IgE and vitamin D status
Brehm et al. [13]	1,024/– Child	Unvalued	–/30	A: 35/–	Unavailable	Negative correlation	Negative correlati- on	No association between skin test reactivity, total serum IgE levels, or eosinophil count and vitamin D status
Montero- Arias et al. [14]	121/– Adult	Unvalued	20/20–30	A:29.8/60.3	Negative correlation	Negative correlation	Negative correlati- on for emergency admission No association for high steroid dose	No association between total serum IgE levels, eosinophil count and vitamin D status
Searing et al. [15]	100/– Child	Unvalued	20/20–30	A:17/47	Unavailable	Unavailable	Negative correlati- on between use of oral steroids and vitamin D status	No association between eosinophil count and vitamin D status Negative correlation between log IgE, number of positive aeroallergen skin prick test responses and vitamin D status

A = Asthma group; C = control groups; F = female; M = male. ^a nmol/l.

trophils and monocytes, enhances microbial killing in phagocytic vacuoles, and has a defined vitamin D-dependent mechanism [21]. The inflammation of airway epithelium caused by viral infections, especially by the respiratory syncytial virus, was found to be decreased by vitamin D replacement [22]. Vitamin D deficiency was related to an increased frequency of respiratory infections [6, 23]. Ginde et al. [23] examined the association between 25(OH)D levels and recent upper respiratory tract infection in 18,883 participants aged ≥ 12 years, and determined a negative correlation. This relationship was more distinct in patients with respiratory tract diseases, such as asthma. It is known that exacerbations of asthma are mostly due to viral infections [1].

The study by Alyasin et al. [7], which was comprised of 50 patients with asthma and 50 controls, did not find a relationship between vitamin D levels and number of hospitalizations. However, Brehm et al. [8] declared a relationship between vitamin D and the number of exacerbations, hospitalizations and systemic glucocorticoid need. The results of studies investigating the relationship between vitamin D and the severity of asthma, hospitalizations, emergency department visits and systemic glucocorticoid need in the previous year are inconsistent (table 4) [5–16].

This study did not confirm any relationship between vitamin D level and atopy markers, such as total IgE level, eosinophil count and sensitivity to allergens, except the sensitivity to dander. Sensitivity to dander was only present in patients with vitamin D insufficiency. A cohort study conducted by Hypponen et al. [24] demonstrated that the supplementation with high daily doses ($\geq 2,000$ IU/day) of vitamin D in the first year of life was associated with increased skin prick test response and allergic rhinitis in 5,007 subjects at age 31 years. Hollams et al. [25] determined that vitamin D insufficiency increased

the risk of atopy. Vitamin D insufficiency at the age of 6 years was shown to relate to increased risk of atopy and asthma development at the age of 14 years. Searing et al. [15] found vitamin D level to be negatively correlated with log₁₀ IgE and the number of positive skin tests, especially with dog dander and house dust mite. Brehm et al. [8] similarly reported a negative correlation with vitamin D and specific IgE for house dust mite and more than one allergen, while there was no difference for eosinophil count. In contrast to these studies, there are studies that are compatible with our study (table 4).

The limited number of participants was the negative aspect of our study. It was designed as a single-center study including patients with asthma aged between 3 and 8.5 years. Vitamin D levels were measured in a single sample obtained in autumn or winter. More than one sample could have been obtained and mean vitamin D levels throughout the year could have been measured in order to minimize the seasonal differences.

Vitamin D levels were not significantly different in patients with asthma, since vitamin D deficiency was common in both the study group and the control group. The clinical severity of disease, suggested by the number of exacerbations, severity of exacerbations and systemic glucocorticoid need, was related to vitamin D levels. Although further studies are needed, we can conclude that vitamin D level measurements should be performed in patients with frequent and severe exacerbations of asthma, and vitamin D replacement could improve the clinical progress of disease.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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