

Does vitamin D deficiency in asthma affect clinical and functional parameters? A Turkish multicenter study

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ABSTRACT

Background: In recent years, interest in the effects of vitamin D on human health and the immune system has increased.

Objective: This study aimed to investigate the relationship of vitamin D with asthma severity, attacks, and clinical and functional parameters in adult patients with asthma who were living in different geographic regions in Turkey.

Methods: A total of 384 patients with stable asthma and 87 control subjects were included. A physical examination and a pulmonary function test were performed, and routine blood analyses and vitamin D levels were evaluated. Asthma Control Test was applied. The number of exacerbations in the previous year, asthma therapy, and medication adherence were recorded.

Results: In our study, vitamin D levels were below the target values in both patients with asthma (median [minimum-maximum] 16.0 ng/mL [3.5–48 ng/mL]) and control subjects (median [minimum-maximum] 20.0 ng/mL [5.8–58.79 ng/mL]). However, it was lower in the patients with asthma than in the control subjects ($p=0.001$). There was a negative relationship between the levels of vitamin D and the severity of asthma (Kendall $\tau = -0.146$; $p<0.001$). Furthermore, the patients with severe asthma were received The Global Initiative for Asthma (GINA) step 5 treatment showed significantly lower vitamin D compared with the patients who received GINA step 4 treatment ($p = 0.037$). Vitamin D levels correlated with forced vital capacity (FVC), forced expiratory volume in the first second of expiration (FEV_1), and peak expiratory flow ($r, 0.221-0.236$; $p \leq 0.001$). In addition, a positive relationship was found between Asthma Control Test and vitamin D ($r = 0.229$; $p=0.001$). However, body mass index (BMI), asthma exacerbation, and hospitalization were inversely related to vitamin D ($r, 0.198-0.233$; $p=0.001$). Multivariable regression analysis revealed that FVC ($p=0.002$), FEV_1 ($p=0.033$), and BMI ($p=0.037$) were independent determinants associated with vitamin D.

Conclusion: This study suggested a high prevalence of vitamin D deficiency in adults with asthma living in different geographic areas in Turkey. Vitamin D deficiency is associated with asthma severity, poor control, and lower lung function.

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Asthma is a heterogeneous disease characterized by its varying severity and intensity of respiratory symptoms and variable airflow restriction, mostly accompanied by airway inflammation and bronchial hyperreactivity.¹ In addition to genetic and environmental factors, nutritional and metabolic pathways have also been shown to contribute to asthma heterogeneity. It is a common chronic respiratory disease with increasing prevalence that affects 1–18% of the population in different countries.¹ Due to the increase in

incidence, studies on vitamin D deficiency have gained momentum.

The interest in vitamin D in human health and the immune system has increased in the past few years. Results of studies showed that vitamin D has regulatory effects on the immune response in the human body.^{2,3} The effects of vitamin D on both allergic and nonallergic asthma were investigated. *In vitro* studies showed that vitamin D suppresses immunoglobulin E (IgE) production from B lymphocytes and increases interleukin (IL) 10 production.^{4,5} In nonallergic asthma, it has been reported to have an inhibitory effect on vitamin D in many stages, such as the release of alarmins (IL-25, IL-33), stimulation of type 2 innate lymphoid cells and activation of eosinophils.^{6–8} Although experimental studies revealed the role of vitamin D in the pathogenesis of asthma, epidemiologic, cross-sectional, and prospective studies provided conflicting results. Although some studies in children reported an inverse relationship between vitamin D deficiency and the incidence of asthma,^{9–11} some studies in adults showed no similar relationship.^{12,13}

Recent clinical trials focused on the vitamin D supplementation effect on asthma outcomes. Most clinical studies showed that vitamin D supplementation does

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not improve asthma control and exacerbation; however, some studies reported that vitamin D replacement reduces severe asthma attacks.^{14–18} A recent Global Initiative for Asthma (GINA) report¹ states that there is no good-quality evidence with regard to vitamin D supplementation improvement in asthma control and exacerbation. Research in this area continues. In this study, we aimed to investigate the relationship of vitamin D with asthma severity, attacks, and clinical and functional parameters in adult patients with asthma who were living in different geographic regions in Turkey.

METHODS

Study Population

As stated in the GINA report,¹ asthma was diagnosed by demonstrating respiratory symptoms, such as cough and wheezing, which change in severity and intensity over time, and variable airflow limitation.¹ Patients who receive steps of treatment are classified as having mild, those who receive three stages of treatment as having moderate, and those who receive four and five stages of treatment are classified as having severe asthma.¹ Inclusion criteria were as follows: patients were included if they (1) were > 18 years, (2) diagnosed with asthma according to the GINA criteria,¹ (3) who had a follow-up diagnosis of asthma for at least 1 year and who are in a stable period, and (4) with a smoking history of <10 pack-years. Exclusion criteria were as follows: having chronic kidney and liver disease and autoimmune disease. Patients who had an attack within the past 1 month and received vitamin D replacement within the past 6 months were excluded. For the control group, individuals of a similar age group who were admitted to our hospital for checkup purposes and did not have asthma or chronic disease were included. All the participants were informed about the nature of the study, and written informed consent was obtained from each participant. The study was planned according to the ethics guidelines of the Declaration of Helsinki, and the study protocol was approved by the institutional ethics committee of the Faculty of Medicine at Balıkesir University (2018/174).

Study Design

This was a cross-sectional single-visit, observational study. Patients with stable asthma, who were admitted to the centers between November 2018 and April 2019, and who met the study criteria were included. This study included a total of 384 patients and 87 control subjects. There were 121 patients from Balıkesir, 142 from two different centers from Istanbul, 71 from Antalya, and 50 from Ankara. A physical examination and a pulmonary function test were performed, and routine blood tests were evaluated. To assess the severity of airflow limitation and to confirm the diagnosis of asthma, lung

function and reversibility were performed in the patients who had episodic symptoms, such as wheezing, cough, shortness of breath, and chest tightness. In these patients, if the degree of reversibility in the forced expiratory volume in the first second of expiration (FEV₁) was 12% and 200 mL from the prebronchodilator value from baseline, after inhalation of 400 µg salbutamol accompanied by airflow limitation, we confirmed the diagnosis of asthma.¹

The Asthma Control Test (ACT) was performed.¹⁹ The Morisky Medication Adherence Scale was completed.²⁰ Respiratory symptoms, rhinitis symptoms questioned, file records reviewed. The ACT and Morisky Medication Adherence Scale assessments were used *via* face-to-face interviews by a pulmonary specialist. In the previous year, the number of emergency admissions and hospitalizations due to asthma attacks and current treatments were recorded. All ongoing use of medications was recorded for each patient, and asthma severity was defined based on the treatment intensity. Inhaled corticosteroids (ICS) (budesonide, fluticasone furoate, fluticasone propionate, beclomethasone), long-acting β -agonist; (salmeterol, formoterol, vilanterol, indacaterol) or long-acting muscarinic antagonist (glycopyrronium, tiotropium), leukotriene receptor antagonist (montelukast, zafirlukast), salbutamol, oral corticosteroids (OCS), and biologic therapy are included in the treatment of asthma. The patients were asked which of these treatments they used, and their current treatments were recorded. For the healthy control group, only a respiratory function test and routine blood analysis were done.

Skin-Prick Test

The skin-prick test (SPT) on the forearm was applied to all the patients by using standardized latex extract that contained high ammonia natural rubber latex and a full set of 25 common allergens. Aeroallergens (SoluprickSQ, ALK-Abello' A/S, Hørsholm, Denmark) were used for the SPTs and included positive histamine and negative (saline solution) controls, house-dust mites, *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, grasses, cereals, tree mix, *Olea*, *Parietaria*, *Artemisia*, *Alternaria*, *Cladosporium herbarium*, *Aspergillus*, *Blatella germanica*, and cat and dog dander. The puncture method with a 1-mm disposable lancet tip was used, and a mean wheal diameter of ≥ 3 mm than the control was considered a positive result.

Blood Analysis

Routine blood tests were examined by taking blood samples from the antecubital vein in the morning after 12 hours of fasting. Blood eosinophil counts were determined on peripheral blood smears, and patients with counts ≥ 300 mm³ were categorized as having eosinophilic phenotypes. Total IgE levels were determined by

Table 1 Characteristics of the patient and control groups

	Patient Group (n = 384)	Control Group (n = 87)	p
Age, mean $\pm$ SD, y	46.14 $\pm$ 14	44.2 $\pm$ 9.6	0.227
Women, n (%)	272 (70.8)	63 (72.4)	0.769
BMI, mean $\pm$ SD, kg/m ²	29.08 $\pm$ 5.5	4.5 $\pm$ 3.5	<0.001
Comorbidities, n (%)			
Any	127 (33.1)	80 (92.0)	<0.001
Allergic rhinitis	240 (62.5)	2 (2.6)	<0.001
Sinusitis	102 (26.6)	5 (6.4)	<0.001
Urticaria	71 (18.5)		
Gastroesophageal reflux	78 (20.3)		
Hypertension	74 (19.3)		
Diabetes mellitus	49 (12.8)		
FVC, mean $\pm$ SD, % predicted	83.7 $\pm$ 20.1	98.4 $\pm$ 10.6	<0.001
FEV ₁ , mean $\pm$ SD, % predicted	78.16 $\pm$ 20.2	98.2 $\pm$ 10.2	<0.001
FEV ₁ , n (%)			
$\geq 80\%$	172 (44.8)		
50–80%	176 (45.8)		
<50%	36 (9.4)		
FEV ₁ /FVC, mean $\pm$ SD, %	75.1 $\pm$ 10.6	85.3 $\pm$ 4.9	<0.001
Vitamin D, median (min-max), ng/mL	16.0 (3.5–48)	20.0 (5.8–58.7)	<0.001
Total IgE, mean $\pm$ SD, IU/L	286.3 $\pm$ 359.2	56.1 $\pm$ 83.0	<0.001
Eosinophil, mean $\pm$ SD, mm ³	313.2 $\pm$ 306.5	133.7 $\pm$ 116.6	<0.001
Skin prick test positive, n (%)	274 (69.3)		
Asthma control, n (%)			
Uncontrolled	256 (66.7)		
Controlled	128 (33.3)		
City, total no. patients/no. patients at step 5			
Balıkesir	121/17	28	
İstanbul	142/20	36	
Antalya	71/48	13	
Ankara	50/5	10	

SD = Standard deviation; BMI = body mass index; FVC = forced vital capacity; FEV₁ = forced expiratory volume in the first second of expiration; min-max = minimum-maximum; IgE = immunoglobulin E.

using the ImmunoCAP-FEIA fluoroenzyme immunoassay with the ImmunoCAP kit (Pharmacia, Uppsala, Sweden). Serum levels of 25 (OH) D were quantified by radioimmunoassay (Cobra-Quantum, Packard, MN) and categorized as sufficient (>30 ng/mL), insufficient (20–30 ng/mL), or deficient (<20 ng/mL).

Vitamin D Status

Vitamin D deficiency is defined as serum levels of 25 (OH) D ≤ 20 ng/mL (≤ 50 nmol/L). Vitamin D insufficiency is defined as serum levels of 25(OH) D from >20 to <30 ng/mL (>50 to <70 nmol/L).^{14–21}

Statistical Analysis

The Kolmogorow Smirnow test, skewness, kurtosis coefficients, and the ratio of standard deviation to mean were used to examine whether the distribution of the data between the groups was normal. The Mann-

Whitney *U* test was used for nonparametric distributed data. For categorical variables, the χ^2 test or the Fisher exact test was used in the presence of cross tables. The Spearman correlation test was applied for the correlation analysis of vitamin D and other parameters. The multivariable regression analysis was performed to identify independent determinants that affect the vitamin D level. A *p* value of <0.05 was considered significant in all analyses. SPSS 15.0 software (SPSS Inc., Chicago, IL) was used for statistical analysis.

RESULTS

The study included 384 patients and 87 control subjects. The mean $\pm$ standard deviation age of the patients was 46.1 ± 14.0 years; 272 were female patients (70.8%). The patients and the control groups were similar in terms of age and gender distribution ($p > 0.05$). The demographic and clinical characteristics of the patient and

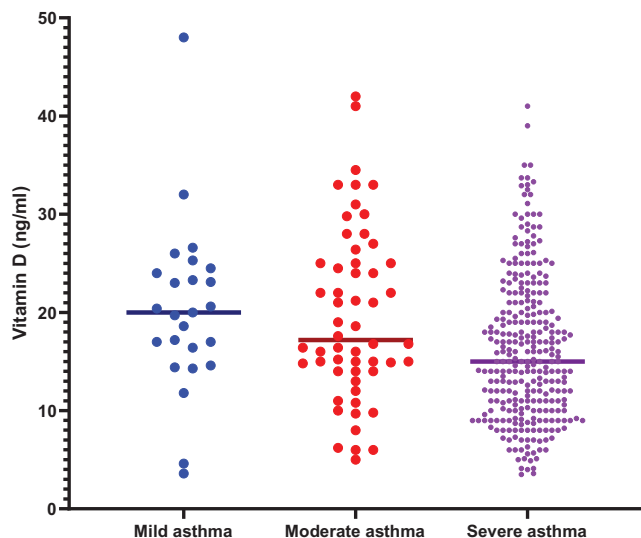


Figure 1. Association between vitamin D level and asthma severity.

the control groups are given in Table 1. Vitamin D levels in both patients (median [minimum-maximum {min-max}] 16.0 ng/mL [3.5–48 ng/mL]) and controls (median [min-max] 20.0 ng/mL [5.8–58.79 ng/mL]) were below the target values determined by the World Health Organization. However, the vitamin D levels were lower in the patients with asthma compared with the controls ($p = 0.001$).

Of the all the patients, 25 had mild asthma, 59 had moderate asthma and 300 had severe asthma. The vitamin D level was found to be significantly lower in the patients with severe asthma (median [min-max] 15.0 ng/mL [3.5–41 ng/mL]) compared with moderate (median [min-max] 17.2 ng/mL [5.0–42.0 ng/mL]) and mild asthma (median [min-max] 20.0 ng/mL [3.6–48.9 ng/mL]) severe asthma compared with moderate and compared with mild asthma ($p = 0.007$, $p = 0.009$, respectively). The vitamin D level decreased as the severity of asthma increased (Kendall $\tau = -0.146$; $p < 0.001$) (Fig. 1). In addition, when patients in the severe asthma group were evaluated within themselves, it was observed that vitamin D levels were lower in the patients with severe asthma who received step 5 treatment ($n = 97$) compared with the group that received step 4 treatment ($n = 203$) ($p = 0.037$). There were no differences with concern to medication adherence between the asthma groups ($p = 0.306$). The vitamin D level (median [min-max] 17 ng/mL [5.0–48.0 ng/mL]) was higher in those who took low-dose ICS than in those who took medium-to-high-dose ICS (median [min-max] 15.3 ng/mL [3.5–41.0 ng/mL]) and those who took OCS (median [min-max] 10.0 ng/mL [3.6–22.0 ng/mL]), low dose ICS than medium-to high dose ICS ($p = 0.018$), and OCS ($p = 0.008$) when we compared the patients according to the doses and kind of ICS they used.

Allergic rhinitis was present in 62.5% of the patients ($n = 240$) and skin prick test positivity in 69.3% of the

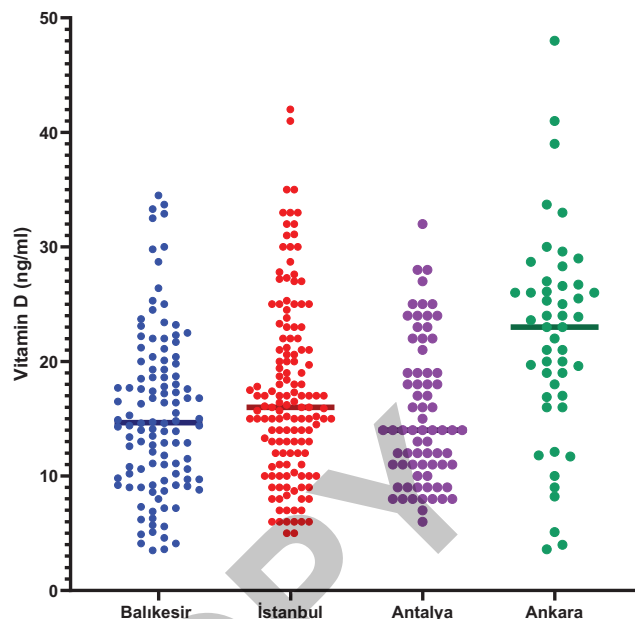


Figure 2. Vitamin D levels in patients living different cities.

total patients with asthma ($n = 274$). According to the skin prick test results, house-dust mite sensitivity was at 52.2%, grass pollen sensitivity was 29.2%, olive sensitivity was 17.2%, cat-dog sensitivity was 20.1%, and mold sensitivity was 14.7%. No significant differences were found in the vitamin D levels in the patients with and in those without allergen sensitivity ($p = 0.741$). In addition, 26.6% of the patients ($n = 102$) had concomitant sinusitis, 18.5% ($n = 71$) had urticaria, 20.3% ($n = 78$) had gastroesophageal reflux, 19.3% ($n = 74$) had hypertension, and 12.8% ($n = 49$) had diabetes mellitus. There was no difference with regard to the vitamin D levels between the patients with and the patients without comorbidities ($p = 0.439$). When we compared the patients in terms of vitamin D levels among the cities, the vitamin D levels were found to be low in Antalya, which is the southernmost part of Turkey, whereas it was higher in Ankara compared with other regions (Balıkesir, İstanbul, Antalya; $p = 0.001$) (Fig. 2). However, when we look at the distribution in terms of disease severity, it was observed that the number of patients with step 5 severe asthma was quite high in Antalya (Table 1).

A positive correlation was found between the vitamin D level and % predicted FVC and % predicted FEV₁ ($r = 0.236$, $r = 0.221$, respectively; $p \leq 0.001$), whereas a negative correlation was found between BMI and vitamin D ($r = 0.198$; $p = 0.001$). In addition, the % predicted peak expiratory flow and the ACT score were positively correlated with the vitamin D level ($r = 0.229$ and $r = 0.201$, respectively; $p = 0.001$); however, asthma exacerbation and hospitalization were negatively related with vitamin D ($r = -0.213$ and $r = 0.200$, respectively; $p = 0.001$). As the number of asthma attacks increased, the vitamin D level

Table 2 Multivariable regression analysis of vitamin D and some variables*

	st β	95% CI	p
Age	-0.065	-0.10 to 0.03	0.328
Body mass index	-0.134	-0.37 to -0.01	0.037
Comorbidity	-0.070	-2.96 to 0.84	0.273
FEV ₁ % predicted	-0.333	-0.21 to -0.01	0.033
FVC % predicted	0.444	0.05 to 0.25	0.002
PEF % predicted	0.146	-0.00 to 0.10	0.070
Eosinophil	-0.007	-0.03 to 0.03	0.911
Total IgE	0.030	-0.02 to 0.03	0.635
Exacerbation	-0.078	-0.58 to 0.23	0.394
Hospitalization	0.075	-0.49 to 1.44	0.341
Asthma Control Test	0.019	-0.16 to 0.22	0.762

st β = Standardized Coefficients Beta; CI = confidence interval; FEV₁ = forced expiratory volume in the first second of expiration; FVC = forced vital capacity; PEF = peak expiratory flow; IgE = immunoglobulin E.

*R² = 0.382; adjusted R² = 0.106; F = 3.599 (p < 0.001).

decreased. In the regression analysis, independent variables that affect the levels of vitamin D were investigated. Age, BMI, comorbidity, FEV₁, FVC, peak expiratory flow, eosinophil count, total IgE value, number of exacerbations, hospitalizations, and ACT were included (Table 2). BMI (95% confidence interval [CI], -0.37 to -0.01; p=0.037), FEV₁ (95% CI, -0.21 to -0.01; p=0.033), and FVC (95% CI, -0.05 to -0.25; p=0.002) have been detected as independent variables that affected vitamin D levels.

DISCUSSION

As far as we know, this was the first large cross-sectional study to evaluate vitamin D levels in adult patients with asthma who were living in different geographic regions in Turkey. Our results indicated that the vitamin D levels were below the expected target values in both the patients with asthma and the individuals without asthma but were significantly lower in the patients with asthma. This situation has shown us that vitamin D levels were also not at the desired level in healthy individuals. Although our country is sunny, in a meta-analysis, vitamin D deficiency stands at 63% for the overall population in Turkey.²² Again, the prevalence of asthma in children and adults in Turkey ranges from 2.7% to 14.8%.²³ In a study conducted in northern Europe, there was no difference in vitamin D levels between patients with asthma and patients without asthma, and there was no deficiency in both groups (66 nmol/L).²⁴ Similarly, in studies conducted in Denmark and Norway, there was no relationship between vitamin D and asthma at baseline and 10-year follow-up.^{12,13} In a Canadian-based cross-sectional

study, a "low level of serum 25(OH) D is related to an increased risk of asthma" was reported.²⁵ Different results between countries and studies can be explained by the differences in the design of the studies, race, genetic and environmental factors, and external intake of supplemental vitamin D.

Individuals who were receiving supplemental vitamin D were not included in our study. A total of 77% of the patients had severe asthma. The reason for the high number of patients with severe asthma was that the centers were upper centers where patients with severe asthma were referred. Asthma severity and vitamin D levels were inversely correlated. Even in the severe asthma group, a significant difference was observed between the GINA¹ step 5 and Step 4 groups. The lowest vitamin D level was in the GINA¹ step 5 group. In some previous studies, insufficiency of vitamin D related to elevated asthma severity was found.²⁶ As the step goes up from GINA¹ steps 1 to 5, the dose of inhaled steroids used by the patient increases. The effect of the low-dose ICS on bone mineral density is not important but it is suggested that it may cause deterioration in bone mineralization as the cumulative dose of ICS increases.^{15,27} It was observed that vitamin D deficiency and bone mineral density decreased in children with asthma who were using OCS.²⁸

Searing *et al.*²⁹ showed that the vitamin D level is lower in patients with asthma by using, not only OCS but also ICS. They also showed vitamin D enhancement of glucocorticoid action in PBMCs in patients with asthma *in vitro*. They explained the relationship between vitamin D and steroids with two hypotheses: first, lower vitamin D levels contribute to increasing asthma severity and a concomitant need for an escalating ICS dose; second, vitamin D insufficiency promotes the need for higher doses of glucocorticoids to achieve the anti-inflammatory effect. In the study, we also observed that, as the ICS dose increased, the vitamin D level decreased, and even lowest in those who used oral steroids. Our results supported both hypotheses. In addition, low vitamin D levels in patients with severe asthma may also be related to a more sedentary life, less time out during the day, and less exposure to the sun.

In vitro studies have shown that vitamin D suppresses IgE production from human B lymphocytes,^{4,5} and serum IgE has been observed to increase in children with vitamin D₃ deficiency.³⁰ Our knowledge of the effect of vitamin D on innate lymphoid cells and eosinophils is more limited.² In a study, it was reported that there was a relationship between sputum eosinophilia and a low vitamin D level.²⁰ Some studies reveal the relationship between atopy and vitamin D,^{26,30} whereas other studies indicate its relationship with nonatopic asthma.³¹ Cherrie *et al.*³¹ showed that vitamin D levels were lower in patients with nonatopic asthma compared with

atopics. In our study, 69.3% of the patients had skin prick test positivity and 53.2% of them had house-dust mite sensitivity. No significant difference was found between the patients who were allergic and patients who were not allergic with regard to the levels of vitamin D. There was also no relationship between allergic rhinitis, eosinophilia, and IgE levels, and vitamin D. In a study conducted in Turkey, it was found to be associated with allergies.³² However, in that study, the vitamin D cut-up value was taken as 10 ng and a comparison was made according to that value.

Notably, the patients with vitamin D deficiency had lower lung function and poor asthma control. Our results suggested that vitamin D deficiency was associated with the increased rate of asthma exacerbation and hospitalization. In one study, it was shown that children with vitamin D deficiency had an increased risk of asthma attacks and hospitalization.³³ A meta-analysis of clinical trials demonstrated that vitamin D supplementation reduced the rate of asthma exacerbation, especially in patients with vitamin D deficiency.^{17,18} In addition, the vitamin D supplementation improvement effect on FEV₁ was reported in patients with asthma with airflow limitation (FEV₁ value < 80%) and vitamin D insufficiency.¹⁷ However, today, there is not enough evidence that vitamin D supplementation has a healing effect on asthma control and attacks.¹ More studies are needed in this area.

Regression analysis showed that FVC, FEV₁, and BMI were independent determinants for vitamin D. A meta-analysis indicates that the prevalence of vitamin D deficiency was more high in subjects with obesity.³⁴ However, obesity is common, especially in patients with severe asthma.³⁵ Excessive use of systemic steroids in severe asthma may be seen as the reason for increasing the prevalence of obesity, but there is evidence that obesity itself increases the severity of asthma.^{36,37} Inflammatory cytokines released from adipocytes, including IL-1 β , tumor necrosis factor α , and IL-6, cause systemic inflammation and affect the lungs.^{38,39} In our study, the high BMI and low vitamin D levels of the severe asthma group suggested that obesity and vitamin D deficiency were common components in the worsening of asthma. In our study, there were no patients who were morbidly obese, but we believe that adipokines and adipokine-associated cytokines, which play a major role in obesity, may play an important role in vitamin D synthesis and regulation.

In terms of geographic regions, Balıkesir and Istanbul are located in the Marmara Sea region, Antalya is in the Mediterranean region, and Ankara is in the central Anatolia region. When we compared the patients in terms of vitamin D levels among the cities, vitamin D levels were found to be low in Antalya, Turkey's southernmost and sunniest place, whereas it was higher in Ankara compared with other regions (Balıkesir, Istanbul, Antalya; $p=0.001$). This can be explained by the high

rate of severe asthma in the cases in the study from Antalya and the low rate of severe asthma in Ankara. In previous epidemiologic studies conducted in our country, the prevalence of asthma was found to be low in Ankara (2.1%) and high in Antalya (9.4%).⁴⁰⁻⁴²

There were limitations of the study. Factors such as the zenith angle, skin color, season, latitude, and longitude, which are the angles at which sunlight reaches the earth, are effective in vitamin D synthesis. Because the study was conducted between November and April, lower values were likely found compared with the summer months. Another limitation of the study was the lack of assessing Pollen-food allergy syndrome. In the literature, the prevalence of pollen-food allergy syndrome has been reported to be high.⁴³

Conclusion

Our results suggested a high prevalence of vitamin D deficiency in adults with asthma who lived in different geographic areas in Turkey. We believe that vitamin D replacement may be useful in inflammation and disease control, and in reducing attacks in patients with vitamin D deficiency, especially in severe asthma.

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