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Evaluation of the Relationship between Serum 25-Hydroxyvitamin D Levels and Pulmonary Functions in Adult Asthma

Serum 25-Hidroksivitamin D Düzeylerinin Yetişkin Astım Hastalarında Pulmoner Fonksiyonlar ile İlişkisinin Değerlendirilmesi

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ABSTRACT

Aim: This study was aimed to determine the relationship between serum 25-hydroxyvitamin D [25(OH)D] levels and the pulmonary functions in adult asthma patients.
Material and Methods: A total of 131 asthmatic patients' general characteristics, asthma symptoms, pulmonary function test, asthma control test (ACT) scores, serum 25(OH)D levels, body weight, and height were recorded. Body mass indexes (BMIs) of the patients were calculated and World Health Organization criteria were used for the classification. Patients with serum 25(OH)D levels below 20 ng/mL were classified as having a deficiency, those with 21-29 ng/mL as having an insufficiency, and those with 30 ng/mL and above as having normal serum vitamin D levels.
Results: The serum 25(OH)D levels of patients in the uncontrolled asthma group, according to the ACT score, were found to be lower than those of patients in the controlled group (p=0.002). It was determined that as the serum 25(OH)D levels of the patients increased, the ACT scores also increased significantly (r=0.280, p=0.001). Additionally it was found that each 1 ng/mL increase in 25(OH)D level was associated with an increase of 0.176 L in forced vital capacity (FVC). In addition it was determined that as the serum 25(OH)D levels increased, the patients' FVCs also increased (OR=1.056, 95% CI=1.003-1.113, p=0.038). Although the change was not statistically significant (p=0.081), as serum 25(OH)D levels increased, the ACT scores also increased.
Conclusion: Vitamin D insufficiency and deficiency were frequently found in adults with asthma and there was a relationship between vitamin D deficiency and pulmonary function.
Keywords: Asthma; pulmonary function; vitamin D deficiency.

ÖZ

Amaç: Bu çalışmanın amacı, yetişkin astım hastalarında serum 25-hidroksivitamin D [25(OH)D] düzeyleri ile pulmoner fonksiyonlar arasındaki ilişkiyi saptamaktır.
Gereç ve Yöntemler: Toplam 131 astım hastasının genel özellikleri, astım semptomları, solunum fonksiyon testi, astım kontrol testi (AKT) skorları, serum 25(OH)D seviyeleri, vücut ağırlığı ve boy uzunluğu verileri kayıt altına alınmıştır. Hastaların beden kütle indeksleri (BKİ) hesaplanmış ve sınıflandırma için Dünya Sağlık Örgütü kriterleri kullanılmıştır. Serum 25(OH)D seviyesi 20 ng/mL'nin altında olan bireyler D vitamini eksikliği, 21-29 ng/mL olanlar D vitamini yetersizliği ve 30 ng/mL ve üstü olanlar ise normal serum D vitamini düzeyi olarak sınıflandırılmıştır.
Bulgular: AKT skoruna göre kontrolsüz astım grubundaki bireylerin serum 25(OH)D düzeyleri, kontrollü gruptaki bireylerden daha düşük bulunmuştur (p=0,002). Bireylerin serum 25(OH)D düzeyleri arttıkça AKT skorlarının da anlamlı şekilde arttığı saptanmıştır (r=0,280; p=0,001). Buna ek olarak serum 25(OH)D seviyesindeki her 1 ng/mL'lik artışın zorlu vital kapasite (forced vital capacity, FVC)'de 0.176 L'lik bir artış ile ilişkili olduğu bulunmuştur. Ayrıca serum 25(OH)D seviyeleri arttıkça, bireylerin FVC düzeylerinin de arttığı tespit edilmiştir (OR=1,056; %95 GA=1,003-1,113; p=0,038). İstatistiksel olarak önemli olmamakla birlikte (p=0,081), serum 25(OH)D seviyeleri arttıkça AKT skorlarının da arttığı belirlenmiştir.
Sonuç: Astım hastası olan yetişkinlerde D vitamini yetersizliği ve eksikliğinin sık görüldüğü ve D vitamini eksikliği ile solunum fonksiyonu arasında bir ilişki olduğu belirlenmiştir.
Anahtar kelimeler: Astım; pulmoner fonksiyon; D vitamini eksikliği.

INTRODUCTION

Asthma is a heterogeneous disease characterized by oversensitivity of the airway and chronic airway inflammation, which develops in response direct or indirect stimuli (1). The World Health Organization (WHO) has reported that 339 million people have asthma worldwide (2). According to WHO estimates, there were 4484.8 deaths (95% CI: 2414.1-7593.1) due to asthma at the global level in the year 2016 (3). Although the presence of atopy, exposure to environmental allergens and smoking are well known to be important risk factors associated with the onset of asthma, in recent years vitamin D insufficiency has been noticed to be a risk factor for asthma (4).

Vitamin D is indicated to be much more than a micronutrient. Vitamin D 1,25-dihydroxy, the active metabolite of vitamin D [$1,25(OH)_2D$] is considered to be a hormone, as it is structurally and functionally similar to steroid hormones (4). Studies have shown that vitamin D reduces proinflammatory markers (interleukin-6 and tumour necrosis factor-α) levels, reduces the antigen delivery of monocyte-macrophage to T cells, prevents the maturation of dendritic cells and shows immunomodulatory effect in addition to the endocrine role as a result of the anti-proliferative effect on lymphocytes (4,5). The effect of vitamin D on the pathogenesis of asthma can also be described as its inhibitory effect on the antigen-providing cells that are essential for the onset and substitution of the cellular immune response. Vitamin D has been shown to inhibit dose-dependent Th1 cells and inflammatory cytokines (such as interleukin-1 alpha-beta, interleukin-12, interferon-gamma), increasing the expression of Th2-dependent cytokines. Vitamin D has also been reported to have anti-proliferative effects on T cells and to suppress antibody production directly or indirectly in B cells; it also reduces the risk of asthma by activating Treg cells and suppressing peripheral autoreactive T cells. Due to these properties, vitamin D is believed to have a role in the reduction of asthma-related morbidity as well as prevention of asthma (6,7). Studies have shown a positive correlation between vitamin D deficiency and severity of asthma in asthma patients, longer hospitalizations and an increased usage of emergency services due to shortness of breath, and a deficiency of vitamin D in asthma patients (8-11). However, these studies have generally been conducted in the pediatric population, and the studies examining the effect of vitamin D insufficiency on asthma are limited. Therefore, this study was aimed to determine the relationship between serum vitamin D levels and the pulmonary functions in adult asthma patients.

MATERIAL AND METHODS

This retrospective study included 131 patients over the age of 18 who had received an asthma diagnosis between 1 March 2019 and 1 June 2019 at the Chest Diseases Polyclinic of the Training and Research Hospital at the University of Health Sciences Antalya. Since serum vitamin D levels may be affected by the time of year, all the patients were selected from patients admitted in the same season (spring). Pregnant, diabetic or cancer patients, vitamin D supplement users and smokers who smoked more than 10 packs/year were not included in the study.

The patient examination information filled in by the chest disease specialist was accessed from the hospital information system: age, gender, underlying chronic diseases, smoking status, asthma symptoms, asthma control test (ACT) scores, serum vitamin D and serum IgE levels and body mass indexes (BMIs) [body weight (kg)/height $(m)^2$] were calculated. The WHO criteria were used for the classification of BMI (12). Patients with serum 25-hydroxyvitamin D [25(OH)D] levels below 20 ng/mL were classified as having a deficiency, those with 21-29 ng/mL as having an insufficiency, and those with 30 ng/mL and above as having normal serum vitamin D levels (13). A Spiro Zan respiratory function test device was used for spirometry evaluations. Forced expiratory volume (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF), forced expiratory volume/forced vital capacity (FEV1/FVC) and forced medium expiratory flow (MEF2575) values were used in the study.

ACT results recorded during the examination were utilized to evaluate the control of asthma-related symptoms. The ACT is a questionnaire that evaluates how well asthma has been controlled, and its Turkish version has been tested for validity and reliability. A score of 20 or more points indicates that the asthma is "controlled" while 19 or fewer points indicates that it is "uncontrolled" (14).

Ethical Committee (Training and Research Hospital, University of Health Sciences Antalya) approval was obtained on 7 November 2019 (Decision no. 24/4).

Statistical Analysis

The descriptive statistics are presented as frequencies, percentage, mean, standard deviation, median, interquartile range, and minimum-maximum values. The relationships between serum vitamin D levels and ACT scores, respiratory function parameters, serum IgE and eosinophil levels were evaluated using the Pearson or Spearman correlation test. The patients were divided into tertile according to serum vitamin D levels. The Shapiro-Wilk test was used in the normality test. The Kruskal-Wallis test was used for non-parametric comparison of numerical variables according to the tertiles, and the Dunn Bonferroni post-hoc test was used for significant cases. The ANOVA test was used to compare the tertiles where there was an assumption of normal distribution. The independent effects of vitamin D on different respiratory function parameters were evaluated using the multiple linear regression model. The effect of insufficient/deficiency vitamin D level on respiratory function parameters and ACT score was examined by logistic regression analysis. The Hosmer-Lemeshow test was used to test the model's goodness of fit. The SPSS v.22.0 package program was used in all statistical analyses and $p<0.05$ was considered statistically significant.

RESULTS

The general characteristics of patients are shown in Table 1. It was determined that the majority of the patients participating in the study (n=79, 60.3%) were female and approximately half of all patients (n=56, 42.7%) were between the ages of 18 and 33. 92 (70.2%) of the patients had had asthma for 1-5 years and more than half of them did not have any other chronic disease. In patients with chronic diseases, hypertension (n=24, 18.3%), psychiatric diseases (n=19, 14.5%) and gastritis/ulcer (n=10, 7.6%) were the most common diseases. More than half of the

patients were found to be overweight (n=49, 37.4%) or obese (n=31, 23.7%). According to the ACT score, the majority of the patients were in the uncontrolled asthma group (n=83, 63.4%) and serum vitamin D levels of 73.3% (n=96) were deficient (≤20 ng/mL). It was determined that as the serum 25(OH)D levels of the patients increased, the ACT scores (p=0.008), FVC (p=0.004) and PEF (p=0.051) levels also increased. Although the BMI values of the patients in the first tertile were the highest (28.1±5.38 kg/m^2) and those of the patients in the third tertile were the lowest (26.6±4.81 kg/m^2), this difference was not statistically significant (p=0.291, Table 2).

Table 3 shows a positive, significant correlation between serum vitamin D level and ACT scores (r=0.295, p=0.001), FVC (r=0.294, p=0.001), FEV1 (r=0.217, p=0.022) and PEF (r=0.180, p=0.040). In the multiple linear regression analysis, it was found that each 1 ng/mL increase in vitamin D level was associated with an increase of 0.176 units in FVC (p=0.005), 0.158 L in FEV1 (p=0.028) and 0.544 point in ACT score (p=0.024, Table 4). Table 5 shows the association of the vitamin D insufficiency with the respiratory function parameters and the ACT score. Accordingly, it was determined that as the serum vitamin D levels increased, the patients' FVCs also increased (OR=1.056, 95% CI=1.003-1.113, p=0.038). Although the change was not statistically significant (p=0.081), as serum vitamin D levels increased, the ACT scores also increased.

Table 1. General characteristics of patients, n (%)

Sex	
Male	52 (39.7)
Female	79 (60.3)
Age (year)	
18-33	56 (42.7)
34-49	41 (31.3)
50-65	34 (26.0)
Asthma Year	
1-5 years	92 (70.2)
≥ 6 years	39 (29.8)
Asthma treatment	
Receiving ICS treatment	107 (81.7)
Not receiving ICS treatment	24 (18.3)
Chronic disease status	
None	78 (59.5)
Hypertension	24 (18.3)
Psychiatric	19 (14.5)
Gastritis/ulcer	10 (7.6)
Body mass index (kg/m^2)	
Normal	51 (38.9)
Overweight	49 (37.4)
Obese	31 (23.7)
Asthma severity	
Controlled (ACT ≥20)	48 (36.6)
Uncontrolled (ACT ≤19)	83 (63.4)
Serum 25(OH)D (ng/mL)	
Deficient (≤20 ng/mL)	96 (73.3)
Insufficient (20.1-29.9 ng/mL)	35 (26.7)

ICS: inhaled corticosteroids, ACT: asthma control test, 25(OH)D: 25-hydroxyvitamin D

Table 2. The asthma control test score, pulmonary function parameters, IgE, eosinophils and body mass index of patients according to serum vitamin D levels

	Tertile 1 (n=43)	Tertile 2 (n=43)	Tertile 3 (n=45)	p
ACT score	19.5±2.8	20.9±3.1	21.5±2.8	0.008
FVC	85 (19) [57-107]	89 (26) [59-125]	94 (13) [56-138]	0.004
FEV1	82.6±14.3	87.5±17.0	89.5±11.9	0.104
FEV1/FVC	103.4±12.9	103.4±11.1	101.2±9.3	0.553
PEF	66.8±17.9	73.3±19.9	75.6±16.4	0.051
MEF2575	71.0±25.5	78.3±26.5	75.4±22.6	0.397
IgE	99 (113) [17-694]	110 (152) [17-603]	141 (130) [17-1660]	0.573
Eosinophils	200 (200) [0-600]	100 (200) [0-1000]	200 (300) [0-1000]	0.285
BMI (kg/m^2)	28.1±5.4	26.7±4.9	26.6±4.8	0.291

Tertile ranges are as follows: Tertile 1: ≤13.89 ng/mL, Tertile 2: 13.9-19.3 ng/mL, Tertile 3: 19.31-29.9 ng/mL, normally distributed variables are presented as mean±standard deviation while not-normally distributed variables are presented as median, interquartile range, and minimum-maximum, ACT: asthma control test, FVC: forced vital capacity, FEV1: forced expiratory volume, PEF: peak expiratory flow, MEF2575: forced medium expiratory flow, BMI: body mass index

Table 3. Correlation between serum vitamin D level and asthma control test score, respiratory function parameters, serum IgE, eosinophils and body mass index

	r	p
ACT score	0.295	0.001
FVC	0.294	0.001
FEV1	0.217	0.022
FEV1/FVC	-0.143	0.140
PEF	0.180	0.040
MEF2575	0.090	0.309
IgE	0.068	0.440
Eosinophils	0.080	0.364
BMI (kg/m^2)	-0.109	0.217

FVC: forced vital capacity, FEV1: forced expiratory volume, PEF: peak expiratory flow, MEF2575: forced medium expiratory flow, BMI: body mass index

Table 4. Multiple linear regression analysis of the relationship between serum vitamin D levels and pulmonary function parameters

	B	SE	Beta	t	p	95% CI	
Constant	6.680	3.110		2.148	0.034	0.525	12.835
ACT score	0.544	0.239	0.275	2.278	0.024	0.071	1.016
FVC	0.176	0.062	0.432	2.844	0.005	0.053	0.298
FEV1	0.158	0.071	0.417	2.222	0.028	0.300	0.017
PEF	0.029	0.034	0.090	0.840	0.403	-0.039	0.097

F=2.403, p=0.010, β: coefficient of regression, SE: standard error, CI: confidence interval, ACT: asthma control test, FVC: forced vital capacity, FEV1: forced expiratory volume, PEF: peak expiratory flow

Table 5. Logistic regression analysis of the relationship between vitamin D insufficiency and deficiency between pulmonary function parameters and asthma control test score

	OR	95% CI		p
FVC	1.056	1.003	1.113	0.038
FEV1	0.955	0.899	1.015	0.138
PEF	1.001	0.973	1.030	0.960
ACT score	1.202	0.977	1.477	0.081

OR: odds ratio, FVC: forced vital capacity, FEV1: forced expiratory volume, PEF: peak expiratory flow, ACT: asthma control test

DISCUSSION

This study found that the prevalence of vitamin D insufficiency in the adult asthmatic population in Turkey (Antalya) was quite high. At the same time, there was a significant relationship between serum vitamin D level and FVC, FEV1 and PEF.

The prevalence of asthma and the rates of vitamin D insufficiency are increasing worldwide. Vitamin D is thought to have a role in asthma pathogenesis because it has immunomodulatory effects such as improving immune system tolerance and maintaining epithelial barrier integrity (15). In Turkey, vitamin D deficiency and insufficiency were found in 76.4% in children with asthma between the ages of 1-4, and in 90.6% of children in another similar study (16,17). Although the number of studies of asthmatic adults is quite limited, the prevalence of vitamin D deficiency found in asthma patients in other research is similar to that observed in our study (18-21). In a study conducted on 435 adult asthma patients in China to determine the relationship between serum vitamin D level and pulmonary function, a significant relationship was found between vitamin D deficiency (50 nmol/L) and FEV1/FVC ratio and FEV1 (18). Similarly, Beyhan-Sagmen et al. (19) suggested that the FEV1 levels of asthmatic patients with serum vitamin D insufficiency in Turkey were low and that there was a significant linear relationship between vitamin D and FEV1. In one study, every 22.7 mL increase in FEV1 was found to cause a 1 ng/mL increase in serum vitamin D (20). Despite this, 91% of adult asthmatic patients in Costa Rica had serum vitamin D levels below 30 nmol/L, and although there was a linear relationship between serum vitamin D levels and FEV1, this relationship was not statistically significant (21). In a study involving 760 asthmatic patients in Norway, a significant correlation between serum vitamin D levels and FEV1 was observed only in males because the males participating had a lower level of lung function than the females (22). In this study, it was determined that as the serum vitamin D levels of the asthma patients increased, the FVC and PEF levels increased, and in multiple linear regression analysis, each 1 ng/mL increase in vitamin D level was associated with an increase of 0.176 L in FVC, 0.158 L in FEV1 and 0.544 point in ACT score. Obesity causes the emergence of asthma as a result of its mechanical and inflammatory effects and increases the severity of asthma over time. Patients with a BMI of 35 or more are reported to be approximately twice as much at risk of asthma (23). There is evidence that the active form of vitamin D modulates intracellular ionized calcium signaling in adipocytes, inhibits uncoupling protein-2 (UCP-2), decreases lipolysis, and increases lipogenesis. Accordingly, vitamin D deficiency is thought to play an important role in the development of obesity (24). In our study, more than half of the patients with asthma were found to be overweight (n=49, 37.4%) or obese (n=31, 23.7%). In addition, although it was determined that patients' BMIs increased as their serum vitamin D levels decreased, this difference was not found to be statistically significant. Sutherland et al. (20) stated that each unit increase in BMI in adult asthmatic patients caused a decrease in serum vitamin D level of 0.71 ng/ml and that there was a strong inverse correlation between serum vitamin D levels and BMI, especially in asthmatic patients not receiving inhaled corticosteroid (ICS) therapy. This was associated with higher obesity rates in asthmatic patients not receiving ICS treatment compared to other groups. Despite this, similarly to our study, Li et al. (18) observed lower serum vitamin D levels in asthmatic patients who were obese, but reported that this relationship was not significant. The fact that the sample of our study was small and that more than one-third of the patients had a normal BMI may explain why this relationship was not significant.

The ACT is the most commonly used test today, is easily understood by patients and their families and shows the severity of the asthma (25). It has been stated that there is a relationship between serum vitamin D levels and clinical parameters such as asthma severity, exacerbation, admission to an emergency department and number of hospitalizations (16,26,27). Studies in children have shown that serum vitamin D deficiency exacerbates asthma by 2.6 times (26) and hospital or emergency department admission by 1.5 times (9) compared to the previous year. Few studies have determined the relationship between asthma control and serum vitamin D levels in adults. While there was no relationship between serum vitamin D level and ACT scores in one study, when classified according to serum 25(OH)D levels, ACT scores were reported to be lower in the group with severe vitamin D deficiency (19). In one study conducted with the elderly, the serum vitamin D levels of patients in the uncontrolled asthmatic group were shown to be lower than those of patients in the controlled group (28). In this study, it was determined that as the serum 25(OH)D levels of the patients increased, the ACT scores also increased, and that there was a low-level, positive and significant relationship between the ACT scores and serum vitamin D level.

In randomized controlled studies, vitamin D supplements at different doses were found to increase serum 25(OH)D levels (29,30), decrease exacerbation rates of asthma and increase ACT scores (28,30,31), and positively affect FEV1 (31,32).

However, some limitations should be noted. First, since the study is retrospective, there was no record of the nutrient consumption of patients and the amount of vitamin D taken in orally could not be calculated. In addition, the patients were not asked about the amount of time they had spent in the sun. Nevertheless, the fact that patients constituting the sample of the study were admitted in the same season (spring) is one of the strengths of the study. Another limitation of the study was the low number of samples and the fact that it was a cross-sectional retrospective study.

CONCLUSION

This study tried to explain the role of vitamin D in adult asthma patients. It was determined that vitamin D deficiency was frequently found in adults with asthma and there was a relationship between vitamin D deficiency and pulmonary function. In addition, it was determined that patients with high serum vitamin D levels have a better asthma course. Since the results of this study are thought to have been affected by factors such as diet, exposure to sun, etc., further studies are recommended that consider multiple factors that may affect the relationship between asthma and vitamin D.

Ethics Committee Approval: The study was approved by the Ethics Committee of Antalya Training and Research Hospital (07.11.2019, 24/4).

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