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THE ROLE OF VITAMIN D ON THE CLINICAL COURSE OF ADULT ASTHMA

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The authors declare that they have no potential conflict of interest including any financial, personal or other relationships with the other people or organizations that could inappropriately influence, or be perceived to influence the presented work.

On behalf of all authors.

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ABSTRACT

Background:

Besides skeletal functions, it has been speculated that vitamin D (vitD) is involved in the pathogenesis of pulmonary diseases. Little is known about vitD in adult asthma or its association with asthma severity and control. As previous studies are inconclusive, the purpose of this study was to determine the prevalence of vitD deficiency in adult asthma and to investigate associations of serum vitD levels with atopy, asthma, and lung function.

Material and Method:

112 (88 stable and 24 exacerbated) asthma patients and similar 94 healthy adults evaluated in this cross-sectional study. Detailed demographic data and clinical features, pulmonary function tests of all participants were recorded. Serum 25(OH)D₃ has been analyzed with high pressure liquid chromatography technique. Serum vitD levels ≤ 20 ng/ml has been accepted as vitD deficiency.

Results:

The mean serum vitD level was 25.19 ± 12.01 and 27.09 ± 12.9 ng/ml in asthma and the control group respectively ($p:0.27$). The prevalence of vitD deficiency and the mean serum vitD level were similar in stable asthma group, exacerbated asthma group and the control group (respectively $p:0.398$, $p:0.363$). Serum vitD levels of female participants (23.89 ± 11.92 ng / ml) was significantly lower than males in asthmatics (29.52 ± 11.48 ng / ml) ($p:0.03$). Forced expiratory volume in first second (FEV₁) and forced vital capacity (FVC) were significantly lower in the vitD deficient group in both asthmatic and control group (respectively in patients $p:0.003$, $p:0.01$, in control group $p:0.04$, $p:0.005$). In stable asthma ($n=88$), mean serum vitD level of obese (22.8 ± 13.3 ng/ml) was significantly lower than non-obese patients (27.9 ± 11.2 ng/ml) ($p:0.024$) and body mass index and serum vitD levels were negatively correlated ($p:0.02$).

Conclusion:

The serum vitD levels and vitD deficiency of asthmatics were not different from control group, but significantly associated with female gender, poor lung function and obesity.

INTRODUCTION

Asthma pathogenesis has not been delineated well yet, so inquires about diagnostic methods, treatment modalities and preventive regimes encourage further investigations. There are numerous well-known risk factors for asthma but recently vitD has been blamed to be responsible for both in development and clinical characteristics of asthma.

VitD is an essential fat-soluble compound that plays a critical role in calcium homeostasis. Beyond this main function, it has been showed to have some immunomodulatory effects on human body. Recent epidemiological studies suggest a causal relationship between vitD and a wide range of disorders such as multiple sclerosis, diabetes mellitus, rheumatoid arthritis, some types of cancer. Along with these recent insight, vitD is found to be associated with a wide range of pulmonary diseases also, including viral and bacterial respiratory infections, asthma, and lung cancer, too. Several researches have reported conflicting associations between vitD and asthma.

It is not well documented that asthma patients have a higher prevalence of vitD deficiency than healthy population. Some studies have not confirmed a positive association between serum vitD level and asthma and supported the concept that vitD is not associated with asthma (1,2, 3), but some have an opposite estimation (4,5).

There has been growing evidence indicating that vitD plays a key role in inflammation (6). VitD suppresses Th2-mediated allergic airway disease and may modulate the function of local regulatory cells (7), and it also plays a key role in the regulation of immune functions (8,9). The underlying mechanisms how vitD metabolism could be linked to the pathophysiology of asthma are often complex and not fully understood (10).

VitD deficiency is common and is found to be possibly associated with a range of illnesses beyond traditional diseases including inflammatory disorders, cancer, infectious disease and long-term conditions and still there is conflicting evidence about the effect of vitamin D on asthma risk factors, clinical course and management. (11, 12, 13,14, 15,). In this cross sectional descriptive study, we aimed to determine the frequency of vitD deficiency in asthma and also figure out the probable effects of vitD on clinical course of asthma and pulmonary functions tests.

MATERIAL AND METHODS

The institutional ethics committee approved the descriptive study (2012/42) and written informed consents were obtained from all of the participants.

STUDY POPULATION

112 asthmatic patients (regardless of asthma control status) and 94 control subjects admitted to Çukurova University Chest Diseases Department enrolled in the study. An informed consent form has been signed up by all participants and detailed sociodemographic data were recorded owing to self-report. Body mass index was calculated on the basis of height and weight measurements. 'Asthma' was diagnosed by a pulmonary specialist based on the clinical history, physical examination and pulmonary function test results. Asthma control test and severity charts examined by the same specialist.

PULMONARY FUNCTION TEST

PFTs were performed by using a calibrated Sensor Medics V-Max 20 Spirometer. None of the patients were receiving oral or inhaled short acting beta 2 agonists 8h before testing. Baseline forced expiratory volume in first second (FEV₁) and forced vital capacity (FVC) was measured 3 times and the best of three measurements was recorded. Total lung capacity was measured using the helium dilution technique (Jaeger MS-PFT Analyser Unit). The transfer factor of the lung for carbon monoxide (T_{LCO}) was measured using the single breath method. The results were presented as the percentages of predicted.

SKIN PRICK TEST

Skin prick test performed on the volar or inner aspect of the forearm avoiding the flexures and the wrist areas. The skin should be clean and free of lotions or creams. A drop of the allergen (extract) solution was placed by each code. A lancet with 1 mm point was used to prick the skin through the drop. A fresh lancet was used for each allergen. The solutions were blotted off the test site. The patient warned not to wipe down the arm to prevent cross contamination. Skin reactions assessed 10-15 minutes after allergen placement. Antihistamines was avoided 48 to 72 hours before the test. Other medication needed to be avoided for example, tricyclic antidepressants and phenothiazines that may lead to false negative results. A positive and negative control included in each series of tests. The negative control solution was the diluent used to preserve the allergen extract. Any reading 2 mm larger than the negative control will then be read as positive. The positive control solution, a 1 mg/ml histamine hydrochloride solution, was used. The reaction graded by measuring the wheal and flare or it was expressed as a percentage of the positive histamine control.

VITD MEASUREMENT

A single measurement of vitD was obtained on 206 subjects by a radioimmunoassay method using stored serum samples that had been frozen after centrifugation of venous blood samples. We categorized vitD levels as deficient(<20ng/ml), insufficient(20–30ng/ml), and sufficient(30ng/ml) (16).

STATISTICAL ANALYSIS

All analyses were performed using SPSS 18.0 statistical software package. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate. Chi-square test was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Kolmogorov-Smirnov test. For comparison of continuous variables between two groups, the Student's t-test was used. For comparison of more than two groups, Oneway ANOVA was used. To evaluate the correlations

between measurements, Pearson Correlation Coefficient was used. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

The asthmatic and control group were similar in sociodemographic, clinical and physiologic characteristics except body mass index and pulmonary function test results. (Table 1) Mean age of asthmatics was $43,7 \pm 14,2$ years.

9 (10.2%) of the participants with asthma had severe persistent, 40 (45,5 %) had moderate, 32(36,4%) had mild persistent and 7(8%) had intermittent asthma. 33(37,5 %) of asthma patients were under control whereas 15(17,0%) were poorly controlled due to asthma control test.

The mean serum vitD level of asthma patients was lower than control group, but this difference was not statistically significant ($25,19 \pm 12,01$, $27,09 \pm 12,9$ respectively $p=0,27$). Furthermore, the both groups were similar in frequencies of vitD deficiency, insufficiency and severe deficiency. (Table 2)

VitD deficiency was more frequent in females in asthma patients. vitD deficiency was similar in patients with either positive or negative skin prick test results. The demographic data of asthmatics according to vitD deficiency is shown in Table 3. Vitamin D deficiency was more frequent in females in asthmatic group ($p=0,24$); gender difference was statistically insignificant in control group ($p=0,24$). In asthmatics group, serum vitamin D level of females ($23,89 \pm 11,92$ ng/ml) was lower than males ($29,52 \pm 11,48$ ng/ml) ($p=0,03$). In control group the gender difference of serum vitamin D level was statistically insignificant ($p=0,24$).

Pulmonary functions of asthmatic patients with vitD deficiency were significantly lower than non-deficient group (Table 4). FEV₁ (L), FVC (L) of vitamin D deficient group was lower and it was statistically significant ($2,09/2,49$ $p=0,003$, $2,68/3,2$ $p=0,001$ respectively).

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In subgroup analysis, the prevalence of vitD deficiency was similar between asthma severity groups and furthermore it was alike between stable and exacerbated groups. (Table 5). Asthma control test points were similar, too.

DISCUSSION

Since several immunomodulator effects of vitD has been recognized recently, it has been linked to many respiratory diseases including viral and bacterial respiratory infections, asthma, COPD and cancer. Vitamin D deficiency has been linked to obesity, race, innercity settings; the epidemiology of vitamin D deficiency appears to correlate with many patterns that have been observed in asthma. (17). Several researchers have reported associations between vitD and asthma, but also some others have reported contrary relationship. And most of studies concerning vitD and asthma have focused on childhood group rather than adults. With the concern about these conflicting results in the causal relationship between vitD and asthma, we aimed to evaluate the effects of serum vitD level and vitD deficiency on the clinical course of asthma.

This study showed that the prevalence of vitD deficiency and the mean serum vitD level were similar in asthma patients and control group. VitD deficiency and the mean serum vitamin D level was similar among asthmatic patients regardless of asthma control status. Serum vitD levels of asthmatic females was significantly lower than males whereas gender difference was insignificant in control group. FEV₁ (L) and FVC (L) levels of vitD deficiency group were significantly low and serum vitD level was positively correlated with FEV₁ (L) and FVC (L) levels in both the asthmatic and the control group. In stable asthma group, mean serum vitD level of obese patients was lower than non-obese and body mass index and serum vitD levels were negatively correlated. These results confirmed that the serum vitD levels and vitD deficiency of asthmatics were not different

from control group, but significantly associated with female gender, poor lung function and obesity in asthma.

Nearly 78% of asthmatics and 71% of healthy subjects had vitD deficiency in cross-sectional vitD analysis. A large adult study conducted the prevalence of vitD deficiency as 82% at base in London (18). We found a slightly lower serum vitD level in asthmatic patients compared to control group, but it was statistically insignificant. The results of a large adult study of B.H.Thuesen et al. reported no statistically significant relation between serum vitD levels with atopy and doctor-diagnosed asthma, too. (19). Our study enrolled only adult asthmatic patients with a mean age of 43 and most of studies reporting a stronger relation about vitD and asthma focused on childhood group rather than adults. Epidemiological studies have shown that low serum vitD levels are associated with a higher risk of respiratory infections and bronchial hypersensitivity in children and there are studies investigating associations between childhood asthma, fetal lung and/or immune development, and maternal vitD intake (20) so the insignificant difference may be the result of the rarer atopic clinical course of asthma in adults. Longitudinal studies have also yielded contradicting results. Large prospective adult studies [21,19] showed no correlation between baseline serum 25(OH)D3 levels and asthma at the follow-up. By contrast, an inverse relationship was found between the vitamin D levels and asthma at older ages in children [22,23], implying that vitamin D may help shape the development of respiratory and immune systems. Tolppanen et al. [24], reported that serum 25(OH)D3 levels were positively associated with risk of wheezing, but not with asthma. On the other hand, the mean serum vitD level of asthmatics in our study was high and may be explained with our geographic characteristics as Adana city is at the southern part of northern hemisphere.

Our study determined a significant relation between vitD deficiency and FEV1(L) and FVC(L) measurements but not with FEV1/FVC ratio. Black and Scragg also discovered the positive correlation between vitD levels and lung function in 14091 adults in the Third National Health and Nutrition Examination Survey (NHANES III). (25). Basically, a rational approach can discuss about the amount of sun light exposure would be lesser in asthmatic group because of dyspnea; but the serum concentration of vitD was still strongly associated with FEV1 and FVC after adjustment for sun light exposure in NHANES III study.

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In both children and adult patients with asthma, serum 25(OH)D3 levels positively correlated with lung function according to many of the studies (26,27, 28,29,30, 4,31), but opposite results were also collected from some fewer reports. (32, 19).

The programming effect of vitamin D on the development of childhood allergic diseases and asthma has been assessed by a number of prospective birth cohort studies. The concentration of vitD assayed in neonatal cord serum or in maternal circulation during pregnancy commonly serves as a surrogate marker for the extent of prenatal exposure to vitamin D. The finding that lower vitamin D status in utero may not increase the risk of asthma in offspring has been demonstrated by studies in which the cord blood (2,33, 34) and the maternal 25(OH)D3 levels (35,36,). However, it is still challenging to fully understand the impact of vitamin D on asthma pathogenesis during early life and over growth.

In our adult asthmatic group, vitD deficiency was similar in asthma regardless of severity and control status. A number of asthma studies in adults demonstrated lower vitamin D levels are associated with worse asthma control (26), more asthma exacerbations, emergency department (ED) visits and hospitalizations (37, 38, 39, 27), whereas Devereux et al. (32) reported in a large case-control study that there was no relationship between asthma severity and serum vitD levels in adult patients asthma. Similarly, most of the available data are consistent in the beneficial role of vitamin D in disease severity and control in asthmatic children (40).

As vitD is fat soluble and it is readily taken up by fat cells, obesity is associated with vitamin D deficiency, and it is believed to be due to the sequestration of vitD by the large body fat pool (41). To our knowledge, no data was available about the association between vitD and obesity

in asthma, and our study showed that vitD deficiency was more common in obese asthmatics, and this linkage was not true for healthy group.

Our cross sectional single vitD measurement is not sufficient to state a causal relationship, but it is generally accepted that vitD effects remodelling, repair systems in all lung development periods (25) and vitD deficiency is linked to increased risk of respiratory infections and to a worse muscle strength. (42) . It would be better to have more than one serum vitD level as it may differ in repeated measurements over time but we enrolled all participants in summer period to eliminate the seasonal changes at least.

The enrollment of patients in a tertiary hospital, lacking evaluation of some factors affecting serum vitD level such as dietary intake, the amount of sun light exposure, physical activity and clothing habits, single vitD measurement and measurement of serum vitD levels with high pressure liquid chromatographic instead of radioimmunoassay are limitations of presented study.

In conclusion,our study do not indicate that serum vitD levels and vitD deficiency influence the clinical course of asthma in adult population. Serum vitD level and frequency of vitD deficiency were similar to normal population. Low serum vitD levels are associated with lower FEV1 and FVC levels. Thus,well-designed larger randomized controlled trials are needed to provide a definitive answer to the hypothesis that vitD could have a role in development, clinical course or treatment of some athma phenotypes.

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Table 1. Sociodemographic, clinical and physiologic characteristics of study population

	Asthmatic group n=112 n(%)	Control group n=94 n(%)	p
Gender			
Female	86(76,8)	62(66)	0,08
Male	26(23,2)	32(34)	
Age * (years)	43,7±14,2	45,1±10,4	0,41
Residential adress			
Bay	3(2,7)	3(3,2)	0,54
Town	1(0,9)	0(-)	
District	26(23,2)	16(17)	
City	82(73,2)	75(79,8)	
Economic status			
Low	39(34,8)	21(22,3)	0,05
High	73(65,2)	73(77,7)	
Smoking habitus			
Never smoked	75(67)	54(57,4)	0,056
Cessated	23(20,5)	16(17)	
Smoker	14(12,5)	24(25,5)	
Cigarette (package/year)*	5,42±11,28	7,36±11,85	0,23
Body mass index* (kg/m ²)	28,95±6,1	27,06±5,26	0,02
Body mass index groups (kg/m ²)			
<18.5	3(2,7)	4(4,3)	0,06
18,5-25	28(25)	33(35,1)	
25-30	33(29,5)	36(38,3)	
30-35	32(28,6)	15(16)	
35-40	11(9,8)	3(3,2)	
>40	5(4,5)	3(3,2)	
Body mass index (kg/m ²)			
≤30	64(57,1)	73(77,7)	0,002

>30	48(42,9)	21(22,3)	
FEV ₁ * (L)	2,33±0,78	2,81±0,69	<0,001
FEV ₁ * (% of predicted)	82,61±18,5	89,13±13,4	0,005
FVC* (L)	3,04±0,96	3,45±0,83	0,002
FVC* (% of predicted)	91,48±16,06	91,33±13	0,94
FEV ₁ /FVC ratio*	75,8±10,67	81,96±4,5	<0,001

*mean±SS

Table 2. VitD deficiency and mean serum vitD levels of study group

	Asthma group	Control group	p
	n=112 n(%)	n=94 n(%)	
VitD level* (ng/mL)	25,19±12,01	27,09±12,9	0,27
VitD level			
Normal (≥30 ng/ml)	35(31,2)	37(39,4)	0,217
VitD insufficiency (20-30 ng/ml)	32(28,6)	28(29,8)	0,210
VitD deficiency (≤20ng/ml)	45(40,2)	29(30,9)	0,165
Severe VitD deficiency (≤10 ng/ml)	10(8,9)	10(10,6)	0,680

*mean±SS

Table 3. The demographic data of asthmatics and control group according to vitamin D deficiency

	Asthmatics Group (n=112)			Control group (n=94)		
	Vitamin D Deficiency (≤ 20 nG/mL)			Vitamin D Deficiency (≤ 20 nG/mL)		
	(+) n=45 n(%)	(-) n=67 n(%)	p	(+) n=29 n(%)	(-) n=65 n(%)	p
Gender						
Male	6(23,1)	20(76,9)	0,042	7(21,9)	25(78,1)	0,24
Female	39(45,3)	47(54,7)		22(35,5)	40(64,5)	
Age (years)	45,89 \pm 15,83	42,16 \pm 12,81	0,17	44,28 \pm 9,04	45,45 \pm 10,9	0,61
Cigarette *(package/yea	2,53 \pm 6,93	7,36 \pm 13,13	0,02	6,83 \pm 10,24	7,59 \pm 12,56	0,774
Skin Prick Test						
(+)	20(43,5)	26(56,5)	0,552	7(26,9)	19(73,1)	0,61
(-)	25(37,9)	41(62,1)		22(32,4)	46(67,6)	

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Table 4. Pulmonary function tests of asthmatic patients

	Asthmatics group (n=112)		
	VitD Deficiency (≤ 20 ng/mL)		P
	(+)	(-)	
	n=45	n=67	
FEV ₁ * (L)	2,09 \pm 0,67	2,49 \pm 0,82	0,003
FEV ₁ * (% predicted)	82,09 \pm 18,15	82,97 \pm 18,86	0,808
FVC* (L)	2,68 \pm 0,72	3,28 \pm 1,02	0,001
FVC* (% predicted)	90,7 \pm 14,28	92,0 \pm 17,24	0,676
FEV ₁ /FVC*	75,57 \pm 10,13	75,96 \pm 11,08	0,852

Table 5. Asthma severity and asthma control status of asthmatic patients according to vitamin D deficiency

	Vitamin D Deficiency		p
	(+)	(-)	
	n=45 n(%)	n=67 n(%)	
Asthma severity			0,322
Intermittant	5(11,1)	2(3)	
Mild persistent	14(31,1)	21(31,3)	
Moderate persistent	19(42,2)	35(52,2)	
Severe persistent	7(15,6)	9(13,4)	
Stable asthmatic group n=88	n=36	n=52	
Asthma control status			0,807
Well controlled	14(38,9)	19(36,5)	
Partially controlled	15(41,7)	25(48,1)	
Uncontrolled	7(19,4)	8(15,4)	
Asthma control test point	19,5±4,75	19,8±4,4	0,762