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Study of serum vitamin D level in adult patients with bronchial asthma

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ABSTRACT

Background: Asthma represents one of the most common chronic diseases and is a major public health problem worldwide. The innate and adaptive immune systems play an important role in the pathogenesis of asthma (Global Initiative for Asthma: GINA Report, 2010). Vitamin D has several effects on the innate and adaptive immune systems that might be relevant in the primary prevention of asthma, in the protection against or reduction of asthma morbidity, and in the modulation of the severity of asthma exacerbations. Vitamin D insufficiency is increasingly recognized in the general population, and has been largely attributed to dietary, lifestyle and behavioral changes. While its musculoskeletal consequences are well established, a new hypothesis links asthma to subnormal vitamin D levels (Ginde et al., 2009).
Objective: Assessment of vitamin D status in patients with bronchial asthma and its relation to disease control and severity.
Patients and methods: This study included 90 subjects divided into two groups, First group included 70 adult asthmatic patients (39 females and 31 males) who attended Chest Diseases Department, AL-Azhar University Hospitals between September 2014 and August 2015, their ages ranged from 18 to 52 years with a mean age of (35.5 ± 8 y). The second group included 20 healthy adult (12 female and 8 male) as a control group, their ages ranged from 20 to 55 years with a mean age of (34.4 ± 6 y). All subjects in this study were submitted to full medical history and clinical examination, plain P-A chest X-ray, routine laboratory investigations, spirometry, calculation of body mass index (BMI) and detection of serum vitamin D level by ELISA (Euroimmun, Germany).
Results: The study showed that serum vitamin D level was significantly decreased in asthmatic patients (19.88 ± 9.6 ng/ml) as compared with the healthy control group (33.5 ± 6.1 ng/ml). Also serum vitamin D level was significantly decreased in uncontrolled asthmatic patients (10.5 ± 5.2 ng/ml) as compared with the controlled patients (20.5 ± 7.5 ng/ml).
Conclusion: There is an important association between adult bronchial asthma and vitamin D deficiency or even insufficiency. A strong correlation between the serum vitamin D level and asthma severity and control was found.

Introduction

Asthma represents one of the most common chronic diseases and is a major public health problem worldwide. The innate and adaptive immune systems play an important role in the pathogenesis of asthma. Many genes involved in inflammation and immunoregulation pathways have been associated with asthma. In the majority of patients control of asthma as defined by guidelines can be achieved with long-term maintenance medications. However, a substantial proportion of patients do not achieve optimal asthma control despite even high dose treatment. In particular inadequately controlled patients with severe persistent asthma are at high risk of severe exacerbations and asthma related mortality. These patients represent the greatest unmet medical need among the asthmatic population today [1].

Vitamin D insufficiency is increasingly recognized in the general population, and has been largely attributed to dietary, lifestyle and behavioral changes. While its musculoskeletal consequences are well established, a new hypothesis links asthma to subnormal vitamin D levels. The immune system is complex in nature with multiple redundant and interfering pathways. Recently, the vitamin D

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pathway has emerged as a new pathway contributing to the outcome of immune responses.

Vitamin D has several effects on the innate and adaptive immune systems that might be relevant in the primary prevention of asthma, in the protection against or reduction of asthma morbidity, and in the modulation of the severity of asthma exacerbations. Cross-sectional data indicate that low 25(OH) D levels in patients with mild to moderate asthma are correlated with poor asthma control, reduced lung function, reduced glucocorticoid response, more frequent exacerbations, and consequent increased steroid use.

An important question is what mechanism does vitamin D use to exert its biologic effects on airway inflammation, remodeling and hyperresponsiveness, and thereby asthma control. The answer to this question will invariably be complicated given the wide-ranging effects of vitamin D on airway epithelium, bronchial smooth muscle, and immune cells central to the pathogenesis of asthma [2].

Aim of the work

Assessment of vitamin D status in patients with bronchial asthma and its relation to disease control and severity.

Subjects and methods

This study included 90 subjects divided into two groups, First group included 70 adult asthmatic patients (39 females and 31 males) who attended Chest Diseases Department, AL-Azhar University Hospitals between September 2014 and August 2015, their ages ranged from 18 to 52 years with a mean age of (35.5 ± 8 y). The second group included 20 healthy adult (12 female and 8 male) as a control group, their ages ranged from 20 to 55 years with a mean age of (34.4 ± 6 y). According to severity of symptoms and FEV1% asthmatic patients group were divided into four subgroups:

Subgroup A: Intermittent asthma. (36 patients, 51.43%).
Subgroup B: Mild asthma. (8 patients, 11.43%).
Subgroup C: Moderate asthma. (12 patients, 17.14%).
Subgroup D: Severe asthma. (14 patients, 20%).

According to asthma control asthmatic patients were divided into:

Controlled (42 patients, 60%).
Partially controlled (15 patients, 21.43%).
Uncontrolled (13 patients, 18.57%).

Inclusion criteria

Asthma was diagnosed by history which include episodic respiratory symptoms and reversible airway obstruction (documentation of reversibility of FEV1 and/ or FVC by 12% or an increase of FEV1 by 200 cc either spontaneously or after inhalation of 400 μg salbutamol).

Classification of asthma severity based on symptoms and asthma therapy as recommended. Asthma control was assessed according to the criteria of the Global Initiative for Asthma to identify controlled, partially controlled, or uncontrolled asthma.

Exclusion criteria

Patients below 18 years, pregnant females, smokers, patients who had a co-morbid disease in addition to bronchial asthma that could affect serum vitamin D level were excluded. Also patients on nutritional support with potential effect on serum 25(OH) D levels were excluded.

All subjects after providing written informed consent were subjected to the following:

- Complete medical history.
- General and local chest examinations.
- Plain P-A chest X-ray.
- Routine laboratory investigations.
- Spirometry: performed for each subject (FVC, FEV_1, FEV1/FVC) using Geratherm Respiratory GmbH Blue Cherry V1.2.2.1 with a built-in computer. Each subject performed at least three spirometry maneuvers and the highest values were chosen. The test was repeated 20 min after inhalation of 4 puffs of salbutamol. Each puff contains 100 mcg salbutamol.
- Body mass index BMI was calculated from measured weight and height.
- Serum vitamin D level: Two milliliters of venous blood was obtained centrifuged; serum was separated and stored at −20 °C until time of assay. Serum levels of 25(OH) D were quantified by ELISA (Euroimmun, Germany) and categorized into sufficient (>25 ng/ml), insufficient (20–25 ng/ml) or deficient (<20 ng/ml).

Serum levels of 25-hydroxyvitamin D are considered the best circulating biomarker of vitamin D metabolic status and reflect contributions from all sources of vitamin D (i.e., diet and sun exposure).

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The following tests were done:

- Independent-samples *t*-test of significance was used when comparing between two means.
- A one-way analysis of variance (ANOVA) when comparing between more than two means.
- Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters.
- Pearson's correlation coefficient (r) test was used for correlating data.
- Receiver operating characteristic (ROC curve) analysis was used to find out the over all predictivity of parameter in and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value.
- Probability (P-value)
  - P-value $\leqslant$ 0.05 was considered significant.
  - P-value $\leqslant$ 0.001 was considered as highly significant.
  - P-value > 0.05 was considered insignificant.

Results

This study included 90 subjects divided into two groups; first group included 70 adult asthmatic patients and the second group included 20 healthy volunteers as a control group. The two groups were age and sex matched.

According to severity of symptoms and FEV1% asthmatic patients group were divided into four subgroups:

- Subgroup A: Intermittent asthma. (36 patients, 51.43%).
- Subgroup B: Mild asthma. (8 patients, 11.43%).
- Subgroup C: Moderate asthma. (12 patients, 17.14%).
- Subgroup D: Severe asthma. (14 patients, 20%).

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According to asthma control asthmatic patients are divided into:

- Controlled (42 patients, 60%).
- Partially controlled (15 patients, 21.43%).
- Uncontrolled (13 patients, 18.57%).

Table 1
Comparison of demographic data (age, sex and BMI) between control group and asthmatic patients group.

Character	Control group (No = 20)	Asthmatic patients group (No = 70)	x^2	P value
Age (years)	34.4 ± 6	35.5 ± 8	0.741	0.626
Male	8 (40%)	31 (44%)	0.096	0.932
Female	12 (60%)	39 (56%)		
BMI (kg/m^2)	29.5 ± 4.5	30.8 ± 5.1	1.601	0.398

This table shows that there was non-significant difference between the studied groups as regard age, sex and BMI.

Table 2
Comparison of serum vitamin D levels between control group and asthmatic patients group.

	Control group No = 20	Asthmatic patients group No = 70	*t*-test	P value
Serum Vit.D level (ng/ml)	33.5 ± 6.1	19.88 ± 9.6	6.995	<0.001 (HS)

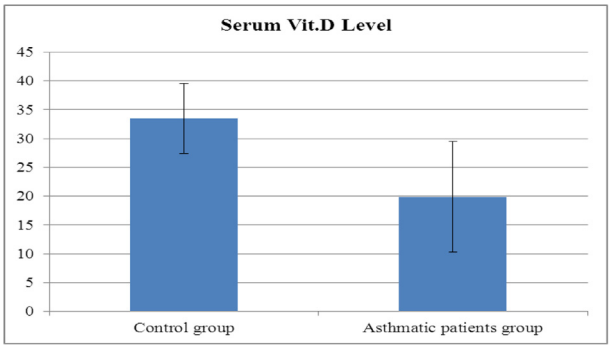

Figure 1. Serum vitamin D level in control group and asthmatic patients group.

Table 3
Comparison of serum vitamin D levels between different asthmatic patients subgroups.

Asthmatic patients	No.	Serum Vit.D level	ANOVA test	p-value
Intermittent asthma (Subgroup A)	36	18.1 ± 8.1	12.474	<0.001 (HS)
Mild asthma (Subgroup B)	8	14.3 ± 6.2		
Moderate asthma (Subgroup C)	12	9.5 ± 2.5		
Severe asthma (Subgroup D)	14	6 ± 2.9		

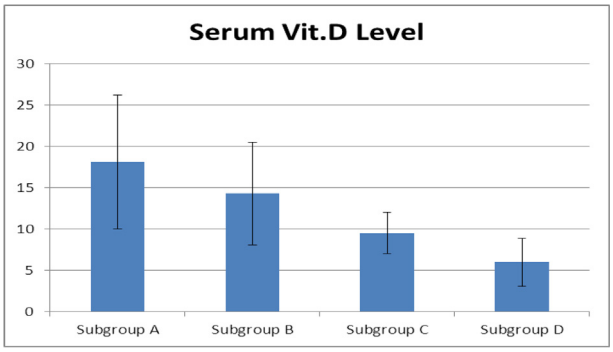

Figure 2. Serum vitamin D level in different asthmatic patients subgroups.

Table 4
Comparison of serum vitamin D levels among controlled, partially controlled and uncontrolled asthmatic patients.

Asthmatic patients	No.	Serum Vit.D level	ANOVA	p-value
Controlled	42	20.5 ± 7.5	9.830	<0.001 (HS)
Partially controlled	15	14.9 ± 5.6		
Uncontrolled	13	10.5 ± 5.2		

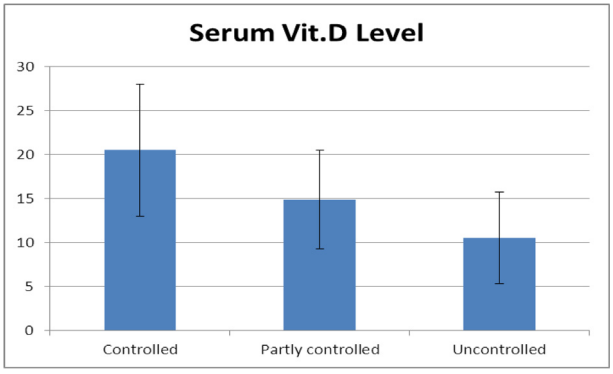

Figure 3. Serum vitamin D level in controlled, partially controlled and uncontrolled patients.

Table 5
Correlation between serum vitamin D levels, BMI and % of predicted FEV1 in asthmatic patients.

		Patients
BMI	*r*	−0.917
	P	<0.001 (HS)
FEV1(% of predicted)	*r*	0.954
	P	<0.001 (HS)

Table 6
Diagnostic performance of Vit.D in discrimination of patients and control.

Cut-off	Sen.	Spe.	PPV	NPV	Accuracy
⩽25	80%	85%	90.3%	70.8%	94.3%

Receiver operating characteristics (ROC) curve was used to define the best cut off value of Vit.D which was ⩽25, with sensitivity of 80% specificity of 85% positive predictive value of 90.3%, negative predictive value of 70.8% with diagnostic accuracy of 94.3%.

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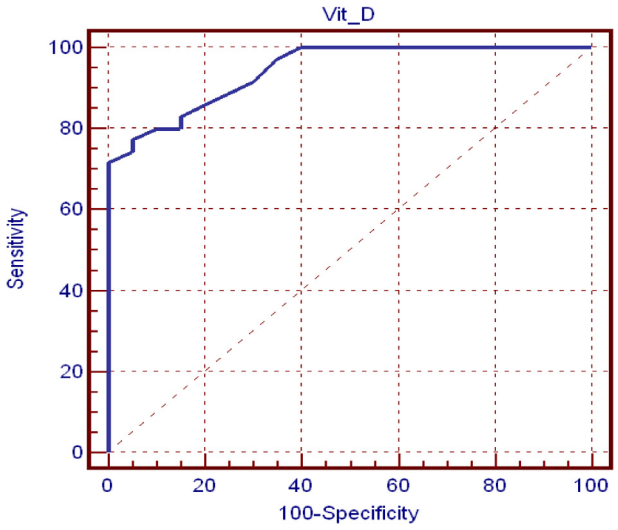

Figure 4. Receiver operating characteristics (ROC) curve.

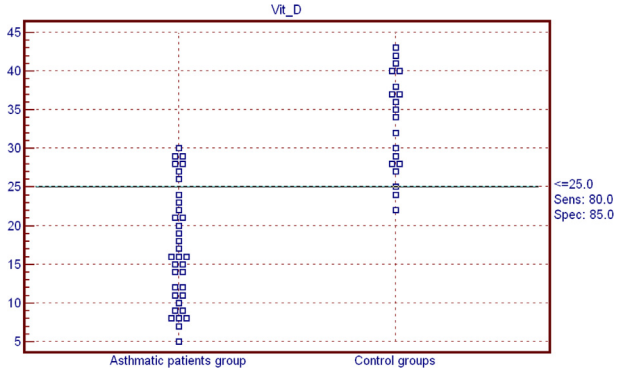

Figure 5. Diagnostic performance of Vit.D in discrimination of patients and control.

Table 7
Comparison between vitamin D states in asthmatic patients group and control group.

Serum Vit.D Level	Patients		Control	
	No.	%	No.	%
Low cut-off 25.0 (deficient)	59	84.29	2	10.00
Above cut-off 25.0 (sufficient)	11	15.71	18	90.00
Total	70	100.00	20	100.00
Chi-square test	x^2	35.978		
	p-value	<0.001 (HS)		

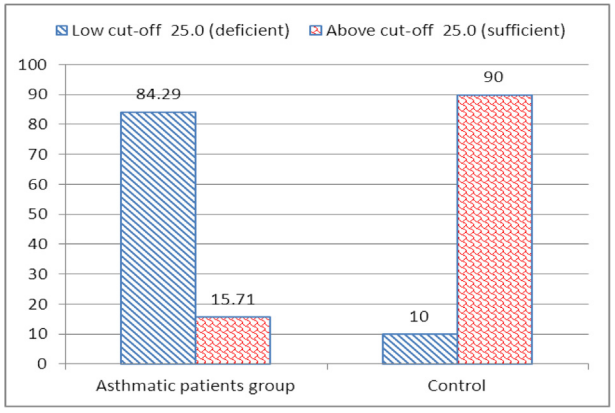

Figure 6. Comparison between vitamin D states in asthmatic patients group and control group.

Discussion

This study included 90 subjects divided into two groups; first group included 70 adult asthmatic patients and the second group included 20 healthy volunteers as a control group.

Regarding demographic data (age, sex and BMI) Table 1, there was non significant difference between asthmatic patients group and control group.

Study of serum vitamin D levels, Table 2, Fig. 1, revealed that there was highly significant difference between control group (33.5 ± 6.1 ng/ml) and asthmatic patients group (19.88 ± 9.6 ng/ml) with p value < 0.001.

This finding agrees with Brehm et al. [3] who found that 25% of asthmatic patients had serum vitamin D levels <25 ng/mL, and 3.4% had levels <20 ng/mL and found a strong inverse association between serum vitamin D levels and asthmatic state. Also a study in Canada involving people between the ages of 13–69 years found that those with vitamin D levels below 20 ng/mL (50 nmol/L) were 50% more likely to have asthma than those with levels between 20 and 30 ng/ml [4]. Also Laura Tamašauskienė et al. [5] in their study on 85 patients with asthma and 73 healthy persons to evaluate the serum vitamin D level in asthmatics with different phenotypes concluded that vitamin D level was lower in asthmatic patients than in healthy individuals.

A number of confounding factors may influence these relationships; one is that the subjects with asthma spend more time indoors, so they may be exposed to less sunlight.

On subdivision of asthmatic patients group according to severity of symptoms and FEV1% into different subgroups (intermittent, mild, moderate and severe asthma) serum vitamin D levels in these asthmatic patients subgroups were (18.1 ± 8.1, 14.3 ± 6.2, 9.5 ± 2.5 and 6 ± 2.9 ng/ml respectively) and statistical analysis showed that there was highly significant difference (p value < 0.001) in serum vitamin D levels among patients of different subgroups, Table 3, Fig. 2.

Also on classification of asthmatic patients group according to asthma control (controlled, partially controlled and uncontrolled asthma) serum vitamin D levels in these asthmatic patients subgroups were (20.5 ± 7.5,14.9 ± 5.6 and10.5 ± 5.2 ng/ml respectively) and statistical analysis showed that there was highly significant difference (p value < 0.001) in serum vitamin D levels among patients of different subgroups, Table 4, Fig. 3.

So, a strong negative correlation was found between serum vitamin D levels and asthma severity as well as asthma control, serum vitamin D was markedly decreased in patients with severe and uncontrolled asthma. This means that the higher the level of vitamin D, the lesser the degree of bronchial asthma severity and the better the control. This highly beneficial finding is in accordance with the work conducted by Litonjua and Weiss [6] that proved that low vitamin D levels were associated with worse bronchial asthma symptoms, more use of medications and poorer lung function measures.

Also this finding agrees with Stephanie Korn et al. [7] who studied serum vitamin D levels in 280 adults with asthma and found that, 25(OH) D concentrations in adult asthmatics were low and vitamin D insufficiency or deficiency was significantly related to asthma severity.

Martineau et al. [8] reported that people given vitamin D experienced fewer asthma attacks needing treatment with oral steroids and the average number of attacks per person per year went down from 0.44 to 0.28 with vitamin D (high-quality evidence). They concluded that vitamin D is likely to offer protection against severe asthma attacks. However, further trials are needed before definitive clinical recommendations can be made.

Similarly Felicia Montero-Arias et al. [9] studied serum vitamin D levels in 121 adults with asthma and noted that, in

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asthmatic patients with low vitamin D levels there was a significant association between vitamin D levels and the risk of severe asthma, the risk of hospitalization or visit to the emergency department due to asthma.

Also this study is in agreement with Liu et al. [10] who conducted a study on 435 adults with asthma and reported that, the concentration of 25(OH) D was low in asthmatic patients.

Also Shaaban and Hashem [11] investigated serum vitamin D levels in 75 adults with asthma and 75 adult healthy controls and demonstrated that, vitamin D deficiency was observed in 78.66% asthmatic patients whereas 85% of healthy control subjects expressed sufficient levels.

Vitamin D deficiency could be involved in asthma pathogenesis through several mechanisms. Vitamin D appears to have regulatory effects on every part of the immune system, with vitamin D deficiency being linked to an array of immunologically based diseases focusing on asthma.

Vitamin D receptors are present in the airways and are thought to inhibit proinflammatory cytokines, with effects on CD4+ T cells, interleukin-2, interferon-gamma, and macrophages. A deficiency of Vitamin D could be associated with an inability to switch off the inflammatory state, following an acute inhalational insult, with up regulation of prostaglandin, leukotrienes, macrophages, and T cell activity and recruitment [12].

Vitamin D also inhibits the formation of matrix metalloproteinase and fibroblast proliferation and influences collagen synthesis; these actions mean that 1,25-dihydroxyvitamin D may influence tissue remodeling and probably lung function. Vitamin D is potentially capable of overcoming the poor glucocorticoid responsiveness in severe asthmatics through the up regulation of interleukin-10 production (a potent anti-inflammatory cytokine) from CD4+ T cells. That is to say that vitamin D restores the capability of regulatory T cells from steroid-resistant patients with bronchial asthma to secrete interleukin-10 in response to steroids [13].

In this study inverse relationship was found between BMI and 25(OH) D levels, Table 5, Obesity has been demonstrated to increase asthma risk, and one of the most significant effects of obesity in asthma relates to its association with an impaired response to glucocorticosteroids. Higher vitamin D levels in adults with asthma are not only correlated with improved lung function and reduced bronchial hyperresponsiveness, but also with an improved in vitro response to glucocorticosteroids. The present findings suggest that reduced 25(OH) D levels in overweight and obese asthma patients may contribute to the reduced glucocorticosteroid response in this population.

A positive correlation was found between 25(OH) D levels and FEV1% of predicted in the studied asthmatic patients, Table 5, this finding agrees with that of Damera et al. [13] who reported that in patients with asthma, higher serum 25(OH) D concentrations were associated with higher FEV1% and explained this finding by that vitamin D inhibits the formation of matrix metalloproteinase as well as fibroblast proliferation and influences collagen synthesis; these actions mean that 1,25-dihydroxy vitamin D may influence tissue remodeling and probably lung function.

Also this study is in agreement with Black and Scragg [14] who reported that serum vitamin D was positively correlated with FEV1 and glucocorticoid response.

Also Searing et al. [15] reported that the serum vitamin D was positively correlated with lung function and enhanced glucocorticoid action in peripheral blood mononuclear cells.

Receiver operating characteristics (ROC) curve was used to define the best cut off value of Vit.D which was <25, with sensitivity of 80% specificity of 85% positive predictive value of 90.3%, negative predictive value of 70.8% with diagnostic accuracy of 94.3% Table 6, Figs. 4 and 5.

In this study about 85%(59 out of 70) of asthmatic subjects had serum vitamin D levels <25 ng/mL compared with 10% (2 out of 20) in the control group ($P < 0.05$) which was statistically significant Table 7, Fig. 6.

Conclusion

There is an important association between adult bronchial asthma and vitamin D deficiency or even insufficiency. A strong correlation between the serum vitamin D level and asthma severity and control was found

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