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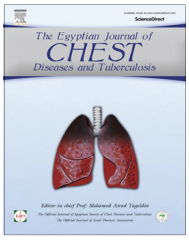

ORIGINAL ARTICLE

Vitamin D and markers of airway inflammation in asthma

Hala Mohamed Shalaby Samaha [a,*], **Amany Ragab Elsaid** [a], **Eman NasrEldin** [b]

[a] *Lecturer of Chest Diseases, Faculty of Medicine, Mansoura University, Egypt*
[b] *Lecturer of Clinical Pathology, Faculty of Medicine, Assiut University, Egypt*

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Abstract *Background:* Vitamin D plays a role in the pathogenesis of asthma as it has a potent immunomodulatory effect acting on the cells of innate immunity. In asthmatic children low vitamin D levels are associated with poor asthma control, reduced lung function, increased medication intake, and exacerbations. Little is known about vitamin D in adult asthma patients or its association with asthma control and inflammatory markers of asthma.

Objective: To establish the relationship between vitamin D serum levels, pulmonary function, asthma control, IgE level and exhaled FE_{No}.

Methods: This study comprised 55 subjects (15 healthy volunteers, 40 asthmatic patient) who underwent history taking, HRCT, pulmonary function test, FE_{NO}, total serum IGE level and serum $25(OH)D_3$ level.

Results: Vitamin D deficiency and insufficiency were observed in uncontrolled asthmatic patients. Patients with vitamin D deficiency and insufficiency had lower pulmonary function, higher serum IgE level, FE_{NO} and higher number of exacerbations in the last year. Total serum IgE level, FE_{NO}, and number of exacerbations showed a negative correlation with serum 25(OH) vitamin D. Serum 25(OH)vitamin D showed a significant positive correlation with pulmonary function in asthmatic patients.

Conclusion: The lower the vitamin D level deficiency or insufficiency, the more the asthma exacerbation, the less the asthma control, the higher the serum level of IgE and higher FE_{NO}. Also low vitamin D associated with airway remodeling is presented by small airway affection and HRCT findings.

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Vitamin D is a seco-steroid hormone important in bone mineralization and calcium homeostasis. Recently, research has found that vitamin D may play a role in multiple chronic diseases such as cancer, autoimmune diseases, infections, and cardiovascular disorders [1,2].

Abbreviations: FEV_1, forced expiratory volume; IgE, immunoglobulin E; HRCT, high resolution computed tomography; FE_{NO}, Fractional exhaled nitric oxide; 25(OH)D, 25-hydroxyvitamin D.

* Corresponding author.

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Vitamin D may also have a role in several diseases involving the respiratory system. Higher vitamin D concentrations, assessed by 25-hydroxyvitamin D [25(OH)D], have been associated with better lung function as measured by forced expiratory volume in 1 s (FEV_1) in a large cross-sectional study of the U.S. population in the NHANES III [3].

Asthma represents one of the most common chronic diseases and is a major public health problem worldwide. In the majority of patients control of asthma as defined by guidelines can be achieved with long-term maintenance medications [4]. 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. Vitamin D insufficiency is increasingly recognized in the general population, and has been largely attributed to dietary, lifestyle and behavioral changes [1,5]. While its musculoskeletal consequences are well established, a new hypothesis links asthma to subnormal vitamin D levels [6–8].

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 [9,10].

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 [11].

Therefore, the aim of this study was to prospectively investigate vitamin D insufficiency and deficiency in adult patients with asthma and its potential relationship with markers of asthma severity and control.

Methods

A cross-sectional case-control study conducted on 55 subjects "15 healthy volunteers, 40 recruited from out patient's clinic diagnosed as asthma". Asthmatic patients included 15 male and 25 female between October 2013 and September 2014, they were diagnosed as controlled, partially controlled and uncontrolled asthmatic patients.

Asthma control was categorized as controlled, partly controlled or uncontrolled in agreement with Global Initiative for Asthma (GINA) guidelines [12]. In particular, levels of asthma control were defined depending on the presence/absence of day time symptoms, limitations of activities, nocturnal symptoms/awakening, need for reliever/rescue treatment, and FEV_1 results.

Exclusion criteria

Smokers, patients using oral corticosteroid or receiving immunosuppressive drugs, patients with chronic liver disease, chronic renal failure, diabetic patient, abnormalities in thyroid or other endocrinal abnormalities, past history of tuberculosis or other connective tissue diseases, overt bone deformities and patient receiving calcium or vitamin D supplements.

All patients were subjected to a complete history taking (age, sex, occupational exposure, asthma duration, current asthma medication, number of acute attack/last year, family history of allergy, phenotypic manifestation) and physical examination. The following were done for each studied subject in the same day: – high resolution CT (HRCT), pulmonary function tests, Fractional exhaled nitric oxide (FE_{NO}).

Laboratory investigation: – Routine investigation included complete blood picture, serum creatinine, liver enzymes, alkaline phosphatase, serum calcium, phosphate. – Measurement of serum total immunoglobulin E (IgE) level, and vitamin D level.

HRCT of the chest: Determination of hyperinflation, mosaic perfusion, tree in bud or central dilation. HRCT of the chest was performed using a 64-row, multiple detector CT scanner (Philips Company, etherland).

Pulmonary function test

Spirometry (BTL-08 spiro, Germany) was performed to determine the lung function measurements and bronchodilator reversibility. Post-bronchodilator FEV_1/FVC% and FEV_1 were measured 15 min after inhalation of 400 μg salbutamol.

Fractional exhaled nitric oxide (FE_{NO}) was measured by the NIOX system (BEDFONT SCIENTIFIC limited 2009) by use of a single-breath on-line method according to European Respiratory Society/American Thoracic Society guidelines [13]. Briefly, the subject inhaled NO-free air to total lung capacity and exhaled through a dynamic flow restrictor with a target flow of 50 mL/s for 10 s. No nose clip was used. The NIOX system was calibrated according to the manufacturer's instructions. FE_{NO} (ppb) < 25 means airway inflammation unlikely, FE_{NO} (ppb) 26–49 mild airway inflammation, FE_{NO} (ppb) > 50 means significant airway inflammation.

Measurement of serum vitamin D level [measured as 25-hydroxy cholecalciferol, 25(OH)D] was made in all subjects, using chemiluminescent microparticle immunoassay "ARCHITECT i1000SR-Abbott diagnostics; Abbott Laboratories, USA". Normal level of vitamin D is defined as a 25-OH Vitamin D concentration greater than 30 ng/mL. Vitamin D insufficiency is defined as a 25-OH Vitamin D concentration of 20–30 ng/mL. Vitamin D deficiency is defined as a 25-OH Vitamin D level less than 20 ng/mL.

Serum level of Immunoglobulin E (total) was estimated using chemiluminescent microparticle immunoassay "ARCHITECT c4000 – Abbott diagnostics; Abbott Laboratories, USA" and expressed as IU/L. It was determined as elevation if serum T-IgE > 100 IU/L.

BMI is defined as body weight divided by the square of their height- with the value universally being given in units of kg/m^2.

Statistical analysis

All statistical analyses were performed using a statistical software package (Statistics Package for the Social Sciences, SPSS 16.0, data are expressed as the mean ± SD (standard deviation). Comparisons of continuous data among groups were performed by the ANOVA test (for normal distribution) or the Kruskal Wallis test (for abnormal distribution). Categorical variables between different groups were analyzed by the $\chi 2$ test. Spearman Correlations were used for

Table 1 Characteristics of patients with asthma and healthy subjects.

	GroupI $N = 15$ healthy	GroupII $N = 13$ Controlled	GroupIII $N = 12$ Partiallycontrolled	GroupIV $N = 15$ Uncontrolled	*P* value
Age	42 ± 10	38 ± 13	40 ± 12	41 ± 9	$P > 0.05$
Sex					
Male	9(60%)	4(31%)	4(33%)	7(47%)	$P > 0.05$
Female	6(40%)	9(69%)	8(67%)	8(53%)	
Family history					
Positive	0 (0%)	2 (15%)	4(33%)	9(60%)	$P < 0.01$
Negative	15(100%)	11(85%)	8(67%)	6 (40%)	
Other allergy					
Positive	0 (0%)	5 (38%)	6 (50%)	6 (40%)	$P < 0.01$
Negative	15(100%)	8 (62%)	6 (50%)	9 (60%)	
Vitamin D					
Sufficient	11(73%)	8 (62%)	3 (25%)	2 (13%)	$P < 0.001$
Insufficient	4 (27%)	5 (38%)	7 (58%)	7 (47%)	
Deficient	0 (0%)	0 (0%)	2 (17%)	6 (40%)	
HRCT					
Normal	15(100%)	10 (77%)	1(8%)	1 (7%)	$P < 0.001$
Hyperinflation	0 (0%)	2 (15%)	6 (50%)	6 (40%)	
Mosaic perfusion	0 (0%)	1 (8%)	1(8%)	3 (20%)	
Central dilation	0 (0%)	0 (0%)	2 (17%)	4 (26%)	
Tree inbud	0 (0%)	0(0%)	2 (17%)	1 (7%)	
NO of acute attack/last year	0	0 (0–3)	1 (0–4)	7 (3–15)	$P < 0.01$
FEV_1% of predicted	94 ± 1.7	92 ± 5.5	79 ± 6.7	48 ± 10.4	$P < 0.001$
FEV_1/FVC	92 ± 2.1	91 ± 5.1	80 ± 6.7	60 ± 13	$P < 0.001$
$FEF_{25-75\%}$	91 ± 3.9	76 ± 23	46 ± 16	30 ± 9.2	$P < 0.001$
IGE	25 (15–49)	52(20–100)	158(47–320)	298(59–500)	$P < 0.001$
FE_{NO}	11 ± 4.2	19 ± 4.2	29 ± 5.1	41 ± 6.1	$P < 0.001$
Duration of asthma	0	12 ± 3.4	14 ± 5.9	15 ± 4.7	$P > 0.05$
BMI	24 ± 4.8	25 ± 3.3	22 ± 3.3	24.8 ± 3.3	$P > 0.05$

correlation analysis. *P* values less than 0.05 were considered as statistically significant.

Results

A total of 55 subjects comprising 40 asthmatic patients (15 male and 25 female) and 15 control (GroupI) were enrolled in this study. The asthmatic patients were divided in 3 groups according to the GINA guideline, group II included 13 controlled asthmatic patients, group III included 12 partially controlled asthmatic patients and group IV included 15 uncontrolled asthmatic patients.

Table 1 showed there was no significant difference between studied groups as regards age, sex, duration of illness and BMI. There was a significant difference between studied groups as regards family history of allergy, other allergic manifestations and HRCT findings.

There was a highly significant difference between studied groups as regards $FEV_{1\%}$ and $FEF_{25-75\%}$ which was much lower in uncontrolled asthmatics.

Vitamin D deficiency and insufficiency were observed in uncontrolled asthmatic patients. IgE level and FE_{NO} were also higher in uncontrolled asthmatic patients.

In Table 2 asthmatic patients were divided into 3 groups according to serum level of 25(OH) vitamin D. Group A included 9 patients (22%) with deficient vitamin D, group B included 19 (48%) asthmatic patients with insufficient vitamin D and group C included 12 patients (30%) with sufficient serum level of vitamin D.

Patients with vitamin D deficiency and insufficiency had lower pulmonary function, higher serum IgE level, FE_{NO} and a higher number of exacerbations in the last year.

Tables 3 and 4 showed a significant positive correlation between serum 25(OH)vitamin D and pulmonary function in asthmatic patients. While serum total IgE level, $FE_{NO,}$ and number of exacerbations showed a negative correlation with serum 25(OH) vitamin D.

Discussion

Our study shows that there is a positive association between vitamin D levels and asthma control as defined by GINA parameters. It is tempting to speculate that this correlation is based on the effect that vitamin D has an immune function. In fact, a number of studies have established that vitamin D is a principal controller of innate immunity, with the production of antimicrobial peptides able to kill viruses, bacteria and fungi [14], and that it exerts an inhibitory effect on the inflammatory response to viral infections [15].

There was a positive relationship between vitamin D status (as reflected by serum 25(OH)D concentrations) and asthma control. Lower 25(OH)D levels are associated with worse lung function, higher levels of exhaled NO, higher serum IgE level, and more changes in HRCT.

Table 2 Characterstics of asthmatic patients according to serum vit-D level.

	Group A Deficient Vitamin D $N = 9$ (22%)	Group B Insufficient Vitamin D $N = 19$ (48%)	GroupC Sufficient Vitamin D $N = 12$ (30%)	P value
Age	35 ± 8.1	43 ± 9.4	35 ± 9.2	$P > 0.05$
Sex				
Male	2 (22%)	9 (47%)	4 (33%)	$P > 0.05$
Female	7 (78%)	10 (53%)	8 (67%)	
Family history				
Positive	3 (33%)	11 (58%)	1 (8%)	$P < 0.05$
Negative	6 (67%)	8 (42%)	11 (82%)	
Other allergy				
Positive	2 (22%)	10 (53%)	5 (42%)	$P > 0.05$
Negative	7 (78%)	9 (47%)	7 (58%)	
BMI	25 ± 1.9	24 ± 3.3	23 ± 3.4	$P > 0.05$
No of acute attack/last year	6 (0–10)	8 (0–15)	2 (0–3)	$P < 0.05$
Duration of asthma	13.3 ± 5.4	16.4 ± 7.3	9.9 ± 4.2	$P < 0.05$
HRCT				
Normal	1 (11%)	5 (26%)	6 (50%)	$P > 0.05$
Hyperinflation	4 (45%)	6 (32%)	4 (33%)	
Mosaic perfusion	1 (11%)	2 (10.5%)	2 (17%)	
Central dilation	2 (22%)	4 (21%)	0 (0%)	
Tree inbud	1 (11%)	2 (10.5%)	0 (0%)	
FEV_1% of predicted	56 ± 18.1	70 ± 21.2	86 ± 10.9	$P < 0.001$
FEV_1/FVC	60 ± 14.4	78.5 ± 15.4	85 ± 9.7	$P < 0.001$
$FEF_{25-75\%}$	40 ± 12	41 ± 19	71 ± 26	$P < 0.001$
IGE	158 (56–500)	168 (47–320)	56 (20–85)	$P < 0.001$
FE_{NO}	47 ± 1.5	29 ± 1.9	19 ± 3.6	$P < 0.001$

Table 3 Correlation coefficients between 25(OH) Vitamin D serum level to clinical and radiological investigated data in asthmatic patients.

	Age	Sex	Duration of asthma	No of acute attack/last year	Family history of allergy	Other types of allergy	BMI	HRCT
R	0.005	0.2	−0.43	−0.53	−0.03	−0.1	0.17	−0.49
P	$P > 0.05$	$P > 0.05$	$P < 0.001$	$P < 0.001$	$P < 0.01$	$P > 0.05$	$P > 0.05$	$P < 0.001$

Table 4 Correlation coefficients between 25(OH) Vitamin D serum level to pulmonary function and laboratory investigated data in asthmatic patients.

	FEV_1%	FEV_1/FVC	$FEF_{25-75\%}$	FE_{NO}	IgE
R	0.54	0.49	0.54	−0.70	−0.65
P	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$

This study is in agreement with that of Eman et al. [16] and Abd ElAety et al. [17] who noted that; there was a positive correlation between 25(OH)D levels and FEV_1%.

The frequency of vitamin D insufficiency was highest in patients with uncontrolled asthma: The findings of the present study confirm and extend in adult patients with various degrees of asthma control in the previous reports in which vitamin D status is associated with asthma severity and control in children [18,19].

There was a strong association between serum level of vitamin D and asthma duration and the number of acute attacks, these findings are in agreement with recent studies showing that insufficient vitamin D status is associated with an increase in the risk of asthma exacerbations in patients of the Childhood Asthma Management Program (CAMP) cohort [20] and with augmented airway responsiveness and increased risk of asthma hospitalization in children with asthma living in Costa Rica [21].

Airway epithelia contain high levels of the enzyme that converts circulating 25-OH-vitamin D3 to its active form, 1,25-OH-vitamin D3. The active form of vitamin D has local effects in response to respiratory infections and might dampen the inflammation that is the consequence of these infections [22]. Reduced vitamin D levels are associated with increased expression of TNF-alpha, suggesting that enhanced expression of this pro-inflammatory cytokine is a potential pathway by which reduced vitamin D levels could exert pro-inflammatory effects in asthma [23,24].

A study with bronchial biopsies demonstrated an inverse association of vitamin D levels and airway smooth muscle mass [18]. In vitro vitamin D influenced airway smooth muscle remodeling by exerting an inhibitory effect on passively sensitized airway smooth muscle growth and contractility [25].

Our study showed patients with uncontrolled asthma have features suggestive of airway remodeling like CT changes, airflow limitation and small airway affection.

Fe_{NO} and serum level of IgE are mirrors of allergic eosinophilic inflammation which reflect allergen exposure and multiple sensitization.

In our study there is strong negative correlation between Fe_{NO} and serum level of IgE and vitamin D status (as reflected by serum 25(OH)D concentrations). Also asthmatic patients with vitamin D deficiency or insufficiency had higher readings of Fe_{NO} and serum level of IgE.

This could be explained that vitamin D had a role in inflammation and allergic reaction. Further, recent data suggest that vitamin D interacts with glucocorticoid signaling pathways in ways that are clinically relevant, and that vitamin D may potentially improve glucocorticoid responsiveness in severe asthmatics by up-regulation of IL-10 production from CD4+ cells [26].

Further studies are needed to investigate the association between vitamin D concentration with asthma control " is this is a consequence of life style, dietary changes or medication" and its relation to asthma mortality. Large follow up studies are needed to study the effect of vitamin D supplementation on airway remodeling and lung function.

Conclusion

The lower levels of vitamin D were associated with reduced asthma control, the more reduced lung function, more exposure to asthma exacerbation, more liability to airway remodeling, and more allergic reactions.

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