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The relationship of Vitamin D in Egyptian Asthmatics

Nadia El-Said[1]*, Nagwa R Abdel Wadoud[2], Nagwa Abd El-Ghaffar Mohamed[3], Hanaa Gamil[4], Aly Saad Rafea[5], and Fifi Helmy[1].

[1]Internal Medicine, AlMataria Teaching Hospital, Egypt.
[2]Clinical Pathology Departments, AlMataria Teaching Hospital, AlMataria Teaching Hospital, Egypt.
[3]Clinical and Chemical Pathology Department, National Research Centre, AlMataria Teaching Hospital, Egypt.
[4]Chest Departments, AlMataria Teaching Hospital, Egypt. , Egypt.
[5]Pediatric Departments, AlMataria Teaching Hospital

ABSTRACT

This study was done to assess the relationship between the serum level of vitamin D and the clinical, functional severity, and atopic markers. Serum 25-hydroxyvitamin D, IgE, and pulmonary function tests were evaluated in thirty asthmatic children, and thirty asthmatic adult patients. Thirty healthy children and adults were conducted as control groups. There were a highly significant decrease in mean serum vitamin D and a highly significant increase in mean serum IgE in comparison with control group in both adult and pediatric patients.There were a negative correlation between vitamin D level and IgE level among adult and pediatric patients with severe asthma and among pediatric patients with moderate asthma. Therefore, changes in 25-hydroxy vitamin D level could be a predictor marker for asthma. Also, our study highlight the concept that the occurrence and the degree of severity of asthma is more related to vitamin D insufficiency among children and more related to vitamin D deficiency in adult in consequences' vitamin D supply to asthmatic children up to adult age might prevent or ameliorate the incidence and severity of asthma. Further studies are recommended to clarify the role of 25-hydroxy vitamin D and asthma severity, exacerbation, treatment and control.

Keywords: Vitamin D, asthma, pulmonary function tests, IgE.

Corresponding author

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INTRODUCTION

Vitamin D is a hormone with multiple physiological actions, many effects of which have been found to occur outside its classical role in calcium homeostasis as its complex effects on pulmonary cell biology and immunity with impact on inflammation and host defense (1).Vitamin D receptors (VDRs) are expressed in many cell types including various immune cells, suggesting the role of vitamin D on immune system hence the increased interest in vitamin D status and its link to several non-skeletal diseases .(2)

Asthma is a chronic respiratory disease characterized by heightened airway inflammation, airway hyper- responsiveness and airflow obstruction in response to specific triggers. Asthma are associated with a numerous aberrant immune responses, for example, T-helper cell type-2 cytokines, such as interleukin IL-4, IL-5, and IL-13, are up regulated in the asthmatic airway and are associated with increased eosinophilia, mast cell degranulation and increased levels of immunoglobulin E (IgE). Impairment of immunogenic tolerance, along with complex interactions between cells and inflammatory mediators, promoting airway injury in a process commonly referred to as airway "remodeling" (3)

Airway epithelial cells have been found to express high levels of 1α-hydroxylase, which converting 25-hydroxyvitamin D to its active form, leading to the increased production of both cathelicidin and the Toll-like receptor co receptor CD14. Vitamin D also enhances the differentiation and recruitment of macrophages, which may lead to an increased ability to fight infection .(4)

A connection between vitamin D status and asthma has been considered since many years and vitamin D deficiency has been blamed as one cause of increased asthma prevalence (5)

AIM OF THE STUDY:

The aim of this study was to assess the relationship between the serum level of 25-hydroxyvitamin D as a major circulating form of vitamin D and the clinical, functional severity, and atopic marker (total IgE) among Egyptian asthmatics

SUBJECTS AND METHODS:

Sixty consecutive subjects who have bronchial asthma will be selected from Chest, Pediatric and Internal medicine Departments Al Mataria Teaching Hospitals. An informed consent was obtained from each subject participating in the study and approval of the ethical committee was also obtained.

Subjects will be divided into:

Group A**:** thirty patients with bronchial asthma and their ages ranged from 20 to 45 years old.
Group B**:** thirty patients with bronchial asthma and their ages ranged from 6 to 12 years old.
Group C**:** thirty apparently healthy adults with matched age and sex as a control group.
Group D: thirty apparently healthy children with matched age and sex as a control group.

All subjects will be submitted for:

- Thorough clinical history including smoking and occupational histories;
- Full general and local clinical examination.
- Radiographical investigations: Plain chest x ray poster-anterior and lateral views;
- Routine laboratory tests including: CBC, ESR, liver functions (ALT, AST, S. bilirubin, albumin & alkaline phosphatase), renal functions (blood urea and creatinine);
- Serum 25-hydroxy vitamin D, serum calcium (total and ionized), and serum phosphorus
- Serum total IgE concentration.
- Ventilatory function tests of the lung.

Inclusion Criteria

- The patient's ages ranged from 6 to 45 years;
- Patients will be non-smokers or ex-smokers for at least 6 months.

Exclusion Criteria

- Patients who have cardiac, hepatic or renal diseases;
- Smokers;
- Patients who received corticosteroid therapy either orally or by inhalation;
- Obesity (Body mass index > 25 Kg/m^2).
- ntIake of dietary supplements containing calcium or vitamin D

According to asthma severity, they were subdivided into mild to moderate and severe (6). Three ml of venous blood samples were collected from each subject participating in the study and were left to clot then the serum was separated by centrifugation at 3000 xg for 10 minutes and stored at -20°C for determination of serum calcium, phosphorous, 25-hydroxy vitamin D and IgE. The determination of serum calcium and serum phosphorous were carried out on Dimension RxL Max analyzer (Siemens Healthcare GmbH - Henkestr. 127, 91052 Erlangen, Germany) by colorimetric techniques. Vitamin D (25-hydroxy vitamin D) was determined using Electro-chemiluminescence binding assay (ECLIA) performed on Cobas e411 immunoassay analyzer (Roche Diagnostics GmbH, D-68289 Mannheim, Germany) vitamin D deficiency should be defined as vitamin D (25-OH) of ≤ 20 ng/ml. Vitamin D insufficiency is recognized as 21-29 ng/ml. The preferred level for vitamin D is recommended to be ≥ 30 ng/ml (7). Total IgE was analyzed using chemiluminescent immunoassays on IMMULITE 2000 (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA) (8).

Statistical Analysis

IBM-SPSS version 20 (Fayetteville, Arkansas, USA) was used for statistical analysis of the data on a personal computer. Normally distributed data were presented as the mean ± SD. The correlation between variables was determined using the Pearson correlation coefficient (*r*). A *P*-value below 0.01 was considered to be significant and a *P*-value below 0.001 was considered to be highly significant

RESULTS

A total of 60 asthmatic patients ,30 children aged between 6 and 13 years (8.28 ±2.02 years) and 30 adults aged between 20 and 45 years (33.14 ± 7.62 years) were studied.

Among the adult group, out of 30 patients, 14 patients had mild to moderate asthma,4 of them had insufficient vitamin D level(28.6%), 10 were with deficient vitamin D level(71.4%), 10 of them had low serum Ca level(71.4%), all had normal serum Ph level , and all had high serum Ig E level . Sixteen of adult patients had severe asthma ,10 out of them had deficient vitamin D level(62.5%), 6 of them had insufficient vitamin D level(37.5%),10 of them had normal serum ca level (62.5%), all have normal serum ph level ,all had high levels of Ig E. All control adult group had normal serum Ca, serum ph, and IgE levels.

Among the pediatric group, 14 patients are with mild to moderate asthma ,12 of them are with insufficient vitamin D(85.7%) , 2 are with deficient vitamin D (14.7%), 12 patients have normal serum Ca level &only 2 have low serum Ca level, while 10 patients have normal serum ph level, only 4 patients have low serum ph level. All of them had high serum IgE level. 16 pediatric patients were with severe asthma , 14 had insufficient or low vitamin D level(87.5%), 2 of them had deficient or very low vitamin D level(12.5%), 12 patients had normal serum Ca ,4 had low serum Ca level, all of them had high levels of IgE. All control pediatric group had normal serum Ca, serum ph, and IgE levels.

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Table (1): Different Laboratory findings among adult subjects (Mean ±SD)

Group / Parameters	Mild-moderate patients (N=14)	Sever patients (N=16)	Control group(N30)	All patients (N=30)	p
Vitamin D(ng/ml)	21.51±3.82	20.61±4.72	37.69±5.19	21.06±4.27	P^a:0.000 P^b:0.000 P^c:0.000 P^d:1.000
IgE (IU/ml)	406.06±91.85	753.76±150.68	16.85±1.73	390.1±100.15	P^a:0.000 P^b:0.000 P^c:0.000 P^d:0.000
Calcium (mg/dl)	7.8±0.34	9.96±4.36	8.97±0.57	8.88±2.35	P^a:1.000 P^b:1.000 P^c:1.000 P^d:0.231
Phosphorus(mg/dl)	3.07±0.33	3.86±0.60	3.75±0.75	3.47±0.47	P^a:0.653 P^b:1.000 P^c:1.000 P^d:0.551

P^a: mild-moderate group vs. control group.
P^b: severe group vs. control group
P^c: asthmatic group vs. control group
P^d: mild-moderate vs. sever adult group.
P>0.05: non-significant. P<0.05: significant P<0.05: significant N=total number

Table 1 revealed a highly significant decrease in mean serum vitamin D and a highly significant increase in mean serum IgE in comparison with control adult group, but no significant difference between different patient groups as regard mean serum vitamin D and a highly significant difference between different patient groups as regard mean serum IgE. There were no significant difference between different groups in mean serum Ca and mean serum ph among adult groups.

Table (2): Different Laboratory findings among pediatric subjects (Mean ±SD)

Group / Parameters	Mild-moderate patients (N=14)	Sever patients (N=16)	Control group (N=30)	All patients (N=30)	p
Vitamin D(ng/ml)	23.04±2.89	23.03±4.95	8.92±0.70	8.24±0.79	P^a:0.000 P^b:0.000 P^c:0.000 P^d:1.000
IgE (IU/ml)	379.67±114.39	756.79±134.95	11.89±1.11	568.23±124.67	P^a:0.000 P^b:0.000 P^c:0.000 P^d:0.000
Calcium (mg/dl)	8.64±0.76	7.84±0.81	8.92±0.70	8.24±0.79	P^a:1.000 P^b:1.000 P^c:1.000 P^d:1.000
Phosphorus(mg/dl)	3.71±0.82	5.09±0.32	5.37±0.91	4.4±0.57	P^a:0.000 P^b:1.000 P^c:0.05 P^d:0.00

P^a: Mild-moderate group vs. control group. P^b: severe group vs. control group.
P^c: asthmatic group vs. control group. P^d: mild-moderate vs. sever adult group.
P>0.05: non-significant. P<0.05: significant P<0.001: highly significant N=total number.

Table 2 revealed a highly significant decrease in mean serum vitamin D and a highly significant increase in mean serum IgE in patient groups compared with control pediatric group. There were no significant difference between different patient groups as regard mean serum vitamin D and a highly significant difference between patients with mild-moderate &severe asthma as regard mean serum IgE. As regard mean serum Ca among pediatric groups revealed no significant difference between different groups. There was a

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highly significant decrease in mean serum ph in patients group with mild-moderate asthma when compared with control group, and a highly significant difference between different groups of patients. There were a significant decrease in all patients group when compared with control group but no significant difference between patient group with severe asthma and control group (Table 2)

Table (3): Different laboratory findings among asthmatic patients (Mean ±SD)

Group / Parameters	Mild-moderate adult patients (N=14)	Sever adult patients (N=16)	Mild-moderate pediatric patients (N=14)	Sever pediatric patients (N=16)	P
Vitamin D(ng/ml)	21.51±3.82	20.61±4.72	23.04±2.89	23.03±4.95	P^a:1.000 P^b:1.000 P^c:1.000 P^d:1.000
IgE (IU/ml)	406.06±91.85	753.76±150.68	379.67±114.39	756.79±134.95	P^a:1.000 P^b:1.000 P^c:0.000 P^d:0.000
Calcium (mg/dl)	7.80±0.34	9.96±4.36	8.64±0.76	7.84±0.81	P^a:1.000 P^b:0.207 P^c:1.000 P^d:1.000
Phosphorus(mg/dl)	3.07±0.33	3.86±0.60	3.71±0.82	5.09±0.32	P^a:1.000 P^b:0.017 P^c:0.000 P^d:1.000

P^a: Mild-moderate adult group vs. Mild –moderate pediatric group.
P^b: severe adult group vs. sever pediatric group.
P^c: Mild –moderate adult group vs. sever pediatric group.
P^d: mild-moderate pediatric vs sever adult group.
P>0.05: non-significant. P<0.05: significant. P<0.001: highly significant. N; total number

Table 3 showed no significant difference in mean serum vitamin D among asthmatic patients. There were highly significant decreases in mean serum IgE in mild-moderate adult group when compared with sever pediatric group and between mild–moderate pediatric group when compared with sever adult. There was no significant difference between different patient groups as regard groups mean serum Ca. There was highly significant decrease in mea serum ph in mild-moderate adult group when compared with severe pediatric group.

Table (4): Correlation between serum vitamin D, serum IgE in different groups

Group / Variable	Sever adult group	Mild –moderate pediatric group	Sever pediatric group
Pearson correlation	-0.916	-0.858	-0.797
Significance (two-tailed)	.001	.013	.018

P is significant at ≤ 0.05 level.

Correlation study revealed that there were a negative correlation between mean serum vitamin D level and mean serum IgE level among adult group with severe asthma(r = -0.916), a negative correlation between mean serum vitamin D level and mean serum IgE level among pediatric group with severe asthma(r =-0.797), and with moderate asthma (r=-0.858) (Table 4).

DISCUSSION

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, new hypothesis links asthma to subnormal vitamin D levels (9). Vitamin D has several effects on the innate and adaptive immune systems (10). Vitamin D also plays an important role in immune regulation

through interactions between 1, 25-dihydroxyvitamin D and VDRs. VDRs are expressed on a variety of airway immune cells, where they function as classic nuclear steroid hormone receptors and ultimately regulate the transcription of numerous genes associated with inflammation and immunomodulation.(11) Vitamin D also plays an important role in respiratory infection by facilitating Toll-like receptor signaling through increased synthesis of human cathelicidin antimicrobial peptide which is cleaved to generate the active cationic peptide, LL-37. While vitamin D can suppress IL-17 and IL-4-mediated expression of IL-13, (12) it can also shift the Th1/Th2 balance toward Th2 dominance (13). These contradictory actions may be due to the direct actions of vitamin D on $CD4^+$ T cells to promote an IL-10-secreting T-regulatory population (14).

Our study involved 30 asthmatic adult, 10 cases were vitamin D insufficient or low (30.3%), 20 cases were vitamin D deficient or very low (66.6%). It also involved 30 asthmatic children, 26 cases were vitamin D insufficient (86.7%), 4 cases were vitamin D deficient (13.3%,),and no one had normal vitamin D level .

A statistically significant relationship was found between asthma severity(in both adult and pediatric groups) and vitamin D sufficiency status: 50% of the adult patients with vitamin D levels below 20 ng/ml (or very low level or deficient) and 60% of the adult patients with vitamin D levels between 20 and 30 ng/ml(or low level or insufficient) had severe asthma in comparison with 0% of the patients with vitamin D sufficiency ,while study done by Montero et al (15), among Costa Rica children who found a 91.4% of the patients with vitamin D levels below 20 ng/ml and 74.0% of the patients with vitamin D levels between 20 and 30 ng/ml had severe asthma in comparison with 50% of the patients with vitamin D sufficiency . Also study done by Li et al (16), where they found that Chinese adults with asthma had vitamin D deficiency was highly prevalent (approximately 90%) and this discrepancy may be attributed to behavioral variables. Furthermore, inherited factors may explain why some populations living at the same latitude but with a distinct genetic background exhibit different vitamin D levels, for example, as a consequence of genetic polymorphisms involved in cholesterol synthesis, hydroxylation, and vitamin D transport (17)

In our study most of adult with moderate or severe asthma were vitamin D deficient while most of children with moderate or severe asthma were vitamin D insufficient this means that the occurrence &the degree of severity of asthma is more related to vitamin D insufficiency among children and more related to vitamin D deficiency in adult.

Comparative study between different asthmatics (either adult or pediatric groups) regarding mean serum vitamin D, revealed a highly significant difference between either moderate or severe asthmatics &control group but no significant difference between moderate and sever asthmatic groups. Korn et al (18) found that there is an inverse relationship between 25 hydroxy vitamin D and asthma severity and a positive relationship between 25 hydroxy vitamin D and both lung function and asthma control.

Elevated serum total IgE is a risk factor for asthma independently of the allergen-specific IgE (19). In our study, mean serum IgE levels were higher in asthmatic groups either adult or children or either patients with severe or moderate asthma. In a British birth cohort, a significantly nonlinear relationship between serum vitamin D and total IgE was observed (20). Although in study done by Li et al (16), they did not observe a significant association between serum 25 hydroxy vitamin D and total IgE.

Comparative study of mean serum IgE level revealed a highly significant difference between moderate or severe group &control group. A highly difference between moderate and severe groups in either adult and pediatric asthmatics. But comparative study between adult patients and pediatric patients revealed no significant difference.

In our study, there were a negative correlation between mean serum vitamin D level and mean serum IgE level among adult group with severe asthma, a negative correlation between vitamin D level and serum IgE level among pediatric group with severe asthma and with moderate asthma with no significant correlation with other parameters. This is in agreement with the findings of Brehm et al (21), in Costa Rica who found that 25- hydroxy vitamin D insufficiency was associated with increased total IgE concentrations, airway hyper responsiveness, and increased symptoms and exacerbations. Similarly, in Italian studies, asthma control, lung function, and airway hyper responsiveness were positively correlated with serum levels of 25- hydroxy vitamin D (22).

Searing et al (23), also noted lower lung function, increased corticosteroid requirements, and increased aeroallergen sensitization in children as a function of decreased 25-hydroxy vitamin D concentrations.

Also the main finding of study done by Montero-Arias et al (15), was the significant association between vitamin D levels, the risk of severe asthma, and the risk of hospitalization or visit to the emergency department due to asthma. These findings are consistent with prior evidence that children with low vitamin D levels have increased asthma severity, more exacerbations, and a concomitant need for escalating pharmacologic intervention (21).

Regarding serum Ca level, there were no significant difference between the different groups of asthmatic patients confirming the influence of vitamin D on the incidence of asthma irrespective of its role on controlling serum ca level.

Regarding serum phosphorus among the pediatric group there were a highly significant difference between asthmatics with moderate severity and control group, and between asthmatics with moderate severity and severe asthmatics, but not between severe asthmatics and control group.

There was a study done by Alamoudi and his colleagues (24), revealed that hypophosphatemia to be one of the most common electrolytes disturbances in patients with chronic, stable asthma and the underlying cause is unclear. Among adult patients there was no significant difference between different groups. Also, there were a highly significant difference between adults with moderate asthma and severely asthmatic pediatrics. Significant difference between adult and pediatric patients with severe asthma this may means the need for further study about the role of serum ph in asthma incidence and severity.

CONCLUSION AND RECOMMENDATION

The present study revealed that serum vitamin D level was significantly decreased in all asthmatic adult and children as compared with the healthy control groups. Our study showed that the asthmatic children and adult had a highly significant increase in asthma markers such as the serum IgE (as a marker of atopy) as compared with healthy control groups. Significant negative correlations were found between the serum vitamin D level the serum IgE level in asthmatic groups. In our study most of adult patients were vitamin D deficient while most of children patients were vitamin D insufficient this means that the occurrence and the degree of severity of asthma is more related to vitamin D insufficiency among children &more related to vitamin D deficiency in adult. So, continuous vitamin D supply to asthmatic children up to adult age may prevent or ameliorate the incidence and severity of asthma. Serum Ca level was not related to the incidence or severity of asthma confirming the influence of vitamin D on asthma severity irrespective of its role on controlling serum Ca level. Serum ph level sometimes related to asthma severity but further studies will be needed. We suggest further clinical trials to determine whether supplementation with vitamin D can reduce or modify asthma severity, associated exacerbation and its pharmacological interaction including their requirement for inhaled steroid, in adults and children. Further studies will be needed about phosphorus or other electrolytes disturbances in relation to asthma incidence or severity.

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