Research Article

Serum Levels of Vitamin D in Children with Bronchial Asthma

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Abstract

Background: the role of micronutrient deficiencies in the etiology of asthma has gained considerable attention in recent years. There is mounting evidence that vitamin D confers a protective effect against asthma risk and severity; however, evidence for an important relationship remains controversial. **Aim:** this study was designed tomeasure vitamin D level in asthmatic patients and to detect if there is a relation between vitamin D deficiency and bronchial asthma. **Patients and methods:** this case control cross-sectional study was conducted on ٦٠ asthmatic patients from outpatient clinics of the Departments of Pediatrics and Chest diseases in El-Minia University Hospitals. Twenty healthy children of matched age and sex were recruited as the control group.According to asthma severity and control patients were classified into mild, moderate or severe persistent asthma and controlled, partially controlled or uncontrolled asthma based on GINA guidelines.Patients and controls were subjected to measurement of serum vitamin D, serum total IgE and Prebronchodilator pulmonary function tests. Asthmatic Patients were subjected tochest X-ray, pre and postbronchodilator pulmonary function tests. **Results:** serum vitamin D levels were found to be significantly decreased in asthmatic children compared with the control group (P< ٠.٠٠٠١). Eighty percent of asthmatic cases were vitamin D defective. Twenty cases were vitamin D deficient (<٢٠ ng/ml), whereas another ٢٨ were vitamin D insufficient (≥ ٢٠ ng/ml to <٣٠ ng/ml). The asthmatic children had a significant increase in the total leukocytic count, eosinophilic count, total immunoglobulin E, and serum alkaline phosphatase. Prebronchodilator pulmonary function tests were significantly decreased in the asthmatic cases compared with the control. Significant negative correlation was found between serum vitamin D levels and the postbronchodilator % predicted forced expiratory volume in one second. A highly significant negative correlation was found between serum vitamin D levels and eosinophilic count and total immunoglobulin E. As the asthma severity increased, vitamin D levels decreased. There was a significant difference between the vitamin D levels in asthmatic children and asthma severity (p < ٠.٠٠١). As vitamin D levels decreased the frequency of controlled asthma cases decreased (p = <٠.٠٠٠١). Asthma severity and control were classified according to the Global Initiative for Asthma (GINA) classification. Vitamin D deficiency was the strongest predictor of asthma (stronger than familial history of asthma or serum IgE levels). **Conclusion:** children with asthma and low vitamin D levels had reduced pulmonary functions, frequent asthma exacerbations, leading to more emergency department visits and more use of health services owing to more hospitalizations. Difficulty in asthma control was observed in asthmatic children with low vitamin D levels. We found a relationship between serum vitamin D levels and asthma; however, this relationship could be influenced by multiple factors such as BMI, seasonal variation, residency, social, cultural, behavioral factors, and eating habits.

Keywords: bronchial asthma, children, pulmonary function tests, vitamin D.

Introduction

Asthma is a highly prevalent chronic respiratory disease affecting ٣٠٠ million people world-wide[١]. The burden of this disease to governments, health care systems, families, and patients is increasing worldwide. The rate of asthma increases as communities adopt western lifestyles and become urbanized. With the projected increase in the proportion of the world's urban population from ٥٥٪ to ٦٩٪ in ٢٠١٥, there will likely be a marked increase in the number of asthmatics worldwide over the next decade. It is estimated that there may be an additional ١٠٠ million persons with asthma by ٢٠٢٥ [٢]**.** Asthma is by far the commonest of all chronic diseases of childhood and estimates from developed countries suggest that it affects between ١١ and ٢٠٪ of all school age children [٣]**.** The prevalence of asthma among Egyptian children aged ٣ - ١٥ years was estimated to be ٨.٢٪. Of major concern is the annual increase in mortality [٤]**.** It is estimated that asthma accounts for about one in every ٢٥٠ deaths worldwide. Many of the deaths are preventable, being due to suboptimal long-term medical care and delay in obtaining help during acute exacerbation.The role of micronutrient deficiencies in the etiology of asthma has gained considerable attention in recent years [٥]. There is mounting evidence that vitamin D confers a protective effect against asthma risk and severity; however, evidence for an important relationship remains controversial [٦].

Patients and methods

This study was conducted on ٨٠ children from outpatient clinics of the Departments of Pediatrics and Chest diseases in El-Minia University Hospitals during the period from January ٢٠١٢ to July ٢٠١٣. The study populations were classified into ٤ groups, their ages ranged between ٦ and ١٨ years.

Group I: included ٢٠ patients suffering from mild persistent asthma.

Group II: included ٢٠ patients suffering from moderate persistent asthma.

Group III: included ٢٠ patients suffering from severe persistent asthma.

Group IV: Included ٢٠ healthy age and sex matched controls.

According to asthma severityand control patients were classified into mild, moderate or severe persistent asthma and controlled, partially controlled or uncontrolled asthma based on GINA guidelines.[٧]

Twenty healthy controls without a history of any allergic disorders in the child or first-degree relatives were also examined. Non-asthmatic controls comprised children with no respiratory disease whose parents had consented for a blood test during an elective surgical procedure. Participants who had a history of consumption of any supplements of vitamin D or drugs that modulate serum vitamin D levels, such as systemic glucocorticoids and anticonvulsants, and those who had chronic pulmonary diseases were excluded.

Patients and controls were subjected to: thorough history taking, complete physical examination, complete blood count, serum calcium, phosphorus, alkaline phosphatase, serum total IgE was analyzed by the Beckman Access ٢ immunoassay analyzer were measured by the Phadia-Immunocap ٢٥٠ analyzer[٨], measurement of vitamin D [measured as ٢٥-hydroxy cholecalciferol, ٢٥(OH) D] by ELISA technique, and Prebronchodilator pulmonary function tests. **Patients with bronchial asthma were subjected to** chest X-ray and pre and postbronchodilator pulmonary function tests.

Pulmonary Function Testing:

Spirometry was conducted using interactive computerized incentive spirometry (Vitalo-graph Pneumotrac, Spirotrac IV software). At least ٣ spirometric-manoeuvres were performed, with at least ٢ reproducible manoeuvres required for each test. The best forced vital capacity (FVC) and forced expired volume in ١ second (FEV١) of the ٣ manoeuvres was selected for data analysis. All spirometry results were compared to appro-priate recent reference ranges. Bronchodilator response (BDR) was assessed by repeating spirometry ١٥ minutes after the administration of nebulized salbutamol ٠.٥ ml plus ٢ ml normal saline via nebulizer. Percentage increases in FEV١, FVC were recorded [٩].

Statistical analysis:
Data were statistically analyzed using Student's t-test, one way ANOVA, and chi-square (linear by linear correlation) tests, as applicable (with a preset probability of P <٠.٠٥). Results are presented as arithmetic mean ± SD. Statistical tests were conducted using the SPSS software package, version ١٦ (SPSS Inc., Chicago, IL, USA) on a personal computer. Additionally, using simple, multiple, and logistic regression analysis, the simultaneous effects of confounding variables such as, age, sex, vitamin D levels, and body mass index (BMI) on the asthmatic state were measured.

Results:

Table (١) showed highly significant differences between children with bronchial asthma and control subjects regarding serum vitamin D levels, eosinophil count, total IgE% predicted FEV١ and FEV١/FVC ratio% (P-value <٠.٠٠٠١ for all) and also it showed significant differences regarding serum calcium, serum phosphorus, alkaline phosphatase, total leukocytic count and % predicted FVC.

Table (٢) shows prevalence of vitamin D deficiency in asthmatic children and control group. Moderate vitamin D deficiency was found in ٤٦.٦٦٪ of asthmatics and ٢٠٪ of controls, while ٢٠٪ of asthmatics had severe deficiency compared to ١٥٪ of controls. In asthmatic children, there was positive family history of asthma (P= ٠.٠٠٤). There were no significant difference between patients and controls regarding age and residence but there was significant difference between them regarding BMI (P=٠.٠٢).

Table (٣) shows predictors for development of asthma in studied patients using multivariate logistic regression analysis. Deficiency in vitamin D level (OR ٤.٨١; ٩٥٪ CI ٢.٣٩–٨.٥٨; p < ٠.٠٠١) was the major predictor of asthma in studied patients. Familial history of asthma and elevated serum IgE are both strong predictors (p <٠.٠٠١ and p = ٠.٠٠٣, respectively) of the disease. Elevated child's BMI (p = ٠.٠٠٤) and parental consanguinity (p = ٠.٠٠٥) were considered as other contributing risk factors.

Figure (١): shows distribution of serum levels of vitamin D in asthmatic children who were classified according to the GINA guidelines of asthma severity. It was ٢٤.٥٦±٧.٠٥, ١٨.٤٢±١٠.١٢, and ١١.١٣±٥.٩٤ in mild, moderate, and severe persistent asthma respectively. As the asthma severity increased, the vitamin D levels decreased. There was a significant difference between the vitamin D levels in asthmatic children and asthma severity (p < ٠.٠٠١).

Figure (٢): shows the distribution of serum levels of vitamin D in asthmatic children classified according to the GINA guidelines of asthma control. It was ٢٦.٢٨±١٠.٥٧, ١٧.٣١±٩.٢٥, and ١٤.٠٤±٧.٥٤ in controlled, partially controlled, and uncontrolled asthmatic patients. As the vitamin D level decreased the frequency of controlled asthma cases decreased (p = <٠.٠٠٠١).

Figure (٣): shows positive correlation between serum vitamin D levels (ng/mL) and prebronchodilator % predicted FEV١ (L).

Figure (٤): shows negative correlation between serum vitamin D levels (ng/mL) and postbronchodilator % predicted FEV١ (L).

Table (١). Baseline serum laboratory parameters and pulmonary function tests among asthmatic and control children

Laboratory parameter	Asthmatics (N=٦٠)	Controls (N=٢٠)	P-value
Serum vitamin D ng/ml	٢٢.٣١±٨.٦٣	٣١.٦٥+١٠.٨٤	٠.٠٠٠١*
Calcium, mmol/l	٩.٣٤±١.٠٨	٩.٨٩±٠.٧٨	٠.٠٣*
Phosphorus, mmol/l	٤.٤٥±٠.٩١	٥.٣٧±٢.٤٦	٠.٠١*
Alkaline phosphatase, U/l	٤٧٥.٢١±٢٤٦.١٩	٣٤٤.٩٢±١٠٩.٧١	٠.٠٢*
Total leucocytic countX١٠٠٠/mcl	٧.٤+٢.٤	٦.٢±١.٩	٠.٠٤*
Eosinophil count, cells/mm٣	٤٠٩.١±١٣٧.٣	١٦١±٥٢.٥	٠.٠٠٠١*
Total IgE, IU/ml	٧٠.٦±٣٦.٤	١٧.٤±٩.٣	٠.٠٠٠١*
Prebronchodilator lung function			
FEV١, L	٧١.١٨ ± ١٥.٢٤	٩٦.٢٣ ± ١٠.٤٥	٠.٠٠٠١*
% Predicted FVC, L	٩١.١٧ ± ١٢.٠٨	٩٧.١٠ ± ١٠.٠٨	٠.٠٤*
% Predicted FEV١/FVC ratio%	٧٢.٢٧ ± ١١.٢٨	٩٦.٢٢ ± ٨.٢٣	٠.٠٠٠١*

**Significant.* *IgE: Immunoglobulin*
FEV ١: Forced expiratory volume ١in one second *FVC: Forced vital capacity*

Table (٢): Prevalence of vitamin D deficiency and assessment of different Covariates among asthmatic patients and controls.

Covariate	Asthmatic patients	Controls	P-value
Vitamin D status			
Moderate vitamin D deficiency (N&%)	(٢٨) ٤٦.٦٦٪	(٤) ٢٠٪	٠.١
Severe Vitamin D deficiency (N&%)	(١٢) ٢٠٪	(٣) ١٥٪	٠.٠٥١
Positive family history of asthma [N (%)]	٣٦ (٦٠)	٤ (٢٠)	٠.٠٠٤
Age in years	٩.٧٨±٢.٦٨	٩.٦٥±٢.١٥	٠.٨٤
Residence [N (%)]			
Rural	٣٨	١١	٠.٦٩
Urban	٢٢	٩	
BMI (Kg/m٢)	١٨.٢٦±٣.٠١	٢٠.٠٢±٢.٩	٠.٠٢*

**Significant* *BMI: Body mass index*

Table (٣): Predictors of asthma in the studied children using multivariate logistic regression analysis.

Independent variable	OR	CI ٩٥٪	P value
Family history of asthma	٢.٣٥	١.٢٩-٤.٢١	٠.٠٠١*
Parental consanguinity	١.٧٤	١.١٣-٢.٥٩	٠.٠٠٥*
BMI (Kg/m٢)	١.٥٢	١.١٢-٢.١١	٠.٠٠٤*
Vitamin D deficiency	٤.٨١	٢.٣٩-٨.٥٨	٠.٠٠١*
Serum IgE level	١.٨٦	١.٢٢-٢.٨٢	٠.٠٠٣*

*Significant OR: Odds ratio,
CI: Confidence interval BMI: Body mass index.

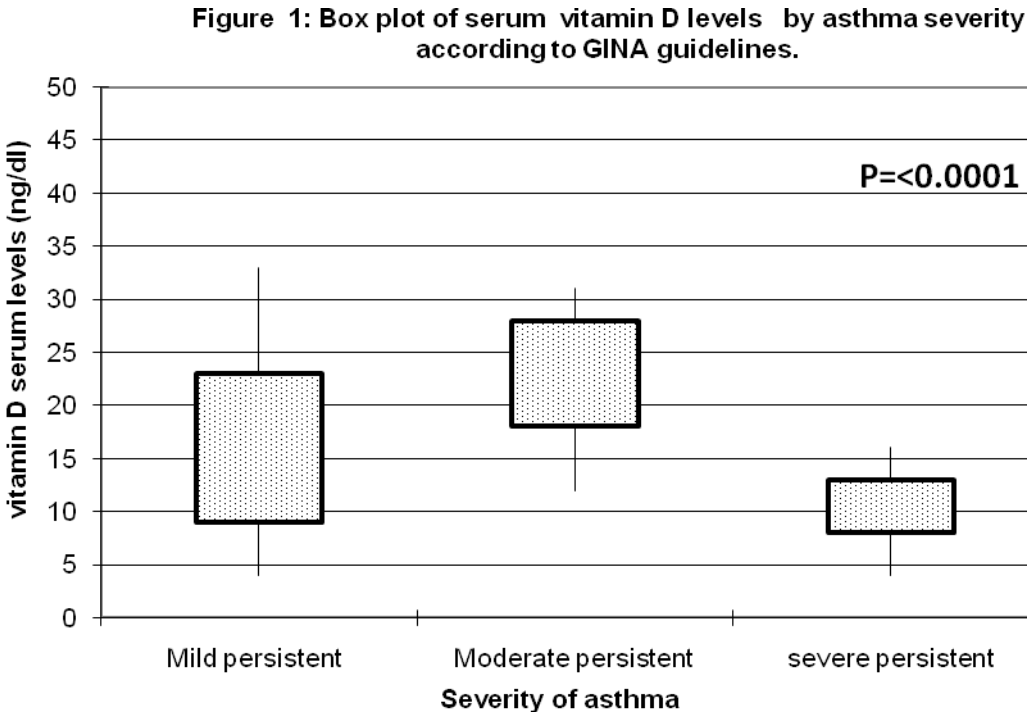


Figure ٢: Box plot of serum vitamin D levels by asthma control according to GINA guidelines

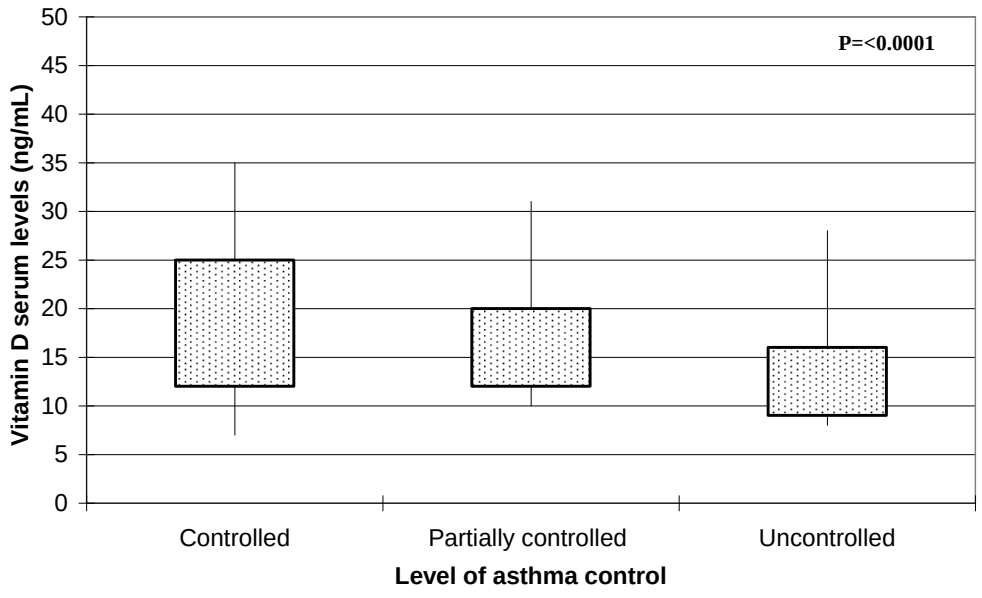


Figure (٣) shows positive correlation between serum levels of vitamin D and prebronchodilator % predicted FEV١ (r =٠.٤١, P= ٠.٠٠١).

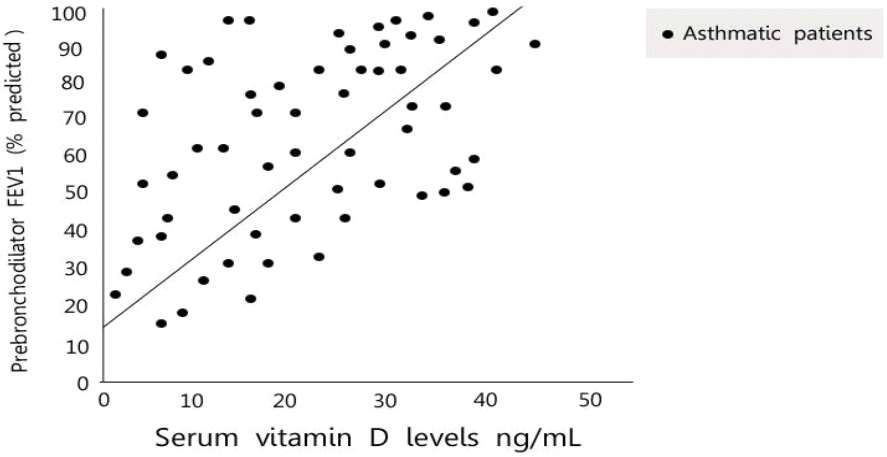
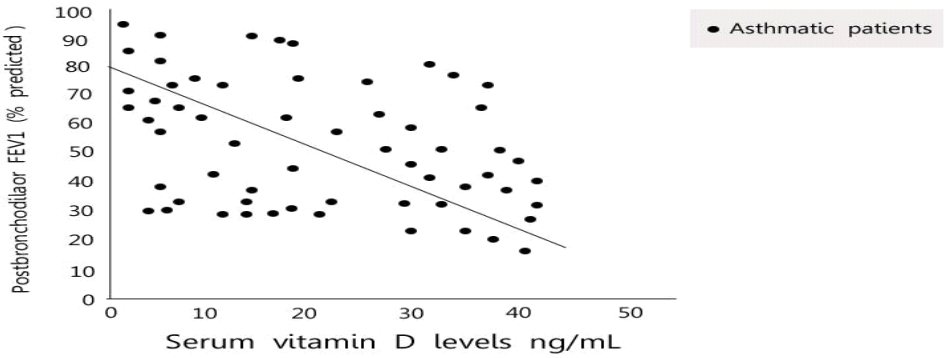


Figure (٤) shows negative correlation between serum levels of vitamin D and postbronchodilator % predicted FEV١ (r =-٠.٤١, P= ٠.٠٠١).



Discussion

We sought to study serum vitamin D levels in asthmatic children to determine the association with asthma prevalence, pulmonary functions and biomarkers for asthma. This study conducted on ٦٠ asthmatic children and ٢٠ control subjects.

The present study revealed that serum vitamin D levels were significantly decreased in all asthmatic children compared to the healthy control group. Although our study performed in Minia Governorate in Upper Egypt which is a sunny area, ٨٠٪ of asthmatic cases were vitamin D defective. These results are in agreement with Elnady et al., and Brehm et al.,[١٠,١١] who explained the cause of vitamin D deficiency by the fact that it does not naturally occur in most foods that humans eat plus the primary sources of this vitamin are natural production in the skin secondary to sun exposure, and secondarily from fortified foods and supplements [١٢].

Although cutaneous production due to ultraviolet radiation is considered the most important source of vitamin D, self-reported sun exposure alone is not a reliable marker of vitamin D sufficiency. In fact, vitamin D deficiency has been documented in healthy subjects despite reports of abundant solar exposure in our population in Minia Governorate as well as in other areas like Honolulu, Hawaii (latitude ٢١٨N)[١٣], Beirut, Lebanon (latitude ٣٣٨N)[١٤], and Australia (latitude ٢٧–٤٣٨S)[١٥]. This is likely due to a combination of behavioral factors (e.g., increased prosperity and adoption of a Western lifestyle, sunscreen use, increased time spent indoors, and clothing coverage) and intrinsic factors such as skin melanin content, decreased cutaneous production of vitamin D, or increased cutaneous destruction of vitamin D. Also the present study is in agreement with Alyasin et al.,[١٦],Checkley et al.,[١٧], Freishtat et al.,[١٨], Awasthi and Vikram[١٩], Uysalol et al.,[٢٠], Kunisaki KM et al.,[٢١] and Gupta et al.,[٢٢]. In contrast to the results of the present study Ozaydin et al.,[٢٣] and Menon et al.,[٢٤], did not detect any significant difference in vitamin D levels in asthmatic patients compared to control group. They explained this contradiction to other studies via a number of limitations in the interpretation of their results. The first shortcoming is the cross-sectional design of the study which makes it difficult to establish causality. Another factor to take into consideration in interpreting their results is the accuracy of documentation of patients' disease state. Devereux et al.,[٢٥], Goleva et al.,[٢٦] and Gergen et al.,[٢٧] found no significant association between serum levels of vitamin D and bronchial asthma. This is against our results.

In this study, which was conducted based on the categorization of vitamin D levels, levels are classified as sufficient (≥ ٣٠ ng/ml), insufficient (≥٢٠ and <٣٠ ng/mL) and deficient (< ٢٠ ng/ml); and these accounted for ٢٠٪, ٤٦.٦٧٪, and ٣٣.٣٣٪ of asthmatic children respectively. Studies conducted in Italy on children with a mean age close to those we studied[٢٨], and in the Middle East[٢٩] showed similar results, whereas the percentages found in a study in Iran were totally different (٨٤٪ sufficient, ١٢٪ insufficient and ٤٪ deficient)[١٦].

Our study classified the level of asthma control based on the GINA guidelines[٧]. There were significant differences in serum vitamin D levels between the levels of asthma control, which is consistent with the results of Gupta et al.,[٢٢] Elnady et al.,[١٠] and Uysalol et al.,[٢٠] who reported that children with uncontrolledwere found to have lower vitamin D levels than those with partially controlled or controlled asthma [٢٠]. Chinellato et al.,[٢٨], investigated the correlation of serum vitamin D levels and asthma control and found a positive correlation between vitamin D levels and the control of asthma symptoms. Krobtrakulchai et al.,[٣٠] and Devereux et al.,[٢٥] reported that there were no signify-cant differences in serum vitamin D levels between the levels of asthma control. This is against our results and may be explained by the lower prevalence of vitamin D deficiency (١٩٪) /insufficiency (٤٤.٨٪) in their studied patients. Another possible explanation for no association of vitamin D statuses with the levels of asthma control may be that this is a cross-sectional study and long-term follow-up studies focusing on changes in vitamin D status and asthma parameters will be needed to clarify the effect of vitamin D status on asthma. Furthermore, many confounding factors can affect vitamin D levels or asthma control. The association between serum vitamin D and asthma control may depend on the genotype or phenotype of asthmatic patient. Awasthi and Vikram,[١٩] found that mean level of serum Vitamin D in controlled cases of bronchial asthma was similar to the control group. However, mean serum vitamin D level of partly controlled and uncontrolled cases of bronchial asthma were significantly lower when compared to controls. Similar findings have been reported by Gupta et al.,[٢٢], who did their study in ٨٦ asthmatic children in London, United Kingdom.

The present study classified asthma severity based on the GINA guidelines[٧], we found a strong inverse relationship between serum levels of vitamin D and asthma severity. This is in agreement with Brehm et al.,[٢١]

who explained this association by the fact that higher vitamin D levels reflect a higher intake of dietary vitamin D, which may be correlated with the intake of other nutrients that may modify asthma severity, such as vitamin E. Higher vitamin D intake may also be related to socioeconomic status (SES). Vitamin D insufficiency was significantly associated with increased risk of severe asthma exacerbations in Puerto Rican and North American children (٣١)which are consistent with our results. Uysalol et al.,(٢٠), Freishtat et al.,[١٨], Alyasin et al.,[١٦] Gupta et al.,[٢٢], and Chinellato et al.,[٢٨], reported that asthma severity increased with vitamin D deficiency. The previous reports are in agreement with our results. Litonjua et al.,[٣٢] proved that low vitamin D levels were associated with worse bronchial asthma symptoms and severity. Menon et al.,[٢٤], found no relationship between serum vitamin D concentrations and steps of asthma severity. This result was different from ours. Their stratification of asthma severity was based on controller medications and their dosages as outlined by the NHLBI's guidelines[٣٣], whereas our study categorized severity based on the GINA guidelines[٧]. Gergen et al.,[٢٧], reported that there is a lack of a relation between serum ٢٥-hydroxyvitamin D concentrations and asthma in adolescents. In their study serum vitamin D concen-trations were not consistently related to multiple measures of asthma severity, including the frequency of asthma exacerbations, the severity of symptoms and the amount of asthma therapy required to achieve control. This also is against our results.

Our study revealed a significant decrease in pulmonary function tests (pre and postbronchodilator FEV١, FVC, and FEV١/ FVC ratio) in asthmatic children. Significant positive correlations were found between the serum vitamin D level and the percent predicted pulmonary function tests in asthmatics (prebronchodilatorFEV١, FVC, and FEV١/FVC ratio). Significant negative correlations were found between the serum vitamin D level and the percent predicted pulmonary function tests in asthmatics (postbronchodilator FEV١, FVC, and FEV١/FVC ratio). These findings suggest the involvement of vitamin D in lung function and the development of airflow limitation. Vitamin D influences tissue remodeling and collagen synthesis by inhibiting expression of matrix metalloproteinase-٩ (MMP-٩) and "a disintegrin and metalloproteinase ٣٣" (ADAM-٣٣) gene. In vitro studies have also shown that Vitamin D has direct anti-proliferative effect on human airway smooth muscle cells. These actions mean that vitamin D may influence tissue remodeling and probably lung function[٣٤]. Sutherland et al.,[٣٥] and Black and Scragg[٣٦], reported that serum vitamin D was positively correlated with FEV١ and glucocorticoid response as vitamin D insufficiency or deficiency was associated with airway hyper-responsiveness. Gupta et al.,[٢٢], detected a positive correlation between serum vitamin D levels and percent predicted FEV١ and FVC. Serum vitamin D levels significantly and inversely correlated with percent BDR and, in a post hoc analysis, BDR (FEV١ improvement of at least ١٢٪). Awasthi and Vikram[١٩], detected a positive correlation between serum vitamin D levels and percent predicted FEV١. Similar results were found by Alyasin et al.,[١٦], from Shiraz, Iran and Searing et al.,[٣٧] from Denver, USA. Alyasin et al.,[١٦], performed a linear association analysis of serum vitamin D levels and measures of lung function which revealed that the direct associations with predicted FEV١ and also with FEV١/FVC ratio were statistically significant. All the previous reports are in agreement with our results. However, Maalmi et al.,[٣٨] from Tunis, Tunisia, Brehm et al.,[١١], Krobtrakulchai et al.,[٣٠], Gergen et al.,[٢٧] and Litonjua et al.,[٣٢] had results contrary to ours.

In our study, only ١٨.٣٣% of children were receiving inhaled corticosteroids and ٨.٣٣٪ were receiving leukotriene inhibitors while ٤٠٪ were receiving oral steroids and ٦٨.٣٣٪ were receiving oral theophylline and this reflects weakness of the health care system in Egypt as these values are much lower than what might be expected based on recent guidelines for treatment of asthma in children. These values are different than those in Latin America[٣٩], Europe[٤٠], Asia

[٤١], and the United States[٤٢]. Current evidence suggests that anti-inflammatory medications are underutilized even in environments in which the ability to afford these medications is not an issue[٤٣], which is the case in Egypt.

Although urgent visits for asthma were high in our population, this is because this variable includes unscheduled visits not only to emergency departments but also to a physician's private clinic, a nebulization room, or a primary health care center. On the other hand, the rate of hospitalization in this study (٢٥٪) is higher than that seen in North America (٥٪) and Europe (٧٪) and likely indicates a more severe asthma exacerbation[١١,٤٠].

There are a number of limitations to be considered in the interpretation of our results. The first is the cross-sectional design of the study which makes it difficult to establish causality between vitamin D status and bronchial asthma. Also all subjects of bronchial asthma are not followed up. We also has a small sample size of asthmatic patients and controls which is inadequate to detect subtle differences between the groups and could have resulted in type ٢ error. Another factor to take into consideration in interpreting our results is the inaccuracy of documentation of patients' disease state and treatment modalities. Also we did not study seasonal variation which affects vitamin D status as well as frequency of asthmatic attacks.

In conclusion, vitamin D deficiency was the strongest predictor of asthma in our patients (stronger than familial history of asthma or serum IgE levels).Long-term follow-up studies with sufficient sample size focusing on changes in vitamin D status and asthma parameters will be needed to clarify the effect of vitamin D status on asthma.Given the emerging association between low vitamin D levels and asthma, strong consideration should be given to routine vitamin D testing in children, particularly those with asthma, and supplementation should be provided accordingly.

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