Does Vitamin D Have a Role in the Inception of Childhood Asthma? - A Comparative Cross-Sectional Study

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ABSTRACT

BACKGROUND
Global prevalence of paediatric asthma has shown a sharp increase in last three decades. Recently vitamin D has been linked with lung function and vitamin D supplementation can lessen the acute exacerbations in asthmatic children. The purpose of the study was to compare lung parameters and vitamin D levels in asthmatic and non-asthmatic children and assess the correlation between vitamin D levels and pulmonary function parameters in children.

METHODS
A cross-sectional study was conducted among 40 asthmatic children and 42 healthy volunteers between the age group of 5 and 18 years attending the paediatric outpatient department (OPD) in a tertiary care centre in Coimbatore. Pulmonary functions were assessed using computerized spirometer and the serum 25-hydroxy vitamin D levels were estimated by Diazyme EZ vitamin D assay latex enhanced immunoturbidimetric method. The results were compared between asthmatics and non-asthmatics to find out the association.

RESULTS
The average age of the study participants was 10.5 ± 2.5 years. Lung parameters and mean vitamin D levels are reduced in asthmatics. There is a positive significant correlation between serum vitamin D levels and forced expiratory volume FEV1 / forced vital capacity (FVC) ($P < 0.05$, $r = 0.781$), and also between vitamin D and FEV1 ($P < 0.05$, $r = 0.28$). Lung parameters like FEV_1, FEV_1 / FVC ratio and peak expiratory flow rate (PEFR) are significantly decreased in asthmatic children.

CONCLUSIONS
Majority of the asthmatics have insufficient vitamin D levels than the normal peers with no asthma. Our study confirms the positive association between vitamin D and FEV_1 and FEV_1 / FVC ratio.

KEYWORDS
Vitamin D, Asthma, Pulmonary Function, Lung Parameters

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BACKGROUND

Bronchial asthma is a major public health concern worldwide with its negative influence in the community with regard to extensive health care costs and deteriorating quality of life.[1] Asthma is chronic reversible airway inflammation with bronchospasm, bronchial hyper responsiveness and mucus production characterized by dyspnoea, wheeze and cough.[2] Children from low-middle income countries (LMICs) particularly suffer a disproportionately higher burden in terms of morbidity, impairment of quality of life, limitation of physical activities and study performance.[3]

Does Vitamin D Deficiency Involve in Asthma Inception?

Vitamin D (1, 25 dihydroxy cholecalciferol), a fat-soluble, sunshine vitamin plays a well-described role in bone formation and resorption by calcium and phosphate homeostasis. Receptors for Vitamin D were found in bronchial smooth muscle and respiratory epithelial cells. 25 (OH) D is converted into 1, 25 (OH) D in respiratory epithelial cells and both VDR and CYP24A1 (a hydroxylase that metabolizes 1, 25 [OH] D) synthesis are increased in bronchial smooth muscle cells.[4,5] Eight single nucleotide polymorphism of the VDR gene have also been associated with asthma and atopy,[6] which clearly depicts an association between vitamin D metabolism, genetics and asthma.

Determination of Vitamin D Status

25-hydroxyvitamin D_3 (calcidiol), the major circulating form has a half-life of about 2 weeks. Committee of the Institute of Medicine had categorized that individuals with serum 25 (OH) D concentrations < 30 nmol / L (< 12 ng / mL) are at risk of vitamin D deficiency. Calcidiol levels ranging from 30 - 50 nmol / L (12 – 20 ng / mL) are classified as vitamin D insufficiency. Individuals with serum 25 (OH) D levels ≥ 50 nmol / L (≥ 20 ng / mL) are considered as normal ones. The committee confirmed that the needs of 97.5 % of the community is covered at the serum level of 50 nmol / L. At the same time, higher levels of 25 (OH) D levels (> 125 nmol / L and > 50 ng / mL) are also linked with potential harmful effects.[7]

A few observational studies suggested that low level of vitamin D has been associated with reduced lung function, worse glucocorticoid responsiveness, poor asthma control, greater exacerbation frequency and substantially more severe asthma symptoms.[8,9] Two studies reported, no protective effects of vitamin D supplementation on asthma lung function.[10,11] Kang, Q. et al.[12] has given a contrasting report that vitamin D levels have no relation with FVC (Forced Vital Capacity), FEV1 (forced expiratory volume in one second), and FEV1 / FVC levels.

To improve clinical outcomes, quality of life and to prevent morbidity in asthmatic patients, methods to dampen asthmatic exacerbations are urgently needed. Having seen debatable analogies, this study was undertaken to assess the correlation between the vitamin D levels and lung parameters in asthmatic and non-asthmatic children.

Objectives

1. To compare lung parameters and vitamin D levels in asthmatic and non-asthmatic children.
2. To assess the correlation between vitamin D levels and pulmonary function parameters in children.

METHODS

This cross-sectional study was conducted in the pediatric asthma clinic of a tertiary care hospital in Coimbatore from 01 February 2018 to 08 September 2018 (1 / 2 / 2018 to 8 / 9 / 2018), after obtaining institutional ethical committee clearance (IHEC / 123 / Physiology / 01 / 2018). Written informed consent from parents or guardian and child assent were obtained before participating in the research. The study was conducted among two groups, forty asthmatic children and forty-two non-asthmatic children aged between 5 - 18 years. Pulmonary function testing using computerized spirometer was done for all the study participants who had FEV1 more than 80 % were classified as non-asthmatics and less than 70 % were classified as asthmatics. Children with acute exacerbation of asthma, on antitubercular or antiepileptic medication, with chronic heart diseases, renal disorders were excluded from the study. In children, the diagnosis of asthma was based on GINA Guidelines 2018.[13] Sociodemographic details, anthropometric measurements, drug history, disease duration, details on remissions and exacerbation were elicited among the study participants.

Sample Collection and Vitamin D Assay

Blood samples were drawn from peripheral vein of all the children and immediately centrifuged to separate the serum which was then stored at - 20^0 C. 25-hydroxyvitamin D was measured by Diazyme EZ vitamin D assay latex enhanced immunoturbidimetric method (Diazyme Laboratories).

Pulmonary Function Tests

Computerized spirometry is the preferred method of diagnosis of airflow obstruction. Lung parameters were obtained using a computerized spirometer (RMS Helios 702 - Recorders & Medicare systems private limited, Panchkula). The participants were allowed to relax for 10 min and then they were instructed to take deep inspiration, close the nostrils with nose clips and expire in to the mouthpiece of spirometer (for a minimum of six seconds). Three trials were recorded and the highest of three trials was noted. The primary signal measured in spirometry may be volume or flow.[14] FEV_1 is the forced expiratory volume in first second. FVC is the volume of air that is expired into the spirometer following forceful inspiration.

An obstructive pattern is characterized by a reduced FEV_1, normal FVC and a low FEV_1 / FVC ratio. Reversibility of FEV_1 by more than 20 % suggests a diagnosis of asthma. PEFR is the sensitive index to respiratory muscles strength and reflects mainly the calibre of the bronchi and larger bronchiole. FEF 25 - 75 % is defined as the mean forced expiratory flow between the 25 % and 75 % of the FVC.[15]

Statistical Analysis

Data was recorded and analyzed using SPSS version 23. Chi-square was used to find out the association between vitamin D level classifications among the study groups. Independent sample T-test was used to compare the difference in mean between different lung parameters and vitamin D levels among asthmatics and non-asthmatics. Linear correlation coefficient was calculated to find out the correlation between serum level of 25-hydroxy vitamin D and pulmonary function parameters. The statistical significance was set at $P < 0.05$.

RESULTS

40 asthmatic and 42 non-asthmatic children were compared for their pulmonary functions and vitamin D levels. Mean age of the study participants was 10.5 ± 2.5 years.

Table 1, depicts the mean ± SD levels of age, Height, weight in asthmatic children (N = 40) and non-asthmatic children (N = 42). Both the groups were similar in terms of age and height. The mean weight of asthmatics was higher compared to the other group with no asthma (38 kg vs. 34 kg) and the result was statistically significant.

Table 2 shows that all the lung parameters and serum vitamin D levels are reduced in asthmatics compared to those with no asthma. There is significant difference ($P < 0.05$) in the mean value between both groups in FEV1, FEV1 / FVC ratio, PEFR and vitamin D levels.

There is a positive significant correlation between serum vitamin D levels and FEV1 / FVC ($P < 0.05$, $r = 0.781$) as in Figure 1, and also a weak positive between vitamin D and FEV1 ($P < 0.05$, $r = 0.28$) as in fig 2. There is no correlation between vitamin D levels and PEFR (Figure 3) and also between vitamin D levels and FEF 25 - 75 % (Figure 4).

Table 3 shows, that 47.6 % of non-asthmatics have a normal vitamin D levels while only 12.5 % of the asthmatics had normal vitamin D levels. The results were statistically significant. There was a weak non-significant negative correlation (r = - 01.154, P = 0.343) between vitamin D levels and FVC.

Variables	Group	Mean	Std. Dev.	Mean diff	t-Value	P-Value
Age (years)	Asthmatics	10.475	2.82	0.025	- 0.045	0.964 NS
	Non-asthmatics	10.5	2.17			
Height (cm)	Asthmatics	139.53	15.54	0.81	- 0.252	0.802 NS
	Non-asthmatics	140.33	13.50			
Weight (kg)	Asthmatics	37.95	10.10	4.05	2.002	0.049 *
	Non-asthmatics	33.90	8.24			

Table 1. Characteristics of the Study Population

* - Significant NS-Not significant

Variables	Group	Mean	Std. Dev.	Mean Diff	t-Value	P-Value
FVC (litres)	Asthmatics	2.18	0.55	0.12	- 1.001	0.320 NS
	Non-asthmatics	2.31	0.611			
FEV1 (litres)	Asthmatics	1.56	0.48	0.39	- 3.665	< 0.001**
	Non-asthmatics	1.96	0.48			
FEV_1 / FVC (%)	Asthmatics	71.91	12.81	13.27	- 5.784	< 0.001**
	Non-asthmatics	85.19	7.38			
PEFR (litres / min)	Asthmatics	2.78	0.63	0.74	- 4.18	< 0.001**
	Non-asthmatics	3.52	0.94			
FEF 25 - 75 %	Asthmatics	2.04	0.69	0.061	- 0.457	0.649 NS
	Non-asthmatics	2.10	0.50			
Vitamin D (ng / ml)	Asthmatics	16.43	4.42	3.94	- 4.7	< 0.001**
	Non-asthmatics	20.36	3.06			

Table 2. Comparison of Lung Parameters and Vitamin D Levels in Asthmatics and Non-Asthmatics

** - Extremely Significant NS - Not significant

Vitamin D Levels	Asthmatics		Non-Asthmatics		Chi-Square Value	P Value
	Frequency	%	Frequency	%		
Vitamin D < 50 nmol / L or < 20 ng / ml (deficiency / insufficiency)	35	87.5	22	52.4	11.923	< 0.001*
vitamin D levels > 50 nmol / L > 20 ng / ml (normal)	5	12.5	20	47.6		

Table 3. Vitamin D Status in Asthmatics and Non-Asthmatics

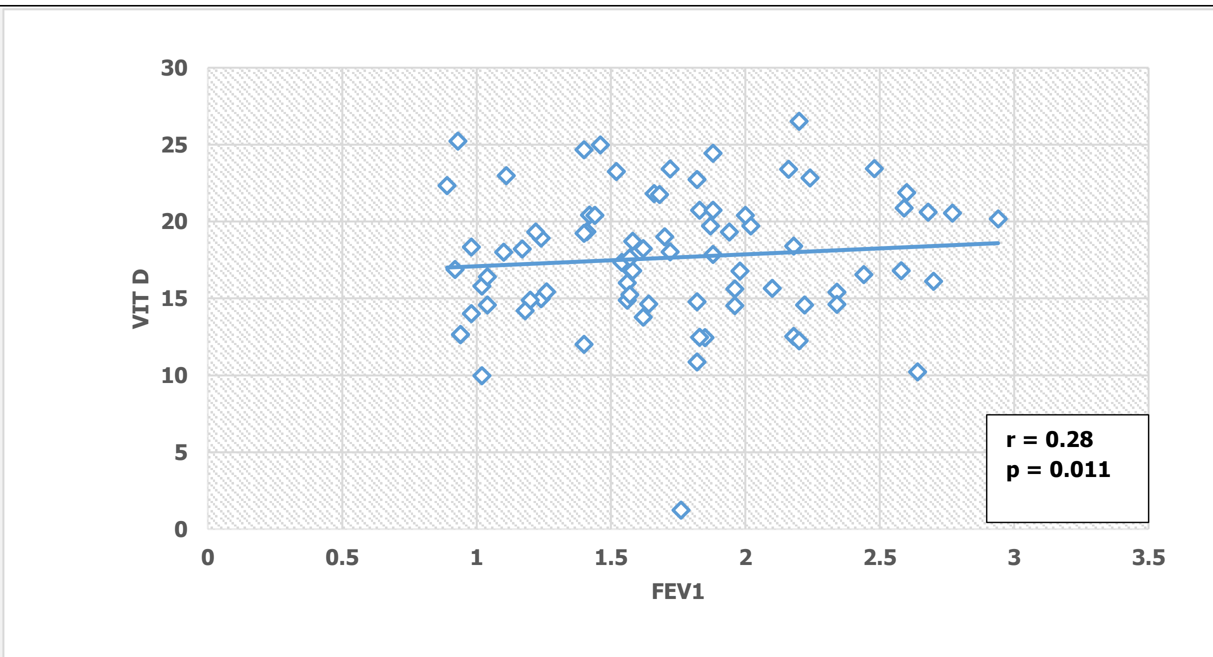

Figure 1. Correlation of Vitamin D and FEV_1 in the Study Participants

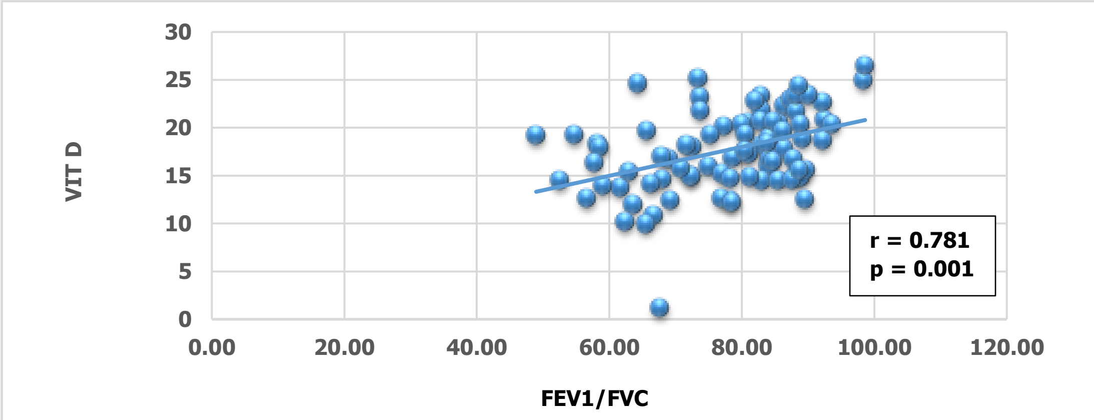

Figure 2. Correlation of Vitamin D and FEV_1 / FVC Ratio in the Study Participants

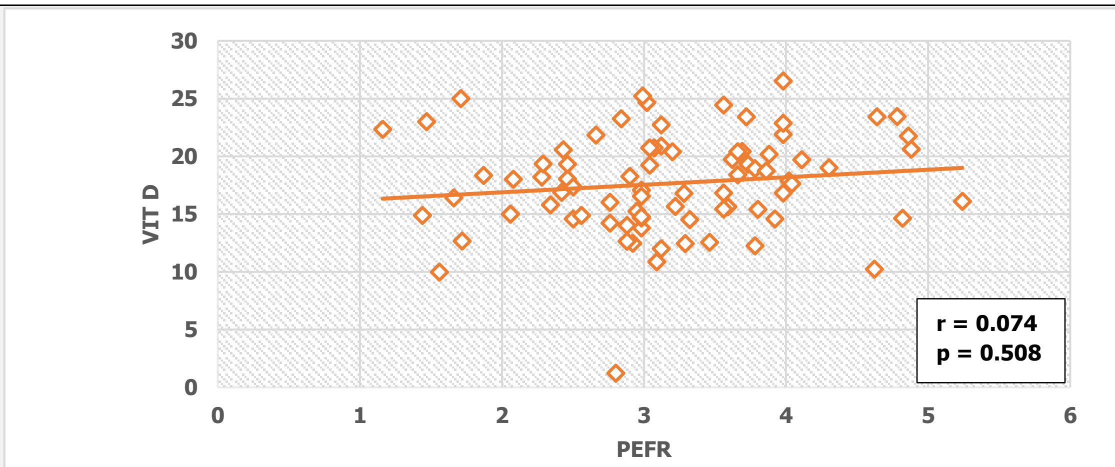

Figure 3. Correlation of Vitamin D and PEFR in the Study Participants

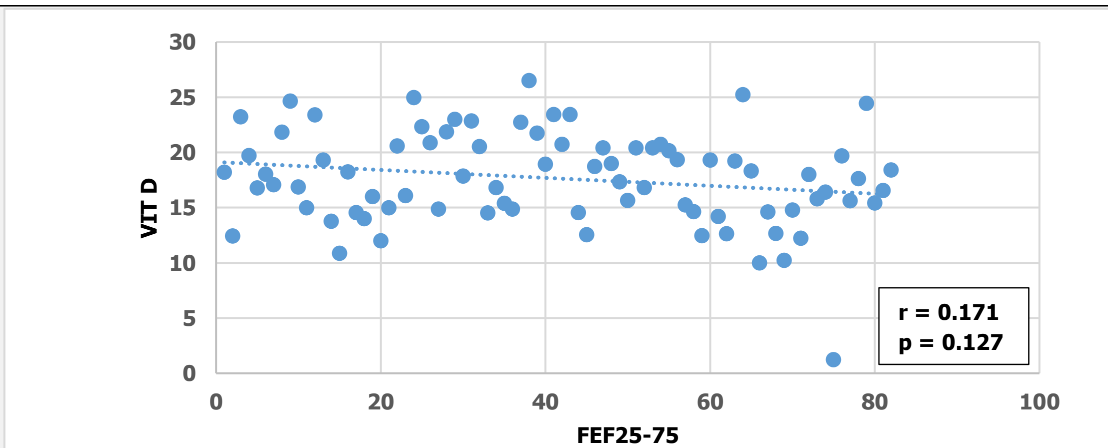

Figure 4. Correlation of Vitamin D and FEF 25 - 75 % in the Study Participants

DISCUSSION

Modern clinical practice has revolutionized to identify and remove the exciting causes of asthma to alleviate the bronchospasm during the paroxysm and to treat complications and sequelae.[16] The potential protective effect of vitamin D against asthma morbidity by dampening atopy, decrease inflammatory markers and proliferation of airway smooth muscles cells, increase the steroid responsiveness and decrease asthma exacerbation was undoubtful.

In the present study, there was a statistically significant difference in mean weight between asthmatics and non-asthmatics (37.95 vs. 33.90 kg, $P < 0.05$), showing that the weight of the asthmatic children was more than the control group (Table 1). This is in accordance with the various studies done in different places. Numerous postulates are available to narrate the mediators streaming in obese conditions like oxidative metabolites causing stress and inflammation. The inflammatory mediators cause airway narrowing and primes the lung for exaggerated responses to environmental triggers which in turn leads to asthma. Obesity related systemic inflammation is due to pro-inflammatory 'adipokines' like leptin, IL 6, adiponectin and TNFα which influence multiple organ systems, including the lung's responses to external stimuli. The greater responsiveness of lung-bronchi and existence of an "obese asthma" phenotype causes reduction in respiratory parameters like FEV1 and FVC [17]

Lung parameters like FEV_1, FEV1, FEV_1 / FVC ratio, PEFR are significantly decreased in asthmatic children.[18] Similarly in our study, there is a statistically significant difference ($P < 0.05$) in the mean value between both groups in FEV_1, FEV_1 / FVC ratio, PEFR and vitamin D levels.

The mean vitamin D concentrations in asthmatics was less compared to non-asthmatics (16.43 + 4.42 ng / ml vs. 20.36 ± 3.06 ng / ml) (Table 2). There is a statistically significant difference in mean vitamin D levels between the two groups. It was observed that there are 87 % (N = 35) vitamin D deficient subjects who are having asthma and 52 % (N = 22) of vitamin D deficient subjects who have no asthma. 12.5 % (N = 5) of asthmatic children do not have vitamin D deficiency. This clearly depicts that, all the vitamin D deficient children are not developing asthma, suggesting the genetical predisposition and the role of triggering factors in the surroundings. (Table 3)

The prevalence of vitamin D deficiency is high among non-asthmatics too. Nowadays, children spend more time at home away from sunlight, causing vitamin D deficiency in them. Vitamin D supplementation in asthmatic children has showed promising results like improvement of FEV_1 % and reduction in the rate of asthma exacerbation.[19,20]

A weak positive significant correlation was observed between serum vitamin D levels and FEV1 ($P < 0.05$, $r = 0.28$), and also between vitamin D and FEV1 / FVC ($P < 0.05$, $r = 0.781$). Positive insignificant correlation was observed between vitamin D and PEFR ($r = 0.074$). In the Third National Health and Nutrition Survey (NHANES III), strong positive relation between serum 25 (OH) D and FEV_1 and forced vital capacity (FVC) were reported.[21] Moghaddassi et al. in their study also have noticed that higher serum vitamin D levels correlate with healthier respiratory volumes.[22]

Negative correlation was observed between vitamin D and forced expiratory flow (FEF) 25 - 75 % and also between vitamin D and FVC. Similar results were obtained in a study done by Menon et al.[23]

Prevalence of vitamin D deficiency and vitamin D insufficiency was higher in asthmatics compared to normal children. Sutherland and colleagues pointed out that for every one nanogram / milliliter increase in vitamin D serum concentration, FEV_1 would experience 22.7 (± 9.3) milliliter increments.[24]

Recently, there was a growing literature suggesting the influence of vitamin D to a wide range of health outcomes including lung maturity, cardiovascular morbidity, insulin resistance-diabetes, cancer and respiratory infection. Our study clearly confirms the positive association between vitamin D and FEV_1 and FEV_1 / FVC ratio.

CONCLUSIONS

This study concludes that 25-hydroxyvitamin D levels are positively associated with pulmonary parameters like FEV_1, FEV1 / FVC and PEFR in the study participants. Vitamin D levels in most of the asthmatic children was found to be lower than the normal set. Prevention is better than cure and hence we conclude by emphasizing that, vitamin D supplementation in children, avoidance of predisposing factors like allergens, passive smoking, pollen and pollutants may reduce the exacerbation of asthma and improve treatment response in asthmatic children. However, larger explorative clinical trials with huge sample sizes and researches on vitamin D receptor are to be undertaken to explain the significance of vitamin D in the prevention of asthma.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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