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Role of Vitamin D and IgE in bronchial asthma in children in Eastern India

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ABSTRACT
Background: *Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. The detrimental effects of vitamin D deficiency in pediatrics have become increasingly apparent and extend beyond skeletal health.*
Aims & Objectives: *This study was carried out to evaluate the level of vitamin D and immunoglobulin E (IgE) in asthmatic patients of paediatric ages during exacerbation and after remission.*
Patients and Methods: *This study was carried out on 56 bronchial asthma children of 4 to 14 years of age group attending the 'Pediatric outpatient department' of ICARE Institute of Medical Sciences, Haldia, with bronchial asthma diagnosed and classified according to Global Initiative for Asthma 2016 and 48 healthy age and sex matched individuals. Serum vitamin D and IgE were measured using enzyme-linked immunosorbent assay for all participants.*
Results: *Serum IgE level was found significantly higher among bronchial asthma subjects with respect to controls (443.2 ± 237.3 versus 139.8 ± 82.06 IU/ml; P < 0.001). Moreover, serum 25 OH vitamin D levels were lower in bronchial asthma cases as compared to controls and were statistically significant (15.83 ± 7.44 versus 23.14 ± 8.29 ng/ml; P < 0.001). Serum vitamin D level showed an inverse correlation with IgE (r = -0.77; P < 0.0001) level among bronchial asthma subjects, but no significant correlation was observed in controls (r = 0.077; P = 0.689).*
Conclusion: *Despite these limitations it has been observed that serum vitamin D levels were lower and IgE levels were higher in patients suffering from bronchial asthma. A clear strong inverse correlation between vitamin D and Ig E also indicates a strong relationship in the pathogenesis of the disease.*
Keywords: *Bronchial asthma, Immunoglobulin E, Vitamin D, Children.*

Introduction

Bronchial asthma is one of the common chronic diseases known to be the leading cause of morbidity in children worldwide[1,2,3]. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation [4]. Hypoxia and hypercapnia is the primary feature of asthma severity. Airway bronchospasm shows diurnal variation of time and intensity with limited expiratory airflow rate [4].

The prevalence of asthma is rapidly increasing to about more than 300 million people in both the developed and the developing countries worldwide. In India, the estimated load of asthma is more than 30 million. In children, reported incidence by 6-7 years and 13-14 years are 2.3% & 3.3% respectively [5-6]. The significant risk factors associated with asthma includes positive atopic status, exposure and sensitisation to environmental allergens and / or family history of allergic diseases. Vitamin D which belongs to secosteroid family plays a role in calcium or phosphate homeostasis along with bone mineralisation is a potent modulator of the immune system also known to be involved in regulating cell proliferation and differentiation [7,9]. Epidemiological evidence also suggests that there is a worldwide epidemic of vitamin D insufficiency or deficiency and lack of vitamin D has been related to increased incidence and severity of bronchial asthma in children [10-14]. It is also said that the vitamin D3 deficiency increases lung airway responsiveness and steroid resistance. A decrease in lung volumes and capacities with decreased therapeutic response has been suggested in vitamin D deficient asthmatics[3]. The major contributors which lead to vitamin D deficiency are prolonged breastfeeding without vitamin D supplementation, maternal vitamin D deficiency, poor diet and/ or limited sunshine exposure [15].

Several studies have been performed to assess the role of vitamin d in bronchial asthma but the association between markers of asthma and vitamin D is still unclear. Thus the aim of our study was to study the role of serum vitamin D levels between asthmatic and non-asthmatic, healthy children and to observe for any associations between vitamin D and development of bronchial asthma in young children.

Methods

The preliminary case- control study included 56 bronchial asthma children and 48 control subjects of 4 to 14 years of age group attending the 'Pediatric outpatient department' of ICARE Institute of Medical Sciences, Haldia, which is a tertiary care hospital in the eastern part of India. The healthy control subjects were age, sex and BMI matched attending the OPD for minor illness with no features of asthma or associated disorders. Informed consent was obtained from every parents of control subject as well as from bronchial asthma patients before enrolling their child for the study. The inclusion criteria having a history of asthma with eosinophilia on blood smear present. The study was cleared by the Institutional Human Ethics Committee according to Helsinki guidelines. All the healthy control subjects were also examined clinically to exclude any asthmatic symptoms. The exclusion criteria for the study was children having clinical rickets, type 1 diabetes mellitus, protein energy malnutrition (PEM), taking drugs which interferes with vitamin-D metabolism like anti epileptic drugs or received vitamin D either oral / injection in last 6 months and children having any chronic liver, kidney or lung or neurological diseases.

About 5 ml venous blood samples were obtained from the patients as well as controls. Non-fasting serum samples of control and asthma subjects were analyzed for routine biochemical parameters immediately after collection while aliquots of the samples were also stored at - 20^0 C for the assay of 25-hydroxyvitamin D or IgE. Serum vitamin D was measured as 25-hydroxyvitamin D is considered as the indicator of vitamin D or IgE was assayed by using commercially available immunoassay ELISA kits.

Statistical analysis of different biochemical parameters was performed by Students' *t*-test. All variables were expressed as mean ± SD (standard deviation). Means obtained from two normally distributed sample groups were compared by Student's unpaired two-tailed "*t*"-test and for nonparametric Mann-Whitney *U* "*t*" test. To find out the correlation between two variables, Pearson's product moment correlation coefficient was used. A value of $P < 0.05$ was considered as statistically significant. All statistical analyses were performed by using Graph Pad prism software (version 5, 2007, San Diego, California, USA). Statistical analysis for sex distributions was evaluated by chi-square test by using statistical software STATA (version 8, Copyright 1984–2003, Stata Corporation, Texas, USA).

Results

The demographic and biochemical profile of the bronchial asthma subjects and healthy controls is presented in Table 1. There was no significant difference in age, sex distribution or BMI in either of the two groups between asthma and control subjects (Table 1). Serum calcium was signify-cantly lower in cases than in controls (Table 1).

Serum IgE level was found significantly higher among bronchial asthma subjects with respect to controls (443.2 ± 237.3 versus 139.8 ± 82.06 IU/ml; $P < 0.001$) (Figure 1). Moreover, serum 25 OH vitamin D levels were lower in bronchial asthma cases as compared to controls and were statistically significant (15.83 ± 7.44 versus 23.14 ± 8.29 ng/ml; $P < 0.001$) (Figure 2). As presented in Figure 3, serum vitamin D level showed an inverse correlation with IgE($r = -0.77$; $P < 0.0001$) level among bronchial asthma subjects, but no significant correlation was observed in controls ($r = 0.077$; $P = 0.689$).

Table 1 Demographic and biochemical profile of subjects.

	Control (n = 48)	Asthma (n = 56)
Age(in years)	8.64 ± 2.1	7.94 ± 1.96
Sex (M/F)	20/28	24/32
BMI (kg/m^2)	16.72 ± 1.64	15.96 ± 3.92
RBS (mg/dl)	82.23 ± 8.52	84.7 ± 11.22
Calcium (mg/dl)	9.39 ± 1.24	8.6 ± 2.32*
Phosphorus (mg/dl)	3.98 ± 0.48	4.28 ± 0.84
Eosinophil (cells/mm^3)	156.3 ± 72.44	588.9 ± 242.3*

RBS, random blood sugar. Age, BMI, and serum levels of biochemical parameters were expressed as the means ± SD. Statistically significant, * p < 0.05 vs Control.

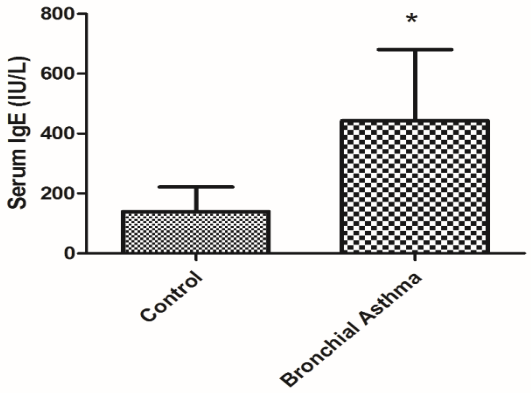

Fig.1 Serum levels of IgE in control and Bronchial asthma subjects.

Serum levels of IgE were determined as described in methods for control and bronchial asthma subjects. Values expressed as the means ± SD.Statistically significant, * p < 0.0001, vs Bronchial asthma.

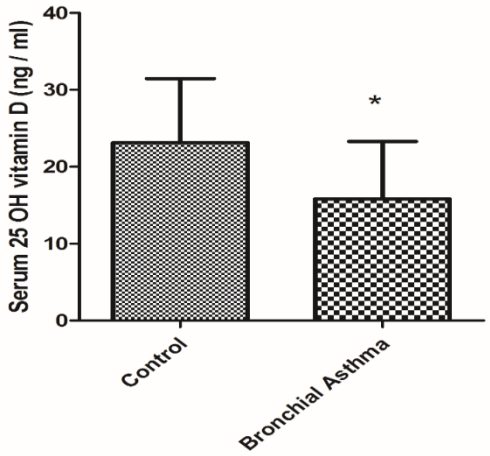

Fig.2 Serum levels of vitamin D in control and Bronchial asthma subjects.

Serum levels of 25 OH vitamin D were determined as described in methods for control and bronchial asthma subjects. Values expressed

as the means ± SD.Statistically significant, * p < 0.0001, vs Bronchial asthma.

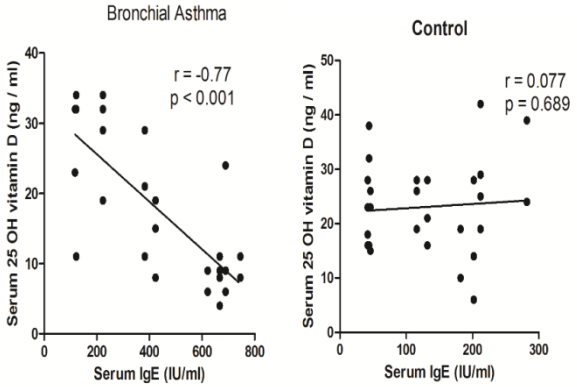

Fig. 3 XY scatter plots between serum levels of IgE and 25 OH vitamin D (A, B) in Controland Bronchial Asthma subjects.

Correlation coefficient (r) represents the degree and nature of correlation between the serum parameters of IgE and 25 OH vitamin D levels in controls and bronchial asthma patients as described in the Materials and Methods. A value of p < 0.05 was considered as statistically significant.

Discussion

The deficiency of vitamin D is emerging to be a global health problem worldwide due to sedentary lifestyle, poor dietary intake, limited exposure to sunshine, excessive clothing coverage, sunscreen use, increased time spent indoors and intrinsic factors such as the skin melanin content and increased cutaneous destruction of vitamin D_3. The deficiency of vitamin D is very common in India despite being a tropical country in all the age groups in both the sexes. Several epidemiological studies have reported about vitamin D deficiency and its association with an increased incidence of asthma and other allergy symptoms [6]. Some studies have found out vitamin D deficiency was the strongest predictor of asthma stronger than familial history of asthma or serum IgE levels and familial history of vitamin D deficiency also being a predictor of asthma [15].

Our study also observed a similar decrease in serum vitamin D levels in bronchial asthma in children and an increase in Ig E levels as compared to control subjects. Moreover, it was also observed a strong inverse correlation between Ig E levels and serum vitamin D level in bronchial asthma children while no correlation was seen in control subjects who signify that vitamin D is associated with asthma and seems to be a major risk factor for the pathogenesis of the disease. Several mechanisms have been suggested to explain the modulation of vitamin D in the pathogenesis of asthma. Vitamin D modulates the function of many immune cells including monocytes, macrophages, lymphocytes, and epithelial cells and may protect one from developing respiratory infections that serve as a trigger for the deterioration of asthma. [16]. One cross sectional study in costa Rica which consists of 616 asthmatic children between 6 to 14 years of age showed insufficient levels of 25 OH vitamin D and also observed its association with total Ig E levels and eosinophil count which supports our study [9]. Another cross sectional study in Italian children aged 5 to 11 years had observed that Vitamin D levels was lower in 53•3% and 37•3% children had insufficient levels while only 9•4% children with asthma had sufficient vitamin D [17]. The control subjects were missing in this study.Moreover, a cross sectional case control study in USA which consists of 6 to 20 years old children with or without asthma showed 86% of cases had insufficient while 54% had deficient vitamin D levels [16]. These studies indicates that low level of Vitamin D is associated with childhood asthma in both developed and the developing countries. The severity of Vitamin D deficiency was found to be associated with severity of childhood asthma. Our finding are also in conformity with other studies which shows that insufficient vitamin D levels are associated with an increase in the risk of asthma exacerbations as found in patients of CAMP cohort and with augmented airway responsiveness and increased risk of asthma hospitalization in children with asthma[15,18]. One study also found an association between serum 25(OH)Vitamin-D levels and risk

of an asthma related emergency department visit or hospitalization and concluded that vitamin D deficiency may be the strongest predictor of asthma, stronger than familial history of asthma or serum IgE levels [7].

A study also reported that polymorphisms in the gene encoding the vitamin D receptor were associated with asthma phenotypes [19]. Vitamin D supplementation was also reported to reduce the risk of disease exacerbations in children with asthma. Moreover, another study found a positive correlation between serum vitamin D with FEV1 and glucocorticoid response as vitamin D insufficiency or deficiency was associated with airway hyper-responsiveness. Some studies observed an association between maternal intake of vitamin D during pregnancy and risk of childhood asthma in the offspring, and thus its supplementation may have beneficial effects during pregnancy, lung growth and development in neonates[20]. Another study found that the serum vitamin D was positively correlated with lung function and enhanced glucocorticoid action in peripheral blood mononuclear cells[21]. Moreover, vitamin D was inversely correlated with total IgE, the degree of atopy and the use of inhaled or oral steroids and might be potentially capable of overcoming the poor glucocorticoid responsiveness in severe asthmatics through the upregulation of interleukin-10 production (a potent anti-inflammatory cytokine) from CD4+ T cells. Thus vitamin D reestablished the capability of regulatory T cells from steroid-resistant patients with bronchial asthma to secrete interleukin-10 in response to steroids.

There were few limitations in our study which needs to be mentioned. The sample size of the study was less. Secondly, few of the patients were taking some other drugs such as antihistamines, topical corticosteroids which might interfere with serum vitamin D levels. Despite these limitations it has been observed that serum vitamin D levels were lower and IgE levels were higher in patients suffering from bronchial asthma. A clear strong inverse correlation between vitamin D and Ig E also indicates a strong relationship in the pathogenesis of the disease. However, supplementation of vitamin D may be beneficial and can be considered as an adjuvant therapy in the prevention of the pathogenesis of bronchial asthma. Moreover, a large longitudinal study needs to be done to conclude the fact.

Conclusion

A clear strong inverse correlation between vitamin D and Ig E also indicates a strong relationship in the pathogenesis of the disease. It would be advisable to measure the vitamin D serum level in children and adults who are part of high risk groups for vitamin D deficiency. Vitamin D supplementation is only recommended for patients who have serum level less than 20 ng/mL. Randomized clinical trials regarding treatment with vitamin D supplementation will help determine the effects on the immune system and any potential role in preventing allergic disease.Additionally, more studies are needed to determine the proper circulating level of vitamin D for optimal immune function.

Conflict of Interest:None declared.

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