

Original Research Article

Vitamin D deficiency in children with asthma

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ABSTRACT

Background: Asthma is one of the most common chronic respiratory diseases worldwide. Its exact cause remains unknown. Vitamin D has been implicated as a critical regulator of immunity and found to be associated with several immune mediated diseases. Recently there has been increasing interest in the possible link between vitamin D and asthma. Hence, we planned this study to assess the existence of any correlation between asthma and vitamin D levels in India.

Methods: Fifty consecutive cases of clinically diagnosed asthma attending asthma clinic and those admitted in IMCH Calicut, Kerala, India were included in the study and administered detailed questionnaire. Routine physical examination and investigation as per the protocol in asthma clinic were done. Blood was drawn for 25 hydroxy cholecalciferol and serum analyzed by Roche Elecsys chemiluminescence assay. Controls were selected only after all fifty cases were selected. Vitamin D levels were assayed in the same manner as in patients with asthma. Vitamin D levels were then analyzed with other parameters and variables. Statistical analysis was performed using SPSS software, version 16.

Results: Prevalence of vitamin D deficiency is high in study population. The difference in vitamin D levels between cases and controls is significant.

Conclusions: More studies need to be done to ascertain the relationship between asthma and vitamin D in developing countries like India.

Keywords: Asthma, Children, Exacerbation, Vitamin D

INTRODUCTION

Asthma is one of the most common chronic respiratory diseases worldwide and has been increasing in prevalence over the last few decades. Its exact cause remains unknown and likely has its origins in complex interactions among multiple genetic and environmental factors. Common risk factors for both asthma and vitamin D deficiency, such as an urbanized, westernized lifestyle, race/darker skin pigmentation and obesity, along with increasing evidence of the immunomodulatory effects of vitamin D, have led to a

hypothesized link between the rising asthma prevalence and low vitamin D.¹

The effects of vitamin D on bone metabolism and calcium homeostasis have long been recognized. Emerging evidence has implicated vitamin D as a critical regulator of immunity, playing a role in both the innate and cell mediated immune systems. Vitamin D deficiency has been found to be associated with several immune mediated diseases, susceptibility to infection and cancer. Recently, there has been increasing interest in the possible link between vitamin D and asthma. Further elucidation of the role of vitamin D in lung development

and immune system function may hold profound implications for the prevention and treatment of asthma.^{2,3}

A number of studies have been conducted in various populations over the world to assess the correlation between asthma and vitamin D levels and so far, many have established a strong inverse relationship between the two.^{1,4,5} In India, it is known that vitamin D deficiency is prevalent, but there are not many studies assessing its relationship with asthma.

Hence, this study is planned as a pilot study to assess the vitamin D levels in asthmatic children and in the normal population, and to see if the correlation between asthma and vitamin D levels exists in India, as well.

The objectives of the study were: to assess Vitamin D levels in newly diagnosed asthmatics, and in non-asthmatic children, aged 1 year to 12 years, in the department of pediatrics, institute of maternal and child health, Calicut, during the period January 2011 to June 2012 and to study the correlation between vitamin D levels and the frequency of asthma exacerbations, acute life threatening episodes, the frequency of infections in these children.

METHODS

This was a case control study which was conducted in the Institute of maternal and child health, government medical college, Calicut, during the period, January 2011 to June 2012. A total of one hundred children were studied, which included fifty cases and fifty controls.

Inclusion criteria

Inclusion criteria of this study were, children with newly diagnosed Asthma, aged 1 year to 12 years, admitted in the wards or attending the asthma clinic of IMCH, Calicut and clinical diagnosis of asthma was used, based on the questionnaire method.

Exclusion criteria

Exclusion criteria of this study were, children with other co-morbidities like heart disease, tuberculosis, epilepsy, cerebral palsy, liver disease and renal disease, children already on treatment for asthma, with preventers and children on vitamin D and calcium supplements. Control group inclusion criteria were normal children, who attended the casualty or outpatient department of IMCH, Calicut and exclusion criteria were children on calcium or vitamin D supplements.

Study methodology

Children with asthma attending the asthma clinic at IMCH, Calicut and those admitted in the wards were included in the study. Fifty consecutive cases of asthma,

diagnosed clinically, were administered detailed questionnaires regarding asthma. Baseline height, weight and clinical examination were recorded. Cases attending the asthma clinic had a profile of investigations already done, which included complete blood count, serum IgE levels and chest X-ray. After ensuring that the children were not on long term inhaled corticosteroids, consent was obtained from the parents, and blood was drawn for 25-hydroxy cholecalciferol (25-OHD, henceforth referred to as vitamin D) estimation. Samples were centrifuged to separate serum, and stored at -20^o C, if there was delay of more than 24 hours in performing the test. Serum was then analysed by Roche Elecsys chemiluminescence assay.

Controls were selected only after all fifty cases were selected. They were age and sex matched controls. All the controls had attended either the emergency department, or the paediatric OPD of Government Medical College hospital, Kozhikode. Blood samples were drawn only when the child was being pricked for another purpose (investigations for the illness with which they were brought to the hospital, clotting time estimation in cases with history of snakebite). Consent was taken from the parents from for inclusion in the study. Vitamin D levels were then assayed in the same manner as above. Vitamin D levels were then analyzed with various parameters as is outlined further. Statistical analysis was performed using SPSS software, version 16.

RESULTS

A total of fifty cases of asthma and fifty age and sex matched controls were studied. The following observations were made.

Baseline characteristics

Gender distribution: in both groups, there were 31 males (62%) and 19 females (38%). Age distribution: in both groups, the children were categorized into three categories less than three years, three to six years and more than six years of age. This was based on the categorization of asthma into transient wheezers, persistent wheezers and late onset wheezers, with age groups as mentioned above, respectively. There were twelve children in each group less than three years of age, twelve in the three to six year age group, and twenty six children older than six years.

Baseline characteristics of children with asthma

Frequency of asthma exacerbations: out of the fifty children diagnosed to have asthma, 20 (40%) had attacks once a month, 13 (26%) had fortnightly attacks, and 5 (10%) had weekly attacks. 10 (20%) had wheezing once in two to three months, while only 2 (4%) had more than one episode of wheeze per week. The frequency of infections in these children also coincided with the frequency of exacerbations of asthma.

Number of hospitalizations with wheeze: out of the fifty children with asthma, 21 (42%) were never hospitalized for wheezing; 22 (44%) had been hospitalized once to thrice and 7 (14%) had been hospitalized more than thrice. Life threatening episodes; out of the fifty asthmatics studied, 13 (26%) had history of life threatening episodes, while 37 (74%) had no such history. Family history of asthma; 34 (68%) of the children with asthma had family history of asthma and 16 (32%) had no relatives with asthma. Degree of relation in those who had family history of asthma; out of those with family history of asthma, twenty one per cent had first degree relatives with asthma, eighteen per cent had first and second degree relatives, and six per cent had first, second and third degree relatives. Fifteen per cent had second degree relatives with asthma, and six per cent had both, second and third degree relatives. Twelve per cent had third degree relatives with asthma. Types of asthma: in the fifty cases of asthma, 13 (26%) had intermittent asthma, 19 (38%) had mild persistent asthma, 14 (28%) had moderate persistent and 2 (4%) had severe persistent asthma. 2 (4%) were found to have cough variant asthma.

Vitamin D levels

Vitamin D levels tested in fifty of the cases showed that 29 (58%) of cases were deficient, 19 (38%) were insufficient and 2 (4%) were sufficient. The mean value of the cases was 18.39±7.14 ng/ml. Among the fifty controls tested for vitamin D levels, 20 (40%) were found deficient, 18 (36%) were insufficient and 12 (24%) were found to be sufficient in vitamin D. The mean value of the vitamin D levels among controls was 22.93±10.74 ng/ml. The differences in vitamin D levels between children with asthma and the controls, with the paired t test, were found to be statistically significant with a p value of 0.008.

Factors which influence vitamin D levels

In the cases, the mean value of vitamin D with adequate vitamin D intake was 18.46 ng/ml, and that of children with poor intake of vitamin D was 21.59 ng/ml. The difference was not statistically significant (p=0.471). The mean vitamin D level in the cases with sunlight exposure was 20.5 ng/ml, while those with poor exposure had a mean value of 15.9 ng/ml. This difference was not statistically significant (p=0.051)

Age and vitamin D levels; among the cases, in analysis of the vitamin D levels between these age groups, the vitamin D levels were significantly higher in children <3 years of age, compared with those in the age groups 3-6 years and >6 years (p=0.022 and 0.001, respectively). There was no significant difference between the age groups 3-6 years and >6 years (p=1.00). In the controls, the difference in vitamin D levels between these age groups was not statistically significant. Gender and vitamin D levels; there was no statistically significant difference in p values between the genders. Occurrence

of life-threatening episodes and vitamin D levels; there was no statistically significant difference in the vitamin D levels between those who had life-threatening episodes and those who did not (p=0.853).

Table 1: Factors which influence vitamin D levels (out of 50 patients).

Variables	Present (%)	Poor (%)	Total (%)
Vitamin D intake	47 (94)	3 (6)	50 (100)
Sunlight exposure	33 (66)	17 (34)	50 (100)

Table 2: Correlation between age and vitamin D.

Variables	Age group (years)	Mean cases (ng/ml)	Mean controls (ng/ml)	P value
Vitamin D levels	<3	24.73	24.64	0.98
	3-6	17.77	23.09	0.074
	>6	15.78	21.99	0.017

Table 3: Correlation between gender and vitamin D levels.

Variables	Gender	Cases	Controls
Vitamin D levels (ng/ml)	Male	19.21	24.96
	Female	17.04	19.60
Significance (p value)		0.300	0.087

Table 4: Correlation between life-threatening episodes and vitamin D.

Life-threatening episodes	Yes	No	P value
Vitamin D levels	18.97	18.54	0.853

Vitamin D and frequency of exacerbations of asthma

On analysis by ANOVA, there was no statistically significant correlation between frequency of exacerbations and vitamin D levels (p=0.853).

Vitamin D and the number of hospitalizations with asthma

Using the pearson correlation coefficient, the relation between vitamin D levels and the number of hospitalizations with asthma exacerbations was analyzed. While there was a positive correlation of 0.240, this was not statistically significant (p=0.093).

Vitamin D and serum IgE levels

Out of the cases, 23 had IgE levels estimated. Out of them, 2 had normal values (less than 60 IU/ml), while 21

had raised levels. The mean IgE level was 1587.24 IU/ml with the lowest value being 6 IU/ml and the highest being 8006 IU/ml. The standard deviation was 2104.

There was a negative correlation between vitamin D levels and serum IgE values (pearson correlation coefficient, 0.477), but the difference was not statistically significant (p=0.054).

Table 5: Vitamin D and frequency of wheezing attacks.

Vitamin D levels	Mean value (ng/ml)
>Once a week	16.74
Once a week	14.05
Fortnightly	20.54
Monthly	19.70
Once in 2 months or more	17.01

Other characteristics

There was no significant difference in vitamin D levels between those who had exercise-induced symptoms and those who did not (p=0.314).

Similarly, there was no statistically significant difference in vitamin D levels between the children who had history of bronchiolitis and those who had no such history (p=0.168).

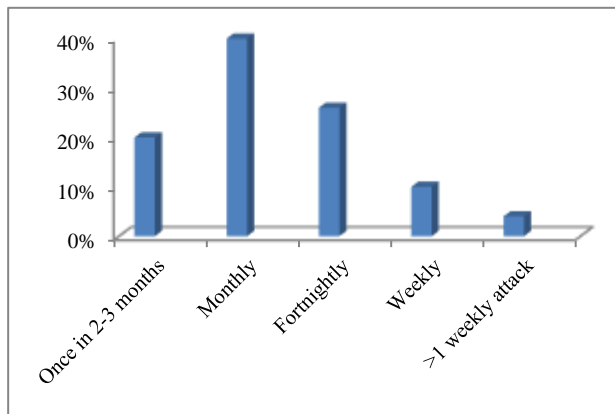


Figure 1: Frequency of wheezing attacks.

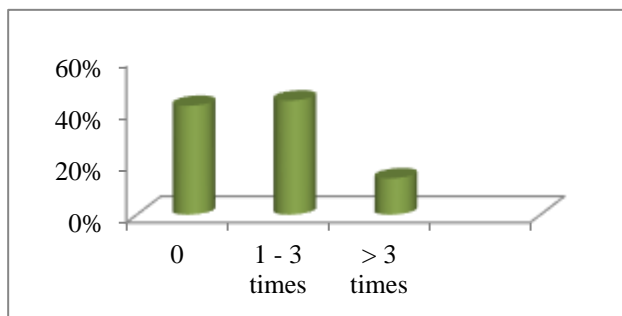


Figure 2: Frequency of hospitalizations.

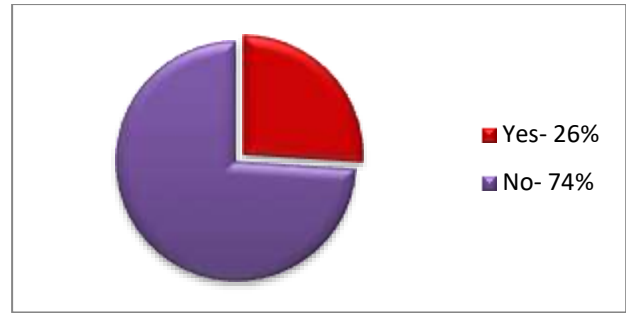


Figure 3: History of life-threatening episodes.

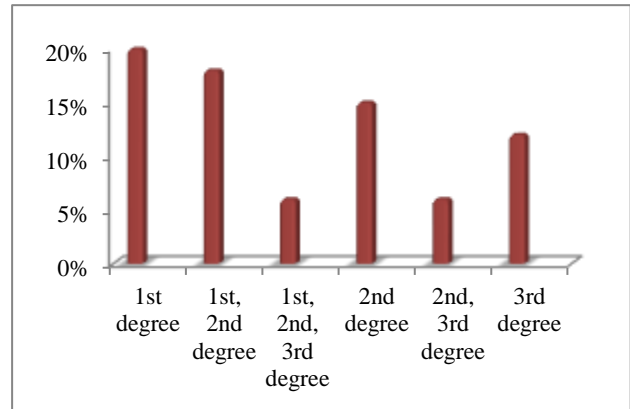


Figure 4: Distribution of degree of relation.

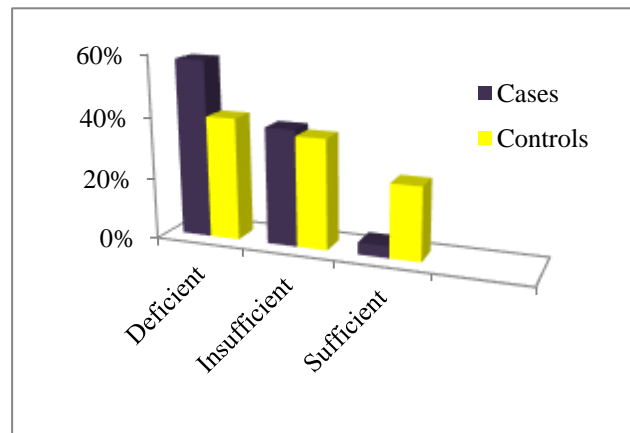


Figure 5: Vitamin D levels in cases and controls.

DISCUSSION

Our study included fifty cases, who were children diagnosed clinically to have asthma, and fifty controls, who were normal children with no significant illnesses. Both groups were not on any vitamin D supplements. The controls were age and sex matched.

The study population included thirty one boys and nineteen girls, in each group. They come from similar socioeconomic groups, mostly from the lower socioeconomic strata. The mean age of both groups was approximately 6.3 years and they were comparable.

The results of our study were similar to those conducted in other countries so far. Even though India is a tropical country, and Kerala is very close to the equator (11°15' N 75°49' E), we found a high prevalence of vitamin D deficiency in the study population.⁶ This correlates with that described in other countries with abundant sunshine, like Lebanon, Costa Rica and Australia.⁷⁻¹⁰ The mean value of vitamin D in cases was 18.39±7.14 ng/ml, and 58% of the fifty studied were deficient (values less than 20 ng/ml), 38 % were insufficient (20-30 ng/ml) and 4% were sufficient. The deficiency noted in this population was much higher than that noted in both, the Costa Rican and Iranian study.^{11,12} Among controls, the mean value was 22.93±10.74 ng/ml, and 40% of them were deficient, 36% were insufficient and 24% were sufficient. This is almost similar to the vitamin D levels noted in Indian children in a study done in Chandigarh, where 32% of normal children were found to be deficient.¹³ Other studies in India have also found a high prevalence of vitamin D deficiency in asymptomatic Indian children.^{6,14} However, the prevalence of deficiency in the control group is higher than that found in the Iranian study.¹²

There was a statistically significant difference in vitamin D levels between the cases and the controls ($p=0.008$). The same was observed in a similar study done in Iran.¹² As of now; there have been no publications from India noting the higher prevalence of vitamin D deficiency in children with asthma. Although the sample size is small, the findings of this study parallel those which were seen in the Costa Rican, Iranian and CAMP studies.^{11,12,15}

With respect to age and vitamin D levels, among cases, it was noted that with increasing age, the mean level of vitamin D decreased. This difference was not significant in controls. The low vitamin D levels may be a reason due to which these children are wheezers. These findings are similar to those seen in the Costa Rican study.¹¹ As the study was a cross sectional study, the improvement (if any) after administering vitamin D to these children, could not be assessed.

When the relationship between gender and vitamin D levels were analyzed, there was no statistically significant difference between girls and boys in both groups. However, in the control group, vitamin D levels were lower among the girls (mean value, 19.60±10.22 ng/ml versus 24.96±10.7 ng/ml among boys). This might be clinically significant. The analysis of the relationship between the number of hospitalizations with asthma and vitamin D levels showed a positive correlation, but not of significance (correlation coefficient, 0.24), and there was no statistical significance either. This was consistent with both, the Costa Rican and Iranian studies.^{11,12}

The relationship between vitamin D levels and the frequency of exacerbations were also studied, and while it was observed that those with greater frequency of exacerbations had lower vitamin D levels, the difference was not statistically significant ($p=0.422$). However, the

lack of significance might also be due to the small sample size.

An attempt was made to study the relationship between sun exposure and vitamin D levels among the cases. As the study was based on random selection of consecutive cases, the distinction between summer and winter levels of vitamin D could not be made. Also, skin pigmentation was not taken into account. However, by the existing standards, it was noted that among the cases, 33 (66%) had adequate sun exposure.¹⁶ There was a clinically significant difference in vitamin D levels between the groups who had adequate sun exposure and those who did not (20.5 versus 15.9 ng/ml, a difference of almost 20%). This was not statistically significant ($p=0.051$). This might be because of the small sample size. But vitamin D was sufficient in only 4% of the cases. This leads us to question whether the “sunshine vitamin” is produced in enough quantities in populations with dark skin colour, even if exposure to the sun is adequate. Another possible reason for this degree of deficiency could be the style of clothing in India, particularly Kerala, where very little skin is exposed. Without further, more accurate studies on this subject, conclusions cannot be drawn. A similar analysis was made with regard to vitamin D intake and vitamin D levels among cases. All the cases were non-vegetarians, and in Kerala, the diet is predominantly fish-based. The fish commonly consumed is sardine, which is small and cheap, but surprisingly, has large quantities of vitamin D in it.¹⁷ A large proportion of the children in the study preferred fried fish to that which was cooked in a curry. Frying is said to decrease the vitamin D levels in foodstuff by almost 50%.¹⁸ Even keeping that in mind, most of the children had an intake of almost 300 IU/day. Bearing in mind that a significant proportion also had adequate sun exposure, the requirement of vitamin D in the diet in these children is around 400 IU/day.¹⁹ It was found that the 47 (94%) who had intake of vitamin D had a mean value of 18.59ng/ml, while the 3 (6%) who did not, had a mean value of 20.5 ng/ml. The skewing of the values may be because of the small sample size, but the presence of insufficiency and deficiency of vitamin D in these children further emphasizes the need for food fortification in our country. At present, in its absence, one cannot ensure adequate vitamin D intake from the diet.¹⁸ At present, there are studies going on to revise the daily recommended intake of vitamin D, as well.¹⁴

A majority of the children included in the study (cases), have been enrolled in the asthma clinic at our hospital. As part of our protocol there, they undergo serum IgE testing as a marker of allergy. However, as it is not done in our hospital, not all the children have this test done. 23 of our cases had serum IgE levels estimated, and the relationship between IgE levels and vitamin D levels was analyzed. A negative correlation was found between the two (Pearson correlation coefficient, -0.477). This was not statistically significant ($p=0.054$), and it may be due to the small sample size. This inverse relationship

between serum IgE and vitamin D levels correlates with that seen in other studies.¹¹

Merits of the study

So far, no studies have been done to assess the relationship between asthma and vitamin D in India, to the best of our knowledge. This study adds to the data that has already been collected in other countries with regard to this subject, and contributes the data of both, normal and asthmatic population from India.

The study has set a platform for further follow-up studies, which may be conducted to assess improvement with vitamin D supplementation in the children in the study group, and also the relationship between steroid requirement and vitamin D levels.

The Indian population is thought to have a high prevalence of vitamin D deficiency, and our control population, though small, shows a high degree of vitamin D deficiency, re-affirming this.^{13,20-22} Food fortification is not done in India, and even though our study population consumes vitamin D-rich food, a majority of them are deficient. Hence, it highlights the need for food fortification in our country to ensure adequate intake of vitamin D in the population.

Limitations of the study

The sample size was small, primarily due to financial constraints, as vitamin D testing is not done free of cost in our hospital.

Lung function testing could not be performed on the subjects, and hence, we could not assess the relationship between vitamin D levels and lung function, as has been done in other studies.

The sun exposure pattern and a detailed dietetic history of the controls were not available, due to the type of controls chosen. In a busy OPD and emergency room, there was no time to get these details. Hence, the relationship between these variables and vitamin D levels of the controls could not be studied.

CONCLUSION

Prevalence of vitamin D deficiency in the study population, both cases and controls, is very high compared to studies done in the west, but similar to the levels in Indian studies. This study showed a significant difference in vitamin D levels between cases and controls which adds to the data that has already been collected in other countries with regards to the study subject and contributes to data of both normal and asthmatic children from India, from where there are little studies on the subject. Indian population is thought to have high prevalence of vitamin D deficiency and our control population, though small, showing high prevalence of

vitamin D deficiency, reaffirm this. This study highlights the need for further in depth study of both these aspects involving large samples which may help health authorities to formulate plans to ensure adequate supply of vitamin D to children and adults including asthmatics, like food fortification, especially in developing countries like India.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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