

Severity of asthma and Vitamin D status in children: A case–control study in a tertiary care center

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Abstract

OBJECTIVE: Studies to find the relation between asthma severity and Vitamin D yielded controversial reports. The objective of the present study is to find the association between severity of asthma and Vitamin D status in children.

MATERIALS AND METHODS: This case–control study was conducted in a tertiary teaching hospital. Details were obtained from children with asthma in the age group of 2–12 years who were under follow-up in the respiratory clinic. They were categorized into two groups according to the Global Initiative for Asthma criteria. Those with moderate-to-severe asthma were grouped as cases, and those with mild asthma were grouped as controls. Vitamin D estimation was done, and levels were analyzed with different levels of asthma severity.

RESULTS: Among 140 children with childhood asthma studied, 64 (45.7%) had mild asthma and 76 (54.3%) had moderate-to-severe asthma. Vitamin D was insufficient in 55 (72.4%) cases and 30 (46.9%) controls. There was a significant correlation between severity of asthma and Vitamin D levels ($P = 0.001$) and peripheral eosinophilia ($P = 0.02$). Logistic regression analysis showed that Vitamin D insufficiency could increase the risk for severe asthma, which remained after adjustment for potential confounders (odds ratio: 2.81 with 95% confidence interval: 1.36–5.82).

CONCLUSION: Screening for Vitamin D insufficiency is suggested for children with severe asthma. Vitamin D supplementation could avoid increasing steroid dose/adding new drugs as controllers.

Keywords: Asthma, children, insufficiency, Vitamin D

Introduction

High morbidity and socioeconomic burden of childhood asthma with its increasing prevalence worldwide prompt researchers to find the remedial measures. The most discussed hypothesis is the relationship between Vitamin D and asthma. The global Vitamin D deficiency epidemic parallels the increased incidence of asthma.^[1] Vitamin D influences the integrity of the airway epithelium, bronchial smooth muscles, and immune cells.^[2] Increased risk of asthma exacerbation, increased need of inhaled steroids, and lower forced expiratory volume in 1 s are seen in Vitamin D-deficient children, and Vitamin D estimation is suggested in asthma, but some studies show conflicting reports.^{[3],[4],[5],[6],[7],[8],[9]} *In vitro* and *in vivo* studies in animals and human studies showed that Vitamin D supplementation improves asthma, but results of clinical trials are controversial which may be related to severity and other confounding factors.^{[10],[11],[12]} There is no high-quality evidence to recommend Vitamin D supplementation in asthma.^{[13],[14]} Further evidence is needed to prove the effects of Vitamin D status in asthma. If proved beneficial, Vitamin D supplementation can avoid the side effects of controllers due to higher dose of steroid and adding new drugs, which is the current practice if asthma remains uncontrolled. The purpose of the study was to assess the relationship between severity of asthma and Vitamin D status in asthmatic children.

Materials and Methods

The participants for this case–control study were recruited from the respiratory clinic of a tertiary care center after getting approval from the institutional ethics committee. Children with physician-diagnosed asthma in the age group of 2–12 years who had been in the follow-up of respiratory clinic for at least previous 6 months were included after getting written informed consent and assent wherever required. Children with comorbid conditions such as liver or renal diseases or on drugs that affect Vitamin D metabolism such as antitubercular drugs and anticonvulsants, on Vitamin D supplementation for the last 6 months, tapering dose of controller as per the Global Initiative for Asthma (GINA) guidelines, noncompliant with controller treatment, or did not give consent were excluded from the study.

Parents and children were interviewed to collect details of illness. Also records of asthma diary were checked to collect details. Then children were categorized according to GINA classification of severity into 2 groups. Those children with

mild asthma ie well controlled with step 1 or 2 of GINA guidelines of asthma treatment were taken as controls. Children with moderate to severe asthma ie well controlled with step 3 to 5 or remained uncontrolled despite treatment were taken as cases. Dietary intake of calcium, Vitamin D and phytate was considered adequate if history of intake of diet rich in these nutrients was there for more than 3 days per week. Physical activity was considered adequate if history of average physical activity for atleast 7 hour per week. Adequate sun exposure is defined as average sun exposure of 6 hour per week between 10 a.m. and 3 p.m. Eosinophil count and 25(OH) Vitamin D levels by chemiluminescence method were measured. Serum levels of Vitamin D ≥ 20 were considered as sufficient, 12–19 as insufficient, and <12 as deficient.^{[15],[16]}

Data were collected in a structured questionnaire and entered into Microsoft Excel. Data were analyzed, and results were summarized as mean $\pm$ standard deviation (SD) for quantitative variables and absolute frequencies and percentages for categorical variables. Categorical variables were compared using the Chi-square test or Fisher's exact test if more than 20% of cells with an expected count of <5 were observed. Odds ratio (OR) was calculated. Logistic regression modeling with the enter method was used to assess the relation between Vitamin D status and severity of asthma with the presence of two confounders: age- and sex-adjusted priori. Statistical analysis of Vitamin D levels with dietary intake, sun exposure, and activity was done. The statistical software R version 3.0 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.URL [https://www. Rproject.org/](https://www.Rproject.org/)) was used. $P = 0.05$ or less was considered statistically significant.

Results

Out of 192 children enrolled for the study, 52 were excluded as per the exclusion criteria or not done Vitamin D estimation. Among 140 children with childhood asthma studied, 64 (45.7%) had mild asthma and 76 (54.3%) had moderate-to-severe asthma according to the GINA criteria; 101 (72.1%) were in the age group of >5 years [Table 1].

	Total (n=140), n (%)	Mild asthma (n=64), n (%)	Moderate-to-severe asthma (n=76), n (%)	P
Age in years (median IQR)	6.00 (4.00-10.0)	6.00 (4.00-8.00)	8.00 (4.00-10.2)	0.065
Sex				
Male	82 (58.6)	33 (51.6)	49 (64.5)	0.170
Female	58 (41.4)	31 (48.4)	27 (35.5)	
Age of diagnosis (years)	2.00 (1.00-3.00)	1.00 (1.00-3.00)	2.00 (1.00-3.00)	0.222
Duration of illness (years)	4.00 (2.00-7.00)	3.00 (1.88-6.00)	4.00 (2.00-7.00)	0.081
Allergic rhinitis	47 (33.6)	20 (31.2)	27 (35.5)	0.723
Infection as trigger	85 (60.7)	35 (54.7)	50 (65.8)	0.244
Family history	68 (48.6)	33 (51.6)	35 (46.1)	0.631
Eosinophilia	43 (30.7)	13 (20.3)	30 (39.5)	0.02
Adequate physical activity (7 h/week)	107 (76.4)	54 (84.4)	53 (69.7)	0.067
BMI	14.0 (12.8-15.6)	14.0 (13.0-15.6)	14.0 (12.7-15.7)	0.719
Vitamin D insufficiency <20 ng/ml, mean (SD)	18.5 (6.68)	20.4 (6.17)	16.9 (6.70)	0.001
Vitamin D <20 ng/ml	85 (60.7)	30 (46.9)	55 (72.4)	0.004
Age group >5 years	101 (72.1)	45 (70.3)	56 (73.7)	0.799

BMI=Body mass index, SD=Standard deviation

Table 1: Characteristic of children according to asthma severity

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Vitamin D level ranged from 4.2 to 38 ng/ml, with a mean Vitamin D level of 18.5 (SD: 6.68) and a median of 18.05 (13.4–22.2) among 140 children studied. Insufficiency of Vitamin D was noticed in 85 (60.7%) children. Vitamin D insufficiency was more in the higher age group. Vitamin D deficiency (<12 ng/ml) was seen in 38 males (60.3%) compared to 25 females (39.7%). Vitamin D was insufficient in 55 (72.4%) cases and 30 (46.9%) controls [Table 2]. Dietary evaluation of Vitamin D-rich food did not correlate with measured Vitamin D levels ($P = 0.395$); total sun exposure hours correlated with Vitamin D levels ($P = 0.033$).

	Total (n=140), n (%)	Mild asthma (n=64), n (%)	Moderate asthma (n=76), n (%)	P (overall)
Vitamin D levels				
Sufficient ≥ 20	55 (39.3)	34 (53.1)	21 (27.6)	0.006
Insufficient 12-19	22 (15.7)	6 (9.38)	16 (21.1)	
Deficient <12	63 (45.0)	24 (37.5)	39 (51.3)	
Vitamin D level, mean (SD)	18.5 (6.68)	20.4 (6.17)	16.9 (6.70)	0.001

SD=Standard deviation

Table 2: Vitamin D status according to severity

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Unadjusted OR of severity of asthma and Vitamin D insufficiency was 2.96, with 95% confidence interval (CI): 1.47–5.99 ($P = 0.0024$). Multivariate logistic regression analysis showed OR of 2.81, with 95% CI: 1.36–5.82. Age and sex did not seem to have any significant effect. Vitamin D insufficiency could increase the risk for severe asthma by 2.8 times.

Discussion

The main finding with clinical implication is an increased risk of asthma severity with Vitamin D insufficiency [Figure 1].^[17] Vitamin D maintains airway epithelial integrity. It acts locally in response to inflammation. Vitamin D decreases inflammatory trigger for asthma exacerbation which, in turn, leads to decreased steroid use/steroid sparing. Vitamin D deficiency or insufficiency causes the downregulation of glucocorticoid pathways which, in turn, leads to the need for increased steroid dose. Studies show improved efficacy of inhaled steroid if Vitamin D is supplemented.^{[18],[19]} Daily intake of oral steroids is reported to lower Vitamin D level.^[2] There were no patients requiring daily oral steroids in our study.

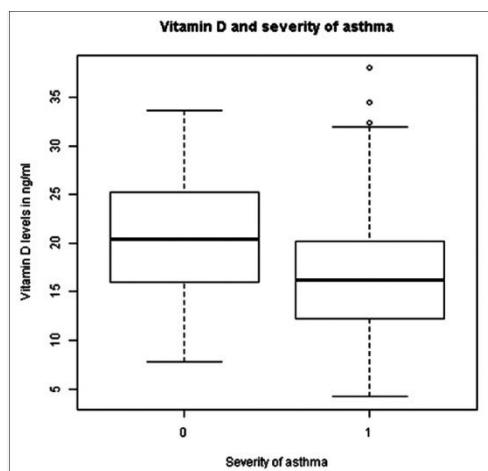


Figure 1: Vitamin D and severity of asthma. 0 – mild asthma and 1 – moderate-to-severe asthma according to the global initiative for asthma criteria

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The prevalence of Vitamin D insufficiency is high in children with asthma in our study similar to previous studies.^{[7],[17]} Vitamin D insufficiency is seen more in the higher age group in our study, actually when there is a high Vitamin D requirement due to a tremendous increase in the bone growth. This may be due to decreased chance of sun exposure during peak hours (10 a.m.–3 p.m.) due to schooling and decreased intake of Vitamin D-rich diet. Vitamin D insufficiency does not show any gender variation in the present study.

Childhood asthma is found to be more common in boys, which is reflected in the present study. The reason can be a smaller lung size in males than in females at birth. Whether Vitamin D insufficiency in children with asthma is primary or secondary is a controversial issue. Children with asthma will be restricted to play outdoors and that can be one reason for Vitamin D insufficiency. However, prolonged duration of illness and Vitamin D insufficiency did not show any correlation in our study.

Allergic rhinitis is a comorbid condition which is also shown to have some association with Vitamin D. In our study, we could not find any significant relation of allergic rhinitis with Vitamin D levels or severity of asthma.^[20]

Eosinophilia is seen associated with severe asthma in the study, which is considered as a risk for future exacerbation.^[21] Vitamin D has got some immunological role in the lung tissue.^[22] Its insufficiency can lead to an increased risk of respiratory infections, which is the common trigger for asthma in children and can increase asthma severity. In our study, we cannot find any relation with low Vitamin D levels and the presence of infection as the trigger.^{[23],[24],[25]} There was a positive correlation between hours of sun exposure and Vitamin D levels; but could not find any correlation between history of adequate intake of vitamin D rich diet and serum vitamin D levels in this study.

Limitation

Normal children were not included in the study as controls because we compared Vitamin D levels among asthmatic children with different levels of severity. Pulmonary function test was not included as we studied children in the age group of 2–12 years. Well-designed randomized double-blind controlled trials are needed to prove the association between Vitamin D status and asthma and to establish the appropriate route, dose, and safety of Vitamin D supplementation for the prevention and treatment of asthma. Seasonal variation of Vitamin D levels was not analyzed; Indian studies did not show a significant difference with sample at different seasons.^[6] Furthermore, we did not take into consideration the seasonal effect on asthma. A follow-up study was done to know the effect of Vitamin D supplementation in those with deficiency.

Conclusion



Vitamin D insufficiency is a correctable risk factor for asthma severity. Vitamin D supplementation in them can avoid the increased steroid dose. We suggest Vitamin D level screening in severe asthmatic children and potential use of Vitamin D as an adjuvant with steroid.

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Conflicts of interest

There are no conflicts of interest.

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