

To study the correlation of serum vitamin D3 level and degree of control in asthmatic children on inhaled corticosteroids

Nithiyantham Ramakrishnan, Shobhana Sivathanu, Andrea Josephine, Sowmya Sampath

From Department of Paediatrics, ESIC Medical College and ESI PGIMS, Chennai, Tamil Nadu, India

Correspondence to: Dr. Shobhana Sivathanu, Department of Paediatrics, ESIC Medical College and PGIMS, K.K. Nagar, Chennai, Tamil Nadu, India. Phone: +91-9841145367. E-mail: shobhana.paed@gmail.com

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ABSTRACT

Background: Childhood asthma is more of a syndrome with complex interplay of gene-environment-lifestyle factors not only for its causation but also for its control with pharmacological therapy. Vitamin D deficiency has been implicated as a risk factor for the causation of asthma and for its poor control in children. **Objective:** To study the correlation of serum vitamin D3 level and degree of control in asthmatic children on inhaled corticosteroids. **Methods:** It was an observational study conducted in the pediatric asthma clinic of a Government Medical College Hospital. The study population consisted of 75 asthmatic children aged 5-15 years. Children with persistent asthma on inhaled corticosteroids were classified into three groups based on global initiative for asthma guidelines. Serum vitamin D levels were measured in all the three groups and an attempt was made to find a correlation between asthma control and vitamin D levels. **Results:** Among the study group, 33% belonged to controlled group, 35% to uncontrolled group and 33% to partly controlled group. 71% of the asthmatic children were found to be either vitamin D deficient/insufficient. Around 81% of uncontrolled asthmatic children were vitamin D deficient, whereas only 12% of well controlled asthmatics had documented vitamin D deficiency. Among the children in controlled group, the majority (72%) were found to have normal vitamin D status. On comparison of asthma control between the groups, there was a statistically significant difference in vitamin D levels between controlled and uncontrolled group ($p < 0.001$). The majority of children in the uncontrolled group constituted girls (69.2%) and 94% of them were vitamin D deficient. **Conclusion:** Vitamin D deficiency/insufficiency is widely prevalent in children with persistent asthma and lower levels of vitamin D are associated with poor asthma control. Girls formed a greater percentage of uncontrolled group and majority of them were vitamin D deficient.

Key words: Asthma control, Children, Correlation, Vitamin D level

Childhood asthma is more of a syndrome with complex interplay of gene-environment-lifestyle factors not only for its causation but also for its control with pharmacological therapy. The genetic factors contributing to asthma, namely vitamin D receptor, human leukocyte antigen genes, human toll-like receptors, matrix metalloproteinase, disintegrin, and metalloprotein-33 are regulated by vitamin D [1]. It is now evident that fetal lung growth and immune system development is dependent on maternal vitamin D intake in pregnancy [2,3]. Camargo et al., in a retrospective cohort study, concluded that increasing maternal vitamin D intake during pregnancy decreased the risk of wheeze in early childhood [2]. Vitamin D plays a key role in the management of asthma, not only by causing upregulation of antimicrobial proteins that are involved in the defense against respiratory infections, which are the most common triggers but also by its anti-inflammatory and anti-proliferative effects on airway smooth muscles.

Vitamin D deficiency has been implicated as a risk factor for several chronic diseases and can be a factor for poor control in children with asthma [4,5]. We planned this study to determine

the correlation of serum vitamin D3 level with the degree of asthma control in children on inhaled corticosteroids.

METHODS

This was an observational study conducted in Pediatric asthma clinic of a Government Medical College Hospital in South India from February 2014 to November 2014. The study protocol was approved by the Institutional Ethics Committee. 75 consecutive asthmatic children aged 5-15 years with persistent asthma who had been on inhaled corticosteroids (as per standard of care) for at least previous 4 weeks were enrolled in the study. Asthmatic children on vitamin D supplementation or those diagnosed to have rickets, chronic inflammatory disorders, chronic systemic diseases, and malignancies were excluded.

After a detailed history, examination and relevant investigations, registered children and their parents were educated on importance of drug compliance and inhaler techniques were demonstrated in a detailed manner. At every review, they were asked to bring the inhaler device and techniques of inhalation

were checked along with history of drug compliance. Peak flow rates were measured using Wrights peak flow meter.

Asthma control was assessed in the study group based on the parameters of global initiative for asthma (GINA) guidelines. The study population was categorized into three groups depending on levels of control. Informed written consent was obtained, and blood samples were taken for measuring serum 25 OH vitamin D₃. Under strict aseptic precautions, 5 ml of venous blood was drawn. Serum 25 OH vitamin D₃ was measured by CLIA method. Vitamin D sufficiency was defined as values ≥30 ng/ml while insufficiency was between 20 and 29 ng/ml and deficiency was <20 ng/ml.

Data were analyzed for correlation between vitamin D levels and the control of asthma. Statistical analysis was performed by one-way ANOVA followed by TUKEYHSD method. Chi-square test and correlation was also done. Based on this data, statistical significance was determined for all the parameters.

RESULTS

A total of 75 children enrolled in the study consisted of 38 boys and 37 girls. The categorization into the 3 groups (GINA guidelines) is shown in Table 1. Peak flow measurements showed a higher mean peak expiratory flow rate (PEFR) in the controlled group (98%) as compared to the uncontrolled group (72%).

The mean vitamin D3 levels showed a marked difference in the 3 groups with minimum levels in uncontrolled and maximum levels in the controlled group (Table 2). Keeping the mean vitamin D3 level as the dependent variable and comparing asthma control between the groups, we found statistically significant difference in vitamin D levels between controlled and uncontrolled group (p<0.001) and also between partly controlled and controlled group (p<0.001). However, such statistical significance was not observed between uncontrolled and partly controlled groups (p=0.120) (Table 3).

On further comparing, the 3 subcategories of vitamin D levels with asthma control, it was seen that nearly 64% of subjects with vitamin D deficiency were in uncontrolled group while only 9%

of such cases were in controlled group. Furthermore, as much as 81% of uncontrolled asthmatic children were vitamin D deficient whereas only 12% of well-controlled asthmatics had documented vitamin D deficiency. Analysis showed a statistically significant relationship (p<0.001) between the vitamin D levels and the level of asthma control (Table 4).

Analysis of vitamin D levels in both sexes revealed that 65% of girls were vitamin D deficient as compared to 24% of boys. Both vitamin D deficiency/insufficiency was much more common in females as shown in Fig. 1. Among the vitamin D deficiency group, 71% of girls and 44% of boys were in the uncontrolled group. Boys constituted the majority of patients in vitamin D sufficient group (18/22) with 83% of them were well controlled. The study revealed that most of the children in uncontrolled group (21/25) had vitamin D deficiency while normal vitamin D levels were seen in the majority of the children in controlled group (22/29).

DISCUSSION

Among the study population, 70.6% of the asthmatic children were found to be either vitamin D deficient/insufficient. Among the vitamin D3 deficient children, 63.6% belonged to uncontrolled group while 81.8% of vitamin D sufficient children belonged to controlled group. Lower vitamin D levels were documented in uncontrolled and partly controlled group as compared to the controlled group. Among the children in controlled group, the majority (72%) were found to have normal vitamin D status. On the contrary, most of the children in uncontrolled group were vitamin D deficient/insufficient (88.5%). We found that 94% of the girls in uncontrolled group were Vitamin D deficient thus reinforcing the fact that vitamin D deficiency may be responsible for persistent symptoms even with adequate pharmacological therapy. The higher prevalence of vitamin D deficiency in girls noted in our study needs to be validated by a larger study. Whether there still exists a gender discrimination in food pattern contributing to vitamin D deficiency in girls or the greater sun exposure among boys as a result of outdoor activities protects them from deficiency or it is just a chance finding because of a small sample size needs to be looked into.

It is reported that in asthmatic children, low vitamin D levels have been associated with poor asthma control, impaired lung function, increased drug usage and increased number of acute

Table 1: Categorization of study population (n=75)

Category of asthma control	Number of children	Male (%)	Female (%)
Uncontrolled	26	8 (30.8)	18 (69.2)
Partly controlled	24	11 (45.8)	13 (54.2)
Controlled	25	19 (76)	6 (24)
Total	75	38	37

Table 2: Mean vitamin D3 levels among the categories

Category of asthma control	Number of patients	Vitamin D levels (ng/ml)		p value
		Mean	SD	
Uncontrolled	26	16.02	8.88	<0.001**
Partly controlled	24	22.02	5.87	
Controlled	25	39.43	14.96	
Total	75	25.74	14.52	

**Statistically significant. SD: Standard deviation

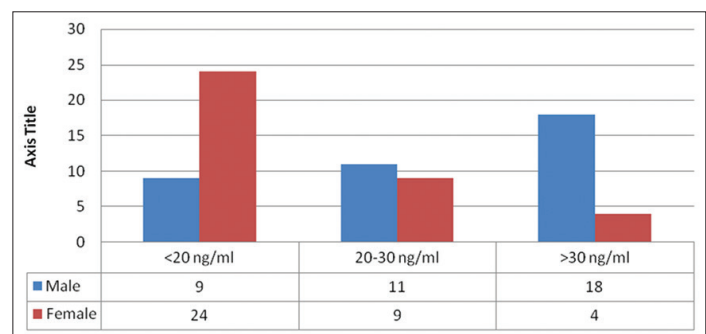


Figure 1: Gender versus vitamin D status

Table 3: Dependent variable: Vitamin D3 (ng/ml)

Level of asthma control		Mean difference in vitamin D level (I-J)	Standard error	p value
I	J			
Uncontrolled	Partly controlled	-6.009	3.01	<0.120
	Controlled	-23.416(*)	2.97	<0.001**
Partly controlled	Uncontrolled	6.009	3.01	<0.120
	Controlled	-17.407(*)	3.03	<0.001**
Controlled	Uncontrolled	23.416(*)	2.97	<0.001**
	Partly controlled	17.407(*)	3.03	<0.001**

**Statistically significant

Table 4: Vitamin D levels with asthma control

Vitamin D levels (ng/ml)	Levels of asthma control (%)			Total (%)	p value
	Uncontrolled	Partly controlled	Controlled		
<20					
Number (%) of patients	21 (63.6%)	9 (27.3%)	3 (9.1)	33 (100)	<0.001*
Asthma control level	80.8	37.5	12.0	44.0%	
20-30					
Number (%) of patients	2 (10.0)	14 (70.0)	4 (20.0)	20 (100)	
Asthma control level	7.7	58.3	16.0	26.7	
>30					
Number (%) of patients	3 (13.6)	1 (4.5)	18 (81.8)	22 (100.0)	
Asthma control level	11.5	4.2	72.0	29.3	
Total					
Number (%) of patients	26 (34.7)	24 (32.0)	25 (33.3)	75 (100.0)	
Asthma control level	100.0	100.0	100.0	100.0	

*p value statistically significant

exacerbations [6,7]. Our study shows that serum vitamin D levels have a significant impact on asthma control, higher levels correlating with better control and lower levels with poor control. Since drug compliance and technique of inhalation were routinely checked these factors are unlikely to contribute towards poor control. Our result is in concurrence with the cross-sectional study done by Chinellato et al. [8]. In their study of 75 Italian children, it was found that vitamin D levels positively correlated with asthma control. Somashekar et al. [9] found a much lower vitamin D levels in asthmatic children. Contrary to our study, Menon et al. [10] Found no significant difference in Vitamin D levels between 263 asthmatic subjects and 284 non-asthmatic controls of ages 2-19 years. In their study, they only found a lower level in obese children both in asthmatic and non-asthmatic group. This correlation of obesity with vitamin D level was not attempted in our study.

Vitamin D deficiency is generally associated with inflammatory and infectious diseases; thus, impairing pulmonary function and contributing to poor control. In a cross-sectional study of 54 asthmatic adults by Sutherland et al., serum vitamin D level positively correlated with FEV1 and glucocorticoid response [11]. In our study too, we found a much higher percentage of children with vitamin D deficiency in the uncontrolled group with much lower PEF. Bener et al. found that 68.1% out of 483 asthmatic children and 36.1% out of 483 healthy controls were vitamin D deficient [12]. They concluded that vitamin D deficiency was

a major predictor of asthma in the study population. In another adult study done by Samrah et al. [13], the severity of vitamin D deficiency correlated with poor asthma control as in our study and the authors had observed the need for more medications to control asthma in such cases.

Although there are study reports of strong association of vitamin D deficiency with causation of asthma and its control, there could be several factors affecting the level of vitamin D itself in these asthmatic children. The confounder in our study could be the use of multiple courses of systemic corticosteroids, especially in the uncontrolled group and other co-morbid conditions which could have contributed to alteration of vitamin D level itself thus limiting the scope.

In spite of strong correlation found between degree of asthma control and vitamin D levels, the design of the study does not allow conclusions about the actual cause-effect relationship and it is difficult to ascertain that vitamin D deficiency alone is responsible for poor asthma control. Interventional studies with larger sample size would be required to prove the cause-effect relationship. Although all children with vitamin D deficiency/insufficiency were appropriately treated with oral vitamin D, we did not reassess the control in our patients after vitamin D supplementation as it was not an interventional study. However, this study group is being followed up after adequately treating them and reassessment of asthma control after supplementation is being planned as a follow-up study. Furthermore, normal

controls were not included to get baseline vitamin D level of the population.

CONCLUSION

In this study, vitamin D deficiency is found to be prevalent in children with persistent asthma (72%), more so in the uncontrolled group and lower vitamin D levels are associated with poor asthma control. In our study, vitamin D deficiency/insufficiency was higher among poorly controlled asthmatic girls.

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