

## The Association between Vitamin D and Wheezing

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### ABSTRACT

**Objective:** To determine the association between vitamin D status and recurrent wheezing.

**Study Design:** Comparative cross-sectional study.

**Place and Duration of Study:** Department of Paediatrics, Pak Emirates Military Hospital (PEMH), Rawalpindi Pakistan, from Aug 2019 to Aug 2020.

**Methodology:** Sixty infants with recurrent wheezing and 60 healthy age-matched infants without acute or chronic illness were inducted into the study. 25 (OH) Vitamin D, immunoglobulin E (IgE) levels and eosinophil counts were measured. In addition, data were analyzed to find the association of vitamin D levels with recurrent wheezing.

**Results:** In the Control-Group, the mean 25 (OH) vitamin D levels were  $25.90 \pm 7.57$  ng/ml and in the Recurrent Attack-Group was  $13.90 \pm 4.63$  ng/ml ( $p = 0.02$ ). The mean IgE levels of the Control-Group were  $22.80 \pm 2.67$  IU/ml, and the Recurrent Attack-Group was  $149.20 \pm 30.60$  IU/ml ( $p = 0.001$ ). Eosinophil count in Recurrent Attack-Group was  $150.40 \pm 23.11$  cells/uL and  $338.95 \pm 33.50$  cells/uL in Control-Group respectively ( $p = 0.08$ )

**Conclusion:** There is a strong association between low vitamin D levels and recurrent wheezing.

**Keywords:** Immunoglobulin E, Vitamin D, Wheeze.

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### INTRODUCTION

Airway obstruction due to inflammation or narrowing of the air passage usually presents with the characteristic recurrent wheezing pattern. Its aetiology is multifactorial. The prevalence of wheezing is high among children and is usually associated with bronchiolitis and asthma.<sup>1</sup> It is a common complication after premature delivery. Recurrent wheeze is defined as three or more episodes of wheezing reported by parents over the last 12 months. The frequency of wheezing in the Pakistani population is 15.3%, as shown by various studies.<sup>2</sup> Allergic disease is a commonly found entity in Pakistan that largely remains undiagnosed. Wheezing can also indicate a serious underlying ailment other than allergic disorders such as COPD, bronchitis, emphysema, lung cancer etc., but these are rare in infancy.<sup>3</sup>

Various risk factors have been associated with recurrent wheezing in infancy and childhood, such as small airway dimensions, insufficient lung functionality at birth, viral infections, pollution, pets, etc.<sup>4</sup> Among the other important risk factors, various animal and human studies have linked low vitamin D levels with atopic diseases and respiratory tract

conditions.<sup>5</sup> However, the pathophysiology behind this association is still unclear. One of the proposed mechanisms can be the balance between humoral response and cellular response is maintained by Vitamin D which modulates the regulation of the immune system via activating macrophages, monocytes, dendrites and natural killer cells via receptors of the active form of vitamin D which are present on the surface of these cells.<sup>6</sup>

There are various forms of Vitamin D. Role of 1, 25-(OH)<sub>2</sub>D<sub>3</sub> in humans has been well established in bone metabolism by maintaining a balance between calcium and phosphate. Its deficiency may lead to the development of osteomalacia in adults and rickets in children. Vitamin-D levels also influence airway remodelling by its effect on the gene-mediated expression of bronchial smooth muscle cells. Genes in calcium-related pathways leading to bronchial smooth muscle contraction are also induced by 1, 25(OH)<sub>2</sub>D.<sup>7</sup>

Insufficiency and deficiency of Vitamin D have been labelled as emerging risk factors for recurrent wheezing in infants. However, few studies have linked low maternal vitamin D intake and recurrent wheezing.<sup>8</sup> Han *et al.* and Parsad *et al.* have linked low vitamin D levels with asthma and recurrent wheezing in children up to 3 years of age.<sup>9</sup> On the contrary, Özyayın *et al.* in their study, demonstrated no

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significant association between vitamin D status and recurrent wheezing in infants.<sup>10</sup> This study was designed to see the association of vitamin D status with recurrent wheezing in infants presenting to our clinical setup. Recurrent wheeze is a very common problem in childhood, and if a strong association is found, then it may provide valuable information and a basis for future studies in preventing illnesses with wheeze in childhood by adequate supplementation of vitamin D.

**METHODOLOGY**

This comparative cross-sectional study was conducted for 12 months, from August 2019 to August 2020, at the Department of Paediatrics, Pak Emirates Military Hospital, Rawalpindi Pakistan. PEMH is a tertiary care referral centre receiving patients from different parts of the country. After taking permission from the Ethical Committee Review, Board (vide letter number A/28/EC/198/2020), written informed consent was taken from the parents of patients. The particulars of patients were endorsed in the proforma. The sampling criteria used was the non-probability consecutive sampling technique.

**Inclusion Criteria:** Patients of either gender, diagnosed by a physician as having recurrent wheezing (>three attacks) 1-12 months of age were inducted into the study.

**Exclusion Criteria:** Patients receiving any vitamin D supplementation or corticosteroids in the last six months, along with those with congenital malformations, respiratory tract infections, and chronic medical and surgical diseases, were excluded from the study.

Healthy, age and weighted-matched individuals visiting for routine check-ups and vaccination were taken as a control population. In addition, 3-4ml of blood was taken via venipuncture into the EDTA tube, and eosinophil count was analyzed using the automated analyzer Sysmex KX21. IgE levels were assessed by using sandwich ELISA. 25(OH) Vitamin D levels were assessed by the chemiluminescence method using ADVIA CENTAUR. Two different cut-off values were used for categorizing the concentration of 25(OH) Vitamin D: 1) Levels between 20-50ng/ml are considered sufficient or normal levels, 2) Levels <20ng/ml are labelled as vitamin deficiency, 3) Levels <10 ng/ml are labelled as extremely deficient.

Statistical Package for Social Sciences (SPSS) version 25.0 was used for the data analysis. Mean and standard deviation were calculated for numerical variables such as age, eosinophil count, 25 (OH) vitamin D

levels and IgE levels. Percentage and frequency were calculated for categorical variables like gender etc. An independent sample t-test was applied to compare the mean levels of 25(OH) vitamin D, IGE and eosinophil count between the two groups. The Chi-square test was used to establish the association between vitamin D levels and the two groups. The *p*-value of ≤0.05 was considered significant.

**RESULTS**

A total of 60 individuals with recurrent wheeze and 60 healthy cases were inducted into the study. The mean age of the patients was 4.50±2.28 months, with a range of 1 to 9 months. The mean age of the Control-Group was 4.53±2.30 months, and the Recurrent Wheezing Attack-Group was 4.48±2.20 months. Of the 120 patients, 63 (52.5%) were males, and 57 (47.5%) were females.

The mean levels of 25 (OH) vitamin D in the Control-Group were 25.90±7.57 ng/ml, and in the Recurrent Attack-Group was 13.90± 4.63 ng/ml (*p*=0.02). The mean IgE levels of the Control-Group were 22.80±2.67 IU/ml, and the Recurrent Attack-Group was 149.20±30.60 IU/ml (*p*=0.001). Eosinophil count in Recurrent Attack-Group was 150.40±23.11 cells/uL and 338.95±33.50 cells/uL in Control-Group respectively (*p*=0.08) (Table-I).

**Table-I: Mean levels of Vitamin D, IgE and Eosinophil in Control and Recurrent Wheeze Group (n=120)**

	Groups	Number of Cases (n)	Mean±SD	<i>p</i> -value
Vitamin D levels(ng/ml)	Control	60	25.90±7.57	0.02
	Recurrent Wheezing	60	13.95±4.63	
IgE (IU/ml)	Control	60	22.88±2.67	0.001
	Recurrent Wheezing	60	149.25± 30.67	
Eosinophil (cells/uL)	Control	60	150.48± 23.11	0.08
	Recurrent Wheezing	60	338.95± 33.55	

Out of total 120 subjects 59(49.1%) patients had normal 25(OH) vitamin D levels (20-50 ng/ml), whereas 46(38.3%) patients had deficiency of 25(OH) vitamin D (<20 ng/ml). 15(25.0%) patients had extremely deficient 25(OH) vitamin D levels (<10 ng/ml). Only 6 (10.0%) patients in the Control-Group showed deficient vitamin D levels, whereas 40 (66.6%) patients in the Recurrent Wheezing-Group had deficient vitamin D levels (Table-II).

**Table-II: Vitamin D Status in Control Group and Recurrent Wheezing Group (n=120)**

Groups	Vitamin D status (ng/ml) Frequency (%)			p-value
	Extremely Deficient	Deficient	Sufficient	
	<10	<20	20-50	
Control (n=60)	0(0)	6(10.0)	54(90.0)	0.001
Recurrent wheezing (n=60)	15(25.0)	40(66.6)	5(8.4)	

**DISCUSSION**

Wheezing in the early childhood period is characterized by three distinct patterns: Transient early wheeze (from the first year of life to early childhood), late-onset wheeze (from the first three years of life to early adolescence) and persistent wheeze (starting in mid-pre-school years continuing into adolescent). One of the challenging problems in infancy is recurrent wheezing due to its associated mortality and morbidity worldwide.

Vitamin D is emerging as a new protective tool in preventing asthma or wheezing due to its antiviral properties, enhancement of response to steroids and down-regulation of atopy. Therefore, assessing its status is very important to assess the reason behind recurrent wheezing in infancy. A study conducted in Turkey demonstrated the prevalence of vitamin D insufficiency in 22.5% and deficiency in 14.5% of children between 1 to 7 years of age.<sup>11</sup> A recent study on the general population in Pakistan suggested that 53.5% of citizens have Vitamin D deficiency, 31.2% of individuals have insufficient vitamin D levels, and only 15.3% have normal levels.<sup>12</sup> However, our study demonstrated that 49.1% of our patients have normal levels. Özaydın *et al.* revealed a high prevalence (90% and 77.8%) of vitamin D deficiency in patients with recurrent wheezing and the control group, respectively.<sup>10</sup> Our study also demonstrated a high prevalence of vitamin D deficiency (91.6%) in patients with recurrent wheezing, with 25% of the patients extremely deficient in vitamin D. Various factors have been associated with these low levels, such as lack of compliance in supplement use, lack or inappropriate duration of exposure to sunlight, diet, skin colour and latitude etc.

Our study revealed a positive correlation between decreased vitamin D levels and recurrent wheezing ( $p=0.02$ ). The mean levels of 25(OH) Vitamin D in the control group were  $25.9\pm7.57$  ng/ml, and in the recurrent attack group was  $13.9\pm4.63$  ng/ml. Litonjua *et al.* showed similar results, assessing vitamin D status at

birth, six months and 1,2,3,4,5 and 10 years. Results suggested a consistent inverse relationship between 25(OH) vitamin D levels and allergic sensitization in early life. They also showed that for ten years, whenever the patients had deficient vitamin D levels, it was positively correlated with the risk of asthma and wheezing.<sup>13</sup> Ozdemir *et al.*<sup>14</sup> also concluded that infants with recurrent wheezing are more likely to be vitamin D deficient than their healthy counterparts. Contradictory results were shown by Wei *et al.* that there is no significant association between Vitamin D status and wheezing in childhood.<sup>15</sup> A recent systematic review Shen *et al.* revealed a significant inverse relationship between childhood asthma and intake of vitamin D.<sup>16</sup> Shen *et al.* also suggested that intake of Vitamin D during pregnancy may play a vital role in protecting the offspring against wheeze.

IgE-mediated hypersensitivity reactions may be a possible cause of wheezing. Thus, when the IgE levels and eosinophil counts were measured for the control and recurrent wheezing groups, a statistically significant difference was seen. The mean IgE levels of the control group were  $22.8\pm2.67$  IU/ml, and the recurrent attack group was  $149.2\pm30.6$  IU/ml ( $p=0.001$ ). Eosinophil count in recurrent attack group vs. control group was  $338.95\pm33.5$  cells/uL and  $150.4\pm23.11$  cells/uL respectively ( $p=0.08$ ). Similar findings were reported by El-Asheer *et al.*<sup>17</sup> Thus, measurement of IgE levels can be a significant predictor in identifying children at risk of recurrent wheezing. Yang *et al.* revealed that IgE levels in the cord blood, male gender and history of passive smoking are the predictive factors for recurrent wheezing.<sup>18</sup>

In addition to the effect of vitamin D on bone mineralization, it also has a steroidlike action and regulates the function of over 200 genes. Most individuals with vitamin D deficiency remain asymptomatic, making its diagnosis challenging. According to the guidelines published based on bonecentric and pleiotropic effects of vitamin D, the recommended target intake ranges from 400-2000 IU/day.<sup>19</sup>

Balanced supplementation varies depending on age, body weight, ethnicity, dietary habits, latitude, and disease status. Randomized control trials are required to prove further the effect of vitamin D deficiency in the patho-genesis of recurrent wheezing in children. The D-wheeze and VDAART trials reported the significant protective effect of vitamin D supplementation in infants at risk of developing asthma and recurrent wheezing.<sup>20,21</sup> However, further

investigations with long-term follow-ups are required to understand the mechanism behind this phenomenon.

### RECOMMENDATIONS

There is a need to do further studies on whether vitamin D deficiency has a direct effect on IgE levels as well as on eosinophil counts. In addition, there is a need to look at the role of vitamin D in developing other atopic diseases in childhood. Long-term follow-up is also desired to determine whether infants treated for vitamin D deficiency would develop atopic conditions like asthma in the future. Therefore, we recommend that vitamin D levels be performed in infants with recurrent wheeze requiring hospitalisations. Vitamin D deficiency, if found, should be adequately treated in this age group. It is also recommended that maternal education regarding nutrition should be undertaken, and mothers must be advised to have a diet adequate in vitamin D.

### CONCLUSION

Vitamin D levels have an indirect relation with recurrent wheezing. Therefore, it is important to maintain optimum vitamin D levels. In addition, raised IgE levels and eosinophil counts may also be an important risk factor in children developing recurrent wheeze.

**Conflict of Interest:** None.

#### Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

MH: Study design, data analysis, critical review, drafting the manuscript, critical review, approval of the final version to be published, QM & QZK: Conception, study design, drafting the manuscript, approval of the final version to be published, JB & MA: Data acquisition, Critical review, approval of the final version to be published.

MI: Data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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