

# Comparison Of Serum Vitamin D Level In Under 5 Recurrent Wheezers And Healthy Children- A Cross-Sectional Study

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## KEYWORDS

Recurrent wheezing;  
Vitamin D

## ABSTRACT

Preschool children are often observed to have wheezing. Many studies have demonstrated that a deficiency in vitamin D increases the chances of recurrent wheezing, while a small number of studies have found no correlation between the two. Our goal was to determine whether there is a correlation between serum vitamin D levels and recurrent wheezing in children under the age of five. This was a cross-sectional study conducted in a tertiary care hospital. Serum vitamin D levels were measured in under-five-year-old recurrent wheezers and age-matched control subjects. The purpose of the data analysis was to determine whether there was a correlation between recurrent wheezing and serum vitamin D levels. We found significant association was between the low serum Vitamin D levels and the recurrent wheeze ( $p=0.002$ ). Larger studies with significantly more sample sizes are required.

## 1. INTRODUCTION

One of the most common causes of hospital visits in infancy is recurrent wheeze (RW), which is a major global burden. About one in every three children have at least one episode of wheezing before 3 years of age and the cumulative prevalence of wheezing is around 50% at six years of age (Tenero et al., 2013). Most studies have shown that there are multiple factors associated with RW and asthma. Various hypotheses have been proposed to explain the rising prevalence of asthma in children, including modifications to lifestyle, diet, and environmental factors (Pearce and Douwes 2013). Thus, the higher frequency of wheezing episodes in children may be partially related to vitamin D insufficiency. Numerous other childhood disorders, including chronic liver disease, chronic kidney disease, malnutrition, and others, may be brought on by low vitamin D levels, even in cord blood, according to previous studies (Camargo et al., 2010; Camargo et al., 2011). The purpose of our study was to evaluate the prevalence of vitamin D insufficiency/deficiency in children who suffer from wheezing frequently in comparison to a sample of healthy children. Despite being a tropical country, current research indicates that 50–90% of Indians have vitamin D inadequacy (Anuradha et al., 2017; Randev et al., 2018; Gupta A 2014). Therefore, we sought to ascertain the association between serum vitamin D levels and RW in our under-five population, utilizing accepted standards.

## 2. MATERIALS AND METHODS

### 2.1. Study population

This was a hospital-based analytical cross-sectional study performed in the Department of Pediatrics of a tertiary care referral hospital from October 2022 to March 2023. After obtaining written informed consent, children with RW between the ages of 6 months and 5 years who presented to the emergency room or outpatient department were enrolled as cases. Healthy age and weight-matched children visiting outdoors for immunization or routine check-ups were included as controls. Infants who were preterm (less than 37th gestational week), had low birth weight (less than 2500 grams), had a history of admission or intubation with assisted ventilation in the newborn intensive care unit due to respiratory distress and children with an underlying cardiopulmonary condition (e.g. congenital heart

disease, symptomatic cardiac anomaly/failure, chronic lung disease, bronchopulmonary dysplasia, pulmonary tuberculosis, aspiration pneumonia, cystic fibrosis, gastroesophageal reflux disease, pneumonia), immunodeficiency, neurologic or metabolic diseases, rickets having received vitamin D supplementation in last six months or congenital malformations, malnutrition or any chronic disorder were excluded.

All the parents were informed about the study and were asked to fill up a detailed questionnaire regarding previous wheezing episodes, the age of onset, their frequency, severity, the need for hospitalization, history of atopic dermatitis in the child, family history of asthma or any allergies, birth details, dietary history including the duration of exclusive breastfeeding and vitamin D supplementation in infancy.

Over half of the population is vitamin D deficient. Therefore, using a power of 0.80 and a confidence interval of 95%, the sample size for each group was determined to be 62. The ethics committee of the Institute gave the study its approval.

## 2.2. Sample collection

Two plain vials were used to collect blood samples (2 mL). Subsequently, the serum was separated by an in-house centrifuge machine and was stored at -4°C. The serum analysis for 25(OH) D3 was completed the same day.

## 2.3. Definitions

"Wheezing" is a high-pitched whistling sound made as air passes through restricted airways in the respiratory tract. It can be caused by several disorders. The term "recurrent wheezer" refers to two or more documented episodes of wheezing since birth (Feketea et al., 2020).

Serum 25(OH) D level of >20 ng/mL was considered sufficient, a level between 12-20 ng/mL as insufficient, and a level <12 ng/mL as deficient (Gupta et al., 2022).

## 2.4. Statistical analysis

Data were collected on structured proforma and managed using Microsoft Excel spreadsheets. Subsequently, SPSS software version 20.0 was used for statistical analysis. Comparison of continuous variables across two groups was done using Student's t-test or Mann-Whitney U test. The statistical significance of categorical variables was determined by the Chi-square test or Fischer-Exact test. P-value of <0.05 was considered statistically significant.

## 3. RESULTS

The study population included 124 children. The study group consisted of 62 children (mean age: 2.11 ± 1.37 months; 38 boys and 24 girls) and the control group had 62 children without wheezing (mean age: 2.17 ± 1.41 months; 32 boys and 30 girls). There was no significant difference between groups regarding age and sex. The demographic characteristics and risk factors are illustrated in Table 1.

**Table 1. Comparison of general characteristics between the groups**

Characteristics	Cases N (%)	Controls N (%)	P value
Age (mean ± SD)	2.11 ± 1.37	2.17 ± 1.41	0.610
Gender n(%)			
Male	38 (54.3)	32 (45.7)	0.277
Female	24 (44.4)	30 (55.6)	
Residence n(%)			
Urban	34 (46.6)	39 (53.4)	0.362
Rural	28 (54.9)	23 (45.1)	
Gestational age n(%)			
Term	55 (49.1)	57 (50.9)	0.544
Preterm	7 (58.3)	5 (41.7)	

Exclusive breast feeding <i>n</i> (%)			
Yes	41 (47.1)	46 (52.9)	0.326
No	21 (56.8)	16 (43.2)	
H/o supplemental Vit D <i>n</i> (%)			
Yes	39 (48.1)	42 (51.9)	0.571
No	23 (53.5)	20 (46.5)	

Table 2 shows the comparison of the characteristics like age of onset, number of wheezing episodes, the requirement of hospitalization, personal history of eczema, and family history of asthma among the cases and controls. The number of wheezing episodes and the requirement of hospitalization along with the family history of asthma were found to be significantly higher in cases as compared to the control group (<0.005).

**Table 2. Comparison of medical history between the groups**

Characteristics	Cases N (%)	Controls N (%)	P value
H/o atopy <i>n</i> (%)			
Yes	10 (58.8)	7 (41.2)	0.433
No	52 (48.6)	55 (51.4)	
Family H/o asthma <i>n</i> (%)			
Yes	20 (74.1)	7 (25.9)	0.005
No	42 (43.3)	55 (56.7)	
Number of wheezing episodes			
≤ 2	44 (41.5)	62 (100.0)	<0.001
> 2	18 (100.0)	0 (0.0)	
Requiring hospitalization			
Yes	36 (97.3)	1 (2.7)	<0.001
No	26 (29.9)	61 (70.1)	
Age of onset ( <i>mean ± SD</i> )	1.18 ± 0.95	0.93 ± 0.57	0.776

The mean levels of vitamin D in the cases were 20.17± 7.08 ng/ml. The mean levels of vitamin D among the controls were 24.10 ± 7.04 ng/ml. The difference in vitamin D levels in the two groups was statistically significant (p = 0.002) (Table 3).

Among the cases 21(33%) were deficient, 19 (30%) were insufficient, and 22 (35%) were sufficient. On the other hand, 5 (8%), 22 (35%), and 35 (56%) of the control population were deficient, insufficient, and sufficient respectively.

**Table 3. Comparison of Vit D levels between the groups**

Characteristics	Cases N (%)	Controls N (%)	P value
Vit D ( <i>mean ± SD</i> )	20.17 ± 7.08	24.10 ± 7.04	<b>0.002</b>

Among the RW group, the mean serum vitamin D level among exclusively breastfed (20.42 +/- 6.88) and those given top feed (19.67 +/- 7.95) was not statistically significant (p-value 0.695). The mean vitamin D level of infants with a history of vitamin D supplementation was 20.63 +/- 6.59; whereas it was 19.38 +/- 7.93 in the other group who were not supplemented with vitamin D in the study group. This difference again was not statistically significant (p = 0.505) (Table 4).

But, there was statistically significant difference in vitamin D levels between children who had a positive history of atopy (p = 0.031) and those who had family history of asthma (p=0.003) or had frequent wheezing episodes (p= 0.017) than those who did not (Table 4).

**Table 4. Comparison of Vitamin D levels with different associated factors within the case group**

Characteristics	Frequency (%)	Vit D level Mean $\pm$ SD	P value
Sex			
Male	38	20.68 $\pm$ 7.38	0.457
Female	24	19.35 $\pm$ 6.63	
H/o EBF			
Yes	41	20.42 $\pm$ 6.88	0.695
No	21	19.67 $\pm$ 7.95	
H/o Supplement			
Yes	39	20.63 $\pm$ 6.59	0.505
No	23	19.38 $\pm$ 7.93	
H/o atopy			
Yes	10	15.77 $\pm$ 3.48	<b>0.031</b>
No	52	21.01 $\pm$ 7.30	
Family H/o asthma			
Yes	20	16.38 $\pm$ 5.82	<b>0.003</b>
No	42	21.97 $\pm$ 6.96	
Episodes of wheeze			
$\leq 2$	44	21.52 $\pm$ 7.80	<b>0.017</b>
$> 2$	18	16.86 $\pm$ 3.08	
Requiring hospitalization			
Yes	36	20.63 $\pm$ 7.34	0.552
No	26	19.53 $\pm$ 6.78	

#### 4. DISCUSSION

Though observational and epidemiological research have demonstrated a strong link between vitamin D insufficiency and viral respiratory infections in certain situations, interventional studies on vitamin D status and/or supplementation have yielded conflicting findings.

It is plausible that increased synthesis of antiviral proteins during very severe viral infections causes 25(OH) hydroxylase inactivation leading to decrease vitamin D while 1 $\alpha$ (OH) hydroxylase activity increases. Consequently, as the concentration of 1,25(OH)D<sub>2</sub> rises in extra-renal tissues, serum 25(OH)D, which is required to generate 1,25(OH)D<sub>2</sub>, is depleted. A severe viral infection during times when vitamin D consumption and sun exposure are minimized may consequently lead to a decrease in serum 25(OH)D. It has not yet been proven in a real-world context that vitamin D levels can be used as a biomarker for the severity of RW and ARTIs.

According to a recent study (Dogru and Seren 2017), individuals with RW exhibited mean serum 25(OH)D levels that were significantly lower than those of a healthy control group. Additionally, there was an inverse correlation between the level and the quantity, duration, and need for systemic glucocorticoids during wheezing episodes. In contrast, Pecanha and colleagues in children with RW did not identify any correlation between 25(OH)D concentration and exacerbations as defined by hospitalizations, emergency visits, and oral corticosteroid use. However, they did discover an association with wheezing beginning before one year of age (Pecanha et al., 2019). Children with wheeze had significantly decreased serum 25(OH)D levels ( $P < 0.001$ ) in comparison to the control group, according to a study by (Alaa Mohamed Abdelkader et al., 2019). However, other research, such as that conducted by Uysalol et al., found no appreciable variation in the study group's serum vitamin D level compared to the controls (Uysalol et al., 2014). They included children of younger age group that is three months to 2 years who might have received supplementation in infancy. Also, their conventional definitions of vitamin D inadequacy and insufficiency, however, differed.

Overall, we found statistically significant variation in the serum levels of vitamin D between the study group and the control group. In comparison to healthy controls, children with wheezing had lower mean serum vitamin D levels in our study. There may be a chance that this discrepancy resulted from the infants' extended stays in indoors during their recurrent illnesses, which limited their exposure to sunlight.

Of the recurrent wheezers in our study, 32.5% had insufficiency and 20.5% had a deficiency in vitamin D. Previous studies also showed that a large percentage of children had inadequate and insufficient amounts of vitamin D. In a study of 122 children, Afreen et al. found that 69 (56.6%) of the participants had vitamin D deficiency (KHAN et al., 2018). Their research cohort was similar in age (less than 3 years), but because vitamin D supplementation has recently gained more attention, the findings may differ.

According to Osman et al., 21% and 32%, respectively, of the preschool-aged children who experienced recurring wheezy episodes had inadequate and deficient serum 25 (OH) vitamin D levels (Osman et al., 2019) which is similar to our results. But they followed the older criteria (<30 ng/dl) for identifying vitamin D deficiency and (<20 ng/dl) for insufficiency were noted in earlier Indian studies (Prasad et al., 2016). These definitions are likely to exaggerate the correlation between vitamin D deficiency or insufficiency and recurrent wheeze.

Newer classifications of vitamin D inadequacy and insufficiency have been advocated by recent Indian guidelines (Gupta et al., 2022). While many children with even florid rickets do not have wheeze, it was found that many children with recurrent wheeze had low vitamin D levels.

Within the group of recurrent wheezers in our study, there was significant correlation found between serum vitamin D levels and factors such as atopy history, family history of asthma, or frequent RW. Though standard definitions have been updated, we found significant relation of low vitamin D level and RW similar to previous studies (AbdelKader et al., 2019; Uysalol et al. 2014; Osman et al., 2019). There may be additional factors influencing vitamin D levels, such as the eating habits of children under five.

In the future, as sample sizes are higher, statistically insignificant relationships may become significant. It's possible that our study's cross-sectional design obscured the precise cause-and-effect link. Furthermore, the families' responses might not be a reliable indicator of our findings. Further research is required to demonstrate the correlation between wheezing and blood levels of trace elements to enhance the clinical course and prevent diseases.

## 5. CONCLUSION

Future research should address the impact of vitamin D on the immune system, as its involvement in chronic wheezers remains contentious. Larger and more rigorous trials are needed to determine the therapeutic effect of vitamin D in the prevention and treatment of wheezing.

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