

Association of Serum Vitamin D Levels with Recurrent Wheezing in Preschool Children

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Abstract

Background: The relationship between the vitamin D level and recurrent wheezing is not clear. There are some studies showed the relationship between recurrent wheezing and vitamin D level. Vitamin D plays a role in development of immune system and lung in the fetus. Vitamin D receptors (VDR) have been found in fetal type II alveolar pneumocytes of rats, and may have the role in lung development, pneumocyte differentiation and surfactant production. It is said that there are some reported data that link between Vitamin D and wheezing episode. The prevalence of asthma is increasing day by day due to vitamin D deficiency though asthma is a multifactorial disease. It may be useful to measure the levels of 25 (OH) vitamin D of the pre-school children with or without recurrent wheezing.

Objective: To observe association between vitamin D status and recurrent wheezing in preschool children.

Methods: Thirty-Seven preschool children with recurrent wheezing response to salbutamol and thirty-seven healthy, similar aged children without any history of acute or chronic illness were included in the study. The clinical features of children were recorded and serum 25-hydroxyvitamin D [25(OH) D] levels were measured. The data was analyzed to find out an association between the serum levels of vitamin D and recurrent wheezing.

Results: The mean value of 25 (OH) D vitamin levels were 34.4 ± 10.1 ng/ml and 26.2 ± 6.5 ng/ml for the control and case group respectively. 16.22% of subjects with recurrent wheezing had deficient vitamin D level (< 20 ng/ml) and 25.4% had vitamin D levels below < 20 ng/ml in the control group. Vitamin D status of the study participants showed that among the cases, 20 (54%) had insufficiency and 11 (30%) had normal vitamin level while among the controls, 13 (35%) had insufficiency and 22 (59%) had normal vitamin D level. This was statistical significance between the two groups.

A strong association between the low serum Vitamin D levels and the recurrent wheeze ($p = 0.001$) was found. The optimal cut-off value for Vitamin D was found to be 28.8 ng/mL.

Conclusion: Low serum 25(OH) D levels are strongly associated with recurrent wheezing in preschool children. So, it is needed to do vitamin D level of all recurrent wheezing with preschool children.

Keywords: Serum Vitamin D Level; Wheezing; Preschool Children

Introduction

About one children in every three have at least one episode of wheezing prior to their third birthday and cumulative prevalence of wheeze is around 50% at the age of six year [1-3]. Recurrent wheeze is defined as three or more episodes of parentally reported wheeze in the past 12 months of life [3]. Its occurrence is quite common and is reported in 6.2% of the Indian children [4]. Although there are many risk factors responsible for the development of recurrent wheezing, recently, vitamin D has some role to develop recurrent wheezing. Some studies reported that low vitamin D levels even in cord blood may be responsible for many childhood diseases [5,6]. Consequently, severe asthma in children [7-9]. Moreover, there are many risk factors including infections and allergy are responsible for development of recurrent wheezing [10,11] recently, vitamin D emerged as significant risk factor for developing wheeze, asthma and also have its immunomodulatory properties [8,9,12].

In tropical country like Bangladesh vitamin D deficiency was thought of uncommon however, contrary to this belief recent studies have shown its prevalence to be as high as 50 - 90% [13-15]. Vitamin D deficiency and insufficiency may be labeling when serum 25(OH) D level is < 20 ng/ml and 20 - 29 ng/ml respectively [16,17].

Previous some studies reported in India shown that there is strong association between vitamin D insufficiency/deficiency with recurrent wheeze [16]. It was also observed that lot of children attending to emergency with recurrent wheeze did not have any underlying etiology except low vitamin D levels, on the other hand many children with even florid rickets doesn't have wheeze.

Aim of the Study

This study was planned to find out the association between serum vitamin 25(OH) D levels and recurrent wheezing in children less than five years of age in Bangladesh.

Materials and Methods

This was a case-control study performed in the Outpatient Department of Pediatrics at BSMMU and biochemical analysis was done in Department of Biochemistry of above mentioned hospital from October 2018 to March 2022. Children less than five years of age, diagnosed with recurrent wheeze response to salbutamol, presenting to outpatient department were enrolled. Before enrollment written informed consent was also taken. Those patient having history of chronic medical or surgical illness, rickets received vitamin D supplementation in last six months or congenital malformations were excluded. Healthy children visiting outdoors for immunization or routine check-up at BSMMU were taken as controls.

After proper approval from the departmental ethical review committee (ERC) of BSMMU, children with recurrent wheezing below five years attending in Asthma centre and admitted into hospital ward of Bangabandhu Sheikh Mujib Medical University Hospital and was respond to salbutamol were selected for case.

Proper informed written consent was taken from the parents or legal guardians. The purpose, procedure, importance and benefit of the study were explained their parents or legal Guardian.

A detailed history was taken from each patient using a predesigned questionnaire containing age, gender, cough, fever, breathing difficulty, history of atopy, family history of atopy, exclusive breast feeding, sunlight exposure and response to salbutamol. Thorough clinical examination including vital signs, anthropometry was done.

With all aseptic precaution 3 ml venous blood was collected from antecubital vein both case and control.

Serum analysis for 25(OH) D, were done on same day with GP-Getein-1100 immunofluorescence analyzer.

Control group without respiratory problem were selected from EPI centre of BSMMU hospital. A detailed history was also taken from control group using a predesigned questionnaire containing age, gender, fever, history of atopy, family history of atopy, exclusive breast feeding, and sunlight exposure. Thorough clinical examination including vital signs, anthropometry was done.

The sample size was calculated using matched case-control study design.

Detailed history of wheezing episodes along with therapy, dietary history, sunlight exposure, respiratory system examination and anthropometry using WHO growth charts were recorded [18].

Blood samples (3 mL) were taken in two plain vials and were sent for analysis for 25 (OH) D and Serum 25 (OH) D was measured by an ELISA kit from DLD Diagnostika GMBH (Alderhost, Hamburg, Germany).

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. Descriptive statistic was used for the characteristics of the study subjects.

Sampling technique

Patients were included in this study by purposive sampling according to inclusion and exclusion criteria. Comparison of continuous variables across two groups was done using Student’s t-test or Mann-Whitney U test. Statistical significance of categorical variables was determined by Chi-square test or Fischer-Exact test and Backward Wald method

Results

A total of 37 cases with recurrent wheeze along with 37 healthy controls were enrolled. The basic demographic characteristics i.e., age, sex, weight, and height (Table 1) was comparable in both the groups.

Baseline characteristics	Case (n = 37)	Control (n = 37)	p value
Age (in months)			
6-23	10 (16.2%)	12 (13.5%)	0.153
24-47	13 (13.5%)	11 (32.4%)	
48-59	14 (70.3%)	14 (54.1%)	
Mean ± SD	27.9 ± 10.2	24.2 ± 8.0	0.088
Gender			
Male	23 (62.2%)	24 (64.9%)	0.809
Female	14 (37.8%)	13 (35.1%)	
Monthly family income			
5,000-10,000	1 (2.7%)	0 (0.0%)	0.607
10,000-20,000	27 (73.0%)	25 (67.6%)	
>20,000	9 (24.3%)	12 (32.4%)	
Weight	11.2 ± 2.2	11.2 ± 1.1	0.947
Height	84.4 ± 9.3	82.8 ± 6.1	0.364

Table 1: Baseline characteristics of the study population (n = 74).

Data expressed as mean ± SD and number (percentage). For statistical analysis, Chi square test, Independent Sample t test and Fisher Exact test were done, where applicable. P < 0.05 was considered statistically significant.

Table 1 showed age distribution of the study participants that in both groups, majority were from 48 - 59 months age group. The mean age of cases and controls were 27.9 ± 10.2 and 24.2 ± 8.0 months respectively which showed no significant statistical difference ($p = 0.088$). Majority of the study participants of cases and controls were male children ($p = 0.809$). Monthly family income was between 10,000-20,000 taka in 27 (73.0%) cases and in 25 (67.6%) controls ($p = 0.607$). No significant statistical difference was observed between cases and controls regarding weight and height as $p > 0.05$.

Risk factors	Case (n = 37)	Control (n = 37)	p value
Atopy			
Present	13 (35.1%)	4 (10.8%)	0.013*
Absent	24 (64.9%)	33 (89.2%)	
Family history of atopy			
Present	16 (43.2%)	6 (16.2%)	0.011*
Absent	21 (56.8%)	31 (83.8%)	
Exclusive breast feeding			
Yes	14 (37.8%)	18 (48.6%)	0.348
No	23 (62.2%)	19 (51.4%)	
Sunlight exposure			
<30 minutes/week	30 (81.1%)	23 (62.2%)	0.071
>30 minutes/week	7 (18.9%)	14 (37.8%)	

Table 2: Distribution of patients by risk factors (n = 74).

Data expressed as number (percentage). For statistical analysis, Chi square test was done. $P < 0.05$ was considered statistically significant.

Table 2 showed atopy was present in 13 (35.1%) cases while in controls, 4 (10.8%). Chi-square test showed that atopy was significantly more in cases compared to controls ($p = 0.013$). Family history of atopy was also significantly more in cases compared to controls ($p = 0.011$). However, no significant statistical difference was observed between cases and controls regarding exclusive breast feeding status and sunlight exposure as $p > 0.05$.

Biochemical parameter	Case (n = 37)	Control (n = 37)	p value
Vitamin D (ng/mL)	26.2 ± 6.5	34.4 ± 10.1	$<0.001^*$

Table 3: Comparison of biochemical parameter among two groups (n = 74).

Data expressed as mean \pm SD. For statistical analysis, Independent Sample t test and Mann-Whitney-U test were done, where applicable. $P < 0.05$ was considered statistically significant.

*= significant.

Table 3 showed the mean vitamin D level was significantly lower in cases (26.2 ± 6.5 ng/mL) compared to controls (34.4 ± 10.1 ng/mL) ($p < 0.001$) but control group was above the normal limit.

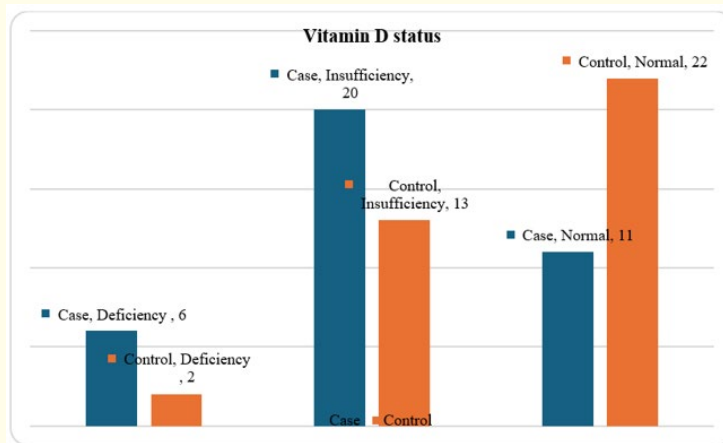


Figure 1: Distribution of vitamin D status in case and control (n = 74).

Figure 1 showed vitamin D status of the study participants showed that among the cases 6 (16.22%) of subjects with recurrent wheezing had vitamin D levels in the deficient range (< 20 ng/ ml) and 2 (25.4%) had vitamin D levels below < 20 ng/ml in the control group, 20 (54%) had insufficiency and 11 (30%) had normal vitamin level while among the controls, 13 (35%) had insufficiency and 22 (59%) had normal vitamin D level.

Frequency of wheeze	Frequency	Percentages
Three times	19	51.4
More than three times	18	48.6

Table 4: Distribution of cases by frequency of wheeze in last year during study period (n = 37).

Among the 37 cases, 19 (51.4%) had wheeze three times in last year while 18 (48.6%) had wheeze four times or more in last year (Table 4).

Frequency of wheeze	Vitamin D level			p value
	Deficiency	Insufficiency	Normal	
Three times	0 (0.0%)	9 (45.0%)	10 (90.9%)	0.001
More than three times	6 (100.0%)	11 (55.0%)	1 (9.1%)	

Table 5: Distribution of cases by frequency of wheeze in last year and vitamin D level.

Among the 6 cases with deficient vitamin D level, all had wheeze four times in last year while among the 11 cases with normal vitamin D level, only one had wheeze four times in last year. Fisher Exact test showed that there was significant statistical difference among the groups regarding frequency of wheeze in last year (p = 0.001) (Table 5).

Criteria	p value	Odds ratio	95% CI
Family history of atopy	0.015*	11.022	1.580-6.898
Vitamin D	0.001*	1.292	1.113-1.499

Table 6: Binary logistic regression model of different independent variables in predicting risk of recurrent wheezing (n = 74).

Analysis was done by Backward Wald method.

*= significant.

A logistic regression was performed to identify predictors of recurrent wheezing. Patients with family history of atopy (odds ratio [OR]: 11.022, 95% CI: 1.580 - 6.898, p = 0.015), Vitamin D level (OR: 1.292, 95% CI: 1.113 - 1.499, p = 0.001) were independent predictors of occurrence of recurrent wheezing.

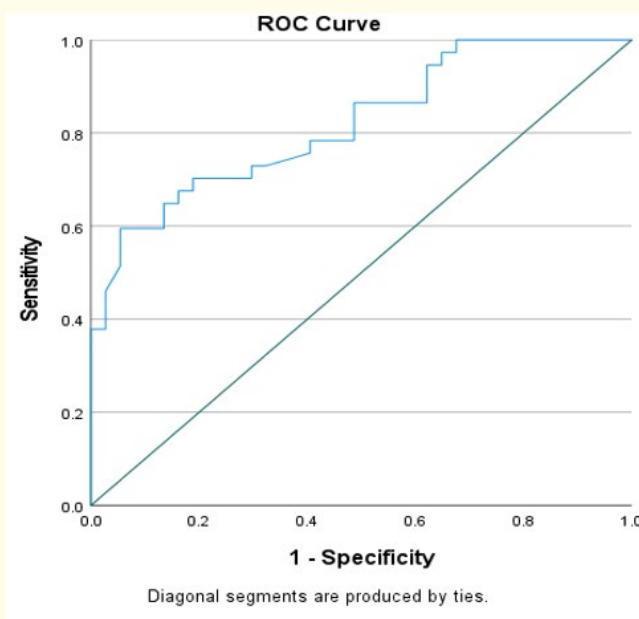


Figure 2: ROC curve analysis performed to predict the best cut off value of vitamin D for recurrent wheezing in children.

ROC curve analysis of serum vitamin D levels for predicting recurrent wheezing in children (n = 74)

Parameters	Value	95% CI
Area Under the Curve (AUC)	0.820	0.726 - 0.914
p-value	<0.001	
Cut-off Value of Vitamin D	28.8	
Sensitivity (%)	70.27%	53.02% to 84.13%
Specificity (%)	81.08%	64.84% to 92.04%
Positive Predictive Value (%)	78.79%	64.86% to 88.20%
Negative Predictive Value (%)	73.17%	61.87% to 82.09%
Accuracy (%)	75.68%	64.31% to 84.90%

Table

The ROC curve analysis reveals that serum vitamin D levels have a strong predictive ability for recurrent wheezing in children, with an area under the curve (AUC) of 0.820, indicating good model performance. The optimal cut-off value for vitamin D was found to be 28.8 ng/mL. At this threshold, the sensitivity was 70.27%, indicating that the test correctly identified 70.27% of children with recurrent wheezing, while the specificity was 81.08%, meaning the test accurately identified 81.08% of children without recurrent wheezing. The positive predictive value (PPV) was 78.79%, and the negative predictive value (NPV) was 73.17%, suggesting that the test has a good balance of identifying true positives and true negatives. Overall, the accuracy of the test was 75.68%, with a 95% confidence interval ranging from 64.31% to 84.90%, demonstrating a reliable association between vitamin D levels and recurrent wheezing.

Discussion

The present study showed a strong association between vitamin D levels and recurrent wheeze in the children below five years of age. Wheezing is quite prevalent in pre-school children and consequently, many children develop asthma [3]. Deficiency of vitamin D is widespread in all parts of the world [14]. 25(OH) D is the major stable and circulating form of vitamin D with a half-life of 2-3 weeks and its level is the best available indicators of vitamin D status [13]. Many cut-offs have been chosen to define deficiency of vitamin D but most of the guidelines meet consensus at a level of < 20 ng/mL, to label as deficient, this cut-off was chosen in concordance to international standards [14].

In this study mean levels of serum 25 (OH) D were significantly lower among cases (26.2 ± 6.5 ng/ml) as compared to controls (34.4 ± 10.1 ng/ml). Similar to other studies, in this study too, most of the children with recurrent wheeze (54%) had vitamin D Insufficiency's Ozdemir, *et al.* studied 186 infants with recurrent wheezing and found that children with recurrent wheeze had significantly lower vitamin D levels and the levels were much less in children who had the propensity to develop asthma based upon Asthma Predictive Index [27].

In present study, this finding reinforces that vitamin D insufficiency is a significant public health problem and there is urgent need of routine supplementation of vitamin D in all age groups along with food fortification. A logistic regression was performed to identify predictors of recurrent wheezing. Patients with family history of atopy (odds ratio [OR]: 11.022, 95% CI: 1.580 - 6.898, $p = 0.015$), Vitamin D level (OR: 1.292, 95% CI: 1.113 - 1.499, $p = 0.001$) were independent predictors of occurrence of recurrent wheezing. This finding is very much similar to the study done [7,9-10,27].

Among the 6 cases with deficient vitamin D level, all had wheeze four times in last year while among the 11 cases with normal vitamin D level, only one had wheeze four times in last year. Fisher Exact test showed that there was significant statistical difference among the groups regarding frequency of wheeze in last year ($p = 0.001$) (Table 5).

This study adds that serum vitamin d level 28.8 ng/ml (AUC-0.820) can be used as a surrogate of vitamin D insufficiency and is an important predictor (sensitivity 70.27%, specificity 81.08%) of recurrent wheeze. The positive predictive value (PPV) was 78.79%, and the negative predictive value (NPV) was 73.17%, suggesting that the test has a good balance of identifying true positives and true negatives. Overall, the accuracy of the test was 75.68%, with a 95% confidence interval ranging from 64.31% to 84.90%, demonstrating a reliable association between vitamin D levels and recurrent wheezing So, it can be used as a substitute in resource-limited settings.

Another finding was that the majority of the wheezing children (37.8%) were exclusively breastfed till six months of age and complementary feeding was not started while the majority of the controls were mixed fed and complementary feeding was started at six months of age. This may be explained by the fact that human milk is a poor source of vitamin D, and in absence of supplementation, those who are exclusively breastfed are likely to develop vitamin D deficiency [28,29].

In this study breastfeeding rates were not significantly higher in wheezers compared to controls, which belief that breastfeeding protects against allergic disorders. This finding is in concordance with a recent systematic review which showed that breastfeeding protects against allergic disorders [27].

Sunlight exposure is an important factor for vitamin D synthesis. In our study, 81.1% of vitamin D insufficiency cases had limited sunlight exposure (< 30 minutes per week), which may have contributed to such a high prevalence. The limited exposure seems to be due to change in life style [29,30]. Studies have shown that a minimum 30-minute weekly sunlight exposure in bright sunlight, over 40% body area for at least four months is required to achieve sufficient vitamin D level by six months of age [29]. The current findings also support this recommendation.

Limitation of the Study

Limitation of this study was a small sample size. Also, detailed information about vitamin D intake was not collected and serum IgE and alkaline phosphate levels were not measured.

Conclusion

Low serum 25(OH) D levels are strongly associated with recurrent wheezing in preschool children but the value not below the deficiency level.

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