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ORIGINAL ARTICLE

Vitamin D Deficiency and Its Association with Recurrent Wheeze in Toddlers

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ABSTRACT

Background: Recurrent wheezing is a frequent respiratory issue in childhood, and may be affected by nutrition, environment, infection, and genetic factors. Vitamin D has a role in immune regulation and in the function of respiratory epithelial cells and in the regulation of airway inflammation. Thus, low levels of vitamin D may make young children more vulnerable to frequent wheezing.

Objective: To determine the frequency of vitamin D deficiency among toddlers and assess its association with recurrent wheeze.

Material and Methods: This hospital-based comparative cross-sectional study was conducted at the Department of Paediatrics, Nowshehra Medical College, Nowshehra, from January 2023 to July 2023. 77 toddlers aged between 12-36 months were recruited using non-probability consecutive sampling. The participants were divided into two groups: recurrent-wheeze and non-recurrent-wheeze. A structured proforma was used to gather the demographic, nutritional, clinical and environmental data. Serum 25-hydroxyvitamin D was analysed and vitamin D status was defined as deficient, insufficient and sufficient. Appropriate statistical tests were used for group comparisons and binary logistic regression was used to determine independent predictors of recurrent wheeze. A p-value of < 0.05 was defined as statistically significant.

Results: The mean age of the participants was 25.8 ± 7.1 months, and 43 (55.8%) were boys. Recurrent wheeze was present in 42 (54.5%) toddlers. Vitamin D deficiency was identified in 44 (57.1%) participants, insufficiency in 20 (26.0%), and sufficiency in 13 (16.9%). The mean serum vitamin D level was significantly lower in toddlers with recurrent wheeze than in those without recurrent wheeze, at 16.8 ± 6.7 ng/mL and 25.6 ± 9.4 ng/mL, respectively ($p < 0.001$). Vitamin D deficiency was present in 73.8% of children with recurrent wheeze compared with 37.1% of those without recurrent wheeze ($p = 0.001$). After adjustment for potential confounders, vitamin D deficiency remained independently associated with recurrent wheeze (adjusted OR = 4.12; 95% CI: 1.42–11.94; $p = 0.009$).

Conclusion: Vitamin D deficiency was common among toddlers and was independently associated with recurrent wheeze. Deficient children also experienced more frequent episodes, emergency visits, and night-time respiratory symptoms. Assessment of vitamin D status may be beneficial in toddlers presenting with repeated wheezing, although prospective studies are required to determine whether vitamin D supplementation can reduce future wheezing episodes.

Keywords: Vitamin D deficiency; recurrent wheeze; toddlers; 25-hydroxyvitamin D; bronchiolitis; airway inflammation.

INTRODUCTION

Wheezing is a common respiratory problem in young children. It is the typical presentation of repeated episodes of a high pitched whistling type sound while breathing due to narrowing of the lower airway. Early childhood respiratory infections, especially bronchiolitis, are frequent triggers, but there may be genetic susceptibility, allergic disease, tobacco-smoke exposure and environmental pollutants that play a role. Chronic recurrent wheezing can lead to hospital admissions, emergency room visits, sleep problems, anxiety for parents and higher health care expenses. Some affected children may get better as they grow older, while other affected children may have respiratory problems to this day and develop childhood asthma (1-3).

Vitamin D is a fat soluble vitamin which can be synthesized in the skin after sunlight exposure, or consumed in small quantities, as in food or supplements. It is known to regulate calcium balance, bone mineralization and skeletal growth in classical functions. But there are also some immune and respiratory processes affected by vitamin D. The presence of vitamin D receptors on immune cells and airway epithelial tissues suggests that vitamin D might modulate antimicrobial defence, inflammatory signalling, and airway responsiveness. Deficiency can impair respiratory epithelial barriers, and diminish production of antimicrobial peptides, which may lead to increased wheezing due to increased incidence of respiratory infections (4-6).

The vitamin D deficiency is more likely in children due to their growth rate, low dietary intake, low sun exposure, staying indoors for longer periods of time, darker skin tone, low vitamin D intake, and maternal vitamin D deficiency. Among toddlers, those who have recurrent respiratory illness may be even more susceptible, as illness may decrease their outdoor exposure and impact on nutrition. Several paediatric populations have been linked to low levels of serum vitamin D and increased rates of lower respiratory tract infections, bronchiolitis, asthma severity and recurrent wheezing. However, the results have been inconsistent, and it is unclear if deficiency alone raises the risk of wheezing or if wheezing is merely a proxy for poor health, reduced exposure to outdoor air and other factors (7-9).

Evidence regarding the relationship between vitamin D status and recurrent wheeze among toddlers in Pakistan remains limited. Local children may have a considerable risk of deficiency despite abundant sunlight because of clothing practices, indoor lifestyles, air pollution, nutritional limitations, and inconsistent vitamin D supplementation. Identifying a potentially modifiable factor could support earlier risk assessment and guide future preventive research. Therefore, the present study was conducted to determine the frequency of vitamin D deficiency among toddlers attending Nowshehra Medical College, Nowshehra, and to evaluate its association with recurrent wheeze after considering relevant clinical, nutritional, hereditary, and environmental factors.

MATERIALS AND METHODS

This hospital-based comparative cross-sectional study was conducted at the Department of Paediatrics, Nowshehra Medical College, Nowshehra, from January 2023 to July 2023. The study aimed to determine the frequency of vitamin D deficiency among toddlers and to examine its association with recurrent wheezing. A

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total of 77 children aged 12–36 months were enrolled through non-probability consecutive sampling. Participants were recruited from the paediatric outpatient department, emergency unit, and paediatric ward during the study period. Toddlers were divided into two groups according to their clinical history: children with recurrent wheeze and children without recurrent wheeze. Recurrent wheeze was defined as three or more physician-documented or caregiver-reported episodes of wheezing during the preceding 12 months.

Children between 12 and 36 months of age who were toddlers (both boys and girls) and whose parents/legal guardians signed an informed consent form could participate. Children with recurrent wheeze were included if wheezing episodes had been recorded by a doctor or if there was some clear history of wheezing with respiratory symptoms and audible wheezing. The comparison group included other toddlers who were not recurrent wheezers and went to the same hospital. Children were excluded if they had congenital heart disease, chronic lung disease, cystic fibrosis, active pulmonary tuberculosis, severe malnutrition, chronic kidney or liver disease, rickets under treatment, immune deficiency or previously known metabolic disorders involving vitamin D metabolism. Other exclusions included toddlers who were taking vitamin D, systemic corticosteroid, anticonvulsant or other medication that is known to affect vitamin D during the last three months.

A structured proforma was developed specifically for this research and used for the collection of data. Parents/guardians were interviewed and information was gathered, supplemented by available medical records. Information recorded consisted of age, sex, residence, birth weight, gestational age, mode of delivery, breastfeeding history, vitamin D supplementation, diet, exposure to sunlight, nutritional status, number of wheezing episodes, age at first wheezing episode, emergency visits, hospital admissions, and bronchodilator and inhaled corticosteroid use. Other potential risk factors included: exposure to biomass fuel, previous bronchiolitis, recurrent respiratory infections, eczema, allergic rhinitis, household crowding, and family history of asthma/ allergic disease. Weight was measured on a calibrated paediatric weighing scale and recumbent length or standing height was measured on an infantometer or stadiometer, depending on the child's age. Indications of nutritional status was measured by the proper weight-for-age, height-for-age and weight-for-height standards.

Venous blood was drawn about 3–5 mL from each participant after the preparation in aseptic conditions. The biochemical marker of vitamin D status was 25-hydroxyvitamin D [25(OH)D] and was separated from the serum by centrifugation. All samples were processed following the manufacturer's instructions and quality-control procedures, and the laboratory analysis was carried out with the assay method commonly used in the institutional laboratory. Vitamin D deficiency was considered to be a serum 25(OH)D level < 20 ng/mL, insufficiency a serum 25(OH)D level between 20 and 29.9 ng/mL and sufficiency a serum 25(OH)D level ≥ 30 ng/mL. In addition, serum calcium, phosphate, alkaline phosphatase, haemoglobin, total leukocyte count, eosinophil count and serum immunoglobulin E were also recorded where clinically indicated and available. To minimize measurement bias, samples were coded and sent to the laboratory without the information of the wheezing status of the participants.

Data were entered and analysed using IBM SPSS Statistics. Quantitative variables like age and serum vitamin D level were presented as mean with SD if normally distributed and as median with interquartile range (IQR) if not normally distributed. Categorical data is reported as frequencies and percentages. Continuous variables were compared between toddlers with and without recurrent wheeze using either the independent-samples t-test or Mann–Whitney U test, which are used to test the difference in continuous variables between two independent groups. To evaluate associations between categorical variables, the chi-square test or Fisher's exact test was used. To assess if the vitamin D deficiency was independently associated with recurrent wheeze, crude and adjusted odds ratios (adjusted for age, sex, prematurity, breastfeeding, sunlight exposure, passive smoking, family history of asthma/allergy, previous bronchiolitis) with 95% confidence intervals were calculated in binary logistic regression analysis. A p-value < 0.05 was considered to be statistically significant.

RESULTS

In total 77 toddlers participated in the study. Their mean age was 25.8 ± 7.1 months, ranging from 12 to 36 months. Of the total participants, 43 (55.8%) were boys and 34 (44.2%) were girls. 42 (54.5%) toddlers reported to have recurrent wheeze, while 35 (45.5%) reported no history of recurrent wheezing. The mean level of 25-hydroxyvitamin D in the whole study population was 20.8 ± 9.1 ng/mL.

The median age of the most participants was 24 to 36 months. There was a family history of asthma or allergic disease in approximately one-third of the toddlers and in 26 (33.8%) children, passive exposure to cigarette smoke was reported. Only less than half were getting enough sunlight and 29 (37.7%) were supplementing with vitamin D regularly during infancy.

The vitamin D deficiency rate was 44 toddlers (57.1%) and vitamin D insufficiency was detected in 20 toddlers (26.0%). 13 (16.9%) children had serum vitamin D levels in the sufficient range. Therefore, 64 (83.1%) of the participants showed either low or inadequate vitamin D levels.

Toddlers who wheezed recurrently had a significantly lower mean serum vitamin D level than toddlers who did not wheeze recurrently, (16.8 ± 6.7 ng/mL vs. 25.6 ± 9.4 ng/mL, respectively; p < 0.001). There was greater vitamin D deficiency in toddlers with recurrent wheeze (31 (73.8%)) than in those without recurrent wheeze (13 (37.1%)) (p = 0.001). Toddlers with recurrent wheeze were also less likely to have been supplemented with vitamin D and to have adequate sunlight exposure. Children with recurrent wheeze were significantly more likely to be passive smokers, to have a family history of asthma or allergy and to have already had an episode of bronchiolitis. There were no significant differences between the two groups with respect to age, sex, LBW or prematurity.

There was a statistically significant association between vitamin D status and recurrent wheeze (p = 0.002). Vitamin D deficiency toddlers who had recurrent wheeze also had higher rates of recurrent otitis media, diarrhoea, and hyperactivity with inattention or hyperactivity-hyperactivity.The vitamin D deficient toddlers who had recurrent wheeze also had higher rates of recurrent otitis media, diarrhoea and hyperactivity with inattention or hyperactivity-hyperactivity. These results showed a steadily increasing trend in recurrent wheezing with decreasing vitamin D status.

The average age of the 42 toddlers with recurrent wheeze at the onset of the first wheezing was 14.9 ± 5.2 months. 17 children (40.5%) had 3 episodes in the previous year and 25 children (59.5%) had 4 or more episodes. 25 (59.5%) Toddlers had been seen in the emergency room for wheezing, and 13 (31.0%) had been admitted to hospital. The commonest trigger for wheezing was respiratory tract infections.

Vitamin D deficient toddlers in the recurrent-wheeze group experienced more of their respiratory symptoms and more severe symptoms clinically. The proportion of the children with vitamin D deficiency who had at least four wheezing episodes per year was higher than children without vitamin D deficiency (71.0% vs. 27.3%, p = 0.011). Vitamin D deficient toddlers were also more likely to have emergency department visits, night-time symptoms and use inhaled corticosteroid.

In the unadjusted analysis, toddlers with vitamin D deficiency had approximately five times greater odds of recurrent wheeze than those without vitamin D deficiency. After adjustment for breastfeeding, vitamin D supplementation, sunlight exposure, passive smoking, family history of asthma or allergy and previous bronchiolitis, vitamin D deficiency remained independently

associated with recurrent wheeze (adjusted OR = 4.12; 95% CI: 1.42–11.94; p = 0.009).

Table 1: Baseline characteristics of the study participants (n = 77)

Variable	Frequency (%) or Mean ± SD
Age, months	25.8 ± 7.1
12–23 months	29 (37.7%)
24–36 months	48 (62.3%)
Male sex	43 (55.8%)
Female sex	34 (44.2%)
Urban residence	47 (61.0%)
Rural residence	30 (39.0%)
Normal birth weight	65 (84.4%)
Low birth weight	12 (15.6%)
Preterm birth	11 (14.3%)
Exclusive breastfeeding for ≥6 months	46 (59.7%)
Vitamin D supplementation during infancy	29 (37.7%)
Adequate sunlight exposure	32 (41.6%)
Passive smoking exposure	26 (33.8%)
Family history of asthma or allergy	24 (31.2%)
Previous bronchiolitis	27 (35.1%)

Table 2: Distribution of vitamin D status among toddlers (n = 77)

Vitamin D status	Serum 25(OH)D level	Frequency (%)
Deficient	<20 ng/mL	44 (57.1%)
Insufficient	20–29.9 ng/mL	20 (26.0%)
Sufficient	≥30 ng/mL	13 (16.9%)
Total		77 (100%)

Table 3: Comparison of toddlers with and without recurrent wheeze

Variable	Recurrent wheeze (n = 42)	No recurrent wheeze (n = 35)	p-value
Age, months	26.4 ± 6.8	25.1 ± 7.4	0.421
Male sex	25 (59.5%)	18 (51.4%)	0.477
Low birth weight	9 (21.4%)	3 (8.6%)	0.121
Preterm birth	8 (19.0%)	3 (8.6%)	0.188
Exclusive breastfeeding ≥6 months	21 (50.0%)	25 (71.4%)	0.056
Vitamin D supplementation	11 (26.2%)	18 (51.4%)	0.023
Adequate sunlight exposure	12 (28.6%)	20 (57.1%)	0.011
Passive smoking exposure	19 (45.2%)	7 (20.0%)	0.019
Family history of asthma/allergy	18 (42.9%)	6 (17.1%)	0.015
Previous bronchiolitis	21 (50.0%)	6 (17.1%)	0.003
Serum vitamin D, ng/mL	16.8 ± 6.7	25.6 ± 9.4	<0.001
Vitamin D deficiency	31 (73.8%)	13 (37.1%)	0.001

Table 4: Association between vitamin D status and recurrent wheeze

Vitamin D status	Recurrent wheeze n (%)	No recurrent wheeze n (%)	Total	p-value
Deficient	31 (70.5%)	13 (29.5%)	44	
Insufficient	8 (40.0%)	12 (60.0%)	20	
Sufficient	3 (23.1%)	10 (76.9%)	13	
Total	42 (54.5%)	35 (45.5%)	77	0.002

Table 5: Wheezing characteristics among toddlers with recurrent wheeze (n = 42)

Wheezing characteristic	Frequency (%) or Mean ± SD
Age at first wheezing episode, months	14.9 ± 5.2
Three wheezing episodes in the previous year	17 (40.5%)
Four to five episodes	16 (38.1%)
More than five episodes	9 (21.4%)
Wheeze-related emergency visit	25 (59.5%)
Wheeze-related hospital admission	13 (31.0%)
Previous nebulization	36 (85.7%)
Bronchodilator use	34 (81.0%)
Inhaled corticosteroid use	15 (35.7%)
Wheeze triggered by respiratory infection	32 (76.2%)
Night-time wheezing or cough	20 (47.6%)

Table 6: Relationship between vitamin D deficiency and severity of recurrent wheeze (n = 42)

Severity indicator	Vitamin D deficient (n = 31)	Non-deficient (n = 11)	p-value
≥4 wheezing episodes/year	22 (71.0%)	3 (27.3%)	0.011
Emergency visit due to wheeze	22 (71.0%)	3 (27.3%)	0.011
Hospital admission	12 (38.7%)	1 (9.1%)	0.067
Night-time symptoms	18 (58.1%)	2 (18.2%)	0.022
Inhaled corticosteroid use	14 (45.2%)	1 (9.1%)	0.035

Table 7: Logistic regression analysis of factors associated with recurrent wheeze

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value
Vitamin D deficiency	4.77 (1.81–12.58)	4.12 (1.42–11.94)	0.009
Passive smoking exposure	3.30 (1.18–9.20)	2.87 (0.91–9.06)	0.072
Family history of asthma/allergy	3.63 (1.25–10.53)	3.18 (1.01–10.01)	0.048
Previous bronchiolitis	4.83 (1.65–14.13)	4.21 (1.31–13.49)	0.016
Adequate sunlight exposure	0.30 (0.12–0.77)	0.38 (0.13–1.10)	0.074
Vitamin D supplementation	0.34 (0.13–0.88)	0.47 (0.16–1.39)	0.173
Exclusive breastfeeding ≥6 months	0.40 (0.16–1.03)	0.55 (0.19–1.59)	0.270

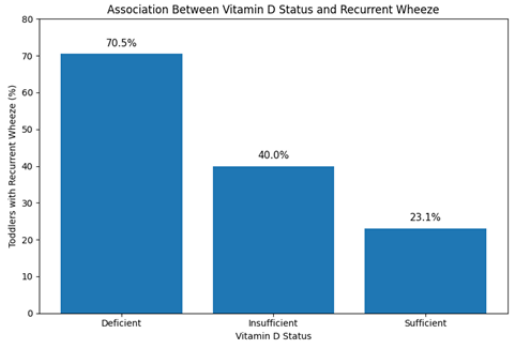

Figure 1: Association between vitamin D status and recurrent wheeze among toddlers.

A family history of asthma or allergy and previous bronchiolitis were also independent predictors of recurrent wheeze. Passive smoking showed increased adjusted odds of recurrent wheeze, although the association did not reach statistical significance after controlling for other variables.

The proportion of recurrent wheeze decreased from 70.5% among vitamin D-deficient toddlers to 40.0% among those with vitamin D insufficiency and 23.1% among those with sufficient vitamin D levels.

DISCUSSION

The present study identified a high frequency of vitamin D deficiency among toddlers and demonstrated a significant association between low vitamin D status and recurrent wheezing. More than half of the enrolled children were vitamin D deficient, while only a small proportion had sufficient serum vitamin D concentrations. Toddlers with recurrent wheeze had markedly lower mean serum 25-hydroxyvitamin D levels than children without recurrent wheezing. Vitamin D deficiency was also substantially more common in the recurrent-wheeze group. These findings suggest that inadequate vitamin D status may contribute to increased susceptibility to repeated wheezing episodes during early childhood (10-12).

There was a gradual association between more severe vitamin D deficiency and recurrent wheeze. Vitamin D deficient toddlers had the highest percentage of affected children, vitamin D insufficient toddlers had the second highest percentage and children with sufficient vitamin D had the lowest percentage. The functions of vitamin D include the regulation of immune response, the maintenance of epithelial integrity in the respiratory tract and regulation of inflammatory response. It can lead to decreased intrinsic immune response to viral and bacterial respiratory infections, a frequent cause of wheezing in toddlers. The observed association could also be due to the fact that insufficient vitamin D levels can also cause airway inflammation and bronchial hyper-responsiveness (13-15).

The presence of recurrent wheeze was associated with vitamin D deficiency, and with markers of worse clinical severity. Deficient children had more wheezing episodes, more emergency visits, more night-time respiratory symptoms and more use of inhaled corticosteroids. Vitamin D-deficient toddlers also were more likely to be admitted to hospital, although this was not statistically significant. These findings suggest that low vitamin D levels may be associated with a more troublesome wheezing pattern. Again the direction of this association needs to be interpreted with caution as the children with recurrent illness might spend less time outdoors and thus have less exposure to sunlight and therefore lower vitamin D levels (16, 17).

There were other factors associated with recurrent wheezing in this study. Previous history of bronchiolitis and family history of asthma or allergic disease were still significant predictors after adjustment for potential confounding factors. Viral bronchiolitis early in life may cause damage or temporary change to the small airways, and may lead to further episodes of wheezing during future respiratory tract infections. Likewise, a positive family history may be a family tendency to airway hyperresponsiveness or atopic disease. Toddlers with recurrent wheeze were also more likely to be passive smokers. Tobacco smoke can irritate airways, reduce local defence mechanisms in the respiratory system, and exacerbate and increase the incidence of respiratory symptoms. Correct exposure to sunlight and vitamin D supplementation seemed to have a protective effect in the unadjusted analysis, but this was less apparent after multivariable adjustment (18-20).

Several strengths of the study include assessing serum vitamin D levels, using a comparison group, evaluating wheezing severity, and adjusting for relevant nutrition, clinical and environmental factors. However, there are some restrictions to be kept in mind. The cross-sectional design does not allow to draw causal conclusions between vitamin D deficiency and recurrent wheeze. The results of this study may not be applicable to other settings or centres due to the relatively small number of samples. The number of wheezing episodes, exposure to sunlight, food and passive smoking was recalled by parents and could be subject to recall bias. The findings could also have been affected by the seasonal fluctuations of vitamin D levels and a susceptibility to respiratory infections. Future larger multi-centre prospective studies are recommended to establish if vitamin D deficiency is a precursor to recurrent wheezing and if vitamin D supplementation can help prevent wheezing episodes or decrease their frequency or severity.

CONCLUSION

Vitamin D deficiency was common among toddlers and was significantly associated with recurrent wheeze. Children with vitamin D deficiency had lower mean serum vitamin D concentrations, more frequent wheezing episodes, increased emergency visits, and more night-time respiratory symptoms. Vitamin D deficiency remained independently associated with recurrent wheeze after adjustment for important clinical and environmental factors. Previous bronchiolitis and a family history of asthma or allergy were also significant predictors. Screening for vitamin D deficiency may be considered in toddlers presenting with repeated wheezing, particularly when additional risk factors are present. However, prospective interventional studies are needed before routine vitamin D supplementation can be recommended specifically for the prevention or treatment of recurrent wheeze.

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