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Original Article

Paediatrics Section

Correlation between Vitamin D Levels and Recurrent Lower Respiratory Tract Infection in Children: A Cross-sectional Study

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ABSTRACT

Introduction: Vitamin D is a vital nutrient with immunomodulatory effects that may impact susceptibility to infections. Lower Respiratory Tract Infections (LRTI) are among the leading causes of morbidity and mortality in children. However, there is limited research exploring the relationship between vitamin D levels and LRTI in children in India.

Aim: To find a correlation between vitamin D levels and recurrent LRTI in children aged 6 months to 5 years.

Materials and Methods: A cross-sectional study was conducted in the Pediatric ward of Bokaro General Hospital in Jharkhand, India, between June 2019 and May 2020. A total of 222 children aged 6 months to 5 years diagnosed with recurrent LRTI were enrolled as cases (n=111), while other children in the same age group who were admitted with different diagnoses and required blood sampling were enrolled as controls (n=111) after obtaining parental consent. The blood levels of 25-hydroxy vitamin D [25(OH)D] were estimated and compared for both groups. Qualitative data were analysed using the chi-square test, while the Pearson's correlation coefficient was used to compute the correlation between quantitative variables.

Results: Among a total of 222 children, the majority 53 (47.7%), exhibited Vitamin D Deficiency (VDD), while most controls, 44 (39.6%) had normal vitamin D levels (p-value=0.03). The mean vitamin D level in the case group was significantly lower (p-value=0.022) compared to the control group. The VDD was found in 36 (39.13%) of the 92 cases with 2-3 episodes of LRTI, whereas it was observed in 17 (89.47%) of the 19 cases with 4-5 LRTI episodes (p-value=0.001). A significant inverse correlation was noted between the number of LRTI episodes and vitamin D levels (r-value=0.53, p-value <0.01).

Conclusion: The present study reinforces the role of VDD and insufficiency in the occurrence of recurrent LRTI in children. Therefore, all children diagnosed with recurrent LRTI should be checked for their vitamin D status and should receive repletion therapy in addition to antibiotic treatment if found to be vitamin D deficient.

Keywords: Immunomodulation, Nutrition, Respiratory infections, Vitamin D insufficiency

INTRODUCTION

Vitamin D is an essential nutritional component with a unique metabolism and physiological effects [1-3]. VDD is considered the most common nutritional deficiency and one of the most frequent undiagnosed medical conditions in the world [4]. Emerging evidence suggests that the consequences of VDD extend beyond its well-known effects on bone metabolism and calcium homeostasis; it also includes alterations in immunity. The immunomodulatory properties of vitamin D may influence susceptibility to infections [5].

The LRTI are among the most significant causes of morbidity and mortality in childhood [6]. LRTI, or pneumonia, affects nearly 120 million children worldwide annually and accounts for 1.8 million deaths in children under five years old each year [7,8]. Acute LRTI is a leading cause of global child mortality, annually causing approximately 1.4 million deaths of children younger than five years [9]. Both VDD and LRTI are significant public health problems in developing countries [10]. VDD is prevalent even in countries with ample sunshine, such as India and Pakistan [7,10]. Low levels of serum Vitamin D are associated with a higher incidence of LRTIs and respiratory syncytial virus disease [10-14].

Studies have shown that children with LRTI have significantly lower mean Vitamin D levels compared to controls, and there is a correlation between Vitamin D levels and the incidence and severity of LRTI [7,15-17]. A case-control study conducted in a tertiary care hospital in Mumbai, India, found that subclinical vitamin D levels were a significant risk factor for Acute Lower Respiratory Infection (ALRI) in Indian children under five years of age, with serum 25(OH)D_3 levels greater than 22.5 nmol/L being associated with a significantly lower odds ratio (OR: 0.09) in children with ALRI [11]. Studies in India have evaluated the Vitamin D status in children with respiratory infections, showing a correlation between VDD and LRTI [7,18-20]. However, the overall role of Vitamin D status in children with recurrent LRTI has not been fully explored. The present study aimed to reinforce the correlation between VDD and insufficiency in the occurrence of recurrent LRTI in children and to contribute to existing literature. Additionally, it highlights the need for serum Vitamin D level assessments in children with recurrent LRTI, alongside routine investigations and antibiotic therapy. Therefore, the present study was conducted to investigate the correlation between Vitamin D levels and recurrent LRTI in children aged six months to five years.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Pediatric ward of Bokaro General Hospital, a tertiary care hospital in Jharkhand, India, over the span of one year (June 2019 to May 2020) after approval from the Institutional Ethics Committee (IEC). Both cases and controls were enrolled after obtaining written consent from their parents.

Inclusion criteria: Children aged six months to five years who were admitted to the Pediatric ward and diagnosed with recurrent LRTIs were included as cases. Recurrent pneumonia was defined as two episodes of pneumonia within one year or three episodes at any point in time [21]. Children of the same age group admitted for other conditions and requiring blood sampling were enrolled as controls. The cases and controls were matched based on age and geographic location.

Exclusion criteria: Children receiving vitamin D supplements, anticonvulsant drugs, anti-tubercular drugs, or steroids, as well as children with congenital skeletal, heart, or lung disorders, or systemic diseases such as diabetes, chronic renal failure, and hypothyroidism, were excluded. Additionally, children whose parents did not provide consent were also excluded.

Sample size calculation: The sample size was calculated based on the following formula:

$n=\{Z^2P\ (1-P)/e^2\}/\{1+\{Z^2P\ (1-P)/Ne^2\}$

$n=\{(1.96)^2\ (0.08)\ (1-0.08)\}/(0.05)^2\}/\{1+\{(1.96)^2\ (0.08)\ (1-0.08)\}/5000\ (0.05)^2\}$

$n=110.55\approx 111$

where, N (total population)=about 5000 paediatric inpatient admissions annually

n (sample size for current study)=111

P=expected prevalence =8%=0.08 (reference article [7])

Margin of error=5%=0.05

Study Procedure

Demographic data, in the form of age and gender, was collected from all the cases and controls. Detailed histories of current and previous LRTI episodes were gathered from the cases. Information regarding current illness, chronic illness, and nutritional supplementation was collected from both cases and controls. Approximately 2 mL of random venous blood was collected from cases and controls to estimate the levels of 25(OH) vitamin D on Elecsys and cobas immunoassay analysers using the electrochemiluminescence technique. The cut-off values for 25(OH) vitamin D levels, according to United States (US) endocrinology guidelines [22], are as follows:

- Potential toxicity levels as >100 nmol/L
- Normal value was taken as 30-100 nmol/L
- Insufficiency as 20 to 29 nmol/L
- Deficiency as <20 nmol/L

STATISTICAL ANALYSIS

Quantitative data was represented as mean±Standard Deviation (SD) and analysed using the t-test. Qualitative data was represented as percentages and analysed using the Chi-square test. The Pearson's correlation coefficient was utilised to compute the correlation between quantitative variables. The significance threshold for the p-value was set at <0.05. All analyses were performed using Statistical Packages of Social Sciences (SPSS) software version 21.0.

RESULTS

The study population comprised a total of 222 children, including 111 cases and 111 controls. The demographic details of the study population has been depicted in [Table/Fig-1]. The majority of subjects 69 (62.2%) cases and 78 (70.3%) controls were in the age group of one to three years. Additionally, there was a higher proportion of males in both the case and control groups. The serum vitamin D levels observed in cases and controls has been depicted in [Table/Fig-2]. The majority of cases 53 (47.7%) showed VDD,

Variables	Groups		p-value
	Cases	Controls	
Age group			
6 months-1 year	12 (10.8%)	3 (2.7%)	0.051
>1-3 years	69 (62.2%)	78 (70.3%)	
>3-5 years	30 (27%)	30 (27%)	
Gender			
Male	58 (52.3%)	58 (52.3%)	1.0
Female	53 (47.7%)	53 (47.7%)	

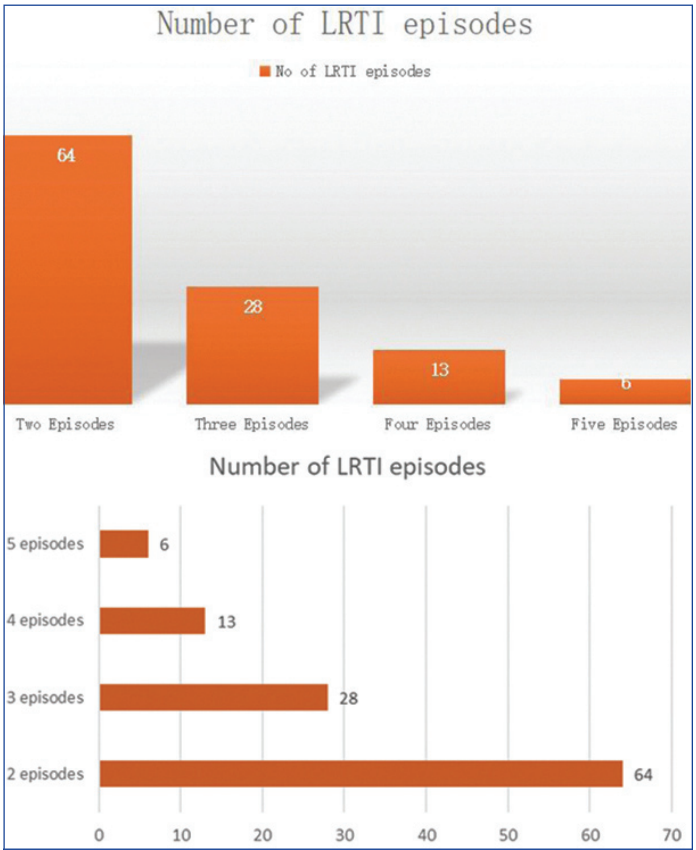
[Table/Fig-1]: Demographics of the study population.
Statistical test used-Chi-square test (N=111)

while most controls 44 (39.6%) had normal vitamin D levels. This difference was found to be statistically significant. The mean vitamin D level in cases (26.32±16.49 nmol/L) was significantly lower (p-value=0.022) compared to controls (31.22±14.96 nmol/L).

Vitamin D	Group		p-value
	Cases (n=111)	Controls (n=111)	
Deficiency	53 (47.7%)	34 (30.6%)	**0.03**
Insufficiency	27 (24.3%)	33 (29.7%)	
Normal	31 (27.9%)	44 (39.6%)	
Mean±SD	**26.32±16.49**	31.22±14.96	**0.022**

[Table/Fig-2]: Vitamin D levels in study population.
Statistical test used-Chi square test (Qualitative) and t-test (Quantitative)

[Table/Fig-3] shows the number of LRTI episodes observed in the study population. The majority of cases 64 (57.7%) had two episodes of LRTI, followed by 28 (25.2%) cases with three episodes of LRTI. The association of vitamin D status with the number of LRTI episodes is shown in [Table/Fig-4]. VDD was observed in 36 (39.13%) cases with two to three LRTI episodes, whereas it was seen in 17 (89.47%) cases with four to five episodes. This difference was statistically significant (p-value=0.001) has been depicted in [Table/Fig-4].

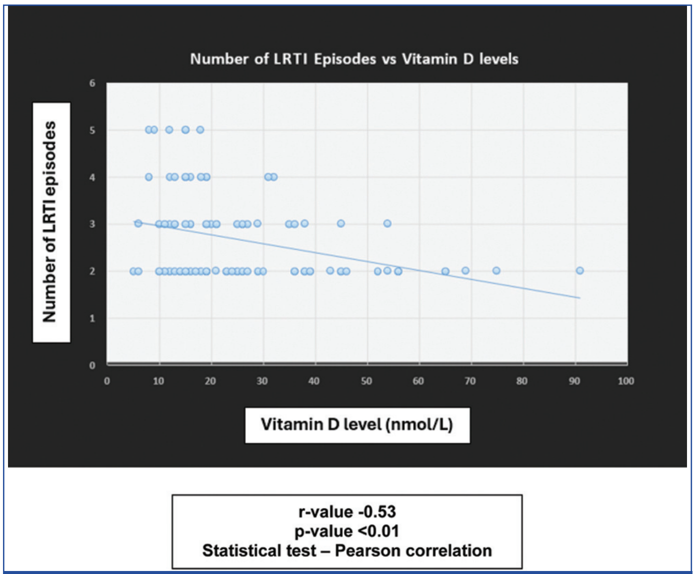


[Table/Fig-3]: Number of LRTI episodes in the study population cases.

Vitamin D status	Number of LRTI episodes (N-111)		p-value
	n (%) Two to three (n=92)	n (%) Four to five (n=19)	
Deficiency	36 (39.13%)	17 (89.47%)	0.001
Insufficiency	27 (29.35%)	0	
Normal	29 (31.52%)	2 (10.53%)	

[Table/Fig-4]: Association of vitamin D status with number of LRTI episodes in cases.
Statistical test used-Chi-square test

The correlation of vitamin D levels with the number of LRTI episodes in cases has been depicted in [Table/Fig-5]. A significant inverse correlation (r-value=0.53 and p-value <0.01) was observed between the number of LRTI episodes and vitamin D levels.



[Table/Fig-5]: Correlation of vitamin D levels with number of LRTI episodes.

DISCUSSION

In present study study, the prevalence of VDD and insufficiency among cases with recurrent LRTI was 47.7% and 24.3%, respectively. A higher prevalence of VDD/insufficiency was observed among study cases compared to controls (72% vs. 60.3%). The mean vitamin D level for the recurrent LRTI subjects was significantly lower (p-value=0.022) than that observed for controls. A significant inverse correlation was found between the number of respiratory episodes and vitamin D levels.

Similar results were found in a case-control study in India by Wayse V et al., which showed that there was a significantly lower odds ratio for having severe acute LRTI with serum 25(OH) D_3 >22.5 nmol/L (OR: 0.09; 95% CI 0.03-0.24; p<0.001) [11]. Another cohort study by Mohamed WAW and Al-Shehri MA, reported significantly low vitamin D levels in infants with LRTI (33.9±2.9 nmol/L) compared to those without LRTI (71.4±2.7 nmol/L) (p-value <0.0001) [17].

The results from present study are comparable to studies by Roth DE et al., Oduwale AO et al., and Alladi YR et al., where significantly lower mean vitamin D levels were found in children with respiratory tract infections compared to those without [12,23,24]. The case-control study by Roth DE et al., in rural Bangladesh concluded that the mean 25(OH)D was significantly lower among ALRI cases than controls (29.1 nmol/L vs. 39.1 nmol/L; p=0.015) [12]. A study by Oduwale AO et al., showed that the mean±SD serum 25(OH)D concentration was 104±59 nmol/L for subjects and 130±107 nmol/L for controls, respectively [20]. Alladi YR et al., reported means vitamin D levels in RRTI as 41.7 nmol/L compared to 64.6 nmol/L in the no RRTI group [23]. A case-control study conducted in New Delhi, India, showed a strong association between low vitamin D levels and recurrent wheezing in preschool children [24].

In contrast, a case-control study conducted in Canada by McNally JD et al., showed no difference in vitamin D levels between the entire ALRI group and control groups. However, significantly more children admitted to the pediatric intensive care unit with ALRI were vitamin D deficient. This difference in results could be attributed to variations in study population demographics, methodology, and inclusion-exclusion criteria [25].

Chandrashekhara and Pampana S conducted a cross-sectional study in Mangalore, India, which revealed a high prevalence of VDD in children with LRTI, particularly among exclusively breastfed children, those born preterm, and children from lower socio-economic backgrounds [18]. It is observed that developing countries like India have a high prevalence of LBW infants and VDD is common among women and children. These LBW infants are at a high risk of respiratory tract infections and other morbidities [15,26,27]. Low-cost interventions, such as improving vitamin D status, are necessary to enhance the health and survival of these infants. More Randomised Controlled Trials (RCTs) are needed to determine the role of vitamin D supplementation in reducing morbidity and mortality in children with respiratory infections and to incorporate an assessment of vitamin D levels in children with recurrent LRTI.

Limitation(s)

The present study contributes to the limited literature on vitamin D status in Indian children with recurrent LRTIs and supports existing evidence highlighting the importance of assessing vitamin D levels in relation to respiratory infections. However, it is important to note that this was an observational, cross-sectional study conducted at a single centre, and the effect of vitamin D supplementation on preventing further respiratory infections was not evaluated.

CONCLUSION(S)

The present study demonstrates that a significantly higher proportion of children with recurrent LRTI had VDD compared to those without it. Additionally, authors observed a significant inverse correlation between vitamin D levels and the number of LRTI episodes. These findings emphasise the need for further research to determine the potential role of vitamin D supplementation in improving morbidity and mortality among children with respiratory infections. Authors also recommend the routine assessment of vitamin D levels in children with recurrent LRTI to better manage their condition. Future research should explore the potential benefits of vitamin D supplementation in reducing the risk of respiratory infections in children.

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