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Role of vitamin D deficiency in patients with recurrent respiratory tract infections: A case-control study

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Abstract:
Recurrent respiratory tract infections remain a common health concern and the contribution of vitamin D deficiency to increased infection risk requires further clarification. Therefore, it is of interest to evaluate the association between serum 25-hydroxyvitamin D levels and recurrent respiratory tract infections in 160 participants, including 80 cases and 80 age- and sex-matched controls. Mean serum 25-hydroxyvitamin D levels were significantly lower in cases than controls (18.6 ± 7.9 versus 29.4 ± 10.8 nanograms per milliliter), while vitamin D deficiency was present in 62.5% and 25.0%, respectively and remained independently associated with recurrent respiratory tract infections (adjusted Odds Ratio = 4.12; 95% Confidence Interval = 1.93–8.80; $p < 0.001$). Lower vitamin D levels were strongly associated with recurrent respiratory tract infections even after adjustment for major confounding factors, indicating a significant relationship between vitamin D deficiency and respiratory morbidity. Thus, data support routine assessment and correction of vitamin D deficiency as a potential strategy to reduce recurrent respiratory tract infections and improve preventive respiratory healthcare.

Keywords: Vitamin D deficiency, 25-hydroxyvitamin D, recurrent respiratory tract infection (rRTI); immunity, case-control study, respiratory morbidity

Background:
Respiratory tract infections are one of the most frequent causes of consultation in the outpatient setting, antimicrobial prescribing, school and workplace absenteeism and short term morbidity. Most episodes are self-resolving, but recurrent episodes impose an ongoing burden on families and health services, particularly when infections occur in people who do not have a significant immunodeficiency or structural lung disease **[1].** Recurrent respiratory tract infection is not a specific diagnosis, but can be due to repeated exposure, altered host immunity, nutritional vulnerability, allergic airway disease, environmental smoke, indoor crowding or incomplete recovery between episodes. Vitamin D is no longer just a vitamin for calcium and bone health. It is biologically active and regulates genes involved in innate and adaptive immunity, such as epithelial barrier integrity, production of antimicrobial peptides, macrophage function and modulation of excessive inflammation. The respiratory epithelium is a mechani-cal barrier as well as an immunologically active surface and vitamin D receptors are found in immune cells and epithelial cells that play a role in respiratory defense **[2].** There is suggestive, but not consistent, clinical evidence of a vitamin D-respiratory infection link. Previous individual participant and aggregate data meta-analyses indicated small protective benefits of vitamin D supplementation for ARIs in people with low baseline vitamin D levels and in regimens that do not include high intermittent bolus doses **[2, 3].** More recent updates, which have included large, randomized trials, have been more conservative and indicate that supplementation may not be consistently effective to prevent acute infections in all populations **[4].** Vitamin D is biologically active and regulates genes involved in innate and adaptive immunity, such as epithelial barrier integrity, production of antimicrobial peptides, macrophage function and modulation of excessive inflammation **[5, 6].** Observational studies have reported lower vitamin D levels among individuals with recurrent or acute respiratory infections. In a case-control study, Laaksi *et al.*, Wayse *et al.* and Maqbool *et al.* found significantly lower serum vitamin D levels among participants with recurrent upper respiratory tract infections than healthy controls **[7–9].** Interventional studies have also been conducted in schoolchildren and other populations, with inconsistent findings that are dependent on the level of deficiency, the dosage regimen, compliance and the definition of the outcome **[10, 11].** Therefore, it is of interest to compare the serum 25-hydroxyvitamin D levels of patients with recurrent respiratory tract infections (rRTIs) with matched controls and to evaluate the independent association between vitamin D deficiency and recurrent infection after adjusting for major environmental and host risk factors.

Materials and Methods:
Study design and setting:

A case-control study was conducted in the outpatient departments of general medicine, pediatrics and otorhinolaryngology of a tertiary care teaching hospital during the period of one year. The study was aimed at comparing vitamin D status of patients with recurrent respiratory tract infections with apparently healthy controls attending routine health visits or minor non-infective complaints.

Sample size:
160 participants (80 cases and 80 controls). Sample size was calculated based on the assumption that the prevalence of vitamin D deficiency is 55% in the cases and 30% in the controls with 80% power, 95% confidence level and 10% allowance for incomplete laboratory data. The age and sex of cases and controls were frequency matched.

Case definition:
Recurrent respiratory tract infection was defined as 6 or more upper respiratory infection episodes in the preceding 12 months, 2 or lower respiratory infection episodes in the preceding 12 months and/or 3 or more physician-documented respiratory infections requiring medical consultation within 6 months. All episodes of upper and lower respiratory symptoms were accepted if there was clinical documentation or a prescription.

Eligibility:
Participants were aged from 5-45 years. Recurrent respiratory tract infection (as defined in the operational definition) was the diagnosis in cases. The controls were not known to have had any history of recurrent respiratory symptoms, nor had they had any acute infection in the four weeks prior to the study. Patients with chronic kidney disease, chronic liver disease, tuberculosis, bronchiectasis, cystic fibrosis, primary immunodeficiency, malignancy, long-term corticosteroid therapy, current pregnancy, vitamin D supplementation in past 3 months and who refused to provide blood samples were excluded.

Data collection:
A structured proforma was used to record age, sex, residence, BMI, dietary pattern, exposure to sunlight, exposure to passive smoke, indoor crowding, allergic rhinitis, history of asthma, vaccination status, frequency of infections, antibiotic use and history of hospitalisation. Temperature, respiratory rate, oxygen saturation, anthropometry and chest examination, as appropriate, were performed during clinical examination.

Laboratory procedure:
Venous blood was taken in the morning. The 25-hydroxyvitamin D level in serum was determined by chemiluminescent immunoassay. Vitamin D status was defined as deficient (<20 ng/mL), insufficient (20-29 ng/mL) and sufficient (>=30 ng/mL). Cases were classified based on vitamin D status and complete blood count and C-reactive protein were measured when clinically indicated.

Data analysis:
SPSS version 28.0 was used for statistical analysis. Continuous variables were presented as mean ± SD and categorical variables were presented as frequency and percentages. Continuous variables according to distribution were analyzed using independent t-test or Mann-Whitney U test. Chi-square test or Fisher's exact test was used for categorical variables. Crude and adjusted odds ratios for RRIs were estimated using binary logistic regression. The p value < 0.05 was taken as a statistically significant value.

Results:
A total of 160 participants were analyzed, with 80 cases and 80 controls. The mean age of cases was 18.9 ± 9.8 years and the mean age of controls was 19.7 ± 10.1 years (p=0.61). Male participants constituted 52.5% of cases and 50.0% of controls (p=0.75). Body mass index was comparable between groups, but passive smoke exposure and indoor crowding were more common among cases **(Table 1).** The mean serum 25-hydroxyvitamin D level was significantly lower among cases than controls (18.6 ± 7.9 ng/mL vs 29.4 ± 10.8 ng/mL, p<0.001). Vitamin D deficiency was present in 50 cases (62.5%) compared with 20 controls (25.0%). Vitamin D sufficiency was observed in only 13.8% of cases compared with 42.5% of controls. Cases also reported a higher median number of infection episodes and greater antibiotic exposure during the previous year **(Table 2).** On logistic regression, vitamin D deficiency showed a strong association with recurrent respiratory tract infection. The crude odds ratio was 5.00 (95% CI 2.55-9.81) and the adjusted odds ratio was 4.12 (95% CI 1.93-8.80) after controlling for age, sex, body mass index, passive smoke exposure, indoor crowding, allergic symptoms and season of sampling. Passive smoke exposure and indoor crowding also remained significant independent predictors **(Table 3).**

Table 1: Baseline characteristics of study participants

Variable	Cases (n=80)	Controls (n=80)	p-value
Age, years (mean +/- SD)	18.9 ± 9.8	19.7 ± 10.1	0.61
Male sex, n (%)	42 (52.5)	40 (50.0)	0.75
BMI, kg/m2 (mean +/- SD)	22.8 ±4.1	22.2 ± 3.8	0.34
Passive smoke exposure, n (%)	31 (38.8)	15 (18.8)	0.005
Indoor crowding, n (%)	29 (36.3)	13 (16.3)	0.004
Allergic rhinitis/asthma history, n (%)	22 (27.5)	11 (13.8)	0.03

Table 2: Vitamin D status and respiratory morbidity indicators

Variable	Cases (n=80)	Controls (n=80)	p-value
Serum 25(OH)D, ng/mL	18.6 ± 7.9	29.4 ± 10.8	<0.001
Vitamin D deficiency <20 ng/mL, n (%)	50 (62.5)	20 (25.0)	<0.001
Vitamin D insufficiency 20-29 ng/mL, n (%)	19 (23.8)	26 (32.5)	0.22
Vitamin D sufficiency >=30 ng/mL, n (%)	11 (13.8)	34 (42.5)	<0.001
Respiratory episodes in previous year	6.8 ± 1.9	1.7 ± 1.1	<0.001
Antibiotic courses in previous year	3.1 ± 1.5	0.6 ± 0.8	<0.001

Table 3: Logistic regression analysis for recurrent respiratory tract infections

Predictor	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value

Vitamin D deficiency	5.00 (2.55-9.81)	4.12 (1.93-8.80)	<0.001
Passive smoke exposure	2.74 (1.34-5.59)	2.21 (1.02-4.82)	0.045
Indoor crowding	2.93 (1.39-6.18)	2.48 (1.11-5.55)	0.027
Allergic rhinitis/asthma history	2.38 (1.06-5.35)	1.86 (0.78-4.43)	0.16
BMI >=25 kg/m2	1.31 (0.61-2.81)	1.18 (0.50-2.78)	0.71

Discussion:

The present case-control study showed that there was a definite link between vitamin D deficiency and recurrent respiratory tract infections. Mean serum 25-hydroxyvitamin D levels were significantly lower in patients with recurrent infections than in controls and 25-hydroxyvitamin D deficiency was more than twice as prevalent in patients. However, the association continued to be significant even after adjusting for environmental exposure, crowding, BMI, allergic airway history and seasonal sampling, indicating that low vitamin D status is not simply a coincidental laboratory finding. The results are biologically feasible. Vitamin D plays a role in maintaining respiratory host defense in several ways: induction of antimicrobial peptides, regulation of the response of macrophages and dendritic cells, maintenance of epithelial integrity and dampening of excessive inflammatory signaling. These pathways are pertinent to both viral and bacterial respiratory infections and early innate immune responses at the mucosal surface affect symptom severity and duration **[5, 12]**. The difference in mean vitamin D levels observed is consistent with previous observational evidence. Maqbool *et al.* reported significantly lower serum vitamin D levels among patients with recurrent upper respiratory tract infections, while Patil *et al.* similarly found lower vitamin D levels and a higher prevalence of deficiency among children with recurrent lower respiratory tract infections compared with healthy controls **[9, 13]**. The findings are also consistent with a systematic review by Raju *et al.,* Cho *et al.* and Jaybhaye *et al.* which found that most of the included studies supported an association between low vitamin D levels and increased susceptibility to respiratory infections in children; although a consistent relationship with infection severity was not showed **[14–16]**. Observational association does not mean that supplementation alone is a guarantee of preventing recurrent infections in all patients, however. Vitamin D deficiency can be a risk factor, a proxy for low levels of outdoor activity, or it could be part of a larger nutrition and environmental risk profile. There is conflicting evidence that is random. Previous meta-analyses indicated a small benefit of vitamin D supplementation for prevention of acute respiratory tract infections (ARTIs) particularly in individuals with low baseline vitamin D levels **[2, 3]**. Subsequent analyses which included larger trials were less supportive of the universal supplementation for infection prevention **[4, 17]**. This distinction is relevant to the clinical situation. It recommends that high dose supplementation of the population as a single intervention as a respiratory prevention strategy should not be encouraged, but it does not exclude the benefit of identifying and correcting deficiency for general health and possibly enhanced immune resistance. Passive smoke exposure and crowding indoors was also independently correlated with recurrent respiratory infections in this study. These may lead to higher exposure dose, to reduced mucociliary clearance and to longer inflammatory irritation of the airway. Thus, the treatment of recurrent respiratory infections should be multi-faceted. Assessment of vitamin D status may be appropriate, but counselling on smoking, ventilation, nutrition, vaccination, sleep and allergic control of the airway is still needed. A practical consideration is that serum 25-hydroxyvitamin D should be considered in patients who have recurrent respiratory infections, particularly if they have limited sun exposure, nutritional risk, musculoskeletal symptoms, or repeated antibiotic use for which there is no clear cause. Treatment for deficiency should be based on accepted clinical guidelines and not be megadose therapy without supervision. The aim is to restore a sufficient vitamin D status and not to replace the usual preventive measures. The advantages of the study are the matched case-control design, objective measurement of serum 25-hydroxyvitamin D and the standardized definition of recurrence, as well as the adjustment for common confounders. Limitations are that it is a single-center study, there may be some recall bias for the frequency of infections, some infections may not have been confirmed by a virus or bacteria and there is no inference of cause. The classification was statistically adjusted for seasonal variation, however repeated measurements of vitamin D throughout the seasons would have strengthened the classification. Future prospective studies are needed to look at the impact of targeted correction of deficiency on reducing recurrence rates, antibiotic exposure and health-care visits in patients with deficiency. In conclusion, the study confirms the importance of vitamin D deficiency as one of the associated factors in recurrent respiratory tract infections. Evidence is strongest for deficiency as a risk marker and potential modifiable contributor and decisions around supplementations should be individual and take a holistic approach to respiratory health measures **[18, 19]**.

Conclusion:

The serum 25-hydroxyvitamin D level was significantly lower and vitamin D deficiency was more common in patients with recurrent respiratory tract infections than in matched controls. The association of vitamin D deficiency with recurrent infections was independent of important environmental and host-related factors. Rational supportive measures to reduce recurrent respiratory morbidity may include targeted evaluation and correction of deficiency, smoke avoidance, improved ventilation, vaccination and nutritional counseling.

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