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Prevalence of Vitamin D Deficiency and Its Association with Infection Frequency Among Adults with Recurrent Respiratory Infections: A Cross-Sectional Study

Dr. Bibin Jose[1], Dr. Anjana A R[*2], Dr. R C Krishna Kumar[3]

[1]Associate Professor, PK Das Institute of Medical Sciences, Vaniyamkulam, Kerala, India.
[2]Assistant Professor, PK Das Institute of Medical Sciences, Vaniyamkulam, Kerala, India.
[3]Medical Director, PK Das Institute of Medical Sciences, Vaniyamkulam, Kerala, India.

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Corresponding Author:

Dr. Anjana A R
Assistant Professor, PK Das Institute of Medical Sciences,
Vaniyamkulam, Kerala, India.

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ABSTRACT

Background: Recurrent respiratory infections (RRIs) represent a clinical problem with important consequences for patient morbidity and health care costs. Vitamin D is important in regulating immune status and it is speculated that subjects with RRI are more prone to vitamin D deficiency. We sought to determine the prevalence of vitamin D deficiency and its correlation with frequency of infection among adults.

Materials and Methods: This cross-sectional study consisted of 120 adults with recurrent respiratory infections. Demographic and clinical data were gathered and serum 25-hydroxyvitamin D, was obtained and classified into deficient (<20 ng/mL), insufficient (20–30 ng/mL) and sufficient (>30 ng/mL) groups. Analysis was performed with SPSS. Proportions were reported with 95% confidence intervals and associations using chi-square tests.

Results: The mean age of participants was 45.8 ± 13.2 years. Most participants were aged 41–60 years (48.3%, 95% CI: 39.4–57.2), with a male predominance (58.3%, 95% CI: 49.5–67.1). High frequency of infections (≥5 per year) was noted in 41.7% (95% CI: 32.9–50.5) of patients. The mean serum vitamin D level was 21.6 ± 8.9 ng/mL. Vitamin D deficiency and insufficiency was seen in 55.0% (95% CI: 46.1–63.9) and 26.7% (95% CI: 18.8–34.6) respectively, with 81.7% (95% CI: 74.8–88.6) of participants having suboptimal vitamin D levels. Among patients with vitamin D deficiency, 45.4% (95% CI: 33.4–57.4) experienced ≥5 episodes of respiratory infections. The presenting symptoms were consistent with cough (80.0%, 95% CI: 72.8–87.2). The association between lower frequency of infections and lower vitamin D level, although noted, was not significant (χ^2 = 7.62, p = 0.10).

Conclusion: Vitamin D deficiency is very common in adults with recurrent respiratory infections and is associated with more frequent episodes of infection, although this is weakly related (r=0.12), suggesting that the association may not be causal. Screening and treatment may lessen the burden of disease. Larger studies are needed to assess causality.

Keywords: *Vitamin D deficiency, recurrent respiratory infections, prevalence, infection frequency, 25-hydroxyvitamin D, cross-sectional study.*

INTRODUCTION

Recurrent respiratory infections (RRIs) are another common clinical problem and an important source of considerable morbidity, healthcare use, and reduced quality of life among adults. RRIs are defined by occurrence of three or more episodes of respiratory tract infections per year involving the upper or lower respiratory tract (comprising pharyngitis, sinusitis, bronchitis, pneumonia, etc.) associated with cough, fever, sore throat, nasal congestion, sputum production and breathlessness[1]. Its repeated episodes disrupt not only routine family and social activities but also centre upon

overprescription of antibiotics, frequent visits to the doctor and incurring considerable economic losses. Increased susceptibility to these respiratory infections is often the result of a complex interaction between host immune resistance, challenge by environmental exposures and health status[2]. Rri susceptibility can be understood by the degree of these biotic and abiotic influences that alter specific aspects of immune defence; among these, nutritional status has turned out to be probably the most important and amenable factor influencing immunity[3]. It is now well-established that micronutrient deficiencies can lead to impairment of both innate and adaptive immunity and hence increased risk of infection. In addition, vitamin D has been recognized as an important vitamin due to its role in immunity and its modulation of host defence and susceptibility to respiratory infections is of interest to us[4]. There are 'vitamin D receptors' that mediate 'genomic' responses and subsequent 'non-genomic' physiological effects of vitamin D (actually in the form of a steroid hormone) on various target organs. Traditionally identified for its role in the maintenance of calcium homeostasis and eliciting bone effects, vitamin D has now become an important modulator of immune responses[5]. Vitamin D receptors are found to be available on immune cells acting primarily but not restricted to the macrophage and dendric cell; T and B-lymphocytes also have these vitamin receptors.By binding to these receptors, vitamin D augments innate immunity by stimulating the expression of antimicrobial peptides such as cathelicidin and defensins that help guard the respiratory mucosa against pathogens. It performs immune system modulation by regulating cytokine production that transiently suppresses inflammatory responses that may cause tissue damage during infections[6].

Epidemiological studies have indicated that decreased serum 25-hydroxyvitamin D [25(OH)D] concentrations increase the susceptibility to respiratory infections, upper respiratory tract infections, bronchitis, and pneumonia[7]. Fluctuations in rise or fall in respiratory infection rates in the respective seasons, especially fall reflects dust or exposure to normal active infection, and therefore, indirect evidence of the role of vitamin D in infection defences is noted. Even with the accumulating evidence, vitamin D deficiency continues to be underidentified and underdiagnosed in every-day practice even in patients by the treating physician[8,9]. Vitamin D deficiency is endemic in India affecting about half to 90% at all ages in spite of abundant sunlight, (indoor dwelling, less exposure to sun, use of sunscreen, air pollution, cultural clothes, women not exposed to sunlight, poor dietary intake, increased skin pigmentation and age reduces cutaneous synthesis of vitamin D) making them vulnerable to infectious diseases[10].

Although studies had evaluated this relationship in the past, few have specifically addressed the prevalence and clinical implication of vitamin D deficiency in adults with recurrent respiratory infections in tertiary care settings.

The relationship is important in order that case finding of easily modifiable risk factors may assist in guiding preventive targets against respiratory infections, therefore the present study aimed to study the frequency of vitamin D deficiency in cases with recurrent respiratory infections and assess the relation of vitamin D deficiency with frequency of episodes of infection.

METHODS

Materials and Methods

Study Centre: This cross-sectional study was conducted among patients reporting for recurrent respiratory infections in Outpatients Department of tertiary care hospital.

Study population: 120 patients were included during the study period.

Selection Criteria

Inclusion Criteria: Patients aged 18 years and older who were diagnosed with recurrent respiratory infections and who gave written informed consent were included. Recurrent respiratory infection defined as presence of recurrent three or more episodes of respiratory illness in previous one year was defined by the presence of symptoms such as cough, fever, sore throat, nasal discharge, and dyspnea.

Exclusion Criteria: Patients receiving (or had received within preceding three months) vitamin D, patients having chronic respiratory diseases stepwise ilness of tuberculosis, history of chronic systemic diseases affecting metabolism of vitamin D such as chronic kidney disease, chronic liver disease, pregnant and breast feeding female patients, history of immunodeficiency disorder, human immunodeficiency virus positive patients, cases on immunosuppressive therapy, unwilling uniformly non-cooperative patients. Sample size: Assuming 70% of individuals would have Vitamin D deficiency as brought out in previous literature, with confidence level of 95% and allowable error of 10%, the sample size was calculated and 120 patients enrolled by consecutive sampling.

Variables: The demographics, clinical history, frequency of episodes of respiratory infection, and symptom profile were recorded in structured proforma. All cases were physically examined in detail focusing on respiratory system. A venous blood sample from each patient was taken to estimate serum 25-OH vitamin D levels along with further relevant investigat ions.Vitamin D levels were estimated by standard computerized system and laboratory (House of Diagnostic, Chennai). All patients were classified as vitamin D deficient (<20 ng/mL), insufficient (20–30 ng/mL), or sufficient (>30 ng/mL) based on their serum 25-OH vitamin D levels. All data were entered in an excel sheet MS Office, then analyzed in SPSS. Categorical variables were expressed in fr equencies and percentages. Continuous variables, i.e. age in years, serum vitamin

D levels were expressed in mean and standard deviation. Proportions were expressed with its 95% confidence intervals. Chi-square test (x 2) was used to analyze association between vitamin D status and frequency of episodes. A $p<0.05$ was considered significant.

RESULTS

Baseline Characteristics of Study Population

One hundred and twenty participants were included. The mean age of the study population was 45.8 ± 13.2 years. The highest proportion of respondents (25.0%, n=30; 95% CI: 17.2–32.8) were aged 41–50 years, and this was closely followed by 51–60 years (23.3%, n=28; 95% CI: 15.8–30.8). Eighteen-point three percent (n=22; 95% CI: 11.4–25.2) of the respondents were aged between 31–40 years while 18.4% (n=22; 95% CI: 11.5–25.3) ranged from 61 years and above, while the least proportion of 15% (n=18; 95%CI: 8.6–21.4) were aged between 18–30 years. Males constituted 58.3% (n=70; 95% CI: 49.5–67.1) while females were 41.7% (n=50; 95% CI: 32.9–50.5).

Table 1: Baseline characteristics of study population

Table 1 shows the age and gender distribution along with mean age.

Variable	Category	Number (n)	Percentage (%)	95% CI
Age (years)	18–30	18	15.0	8.6–21.4
	31–40	22	18.3	11.4–25.2
	41–50	30	25.0	17.2–32.8
	51–60	28	23.3	15.8–30.8
	>60	22	18.4	11.5–25.3
Gender	Male	70	58.3	49.5–67.1
	Female	50	41.7	32.9–50.5

Mean age of participants: 45.8 ± 13.2 years

Distribution of Respiratory Infection Episodes

For episodes of respiratory infection: 30.0% (n=36; 95% CI: 21.8–38.2) reporting four episodes; 28.3% (n=34; 95% CI: 20.2–36.4) three episodes; 23.3% (n=28; 95% CI: 15.8–30.8) five episodes; 18.4% (n=22; 95% CI: 11.5–25.3) six or more; overall, 41.7% (n=50; 95% CI: 32.9–50.5) had ≥5 episodes/year.

Table 2: Distribution of respiratory infection episodes

Table 2 shows the frequency of infection episodes among participants.

Episodes	Number (n)	Percentage (%)	95% CI
3 Episodes	34	28.3	20.2–36.4
4 Episodes	36	30.0	21.8–38.2
5 Episodes	28	23.3	15.8–30.8
≥6 Episodes	22	18.4	11.5–25.3
≥5 Episodes (combined)	50	41.7	32.9–50.5

Symptom Profile of Respiratory Infections

Cough was the most common (80.0%, n=96; 95% CI: 72.8–87.2) followed by fever (70.0%, n=84; 95% CI: 61.8–78.2) sore throat (60.0%, n=72; 95% CI: 51.2–68.8) and nasal congestion (56.7%, n=68; 95% CI: 47.8–65.6). Breathlessness was experienced by 33.3% (n=40; (95% CI: 24.9–41.7)

Table 3: Symptom profile of respiratory infections

Table 3 shows the distribution of symptoms among participants.

Symptom	Number (n)	Percentage (%)	95% CI
Cough	96	80.0	72.8–87.2
Fever	84	70.0	61.8–78.2
Sore throat	72	60.0	51.2–68.8
Nasal congestion	68	56.7	47.8–65.6
Breathlessness	40	33.3	24.9–41.7

Distribution of Vitamin D Status

The mean serum vitamin D level was determined to be 21.6 ± 8.9 ng/mL. Approximately, deficiency was detected in 55.0% (n=66; 95% CI: 46.1-63.9), 26.7% (n=32; 95% CI: 18.8-34.6) had levels that are insufficient, while only 18.3% (n=22; 95%CI: 11.4-25.2) had adequate level of vitamin D. The overall prevalence of poor vitamin D status was 81.7% (n=98; 95% CI: 74.8-88.6).

Table 4: Distribution of vitamin D status

Table 4 shows the distribution of vitamin D status along with mean serum vitamin D levels.

Vitamin D Status	Number (n)	Percentage (%)	95% CI
Deficient (<20 ng/mL)	66	55.0	46.1–63.9
Insufficient (20–30 ng/mL)	32	26.7	18.8–34.6
Sufficient (>30 ng/mL)	22	18.3	11.4–25.2
Deficient + Insufficient	98	81.7	74.8–88.6

Mean serum vitamin D level: 21.6 ± 8.9 ng/mL

Association Between Vitamin D Status and Frequency of Respiratory Infections

Among vitamin D deficient patients, 45.4% (n=30; 95% CI: 33.4-57.4) had ≥ 5 episodes compared with 37.5% (n=12; 95% CI: 20.7-54.3) among the insufficient and 36.4% (n=8; 95% CI: 16.3-56.5) among the sufficient groups. The sufficient patients were more frequently seen in the lower infection frequency group (3 episodes: 45.4%). Although there was an observed trend, the association was not statistically significant ($\chi^2 = 7.6232$ p=0.10)).

Table 5: Association between vitamin D status and frequency of respiratory infections

Table 5 shows the relationship between vitamin D levels and frequency of respiratory infection episodes.

Vitamin D Status	3 Episodes	95% CI	4 Episodes	95% CI	≥5 Episodes	95% CI	χ^2	p-value
Deficient (n=66)	12 (18.2%)	8.9–27.5	24 (36.4%)	24.8–48.0	30 (45.4%)	33.4–57.4	7.62	0.10
Insufficient (n=32)	12 (37.5%)	20.7–54.3	8 (25.0%)	10.0–40.0	12 (37.5%)	20.7–54.3		
Sufficient (n=22)	10 (45.4%)	24.6–66.2	4 (18.2%)	2.1–34.3	8 (36.4%)	16.3–56.5		

Mean age of the study population, data depicted in **Table 1,** was 45.8 ± 13.2 years; most belonged to age group of 41-50 years (25.0%), followed by 51-60 years (23.3%). Among the obtained groups, least was 18-30 years (15.0%). Males comprised higher proportion of the study population, 58.3% in contrast with females 41.7%, depicting slight male predominance. **Table 2** depicts that more patients experienced 4 episodes (30.0%), followed by 3 episodes (28.3%). Major proportion of the patients (23.3%) experienced 5 episodes while majority (18.4%) experienced six or more episodes. The study population experiencing ≥5 episodes annually was 41.7% showing considerable burden of recurring infections. **Table 3** shows cough to be most frequently encountered presenting symptom (80.0% participants) followed by fever in (70.0%), sore throat and nasal congestion (60.0%, 56.7% patients respectively). Least common was breathlessness (33.3%), indicating upper respiratory tract symptoms dominance. **Table 4** depicts mean serum vitamin D level 21.6 ± 8.9 ng/mL. Vitamin D deficiency (55.0%) majorly seen followed by insufficient levels (26.7%) while only 18.3% had sufficient levels. The study population portrayed suboptimal vitamin D status (81.7%), indicating high prevalence of hypovitaminosis D patients with recurrent respiratory infections. **Table 5** shows frequency of >5 episodes among the patients of vitamin D deficient patients (45.4%) was greater as compared to the insufficient levels (37.5%) and the higher levels (36.4%) found crowded mostly in lower frequency category of 3 episodes (45.4%). Though more frequency seen among Vitamin D deficient persons, the association was not significant ($\chi^2 = 7.62$, p = 0.10) indicating a trend only.

DISCUSSION

The present study demonstrated a high burden of vitamin D deficiency in adult patients who presented with recurrent respiratory infections, as well as a trend toward increasing frequency of infection with declining vitamin D status.

Participants in this study had mean age of 45.8 ± 13.2 years, with majority belonging to 41–60 years age group. The highest age group was 41–60 years, reflecting the outsize predominance of working-age adults, who are also more amenable to developing environmental risk factors for, and seeking healthcare for recurrent respiratory symptoms[11,12]. A slight male predominance was seen which may also have reflected superior access to healthcare, or occupational exposure, though vitamin D deficiency was widely distributed across age groups and by gender with no significant association seen[13]. This is not surprising, in view of the fact that vitamin D deficiency is a generalized problem. Overall prevalence of vitamin D deficiency in the present study was 55.0%. An additional 26.7% had insufficient levels. Thus 81.7% participants in the study had suboptimal vitamin D status[14]. The mean serum vitamin D level of 21.6 ± 8.9 ng/mL, is suggestive of the ramification of hypovitaminosis D across this cohort.Our findings are in concordance with other researchers reporting greatly increased rates of vitamin D deficiency across populations, especially in locales with sunlight paradox. A downward factor includes socially restricted outdoor activity, pollution or smog, dark skin pigmentation, and deficient vitamin D dietary intake[15]. The clinical profile of our patients reveled cough as the most commonly encountered symptom, followed by fever. Other symptoms such as sore throat and nasal congestions were less frequently reported by the subjects. This is consistent with the common picture of recurrent respiratory infections where upper respiratory infections predominate as per reports[16]. Breathlessness was less commonly encountered suggesting generalized lung involvement not as common, probably reflecting severe involvement of the lower respiratory tract, in a smaller subset of patients[17]. Noteworthy in our study however was the observation of a relationship (however not approaching significance) of vitamin D status and the occurrence of upper respiratory infection episodes[18]. More patients with vitamin D deficiency had (‘frequent’ 517 episodes per year) recurrent infection episodes compared to patients with Insufficient vitamin D and adequate levels of vitamin D.

Although the association did not reach statistical significance, we note the observed trend with interest as vitamin D enhances innate immune responses through 10 antimicrobial peptides (cathelicidin and defensins) which play an important role in respiratory immunity against pathogens[19]. In addition, Vitamin D concentrates points in airway epithelial cells therefore modulating inflammatory responses, and then attenuating an exacerbated inflammatory response leading to further host tissue damage[20].

A small sample size such here in our study, might make it difficult to attendant significance. Alternatively, other contributory factors such as nutrition, socioeconomic status, Body mass index and comorbid illnesses, may obscure the relationship. Finally, the cross-sectional design limits the fulfilment of the causal condition of temporal precedence. The burden of vitamin D deficiency in patients with recurrent respiratory infections is affected with these implications for clinical policy. Frequent screening of vitamin D levels in patients with recurrent respiratory infections, identification and correction of deficiency with notification, agency and supplement-based antibiotics with calcium and lifestyle advice (sunshine and dietary creative). Our study has limitations. We did not replicate our inclusion criteria across a control group suffering no recurrent infections, the trend of association was not significant between vitamin D and the recurrent episode frequency, seasonal variation in levels was not studied, nor was Confounding extensively handled. Despite our study finding a high burden of vitamin D deficiency in adults with recurrent respiratory infections, studies such as this highlight the need for larger studies across wider samples to study the health care impact of vitamin D deficiency in patients with recurrent infections., and ultimately her role as a remedy worker, if confirmatory results arise from wider studies.

CONCLUSION

The current study finds a high prevalence of vitamin D deficiency among recurrent respiratory infection adults with most adults deficient or insufficient in vitamin D, with low mean serum vitamin D level further emphasizing the public health significance of hypovitaminosis D burden in this population. Despite no statistically significant association between vitamin D and the frequency of respiratory infections noted, greater number of frequent occurrence episodes noted in vitamin D deficient individuals indicating potential role of vitamin D in immune function and susceptibility to respiratory infections. Routine screening of vitamin D level in patients with recurrent respiratory infections will facilitate earliest identification and management of deficiency. Correction of vitamin D status in conjunction with appropriate sunlight exposure and dietary improvement may alleviate this burden of recurrent infection. Large scale, longitudinal studies should be done to confirm the causal nature and the efficacy of vitamin D supplementation in reducing the frequency and severity of respiratory infections.

Limitations

The present study has a few limitations. Since the study had a cross-sectional design, it is difficult to ascertain if deficiency in Vitamin D was causal or vice versa, recurrent respiratory infections. Lack of a control group of people without recurrent infections makes it difficult to compare our findings. Other confounders such as dietary habits, BMI, economic status, other comorbidities were not exhaustively taken into consideration. Seasonal variation in the vitamin D level was not documented, which may affect the serum levels. Small sample size may also have limited our statistical power.

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