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ORIGINAL ARTICLE

# Vitamin D - An Elixir for Recurrent Upper Respiratory Tract Infection

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## Abstract

**AIM** The aim of this study was to assess and compare the level of serum vitamin-D in participants affected with recurrent upper respiratory tract infections and in healthy population and to know whether vitamin-D deficiency is factor contributing to recurrent upper respiratory tract infections (URTI).

**Materials and Methods** A case control study was conducted on 52 subjects with recurrent URTI and 52 controls. Frequency and severity of infections in the previous 6 months were assessed and documented among the case group. Vitamin D level was assessed in all the participants among case and control group and statistical analysis was done.

**Results** Mean serum vitamin D was 10.67 ± 3.58 ng/mL in the study group and 20.10 ± 7.73 ng/mL in the control group, the difference in value was statistically significant. None of the study group participants belonged to vitamin D sufficient group, and majority (98%) were in vitamin D deficient, except for 2% who were in insufficient group. In the control group, 10%,29%,61% were in sufficient, insufficient and deficient group respectively. Mean serum vitamin D was not significantly associated with severity and type of infection.

**Conclusion** Significant number of participants in both study and control had serum vitamin D deficiency. This study also observed that a significant number of participants with recurrent URTI had serum vitamin D deficiency than the control group which suggest that hypovitaminosis D is a factor contributing to recurrent URTI.

## Introduction

Vitamin D is a fat-soluble vitamin, predominantly synthesized in the skin in the presence of ultraviolet B (UVB) radiation [1]. Vitamin D is found in two forms in the human body, vitamin-D3 (cholecalciferol) and vitamin-D2(ergocalciferol). Vitamin-D3 (cholecalciferol) is synthesized in the skin and is also obtained from diet like fatty fishes whereas Vitamin-D2 (ergocalciferol) is obtained from the plant-based sources. Dietary sources alone is not sufficient to meet the daily requirement of this vitamin [2]. The level of 25(OH)vitamin D in the bloodstream is the best indicator for defining an individual's serum vitamin D status [3].

Vitamin D has a vital role in regulating immune system in addition to its key role in maintaining calcium homeostasis. Vitamin D receptors are found on immune cells including antigen-presenting cells (e.g., macrophages), T-cells and B-cells, which have the ability to synthesize and respond to the active form of vitamin D (1,25-dihydroxyvitamin D) [4].

Even though the major source of Vitamin D is cutaneous synthesis, hypovitaminosis D is prevalent even in the areas with adequate sunshine [5]. Vitamin D deficiency can be caused by a variety of factors, including decreased vitamin D synthesis and absorption in the skin, as well as acquired and hereditary abnormalities of vitamin D metabolism and response [6].

The US Endocrine Society recommends a cut-off level of less than 20 ng/ml (50 nmol/L) for serum vitamin D deficiency, between 21 and 29 ng/ml (50– 75 nmol/L) for insufficiency, and a safety margin of 100 ng/ml (250 nmol/L) for serum 25 hydroxyvitamin D to prevent hypercalcaemia [7].

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Low Vitamin-D level is linked to recurrent infections according to the new studies. If vitamin-D supplementation can reduces the recurrence of upper respiratory tract infections, it can improve the standard of living for the patient. The purpose of this study is to know whether vitamin-D deficiency is associated with recurrent upper respiratory tract infections and to put forward a recommendation in clinical practice.

## Materials and Methodology

This is a case control study done in a tertiary care hospital over a period of 18 months. This study was conducted after approval from the Institutional Ethics Committee (YEC 2/248) under tenets of Declaration of Helsinki as per national Ethical Guidelines for Biomedical Research involving human participants of the Indian Council of medical research (ICMR),2017.

Participants were selected using convenient sampling technique. Subjects attending otorhinolaryngology department with clinical diagnosis of recurrent tonsillitis, recurrent pharyngitis, recurrent rhinosinusitis, otitis media with or without effusion, were enrolled in to the study. Age and sex matched control group was also selected. A detailed written informed consent was obtained from all subjects enrolled to the study. Subjects with chronic diseases like diabetics, CKD, COPD, bronchial asthma, acquired or congenital immunodeficiency, hypercalcemia or nephrolithiasis, malignancy, who were pregnant or planned pregnancy during the study period, smokers, those who are on vitamin-D supplementation in the past 6 month's period and who use immunosuppressant or medications that interfere with vitamin D metabolism were excluded from the study. Subjects who were having minimum, 4 episodes of infections in a year were enrolled to the study.

All the patients with acute symptoms were treated conservatively. There were 52 subjects in the study group. All subjects in the case group were asked for the frequency of infections in the previous 6 months and also about the average severity of symptoms based on 1 to 10 point scale at the time of enrollment to the study and serum vitamin D (25 hydroxyvitamin-D )level was assessed at the same time. Subjects with vitamin D level < 30 ng/mL, were supplemented with 60,000 IU of oral Vitamin-D weekly once for 12 weeks. Control group had 52 age and sex matched subjects with no history of recurrent upper respiratory tract infection. Serum vitamin-D level was assessed in them and those with deficiency were given oral supplementation.

Serum 25 hydroxyvitamin-D was analyzed on Siemens ADVIA Centaur which is standardized against ID-LC/MS/MS, as per the Vitamin D Standardization Program (VDSP).

**Table 1** Division of the case group based on the frequency of symptoms (n = 52)

| Sub groups | Frequency of Symptoms | Number of Participants |
|---|---|---|
| **Group 1** | 2 episodes in last 6 months | 2 (both female) |
| **Group 2** | 3 episodes in last 6 months | 25 (9 males and 16 females) |
| **Group 3** | 4 episodes in last 6 months | 23(10 males and 13 females) |
| **Group 4** | > 4 episodes in last 6 months | 2 (both females) |

## Results

There were 52 subjects in the study group who met the inclusion criteria and an equal number of controls. This study comprised of 19 males (36.5%) and 33 females (63.5%) in both study and control groups, with a majority of female participants. Cases and controls were gender matched without significant difference. ($\chi2 = 0.000$, $p = 1.000$) (Table 1).

Participants in the study group, ranged from 19 to 57 years of age with a mean age of $26.69 \pm 8.27$ and in the control group, participants ranged from 19 to 54 years of age, with a mean age of $26.62 \pm 7.06$. There was no significant difference between the case and control groups in terms of age distribution (Years) ($W = 1288.500$, $p = 0.680$).

Participants in the case group were divided into 4 groups, according to the frequency of symptoms in the previous 6 months at the time of enrollment to the study, which is depicted in Table 1.

In this study, we observed only 2 types of recurrent respiratory tract infections, chronic pharyngitis/ tonsillitis and chronic rhinosinusitis. As all the subjects with tonsillitis had pharyngitis they were included in pharyngotonsillitis group. There were 32 (61.5%) in pharyngitis/tonsillitis group and 20 (38.5%) in chronic rhinosinusitis. Majority of the study participants presented with throat pain, other symptoms were post nasal discharge, facial pain/paranasal sinus tenderness and running nose.All subjects in the study group were assessed based on a severity score (baseline) ranging from 1 to 10. Average severity score was measured in each subgroup and it was statistically analyzed in the 4 subgroups of the cases.**(**Table 2**)** There was no significant difference between the groups in terms of Severity Score (Baseline) ($\chi2 = 0.252$, $p = 0.969$). Strength of association (Kendall's Tau) = 0.05 showed minimal / no association.

The vitamin D (ng/mL) in the study group ranged from 5.52 to 25.9 with a mean value of $10.67 \pm 3.58$ ng/mL whereas in control group ranged from 9.1 to 43 with a mean value of $20.10 \pm 7.73$ ng/mL. The median value (IQR) of serum Vitamin D (ng/mL) was 10.34 (8.13–12.32) and 18.75 (15.09–23.26) in the case group and control group respectively. There is a significant difference between the

**Table 2** Comparison of the 4 Subgroups in Terms of Severity Score (Baseline) (n = 52)

| Severity Score (Baseline) | Frequency Of Symptom In 6 Months-Subgroups | | | | Kruskal Wallis Test | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | 0.252 | 0.969 |
| Mean (SD) | 5.50 (0.71) | 5.48 (1.85) | 5.61(1.59) | 6.00(1.41) | | |
| Median (IQR) | 5.5 (5.25–5.75) | 5 (4–7) | 6(5–7) | 6(5.5–6.5) | | |
| Range | 5–6 | 3–8 | 2–8 | 5–7 | | |

**Table 3** Association of parameters in Case and Control Groups

| Parameters | Group | | p value |
|---|---|---|---|
| | **Case (n = 52)** | **Control (n = 52)** | |
| **Age (Years)** | 26.69 ± 8.27 | 26.62 ± 7.06 | 0.680[1] |
| **Gender** | | | 1.000[2] |
| **Male** | 19 (36.5%) | 19 (36.5%) | |
| **Female** | 33 (63.5%) | 33 (63.5%) | |
| **Mean Vitamin D (ng/mL)*** ** | **10.67 ± 3.58** | **20.10 ± 7.73** | **< 0.001[1]** |
| **Vitamin D*** ** | | | **< 0.001[3]** |
| **Sufficient**(> 30ng/dl) | 0 (0.0%) | 5 (9.6%) | |
| **Insufficient**(20 > x < 30) | 1 (1.9%) | 15 (28.8%) | |
| **Deficient**(< 20) | 51 (98.1%) | 32 (61.5%) | |

***Significant at p < 0.05, 1: Wilcoxon-Mann-Whitney U Test, 2: Chi-Squared Test, 3: Fisher's Exact Test

2 groups in terms of Vitamin D (ng/mL) (W = 247.500, p = < 0.001), with the mean and median Vitamin D (ng/mL) being lowest in the case group.**(**Table 3**)** Participants were divided into 3 group based on serum vitamin D levels, sufficient group with a serum vitamin D (> 30ng/ml), Insufficient group (between 20 and 30 ng/ml) and Deficient group (less than 20ng/ml). In case group, 98% (51 participants) belonged to deficient and remaining 2% (1 participant) in insufficient group whereas in control group, 10% (5 participants) were in sufficient group, 29% (15 partcipants) were in insufficient group, and majority (62% − 32 participants) belonged to deficient group. Distribution of subjects in each group among case and control is depicted in **(**Table 3**).** There was a significant difference between the various groups in terms of distribution of Vitamin D ($\chi 2 = 21.599$, p = < 0.001, Fisher's exact test). (Table 3)

To summarize the association between serum vitamin-D level in case and control group, it was found that 100% of vitamin-D sufficient and majority of insufficient participants belonged to the control group, whereas major proportion of the case group consisted of vitamin D deficient participants(98%).**(**Chart 1**)** There was a significant

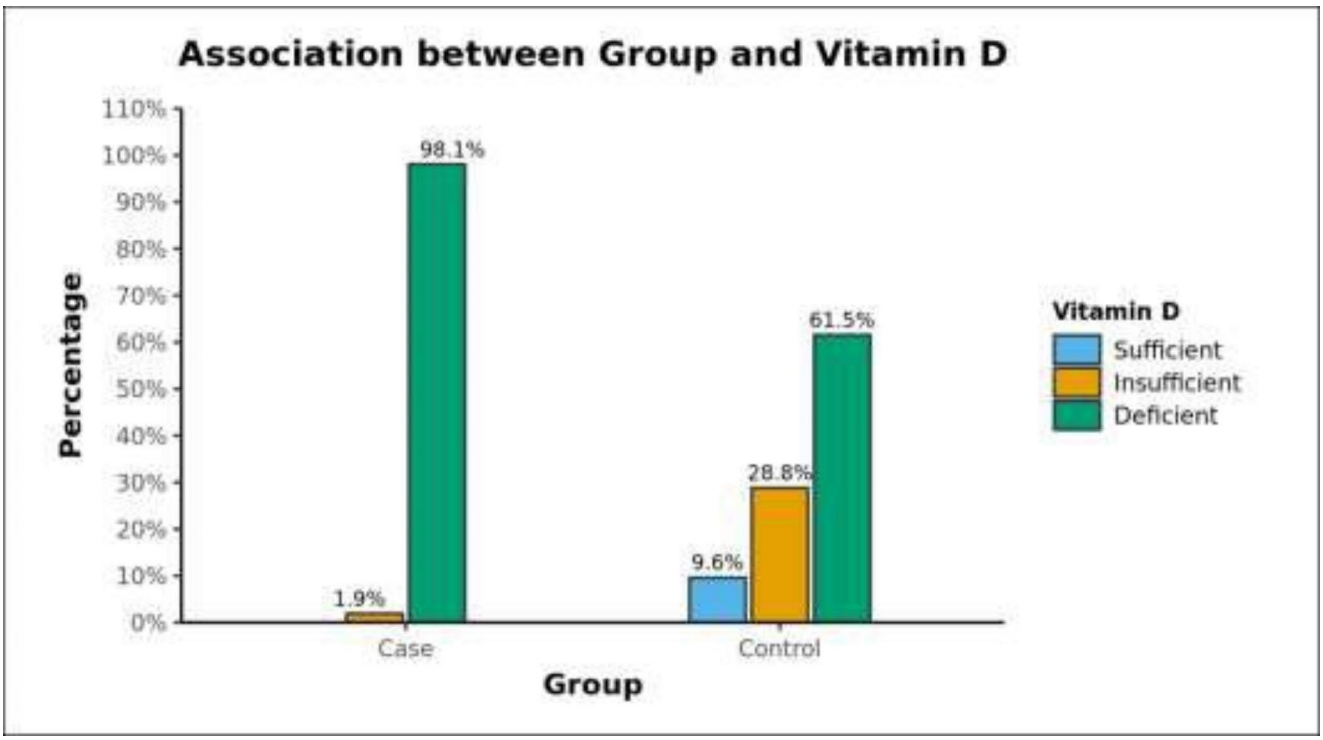


**Chart 1** Graph depicting serum vitamin D status in case and control group

**Table 4** Association between mean serum Vitamin D (ng/mL) and Parameters in case group

| Parameters | Vitamin D (ng/mL) | p value |
|---|---|---|
| **Gender** | | 0.113[2] |
| **Male** | 11.22 ± 2.97 | |
| **Female** | 10.36 ± 3.90 | |
| **Frequency Of Symptom In 6 Months** | | 0.842[3] |
| **Group 1** | 9.81 ± 6.07 | |
| **Group 2** | 10.20 ± 2.29 | |
| **Group 3** | 11.41 ± 4.60 | |
| **Group 4** | 8.89 ± 0.05 | |
| **Diagnosis** | | 0.679[2] |
| **Chronic Tonsillitis/Pharyngitis** | 10.95 ± 4.02 | |
| **Chronic Rhinitis/Sinusitis** | 10.23 ± 2.77 | |

***Significant at $p < 0.05$, 1: Spearman Correlation, 2: Wilcoxon-Mann-Whitney U Test, 3: Kruskal Wallis Test

**Table 5** Association between Vitamin D (ng/mL) and gender in control group

| Parameters | Vitamin D (ng/mL) | p value |
|---|---|---|
| **Age (Years)*** ** | **Correlation Coefficient (rho) = -0.31** | **0.027[1]** |
| **Gender** | | 0.778[2] |
| **Male** | 20.07 ± 5.70 | |
| **Female** | 20.12 ± 8.77 | |

difference between the case and control groups in terms of distribution of participants in Vitamin D sufficient, insufficient and deficient groups ($W = 247.500$, $p = < 0.001$). (Chart 1).Mean vitamin D in differrent parametres among case group is depicted in Table 4.

## Discussion

Neils Ryberg Finsen won the Nobel Prize for his work on lupus vulgaris using phototherapy in 1903. Since then, different studies have been conducted to treat and cure infection by sun light. The Indian subcontinent, which is located between 8°4' north and 37°6' north latitude and 68°7' east and 97°25' east longitude, receives ample sunlight throughout the year and hence should not suffer from low vitamin D levels. Winter is shorter in India and there is little seasonal variation of the peak intensity of sunlight. Still we find majority of the population are deficient or insufficient in serum vitamin D [8]. In our study we have estimated serum vitamin D level in 104 participants. In this 52 subjects were having recurrent upper respiratory tract infection who constituted the case group and the other 52 subjects were healthy participants without recurrent respiratory infection who constituted the control group. We observed that, in the case group none of them belonged to the vitamin D sufficient group and except for 1 participant who was having serum vitamin D as insufficient level, all others (98%) were in the vitamin D deficient group. In the control group also it was found that majority of participants were in deficient group and 15 of them were in insufficient group and only 5 were having serum vitamin D level in sufficient level. To summarize, out of 104 participants, only 5 of the participants were having a sufficient level of serum vitamin D.

There are multiple factors which can contribute to vitamin D deficiency. It is caused by a variety of factors, including decreased vitamin D synthesis and absorption in the skin, as well as acquired and heritable abnormalities of vitamin D metabolism and response as well as environmental pollution blocking UVB radiation. Some of the causes of vitamin D deficiency includes, reduced skin synthesis doe to use of sunscreen, skin pigmentation, aging, season, latitude and time of day; decreased bioavailability due to malabsorption and obesity; breast feeding (poor vitamin D content in human milk); decreased synthesis of 25- hydroxyvitamin D in condition like liver failure; increased urinary loss of 25-hydroxyvitamin D like in nephrotic syndrome; decreased synthesis of 1,25 dihydroxyvitamin D as in chronic kidney disease, hyperphosphatemia; heritable disorders like pseudovitamin D deficiency rickets, vitamin D resistant rickets, vitamin D dependent rickets, autosomal dominant hypophosphatemic rickets, X-linked hypophosphatemic rickets; acquired disorders like tumor induced osteomalacia, primary hyperparathyroidism, granulomatous disorders, sarcoidosis, tuberculosis and hyperthyroidism [6, 9].

Vitamin D deficiency and insufficiency is a worldwide health problem affecting over one billion children and adults. Among western population despite using fortified milk its very common due to seasonal variation, due to decrease in milk consumption ,increased use of sunscreen, increased incidence of obesity. Whereas in India, where there is abundant of sunshine throughout the year, people should not be deficient in vitamin D. On the contrary, epidemiologic studies from several parts of India found that vitamin D deficiency [25(OH)D < 20ng/mL] is prevalent in all age categories, including toddlers, schoolchildren, adult males, pregnant women and their neonates, with a prevalence of more than 70% [10]. A survey in Delhi found that 91% of schoolgirls were vitamin D deficient with prevalence similar in upper and lower socioeconomic group [11].

Another study showed that 70% of healthy volunteers (n = 1,137) in Mumbai, showed vitamin D deficiency [mean 25(OH)D levels = 17.6 ± 9.2 ng/mL], with females being more affected than males (79%) [8].

In this study among case group, women( 10.36 ± 3.90) have a lower serum value than men (11.22 ± 2.97) whereas in the control group mean value is similar in both groups. Reason for low serum level of vitamin D in women is not

clear. It is likely that women absorb less vitamin D or that their behaviour patterns like use of sunscreens, such as p-aminobenzoic acid, hinder vitamin D production in the skin [12]. Religious, lifestyle, and nutritional differences are linked to variations in serum vitamin D levels among people living in the same city or nation [13, 14].

Its found that as age advances vitamin D level decreases due to decreased skin thickness and due to less outdoor activities [15]. Although it is not statistically significant, in the present study we observed that older age group has lower level of vitamin D.

In our study conducted in South India, mean serum vitamin D among case group is 10.67(3.58) ng/mL whereas mean value in control group is 20.10 (7.73)ng/mL. The difference in mean value among case and control group is statistically significant (p value < 0.001). Serum vitamin D was found deficient in 98.1% of participants in case group and 61.5% of the control group. Majority of the participants in both case and control groups belonged to the deficient group which proves that vitamin D deficiency is highly prevalent in the Indian population. The reasons could be lack of outdoor activities, nutritional deficiency, dressing habits and use of sunscreens. Sunscreens, such as p-aminobenzoic acid, hinder vitamin D production in the skin which could also be a reason for low level.

Recent researches have shown antimicrobial action of vitamin D and its role in both adaptive and innate immunity. The active form of vitamin D(1, 25-dihydroxy vitamin D) increases the production of antimicrobial peptides in monocytes, neutrophils and epithelial cells such as cathelicidin and β-defensin-2 [16]. The gene encoding the antimicrobial peptides, cathelicidin and β-defensin-2 are similar to vitamin D receptor genes. Vitamin D acts on these receptors and increases cathelicidin production. Cathelicidin has a broad spectrum of bactericidal activity. Cathelicidin has been identified in upper and lower respiratory tract epithelium [1].

Vitamin-D deficiency is one of the cause for chronic respiratory tract infection over time. In Auckland, a study done on children who underwent adenotonsillectomy, observed that chronic adeno tonsillitis was associated with serum vitamin D of less than 30 ng/mL [17]. In another study it was found that adult patients with higher vitamin D concentrations had improved lung function than those with lower concentrations [18]. Long-term economic impact of vitamin D deficiency is considerably greater on the patient. So supplementation with vitamin D can lower the frequency of infections and sequelae and complications associated with it as well as it may bring down the need for surgery as well as the antibiotic resistance.

The association between vitamin D deficiency and COVID 19 is also well studied. Among several factors such as age, healthcare system quality, general health condition, socioeconomic position, and so on, it appears that one of the underexplored factors that may be connected with COVID-19 outcome was low serum vitamin D status. Individuals with vitamin D deficiency had a three-fold higher likelihood of contracting SARS-CoV-2 and a five-fold higher chance of having the severe disease. Vitamin D deficiency, on the other hand, had no effect on mortality rates in these types of patients [19]. Kaufman et al. retrospectively investigated the relationship between SARS-CoV-2 positive rates and circulating serum vitamin D in 191,779 patients. Patients with vitamin D deficiency had the highest rate of SARS-CoV-2 positivity. Overall, this study provided the evidence for the inverse relationship between SARS-CoV-2 positivity rate and serum vitamin D levels in COVID-19 patients [20].

In our study, 61.5%(32) of the participants had throat pain as symptoms and they were diagnosed as chronic tonsillitis/pharyngitis. Post nasal discharge, running nose and facial pain were observed in 38.5% (20), 5.8% (3) and 38.5% (20) respectively who were diagnosed with chronic rhinosinusitis. The mean serum vitamin D level was found to be $10.95 \pm 4.02$ ng/mL and $10.23 \pm 2.77$ ng/mL in chronic tonsillitis/pharyngitis and chronic rhinitis/sinusitis respectively which is not statistically significant (p value 0.679). Mean serum vitamin d among each subgroup of case group was compared and found not to be statistically significant. This proves that vitamin D deficiency make a person prone to get repeated upper respiratory tract infection but not to a specific type of infection and it does not have any relationship with the severity of infection too. Vitamin D level is low in both groups, when compared to that of control groups who had a mean level of $20.10 \pm 7.73$ ng/mL, the case group had a very low level and the difference in value is statistically significant. So vitamin D deficiency is one of the reason for recurrent upper respiratory tract infection among other factors for recurrent URTI like close contact with patients, immunodeficiency, smoking, obesity, etc. Among the above factors vitamin D deficiency is a preventable cause for recurrent infection. Recurrent infection has been a reason for over prescription of antibiotics which can eventually lead to antibiotic resistance.

For the Indian population, the ICMR recommends 400 IU/day because of the minimal exposure to sunlight but has not set a recommendation for a monitored food fortification programme. ICMR also suggest a minimum 5 min outdoor activity in a day for optimal level of vitamin D in serum. This also controls the overweight and obesity in the population [21]. Vitamin D intake should be 400 IU/day for people under 50 and 800 IU/day for those over 50, according to the updated Dietary Reference Intake (DRI) for the United States and Canada [22]. In our present research all subjects with vitamin D less than 30ng/ml were supplemented with

weekly doses of 60,000 IU of oral Vitamin D for 3 months. This study proves that hypovitaminosis D is one of the factor responsible for recurrent infection, but it does not have any relationship to the type as well as the severity of upper respiratory infections.

## Conclusion

Vitamin D deficiency is a factor contributing to recurrent upper respiratory tract infection. Vitamin D toxicity being rarely reported and deficiency being highly prevalent in our society, we would like to recommend/ suggest vitamin D supplementation to be initiated for all patients with recurrent upper respiratory tract infections, even without serum estimation, to reduce the financial burden on population.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s12070-022-03220-z.

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