Original Article

Severe Vitamin D Deficiency as a Risk Factor in Newly Diagnosed Tuberculosis Patients: Comparative Study on Inhabitants of High Altitude Region

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Abstract

Background: The present study was conducted to find the association between tuberculosis and vitamin D levels and assess severe vitamin D deficiency (VDD) as a risk factor for developing tuberculosis at high-altitude regions. **Methods:** This cross-sectional study was carried out at a tertiary care hospital situated at an average altitude of 5,412 feet above sea level. Newly diagnosed active cases of tuberculosis (Group A) and unmatched healthy individuals (Group B) were recruited in the study. Serum samples were analyzed for Vitamin 25(OH) D levels and correlated between the groups. **Results:** The study included 54 newly diagnosed tuberculosis patients (Group A) (47 pulmonary and 7 extrapulmonary tuberculosis) and 87 healthy controls (Group B). Of the total 141 participants, 69 (49%) had severe VDD and 44 (31%) had VDD. The mean (SD) vitamin D level was significantly lower in patients having tuberculosis (12.6 ± 7 ng/mL) as compared to Group B (15.9 ± 7 ng/mL). The risk of tuberculosis infection was 2.13 times higher among those who had VDD (odds ratio = 2.13) (*P*-0.106), whereas those with severe VDD were at 3.2 times higher risk of developing tuberculosis (crude odds ratio = 3.2) ($P = 0.001$) and severe VDD independently contributed to being diagnosed with tuberculosis (adjusted odds ratio = 3.1) ($P = 0.002$). **Conclusions:** Vitamin D levels are significantly low in tuberculosis patients and severe VDD independently contributes to developing tuberculosis infection.

Keywords: *High altitude, tuberculosis, vitamin D, vitamin D deficiency*

Introduction

Tuberculosis has been a disease of concern for mankind for many centuries. According to the World Health Organization (WHO) Global TB Report 2020, India accounts for 26% of total tuberculosis cases in the world.[1] Similarly, although Vitamin D is photosynthesized, Vitamin D deficiency (VDD) is widespread globally. Available data on vitamin D status worldwide suggest widespread VDD, with a high degree of geographic variability, regardless of a country's human development index and latitude.[2] Reported adult prevalence of VDD ranges from 10% in North America to >80% in parts of Asia.[3] The community-based Indian studies of the past decade done on apparently healthy controls reported a prevalence ranging from 50% to 94% (with the cut of value of <20 ng/mL).[4-6] It is known that VDD has a bearing not only on skeletal but also on extraskeletal diseases. Biochemical studies have implicated VDD in many chronic diseases including, but not limited to, infectious diseases, autoimmune diseases, cardiovascular diseases, diabetes, and cancer.[7]

The first evidence of the role of vitamin D in immunological control of *Mycobacterium tuberculosis* was given by Rook *et al*.,[8] in 1986, by showing reduced proliferation of mycobacterium tuberculous bacilli in macrophages treated with 1,25 dihydroxy vitamin D3. Since then, numerous cluster studies have been done correlating tuberculosis and vitamin D deficiency. However, such studies from the region of India are sparse and especially from high-altitude regions in eastern Himalayan states are nil. Considering the fact of high prevalence of both tuberculosis and Vitamin D deficiency individually in India, we hypothesized that TB patients have lower serum levels of vitamin D than healthy individuals and VDD is a risk factor for developing TB.

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Methods

Study participants and methodology

This cross-sectional study was carried out at a tertiary care hospital in Gangtok, Sikkim. Gangtok is situated at an average altitude of 5,412 feet above sea level. Being a part of the Himalayas, Sikkim has predominantly longer winters and rainy seasons, which influence the clothing pattern of its inhabitants as well as sunlight exposure. To avoid seasonal variation in vitamin D levels as a confounding factor, the study was planned in the months of March, April, and May (when sun exposure is adequate in this region) for 2 consecutive years (a total of 6 months). Newly diagnosed laboratory-confirmed (positive for acid fast bacilli [AFB] and/or cartridge-based nucleic acid amplification test [CBNAAT]) active cases of tuberculosis (both pulmonary and extrapulmonary) who presented to the department of respiratory medicine were recruited in the study. CBNAAT was used to detect the drug sensitivity of these patients. Patients who reported a past history of tuberculosis, taking anti-tubercular medicine, co-infection with human immunodeficiency virus, those who were on Vitamin D supplementation or with co-morbid conditions that are associated with Vitamin D deficiency (diabetes mellitus, chronic kidney disease, and autoimmune conditions), pregnant women, and non-ambulatory for more than 2 weeks, were excluded from the study.

After screening for these, 54 such newly diagnosed patients with informed written consent, were included in Group A. Unmatched 87 healthy individuals, primarily consisting of participants in blood donation camps at the hospital and health workers, were included in the comparison group (Group B), following the same exclusion criterion as Group A. Basic demographic data and lifestyle habits such as regular tobacco smoking, regular alcohol consumption, the average duration of sunlight exposure in a day were collected using a questionnaire. Casual sunlight exposure for a duration of more than 1 h in a day was considered as 'adequate exposure' and data were dichotomized as adequate exposure present or not.[9]

Morning fasting venous blood sample was obtained from participants of both groups, as per institutional guidelines. Through centrifugation at 3000 rpm for 5 min serum was separated and stored at − 20°C. Serum samples were tested for Vitamin 25(OH) D levels, using the VIDAS® 25 OH Vitamin D Total kit (reference number-30463), which is an automated quantitative test to determine the total serum 25-hydroxyvitamin D levels using the enzyme-linked fluorescent assay (ELFA) technique. Test kit prescribed levels were taken as cut off and accordingly, a level above 30 ng/mL was considered sufficient or normal, 21–30 ng/mL was considered insufficient, and a level below 20 ng/mL was considered a deficiency. The kit does not describe cut off value for severe vitamin D deficiency; however, studies have shown that vitamin D levels less than <25 or <30 nmol/L (or 10/12 ng/mL increases the risk of health hazard [skeletal health and respiratory infection]) dramatically; hence, a serum vitamin 25(OH) D level less than 12 ng/mL was considered as severe vitamin D deficiency.[10,11]

Statistical analysis

Data collected were analyzed using Statistical Package for Social Sciences (SPSS) version 20 for Windows10 (IBM®). Data were reported as frequency and percentage for categorical variables and mean and standard deviation (SD) for the normally distributed continuous variables. Categorical variables were analyzed using the Chi-square test. Continuous variables between two groups were compared using 'independent sample *t*-test.' Pearson's correlation test was used to correlate Vitamin D levels and other variables. The crude odds ratio (COR) was calculated by Chi-square test and binary logistic regression. The adjusted odds ratio (AOR) was calculated by entering variables with a P value of <0.2 in the bivariate analysis to a multivariable binary logistic regression analysis to identify the independent risk factor for tuberculosis. Both COR and AOR with a corresponding 95% confidence interval (CI) were used to investigate the strength of the association. Statistical significance was considered at a 95% level of confidence and P value ≤ 0.05.

Ethical clearance

Ethical clearance was obtained by the institutional ethics committee (SMIMS IEC Registration no: IEC/522/19-51). Informed written consent was obtained by all participants before the study.

Results

Socio-demographic and clinical characteristics of study participants

The study group consisted of 141 subjects including 54 newly diagnosed tuberculosis patients (21 males and 33 females) and 87 community controls (31 males and 56 females). The mean (SD) age of TB patients and healthy controls was 33.5 ± 15 years and 32.6 ± 9 years, respectively [Table 1]. Of the 54 newly diagnosed cases of tuberculosis, the majority (88%) were of pulmonary tuberculosis and the rest were extrapulmonary TB. A majority (64%) of tuberculosis patients were cases of multidrug resistance (MDR) TB.

Serum vitamin D levels among TB patients and controls

The Vitamin D assay was done using the VIBAS Enzyme-Linked Fluorescent Assay technique. In the study, it was observed that of the 141 participants, 69 (49%) had severe VDD, 44 (31%) had VDD, 22 (15%) had vitamin insufficiency, and only 6 (4%) had sufficient levels of Vitamin D [Table 2].

The mean (SD) Vitamin D level was significantly lower in patients having tuberculosis (12.6 ± 7 ng/mL) as compared

to the normal control population (15.9 ± 7 ng/mL) (P = 0.009). Also, 47 (87%) of the subjects in Group A had VDD as compared to 66 (76%) in Group B. However, this was not statistically significant (P-0.106). On dichotomizing participants as those having severe (<12 ng/mL) and non-severe (13–20 ng/mL) deficiency, it was seen that severe VDD was significantly more in patients of tuberculosis (34 [63%] of Group A, 35 [40%] of Group B participants)] (P = 0.04) [Table 2].

Vitamin D levels had a significant association between sunlight exposure (r = 0.18, P = 0.019) and being diagnosed with tuberculosis (r = −0.3, P = 0.009). However, there was no significant change in Vitamin D level with age, sex, smoking, or alcohol. Among those who had tuberculosis, there was no statistically significant association of vitamin D levels between those with pulmonary and extrapulmonary tuberculosis nor with multidrug resistance and drug sensitivity [Table 3].

Table 1: Socio-demographic and clinical characteristics of study participants

Variables	Group A TB patients (n=50)	Group B Community controls (n=87)	Significance (P)
a) Gender			
Male	21 (39%)	31 (36%)	0.697
Female	33 (61%)	56 (64%)	
b) Mean age in years (SD)	33.5±14.9	32.6±8.82	0.624†
c) Alcohol use			
Yes	26 (48%)	39 (45%)	0.721
No	28 (52%)	48 (55%)	
d) Smoking			
Yes	25 (46%)	26 (30%)	0.049*
No	29 (54%)	61 (70%)	

*P<0.05 was considered as significant. †'independent t- test' is used to compare continuous data

Risk of tuberculosis and vitamin D deficiency

To assess the risk of tuberculosis and Vitamin D deficiency, the COR was calculated using the Chi-square test and Binary logistic regression model. It was seen that the risk of being diagnosed with tuberculosis was 2.13 (COR = 2.13, CI- 0.84 to 5.43) times higher among those who had VDD than controls, which, however, was not significant statistically (P-0.106). As smoking showed a significant association with tuberculosis (P = 0.049), the AOR was calculated using smoking as a confounding factor. After adjusting for confounding, it was seen that VDD was an independent risk factor for TB (AOR = 2.1). However, this was not found to be statistically significant (P-0.124), whereas those with severe VDD were at 3.2 times more at a risk of developing tuberculosis (COR = 3.2, CI-1.57 to 6.62) (P = 0.001), and after adjusting for confounding, it was seen that severe VDD, independently and significantly contributed to being diagnosed with tuberculosis (AOR = 3.1) (P = 0.002). It was also noted that with each level increase in vitamin D, the probability of not having tuberculosis increased by 9%, which was statistically significant (P = 0.019) [Table 4].

Discussion

Role of vitamin D in tuberculosis

The association between Vitamin D deficiency and tuberculosis infection is not new to the scientific world. Several mechanisms have been identified by which vitamin D might have an anti-tuberculosis effect. Among the few of the earliest explanations, Rook *et al*.[8] showed that human monocytes, which have the receptor protein for 1,25(OH) 2D3 at the physiologically reasonable concentration of 10^{-9}

Table 2: Correlations between tuberculosis and vitamin D

	Group A	Group B	Significance (P)
a) Mean Vitamin D level :	12.6±7 ng/dL	15.9±7 ng/dL	0.009**†
b) Vitamin D deficiency :			
Yes	47 (87%)	66 (76%)	0.106
No	7 (13%)	21 (24%)	
b) Extent of vitamin D level:			
Severe deficiency (<12 ng/dL)	34 (63%)	35 (40%)	0.040*#
Deficiency (13-20 ng/dL)	13 (24%)	31 (36%)	0.034*#
Insufficiency (21-30 ng/dL)	5 (9%)	17 (19%)	0.460
Sufficient (30-100 ng/dL)	2 (4%)	4 (5%)	0.070
c) Sunlight exposure per day:			
< 1 h	45 (83%)	56 (64%)	0.128
1-2 h	7 (13%)	18 (21%)	
2-3 h	2 (4%)	9 (10%)	
3-4 h	0	3 (3%)	
>4 h	0	1 (1%)	

**P<0.01,†Independent t-test was used to compare continuous variables, #binary logistic regression was used to compare categorical variables within the independent variable.*P<0.05 is considered as significant

Table 3: Factors affecting vitamin D level

Variable	Correlation coefficient®	Statistical significance (*P*)
Age	0.02	0.337
Sex	0.09	0.461
Regular smoking (no-0, yes-1)	-0.06	0.597
Regular alcohol intake (no-0, yes-1)	-0.02	0.446
Adequate duration of sunlight exposure (no-0, yes-1)	0.18	0.019*
Tuberculosis (no-0, yes-1)	-0.3	0.009*
Drug sensitive TB vs. MDR TB	0.05	0.803
Pulmonary TB vs. extrapulmonary TB	0.10	0.094

Statistical correlation between the factors affecting vitamin D level. Pearson correlation was used to analyze the significance. *P<0.05 was considered significant

Table 4: Risk analysis for tuberculosis infection

Variable	COR	95%CI		*P*	AOR	*P*
		Lower	Higher			
VDD	2.13	0.84	5.43	0.106	2.100	0.124
Severe VDD	3.23	1.57	6.62	0.001**	3.140	0.002**
Smoking	2.02	0.99	4.09	0.049	1.9	0.08
Vitamin D level as a factor for not developing tuberculosis#						
	B	**SE**		**Exp (B)**		***P*#**
Adjusted risk	0.089	0.038		1.093		0.019**

VDD- vitamin D Deficiency. COR- Crude Odd's Ratio, calculated using Chi-square test. AOR-Adjusted Odds Ratio, calculated by the binary regression model. #binary regression model for risk analysis of continuous variable. *P<0.05. **P<0.01

M, can inhibit the growth of *M. tuberculosis,* and the effect is additive with the weaker effect of gamma interferon. Crowle *et al*.[12] demonstrated that 1,25(OH)- vitamin D inhibited the multiplication of virulent tubercle bacilli in cultured human macrophages and proposed membrane and cytosol Gc as possible targets. It has also been shown that 1,25(OH) 2D3 activates vitamin D receptor (VDR) signaling and induces antimicrobial responses such as the induction of autophagy, phagolysosome fusion, release, and activation of the antimicrobial peptide cathelicidin, and killing of intracellular *M. tuberculosis*.[13-15]

Based on these findings, several studies have been done to assess vitamin D deficiency in tuberculosis and have shown that vitamin D levels are significantly low in patients with tuberculosis as compared with healthy controls and household contacts of TB patients.[16,17] However, such studies in the Indian sub-context are sparse, and none at higher altitudes. Among the earliest studies from India, Sasidharan *et al*.[18] reported that patients with tuberculosis had significantly low mean vitamin D levels (10.7 ng/mL) as compared to healthy control group (19.5 ng/mL). Subsequent studies done on the Indian population have shown that tuberculosis patients have lower vitamin D levels ranging from 11 ng/mL to 19 ng/mL.[19,20] Similar to these studies, we found that mean levels of vitamin D were significantly low in active TB patients (12.6 ± 7 ng/mL) (P = 0.009) as compared with normal controls (15.9 ± 7 ng/mL). It is noteworthy that in our study, the mean vitamin D levels in the normal control group were considerably lower than in the healthy control groups of these similar studies done in India (19.5 ng/mL,[18] 21 ng/mL,[19] 25 ng/mL[20]). Interestingly, the mean vitamin D levels of normal healthy individuals in our study were similar to the findings of the studies by Sharma *et al*.,[21] and Zargar *et al*.,[22] done at higher altitude regions of India where they found the mean vitamin D level in healthy population to be 14.7 ng/mL and 15 ng/mL, respectively, which could suggest that high altitude inhabitants in India are at the risk of VDD.

Risk of TB infection in VDD

The present study to evaluate the relation between VDD and risk of TB infection in residents of Sikkim was prompted by the idea that inhabitants of Sikkim being nestled in the eastern Himalayan area at an average altitude of 5,412 feet above sea level are prone to have VDD due to prolonged winters and clothing patterns. The Sikkim state is placed fourth in TB notification rate in India (218 cases per one lakh population).[23] Thus, we hypothesized that vitamin D levels are low among tuberculosis patients and VDD is a risk factor for TB. The existence of VDD in TB patients can both be the cause and effect of TB, Huang *et al*.,[16] in their meta-analysis, revealed that VDD was significantly associated with an increased risk of TB (OR = 2.57), and specifically the Asian population has a higher risk of having TB (OR = 2.62) as compared to the African population (OR = 1.89). Similarly, we found that the risk of being diagnosed with tuberculosis was higher among those who had VDD (AOR = 2.1) but this was not significant, whereas the risk of TB infection was significantly higher in patients with severe VDD (AOR = 3.14) (P-0.002) as compared to normal controls. Aibana *et al*.,[24] in their meta-analysis, found similar results, where the AOR for TB risk among participants with baseline vitamin D deficiency compared to sufficient vitamin D was 1.63, which was not significant but, severe VDD, however, contributed significantly as a risk factor for TB (AOR = 2.05, P-0.02). They concluded that vitamin D predicts TB disease risk in a dose-dependent manner and that the risk of TB disease is the highest among HIV-positive individuals and with severe vitamin D deficiency. Similarly, it was also noted in our study that with each level increase in vitamin D, the probability of not having tuberculosis increased by 9%, which was statistically significant (P = 0.019) suggesting that a low level of vitamin D might increase the susceptibility to tuberculosis in a dose-dependent manner.

Although a few studies have found significantly lower levels of vitamin D among patients with MDR-TB, as compared to drug-sensitive TB patients and healthy

population,[25,26] our present study did not show significant correlations between vitamin D levels and drug sensitivity or extrapulmonary tuberculosis infection. However, it is noteworthy that 64% of cases in the present study were of MDR-TB, which is a flag sign for us and calls for focus on the prevention of tuberculosis infection by identifying correctable risk factors. One such measure could be supplementation of vitamin D for the general population in the form of food fortification or periodic medical supplementation and also increase the knowledge attitude practice among people about vitamin D as well as TB infection.

Limitations of the study: The study was conducted at a single center with a limited sample size, which would limit its ability to generalize its results to the general population of different terrain and ethnic as well as cultural differences. Further multicentric studies involving a larger population of different geographic terrains are needed for further validation of the cause-and-effect relationship between VDD and tuberculosis infection.

Conclusions

The present study could demonstrate that vitamin D levels are significantly low among patients with tuberculosis as compared with healthy individuals. As vitamin D levels reduce, the risk of tuberculosis increases significantly, and severe VDD independently increases the risk of being diagnosed with tuberculosis.

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Conflicts of interest

There are no conflicts of interest.

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