Vitamin D Deficiency in Medical Patients at a Teaching Hospital in North India

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Abstract

**Background:** While vitamin D is critical for calcium homeostasis, current literature also highlight role of vitamin D deficiency (VDD) in diseases other than the metabolic bone disorders. Only few studies on role of vitamin D in tuberculosis have been done in Asian populations. There is paucity of literature addressing this issue in Indian population as well.

**Aim:** We planned to study prevalence of vitamin D deficiency in patients with tuberculosis and to compare it with patients who had non-tuberculosis medical illnesses and healthy individuals with the hypothesis that patients with tuberculosis might have higher prevalence of hypovitaminosis D.

**Methods:** In this descriptive cross-sectional study, there were three groups of study participants. Group 1 consisted of newly diagnosed sputum-positive pulmonary tuberculosis patients of either sex aged 18–60 years. Group 2 comprised of age and sex matched hospitalized patients of other medical illnesses. In group 3 healthy controls were recruited from the general population amongst patient's attendants and hospital staff with the same socio-economic status and ethnic background as that of the patients. Their routine hematological and biochemical parameters along with vitamin D status was assessed.

**Results:** Mean vitamin D levels were significantly low (11.2±6.5 ng/ml) and prevalence of hypovitaminosis D was highest (92%) in patients with pulmonary tuberculosis than other groups. Sputum smear conversion time revealed a significant negative correlation with vitamin D levels (Spearman's p coefficient −0.24, \( P = 0.02\)).

**Conclusion:** Vitamin D deficiency is highly prevalent among hospitalized patients especially patients with pulmonary tuberculosis as compared to patients with other illnesses and healthy individuals. Hypovitaminosis D might be linked to severity of the tuberculosis and also response to treatment.

Introduction

Role of vitamin D in skeletal health is well described. In recent years, it has been recognized that in addition to this classical function, vitamin D modulates a variety of processes including host defense, inflammation, immunity and repair. While vitamin D is critical for calcium homeostasis, current literature also highlight role of vitamin D deficiency (VDD) in diseases other than the metabolic bone disorders.¹-³

Tuberculosis (TB) is a global epidemic and an important public health problem in India. In 2010, an estimated 8.8 million new cases were diagnosed worldwide (around 2 million in India).⁴ Role of vitamin D deficiency (VDD) in predisposition of tuberculosis has been suspected since a long time. Before the etiologic cause of TB was determined in 1903 by Robert Koch, cod liver oil and sun exposure, both sources of vitamin D, were commonly used in treatment of tuberculosis in the pre-antibiotic era.⁵ The active form of vitamin D is 1,25(OH)2D3 which has been shown to inhibit growth of Mycobacterium tuberculosis through stimulating cell-mediated immunity.⁶

Several studies across ethnic...
backgrounds have demonstrated a positive association between prevalence of TB and vitamin D deficiency. A meta-analysis of 7 observed studies noted a reduced risk of active tuberculosis in those with the highest versus the lowest values of 25(OH) D. Two recent randomized controlled trials have investigated vitamin D supplementation as an adjunctive treatment in active TB.

Only few studies on the role of vitamin D in tuberculosis have been done in Asian populations. There is paucity of literature addressing this issue in Indian population as well. Since there is no clinical data comparing the vitamin D status in patients with tuberculosis, to patients with non-tuberculosis medical illnesses and healthy individuals we planned this study with the hypothesis that patients with tuberculosis might have higher prevalence of hypovitaminosis D.

**Patients and Methods**

Our hospital serves a population from predominantly rural and peri-urban areas. In this descriptive cross-sectional study, there were three groups of study participants. Group 1 consisted of newly diagnosed sputum-positive pulmonary tuberculosis patients of either sex aged 18–60 years who were recruited between July 2012 and January 2013 from medical and tuberculosis wards of Era’s Lucknow Medical College. Strict exclusion criteria were applied: presence of secondary immunodeficiency due to corticosteroid or other immunosuppressant use, diabetes mellitus, malignancy, co-infection with the human immunodeficiency virus, hepatitis B or hepatitis C, extra-pulmonary TB in the absence of pulmonary involvement, concurrent cytotoxic chemotherapy, pregnancy or lactation, sarcoidosis, hyperparathyroidism, current or recent (<1 year) use of vitamin D and/or calcium supplements, and patients on anticonvulsants, thiazide or any other drug interfering with vitamin D. Patients with chronic liver disease, renal disease, gastric or bowel resection, malabsorption states such as chronic pancreatitis and inflammatory bowel diseases were also excluded. Group 2 comprised of age and sex matched hospitalized patients of other medical illnesses. Healthy controls were recruited from the general population amongst patient’s attendants and hospital staff with the same socio-economic status and ethnic background as that of the patients and named as group 3. All screened negative for personal history of TB and had normal chest radiographs, hematological profile, liver and kidney function. The Institutional Ethics Committee approved the study protocol. Written informed consent was obtained from all subjects.

Plain postero-anterior chest radiograph was used to assess radiographic severity. At least two baseline sputum samples, including one early morning sample, were obtained from each patient, as per Revised National Tuberculosis Control Programme (RNTCP) guidelines. All samples were examined for the presence of *Mycobacterium* using Ziehl-Neelsen staining. Bacillary load was graded using World Health Organization (WHO) guidelines. Sputum examination was repeated every week after 4 weeks.

Demographic data and full medical history, including personal history of and/or contact with TB, drug and alcohol history, were recorded. All participants also underwent baseline anthropometric measurements of weight and height for calculation of the body mass index (BMI). Prior to initiation of anti-TB treatment, blood was drawn for measurement of the serum 25(OH)D concentrations, complete blood count, serum albumin and calcium concentrations, glucose, renal function tests (serum urea and creatinine) and liver function tests (alanine transaminase (ALT) and alkaline phosphatase (ALP) concentrations), HIV serology and viral markers. The serum 25(OH)D concentrations were determined by an immunoassay technique using the Elecsys vitamin D3 assay. It is an electrochemiluminescence immunoassay supplied by Roche diagnostics. It measures the serum 25(OH)D concentrations in the range of 4–100 ng/ml. Its intra-assay and inter-assay CV was 4.3%-5.9% and 6.2%-9.7%, respectively.

Vitamin D status of the study participants was defined as per the Endocrine Society clinical practice guidelines by Holick et al on evaluation, treatment and prevention of vitamin D deficiency. Vitamin D deficiency, severe vitamin D deficiency, vitamin D insufficiency and normal vitamin D levels were defined as serum 25(OH)D concentrations ≤20 ng/ml, <10 ng/ml, <5 ng/ml, 21–29 ng/ml and ≥30 ng/ml, respectively. The formula below was used in correcting serum calcium concentrations for the albumin levels. Normal serum albumin concentration was defined as a level of 40 g/L.

**Statistical Analysis**

Data analysis was carried out using an SPSS software version 15 (SPSS, Chicago, IL). The χ²-test was used for comparison of categorical variables among groups. In univariate analysis, differences in the means of continuous variables among the groups were analyzed by one way analysis of variance. Multiple logistic regression analyses were used to assess
We had three groups of study participants. Group 1 (n=100) comprised of patients with pulmonary tuberculosis, group 2 (n=96) comprised of hospitalized patients who had non-tuberculosis medical illnesses and group 3 (n=100) comprised of age and sex matched healthy controls. Table 1 shows demographic and clinical characteristics of subjects in three groups. There were no significant differences in age and gender of participants of the different groups. BMI was significantly low in patients with pulmonary tuberculosis. Prevalence of smoking was significantly higher in patients with tuberculosis than other groups.

Vitamin D status in participants of the three groups is being shown in Table 2. Prevalence of hypovitaminosis D was highest (92%) in patients with tuberculosis. Vitamin D deficiency was also significantly higher in patients with tuberculosis than other groups. Severe vitamin D deficiency was 16% and 6% in patients with tuberculosis and patients with other illnesses respectively.

Mean vitamin D levels were significantly low (11.2±6.5 ng/ml) in patients with pulmonary tuberculosis than non-tuberculosis patients and healthy controls. It was observed that the patients with severe vitamin D deficiency had bilateral extensive pulmonary lesions.

Sputum smear conversion time revealed a significant negative correlation with vitamin D levels (Spearman’s ρ coefficient −0.24, \( P = 0.02 \)). The patients of pulmonary tuberculosis who were vitamin D sufficient had sputum conversion time 0.8±0.76 months vs 1.7±0.5 months, \( P = 0.02 \) significantly lower than patients with hypovitaminosis D.

Univariate analysis of hypovitaminosis D has been shown in Table 3.

In multivariate analysis of the combined data set having participants of all the three groups, presence of tuberculosis (OR 3.59, 95%CI 1.61–4.32, \( P = 0.001 \)) and hypocalcaemia (OR 2.12, 95% CI 1.72–4.30, \( P = 0.01 \)) were independent predictors of vitamin D deficiency. Presence of anemia or hypoalbuminemia were not found to be independently associated with low vitamin D levels in regression analysis.

Discussion

Despite the immune-regulatory properties of vitamin D, there is a scarcity of data on the vitamin D status in low-income populations exposed to infectious diseases and on the role of vitamin D deficiency in the susceptibility to specific infections. Vitamin D is a low-cost intervention that is easy to administer in resource-poor settings. Vitamin D has been attributed an important role in host immune defense against *Mycobacterium tuberculosis*.\(^{23}\) It has been shown by Liu et al\(^7\) that vitamin D supplementation results in increased expression of antimicrobial peptide ‘cathelicidin’ in the macrophage culture, which could result in killing of the intracellular *Mycobacterium tuberculosis*. This is a potential mechanism which could logically explain role of vitamin D in enhancing innate immunity in patients with tuberculosis.

Several studies from different parts of our country have pointed towards widespread vitamin D deficiency in Indians of all age groups residing in rural or urban areas.\(^{24–27}\) Skin complexion, poor sun-exposure, vegetarian food habits and lack of vitamin D food fortification programme in the country explain the high prevalence of VDD in India despite its sunny climate.\(^4\)

The association of vitamin D and tuberculosis has been shown in various studies. Studies in Gujаратí Asians living in the UK found that lower levels of vitamin D were associated with an increased risk of pulmonary tuberculosis.\(^{28}\) VDD is widely prevalent in India but little is known about the prevalence of VDD in tuberculosis patients in India. Therefore, we planned this study that included not only patients...
with pulmonary tuberculosis but also patients having other medical illnesses along with age and sex-matched healthy controls to evaluate and compare presence of hypovitaminosis simultaneously in the three different groups of the participants. This is the strength of our study since there are no such studies available in our population.

The prevalence of vitamin D deficiency in our study was significantly higher in patients with tuberculosis than other groups. Low vitamin D levels were inversely correlated with bilateralism and extensiveness of the pulmonary lesions. The patients with tuberculosis were followed to see the sputum conversion and we found that mean sputum conversion time also inversely correlated with vitamin D levels.

Sasidharan et al in a small study on patients with tuberculosis also observed a statistically significant difference in mean vitamin D levels between controls and study subjects. They found low vitamin D levels in the study population despite adequate sun-exposure, concluding that diet was the more important factor.

Another study from India by Rathored et al concluded that VDR gene polymorphisms and hypovitaminosis D may predispose to MDR-TB. Lower serum 25(OH)D may increase time to MDR-TB sputum smear negativity. Kota et al studied patients with tuberculosis and diabetes mellitus and suggested that vitamin D can serve as adjuvant treatment of tuberculosis in diabetics with vitamin D.

Non-tuberculosis medical patients in present study were of other chronic illnesses such as congestive cardiac failure, diabetes mellitus, stroke and pneumonia. Cardiovascular disease and diabetes have also been reported with hypovitaminosis D.

Risk factors for hypovitaminosis D in our study were low BMI and nutritional factors. Our patients were undernourished, had low BMI (lack of adipose tissue leading to poor stores of vitamin D) and low self-reported consumption of vitamin D-containing foods which was due to their poor socioeconomic status. Although malnutrition might be expected to be associated with vitamin D deficiency, anemia or hypoalbuminemia were not found to be independently associated with low vitamin D levels in regression analysis. Our patients predominantly belonged to rural areas and had good sunlight exposure although not estimated exactly.

Prevalence of smoking was higher in patients with tuberculosis which is a risk factor for tuberculosis disease. Although vitamin D is important for calcium absorption which is impaired by smoking, there is no evidence to suggest that vitamin D absorption is impaired directly by smoking.

We have several limitations of our study. We were unable to do detailed dietary assessment of the intake of vitamin D. One potential bias in this study was selection bias since it was a hospital-based study that recruited only admitted patients who are frequently critically ill. We used an electrochemiluminescence immunoassay which has been shown to underestimate or overestimate vitamin D concentrations. Being a cross-sectional study, the temporality between TB and VDD could not be clearly established.

### Conclusion

Despite presence of abundant sunshine, vitamin D deficiency is highly prevalent among hospitalized patients especially patients with pulmonary tuberculosis as compared to patients with other illnesses and healthy individuals. Hypovitaminosis D might be linked to severity of the tuberculosis and also response to treatment. Other potential associations between tuberculosis and vitamin D status need to be explored in larger studies; with prospective data collection. Randomized controlled clinical trials are needed to evaluate the effect of vitamin D replacement as adjuvant therapy on clinical outcomes and treatment of tuberculosis in our population.

### References


