ORIGINAL ARTICLE

Prevalence of Vitamin D Deficiency in Pulmonary Tuberculosis: A Prospective Cross-sectional Study

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Abstract

Objective: The current cross-sectional study examined the extent of vitamin D (Vit-D) deficiency among pulmonary tuberculosis (TB)–affected patients and explored the potential associations of demographic factors with Vit-D status.

Methodology: Conducted from 1st August 2014, to 1st February 2016, at a tertiary care center, the study included patients aged 18–60 years. Ethical approval was obtained, and exclusion criteria such as category II or multidrug-resistant TB, secondary immunodeficiency states, and extrapulmonary TB were applied. Clinical and laboratory data, including Vit-D levels, were collected. Statistical studies employed ANOVA, Chi-squared tests, and one-sample *t*-tests.

Results: Among the 72 patients with TB, the majority were aged 50 years and above, with male preponderance (62%). Fifty-two (75%) TB patients had Vit-D deficiency, with an average Vit-D level of 16.68 ng/mL. The prevalence of Vit-D deficiency was significantly higher in women compared to men (92.6 vs 64.4%; $p = 0.026$). All patients with bilateral lung lesions had Vit-D deficiency compared to 59.3% in unilateral lung lesion patients ($p = 0.002$). Sputum microscopy and culture contributed to 65.28% of TB diagnoses. Vit-D deficiency prevalence was 75%, with an average Vit-D level of 16.68 ng/mL.

Conclusion: The study highlights gender- and lesion-associated vulnerabilities to Vit-D deficiency among pulmonary tuberculosis patients. Despite limitations, the findings suggest the need for Vit-D screening in TB care and further clinical trials to explore the role of Vit-D levels in management.

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Introduction

Tuberculosis (TB) continues to pose a significant global threat, surpassing human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) as the primary cause of death from infectious diseases.[1,2] With over 25% of the global population affected,[3] the impact of TB is particularly pronounced in Southeast Asia, the Western Pacific, and Africa.[4] Major contributors to the TB epidemic include poverty, drug resistance, and HIV, predominantly affecting developing countries (95% of cases).[5] While global TB incidence has gradually declined since 2003, with an approximate 2% annual deceleration, significant challenges persist.[6]

Despite the World Health Organization (WHO) setting ambitious targets to end the TB epidemic by 2030,[1] the challenges in achieving these targets have been exacerbated by the COVID-19 pandemic, the HIV epidemic, and the emergence of extensively drug-resistant (XDR) and multidrug-resistant (MDR) TB strains. This increases infection rates and also contributes to increased morbidity and mortality among TB patients.

The rate of recovery for TB patients affected by drug-susceptible strains can exceed 90% with proper infrastructure for diagnosis and treatment. MDR-TB cure rates are notably lower, reaching, at best, 57%, according to the latest WHO estimates.[7] Factors influencing TB incidence and treatment outcomes include socioeconomic conditions, healthcare access, adherence to medication, and the emergence of drug-resistant strains.[7] Examining supplementary treatment approaches becomes essential to improve clinical outcomes for tuberculosis cases that are drug-resistant as well as drug-susceptible.

Vitamin D (Vit-D) levels are among the major factors known to influence the incidence and progression of TB.[8–10] In addition to its important role in bone metabolism, Vit-D also plays a crucial role in preventing infections.[11] As early as the 1930s, Vit-D obtained from cod liver oil was used in the treatment of TB. However, the advent of anti-infective chemotherapy in the 1950s supplanted the use of Vit-D in TB.[12] Recent epidemiological research has indicated associations between reduced Vit-D levels and an increased risk of infections, including septic shock,[13] influenza,[14,15] and respiratory infections.[14] Numerous studies highlight that the binding of the biologically active form of Vit-D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), to the Vit-D receptor (VDR) activates signaling that induces antimicrobial responses. This stimulates autophagy, activates antimicrobial peptides, and intracellular killing of TB bacteria[16,17] (Fig. 1).

Vit-D has a vital role in the maintenance of calcium homeostasis and bone metabolism. During prolonged or severe shortage due to reduced intestinal absorption of calcium and phosphorus, there is increased susceptibility to hypocalcemia and secondary hyperparathyroidism. The secondary hyperparathyroidism-induced phosphaturia further aggravates bone demineralization. The cascading effects of this process may lead to conditions such as osteomalacia and osteoporosis in adults and osteomalacia and rickets in children.[18]

While previous studies have emphasized the significance of Vit-D in preventing various infections, its specific influence on pulmonary TB remains less explored. In this context, the aim of the current cross-sectional study is to explore the occurrence of Vit-D deficiency among patients diagnosed with pulmonary tuberculosis and investigate its potential role in the context of TB.

Methodology

Study Duration

This cross-sectional study was conducted from 1st August 2014, to 1st February 2016, at a tertiary care center.

Study Population

The study included patients who were seen in the outpatient and inpatient departments of the department of general medicine and respiratory medicine.

Inclusion Criteria

Patients of either sex with pulmonary TB aged between 18 and 60 years.

Exclusion Criteria

Patients excluded from this cross-sectional study were those diagnosed with category II or multidrug-resistant TB (MDR-TB). Furthermore,

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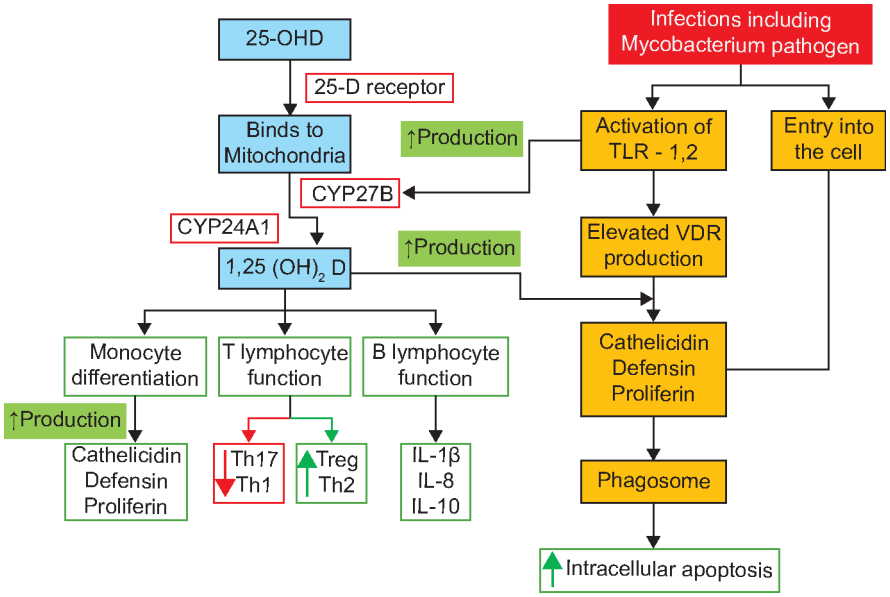

Fig. 1: 25-OHD, 25-hydroxyvitamin D; 1,25-dihydroxyvitamin D; TLR, toll-like receptors

Table 1: Distribution of age and gender in the study population

Age-group/gender	*Number (n)/percentage*
<30	9
31–40	13
41–50	10
>51	40
Total	72
Male	62%
Female	38%

Table 2: Relation between age, gender, and Vit-D levels

Age-group	*Total*	*Deficient*	*Insufficient*	*Sufficient*	*p-value*
≤30	9	5	4	0	0.473
31–40	13	9	3	1	
41–50	10	9	1	0	
>51	40	31	6	3	
Gender	*Total*	*Deficient*	*Insufficient*	*Sufficient*	*p-value*
Male	45	29	12	4	0.026
Female	27	25	2	0	

individuals with secondary immunodeficiency conditions such as HIV, organ transplantation, malignancy, corticosteroid treatment, hepatitis B or C positivity, extrapulmonary TB, or those requiring surgical intervention were not included. Exclusion criteria also encompassed patients currently or recently (within the last 3 months) undergoing cytotoxic therapy, pregnant or lactating individuals, those with a known seizure disorder, symptomatic cardiac disease, abnormal renal function, hepatic dysfunction, hematological abnormalities, serious illness, or those unable to comply with the treatment regimen. Furthermore, individuals with a history of alcohol or drug abuse were excluded.

Sample Size Determination

Based on a study by Talat et al.,[19] the sample size was determined to be 72 using the formula $n > z^2\ pq\ /\ d^2$, with a confidence coefficient (z) of 1.96, error of estimate (d) of 10%, and an incidence rate (p) of 76%.

Ethical Approval and Informed Consent

The Institutional Ethics Committee approved the trial, and the patients' next of kin gave their informed permission.

Data Collection

Simple random sampling was used to recruit patients. Clinical details were recorded in a well-designed proforma, including sociodemographic data, medical and drug history, and laboratory variables. Criteria such as the presence of acid-fast bacilli in sputum smears, culture positivity for Mycobacterium tuberculosis, TB PCR positivity, or evidence of persistent caseating granulomatous inflammation were used to confirm the diagnosis of tuberculosis.

Laboratory Measurements

Blood samples were collected for a range of assessments, including complete blood count, serum 25(OH)D, albumin, and calcium levels. Additionally, renal function tests, including serum creatinine and urea, and liver function parameters, including ALP and ALT, were estimated. The Elecsys Vit-D_3 assay was utilized to determine serum 25(OH)D concentrations.

Vitamin D Status Definition

Vitamin D status was categorized based on the Endocrine Society clinical practice recommendations.[20] Baseline serum 25(OH)D values of ≥30 ng/mL, 21–29 ng/mL, and ≤20 ng/mL were used to define normal, insufficiency, and deficiency of Vit-D, respectively.

Statistical Analysis

Continuous and categorical measurements were subjected to descriptive statistics, while significance testing utilized analysis of variance (ANOVA) and the Chi-squared test. One-sample *t*-test was used for analyzing Vit-D deficiency. Confidence intervals and significance levels were determined, and statistical software such as IBM SPSS version 20 and Microsoft Word and Excel were utilized for data analysis and presentation.

Results

The cross-sectional study included 72 pulmonary tuberculosis patients selected from the department of pulmonary and general medicine. The study population had a majority of individuals belonging to the >51 age-group, with a distribution of 62% males and 38% females (Table 1).

The incidence of Vit-D deficiency was notably higher in the >51 age-group ($p = 0.473$), and a substantial association was found between gender and Vit-D deficiency, with females exhibiting a higher prevalence ($p = 0.026$) (Table 2).

The study also identified a noteworthy association between the site of lung lesion, area of residence, and Vit-D level (Table 3). Vit-D deficiency showed a clear association with unilateral or bilateral lung lesions ($p = 0.002$), but there was no statistically significant

Table 3: Association between site of lung lesion, area of residence, and Vit-D level

Parameter	*Vit-D level*			*p-value*
	Deficient	*Insufficient*	*Sufficient*	
UL	32 (59.3%)	14 (100%)	4 (100%)	0.002
BIL	22 (40.7%)	0 (0%)	0 (0%)	
N = 22	22 (100%)	0 (0%)	0 (0%)	
Rural	29 (53.7%)	7 (50%)	3 (75%)	0.829
Urban	25 (46.3%)	7 (50%)	1 (25%)	

Table 4: Prevalence of Vit-D deficiency in study population

Vit-D status	*Frequency*	*Percentage*
Deficient	54	75%
Insufficient	14	19.44%
Sufficient	4	5.56%

correlation between Vit-D deficiency and the place of residence (p= 0.829).

Regarding the diagnostic method, sputum microscopy and culture contributed to 65.28% of TB diagnoses, while BACTEC culture played a role in 34.72%. The average Vit-D level observed in the study population was 16.68 ng/mL. The incidence of Vit-D deficiency in the study population was 75%. Additionally, 19.4% had insufficient Vit-D, with only 5.6% having normal levels of Vit-D (Table 4).

Discussion

This study aims to investigate the prevalence of Vit-D deficiency among pulmonary tuberculosis (TB) patients, assessing various demographic factors and their potential correlations with Vit-D status. This study, conducted from 1st August 2014, to 1st February 2016, involved 72 randomly selected patients.

Our findings revealed a notable age skew, with a majority of patients falling into the >51 age-group. This observation aligns with the known demographic vulnerability of older individuals to TB. Moreover, the study highlighted a significant gender disparity, with females exhibiting an elevated incidence of Vit-D deficiency in comparison to males (p = 0.026). The prevalence analysis revealed a substantial burden of Vit-D deficiency among the study population, with 75% of participants exhibiting deficiency, 19.44% having insufficient levels, and only 5.56% being sufficient (p < 0.001).

The examination of Vit-D levels and age-groups showed an interesting pattern, with those in the >51 cohort showing the highest frequency of insufficiency, although statistical significance was not reached (p = 0.473). This observation aligns with existing literature that suggests a potential age-related susceptibility to Vit-D deficiency.[21] The study by Giustina et al. recommends combining Vit-D with calcium to reduce fractures, establishing a goal of 25(OH)D > 50 nmol/L. It favors daily low-dose regimens for fall prevention in the elderly and emphasizes Vit-D supplementation effectiveness over alternative strategies for achieving sufficiency in the aging population.[21]

Vit-D deficiency was observed to be higher among women in the current study. About 93% of women had Vit-D deficiency compared to 64.45% of men (p = 0.026). A study revealed a strong correlation between Vit-D levels and gender, particularly highlighting a substantial prevalence (71.2%) in women aged 19–39 years.[22] This discrepancy can be attributed to reduced sunlight exposure due to veiling, insufficient intake of dietary Vit-D, residing in urban areas, and parity in women, as reported in different studies. Factors associated with hypovitaminosis D include covering arms from sunlight, inadequate Vit-D supplementation in postmenopausal women, elevated BMI levels, and low education levels. In contrast, season, sun exposure, and dietary Vit-D were not identified as significant predictors.[23]

A notable discovery in this study arose regarding the association between the site of lung lesions and Vit-D deficiency. Patients with unilateral or bilateral lung lesions exhibited a significantly higher prevalence of deficiency (p = 0.002). In a prospective study, it was found that Vit-D deficit was linked to an augmented risk of total and respiratory mortality, highlighting its potential role in influencing health outcomes in older men with varying lung function statuses over a 20-year period. The underlying mechanisms linking lung lesions and Vit-D deficiency were not explored in this study and warrant further investigation.[24]

The results of this investigation did not show a statistically significant correlation between Vit-D insufficiency and residential area (rural vs urban). Rural regions had a higher prevalence of Vit-D insufficiency (53.7%) than urban areas (46.3%), although the difference was not statistically significant (p = 0.829). Marzban et al. also observed a high prevalence of Vit-D deficiency in their study conducted among rural populations in the province of Bushehr.[20]

The mean Vit-D level observed in the population was 16.68 ng/mL, shedding light on the overall Vit-D status among tuberculosis patients. To facilitate further comparison and contextualize the findings, the widely recognized categorization of Vit-D status as defined by the Endocrine Society guidelines was adopted. Normal Vit-D levels are considered sufficient if 25(OH)D ≥30 ng/mL, insufficiency as 20–29 ng/mL, and deficiency as <20 ng/mL.[25] This average provides a quantitative measure that can serve as a reference for healthcare providers in assessing and managing Vit-D deficiency in this patient group.

This research echoes existing evidence on the beneficial effect of Vit-D supplementation in the treatment of pulmonary tuberculosis. The study population's significant incidence of Vit-D insufficiency is consistent with other findings, highlighting the need to address Vit-D status in tuberculosis therapy. The positive clinical outcomes observed in TB-infected children in a study[13] further support the potential of Vit-D as an adjunctive therapeutic strategy. The results highlight the necessity for additional clinical studies to ascertain the optimal role and dose of Vit-D in tuberculosis treatment. In the context of providing holistic care to TB patients, routine testing and adjustment of Vit-D levels may be considered, which might improve treatment response and overall outcomes.

Limitations

One of the study's drawbacks is that it included only 72 individuals with pulmonary TB, which may have limited the generalizability of the results. Furthermore, creating a CONSORT flow diagram was not possible because of the absence of information on the patients who were omitted.

Conclusion

In conclusion, the study emphasizes the imperative for further clinical trials aimed at delineating the optimal role and dosage of

Vit-D in tuberculosis therapy. Considered as an essential part of the comprehensive care given to patients with TB, frequent testing and adjustment of Vit-D levels may improve treatment responses and general health.

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