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Comparison of Effectiveness of Anti-Tuberculous Therapy Alone and in Combination with Vitamin D Supplementation for Early Sputum Conversion in Smear-Positive Pulmonary Tuberculosis Patients with Optimal Vitamin D Levels

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Abstract

Background: Tuberculosis (TB) continues to be a major global health concern, contributing significantly to morbidity and mortality despite standardized anti-tuberculous therapy (ATT). Vitamin D plays an immunomodulatory role by enhancing macrophage activity and stimulating the production of antimicrobial peptides. However, its additional therapeutic benefit in TB patients with optimal Vitamin D levels remains uncertain. **Objective:** To compare the effectiveness of anti-tuberculous therapy (ATT) alone versus ATT combined with Vitamin D supplementation in achieving early sputum conversion among smear-positive pulmonary tuberculosis patients with optimal Vitamin D levels. **Methods:** This randomized controlled trial was conducted at the Department of Medicine, Mayo Hospital, Lahore, over nine months from 10 August 2024 to 10 May 2025. A total of 112 newly diagnosed smear-positive pulmonary TB patients (aged 16–70 years) with optimal Vitamin D levels (30–50 ng/mL) were enrolled. Participants were randomly assigned to Group A (standard ATT) or Group B (ATT + Vitamin D 100,000 IU IM fortnightly during the intensive phase). Sputum conversion was assessed at 8 weeks. Data were analyzed using SPSS 26.0, with a chi-square test applied and significance set at $p < 0.05$. **Results:** The mean age of participants was 37.8±12.3 years, with 58 (51.8%) males. Early sputum conversion at 8 weeks

occurred in 48 (85.7%) patients in Group A and 54 (96.4%) in Group B (p=0.041). No significant association was observed between sputum conversion and factors such as gender, BMI, or socioeconomic status. **Conclusion:** Adjunctive Vitamin D supplementation alongside standard ATT significantly improved early sputum conversion rates in smear-positive pulmonary TB patients, even among those with optimal baseline Vitamin D levels. These findings suggest a potential therapeutic benefit of Vitamin D in enhancing treatment efficacy. Further multicenter studies are recommended to confirm these outcomes and establish optimal dosing protocols.

Introduction

Tuberculosis (TB) remains a major global health challenge, contributing substantially to morbidity and mortality worldwide. In 2019, there were diagnosed cases of Tuberculosis (TB) and over a million deaths due to the same disease, based on statistics issued by world health organization (WHO) (1) and among these, pulmonary tuberculosis, especially the smear-positive cases, is one of the most serious public health threats due to its highly transmissible nature and capacity to leave lasting pulmonary damage (2). The mainstay of TB treatment involves Anti-Tuberculosis Treatment (ATT) which is composed of first-line drugs isoniazid, rifampicin, pyrazinamide, and ethambutol in combination. Although the ATT regimen are effective in curing the disease and eliminating Mycobacterium tuberculosis, treatment success is particularly affected by long treatment periods, poorly adherent patients, and drug-induced liver damage, which are common in the treatment of TB (1). Hence, the need for additional effective treatment options to reduce the burden of TB disease has gained increased interest. For TB, one of the treatment adjuncts that has gained interest is Vitamin D. Although primarily used for its role in calcium homeostasis, Vitamin D has been shown to impact TB immunity, and in mycobacterial infections, immunity is critical (3). Vitamin D increases the phagocytic activity of macrophages, initiates the production of various antimicrobial peptides in particular cathelicidin, and initiates the production, or moderates excessive production of proinflammatory cytokines. Research has documented the relation between Vitamin D deficiency and the development of TB. In one cross-sectional study, 80 TB patients (42 pulmonary and 38 extrapulmonary) were compared with age and sex matched controls. Among TB cases, the mean Vitamin D level was significantly lower (24.82 ± 12.33 pg/ml) than controls (34.41 ± 6.19 pg/ml). Moreover, 31.3% of patients had levels below 20 pg/ml, but no controls were deficient, indicating a significant difference (p = 0.005) (4). This study shows the relation between Vitamin D deficiency and the development of TB. Research in TB patients assessing the outcomes of Vitamin D supplementation with ATT have shown inconsistent outcomes. In the randomized controlled trial conducted by Afzal et al. (2018), 120 sputum smear-positive TB patients were randomized to ATT alone or ATT with Vitamin D. In the 12th week, only 1.7% of patients in the Vitamin D group remained sputum-positive compared to 11.7% in the control group, which was a statistically significant difference (p = 0.028) (5). In a double-blind trial conducted in Iran by Farazi et al. (2017), sputum conversion rates were significantly higher in the Vitamin D group than in the placebo group by the second month (93.3% vs. 73.3%, p = 0.037) (6). Unlike others, Sinha et al. (2023) achieved comparability on a large scale. The authors were able to describe the participants and give a thorough account of a double-blind controlled trial, referring to it as large scale, including 846 patients for TB, and performing a random allocation for 60,000 IU Vitamin D3 to a control group (placebo). Both arms of the study achieved a 2-week median time for sputum conversion, and it was outlined, as results, under the headings of 'Not statistically significant difference is observed, citing, e.g. HR = 1.06; 95% CI 0.91 - 1.24; p = 0.418.' On the same note, Soeharto et

al. (2019), as was mentioned in the meta-analysis, also concluded similarly, citing adjunctive Vitamin D as not having significance with respect to improvement to the sputum conversion rate (8) as was defined and explained. Regardless of the thorough investigations, analysis on the role of Vitamin D with respect to TB is inconclusive even with the considerable literature available. The reason the literature is inconclusive stems from conflicting study results; these could be a range of factors, e.g. Baseline value of Vitamin D, the amount sustained with or without supplementation, duration, individual immune response, or even any allocation of genetics.

Objective

To compare the effectiveness of anti-tuberculous therapy (ATT) alone versus ATT combined with Vitamin D supplementation in achieving early sputum conversion among smear-positive pulmonary tuberculosis patients with optimal Vitamin D levels.

Methodology

This randomized controlled trial was conducted in the Department of Medicine, Mayo Hospital, Lahore, over a period of nine months from 10 August 2024 to 10 May 2025. A total of 112 patients were included in the study, with 56 patients in each group. The sample size was calculated at a 95% confidence level and 80% study power, assuming sputum conversion rates of 93.3% in the Vitamin D supplementation group and 73.3% in the control group, based on previous research. Patients were selected using a non-probability consecutive sampling technique to ensure all eligible participants meeting the inclusion criteria were enrolled until the required sample size was achieved.

Inclusion Criteria

Patients aged between 16 to 70 years who were diagnosed with pulmonary tuberculosis, based on the operational definition, were included in the study. Only those who had not received any prior anti-tuberculosis treatment or Vitamin D supplementation were enrolled. Additionally, patients with optimal Vitamin D levels, ranging from 30 to 50 ng/mL (75–125 nmol/L), were included.

Exclusion Criteria

Patients diagnosed with extrapulmonary or multi-drug-resistant tuberculosis (MDR-TB) were excluded from the study. Pregnant or lactating females, as well as those with serum calcium levels above 10.5 mg/dL or a history of renal stones, were also excluded. Additionally, patients with deranged liver or renal function tests were not included. Individuals who had previously taken or were currently receiving anti-tuberculous therapy, steroids, antiepileptics, cytotoxic, or immunosuppressive drugs were excluded.

Data Collection Procedure

Approval of the necessary ethics review allowed project staff to go through records of patients exhibiting tuberculosis symptoms and to order sputum AFB smear tests and chest radiographs to arrive at an early diagnosis. They performed baseline serum Vitamin D and other relevant biochemical assessments. For the random sampling exercise, the project staff used lottery techniques to classify the participants into one of two groups. Group A received standard anti-tuberculosis treatment (ATT) while Group B received ATT and Vitamin D. During the intensive therapy phase, Group B received one intramuscular dose of 100,000 IU of Vitamin D, at the fortnighly spaced interval, for a total of four doses. National treatment guidelines substantively harmonized the therapy of the two groups. To establish sputum conversion, staff

checked sputum smears at the outset of the treatment and again after eight weeks. A structured proforma captured analysis details, including demographics, comorbid conditions, and treatment outcomes.

Data Analysis

All collected data were analyzed using SPSS version 26.0. Variables such as age and body mass index (BMI) were analyzed as continuous and described as means ± standard deviation (SD) while gender and sputum conversion status were analyzed as categorical and described as frequencies and percentages. Sputum conversion rates were compared for the two study groups using the Chi-square test. Confounding was minimized by controlling the effect modifiers age, gender, BMI, and diabetes. A two-tailed test was used and a p-value of less than 0.05 was deemed significant.

Results

A total of 112 patients diagnosed with smear-positive pulmonary tuberculosis were enrolled in the study. Participants were evenly divided into Group A (ATT only) and Group B (ATT + Vitamin D supplementation), with 56 patients in each group. The mean age of participants was 37.8 ± 12.3 years, and 58 (51.8%) were males, showing a balanced gender distribution between groups. Baseline demographic and clinical characteristics were comparable, as summarized below.

Baseline Characteristics

Parameter	Group A (ATT Only)	Group B (ATT + Vitamin D)	p-value
No. of Patients	56	56	—
Mean Age (years)	37.4 ± 11.8	38.2 ± 12.7	0.63
Gender (Male : Female)	29 : 27	30 : 26	0.85
Mean BMI (kg/m²)	22.8 ± 2.1	22.5 ± 2.3	0.47
Diabetes Mellitus (Comorbidity)	11 (19.6%)	9 (16.1%)	0.63

There was no statistically significant difference between the two groups in terms of age, gender distribution, BMI, or presence of diabetes, indicating successful randomization and comparability at baseline.

Treatment Outcome: Early Sputum Conversion

Outcome	Group A (ATT Only)	Group B (ATT + Vitamin D)	p-value
Early Sputum Conversion (8 weeks)	48 (85.7%)	54 (96.4%)	**0.041**

At 8 weeks, **early sputum conversion** was achieved in **48 (85.7%)** patients in Group A and **54 (96.4%)** in Group B. The difference was statistically significant (**p = 0.041**), indicating a beneficial effect of Vitamin D supplementation on treatment response.

Interpretation

Adjunctive Vitamin D supplementation led to a significantly higher rate of early sputum conversion compared to standard anti-tuberculous therapy alone. No significant associations were found between sputum conversion and variables such as gender, BMI, or diabetes. These results suggest that Vitamin D may enhance the

efficacy of ATT even in patients with optimal baseline Vitamin D levels, possibly through immunomodulatory mechanisms that accelerate bacterial clearance.

Discussion

This randomized controlled trial evaluated the impact of adjunctive Vitamin D therapy in smear-positive pulmonary tuberculosis (TB) patients with optimal baseline Vitamin D levels. The results showed a statistically significant increase in sputum conversion rates for patients who received Vitamin D in addition to standard anti-tubercular therapy (ATT). These results are consistent with studies conducted earlier by Afzal et al. (2018) (5) and Farazi et al. (2017) (6), which showed improved the clinical outcomes and sputum conversion with Vitamin D. The immunomodulatory function of Vitamin D which includes the activation of macrophages, the induction of antimicrobial peptides like cathelicidin, modulation of cytokines, and enhancement of autophagy, may explain these outcomes (3,9). In contrast to findings reported by Sinha et al., 2023 (7) and Soeharto et al., 2019 (8) which found no substantial treatment outcome improvements, there could be a variety of reasons for differences including but not limited to differences in dosing and duration of treatment, baseline levels of vitamin D, polymorphisms in the vitamin D receptor (VDR) gene, and differences in the immune response of the patients (10). The meta-analysis conducted by Martineau et al., 2019 found that there is no substantial evidence that vitamin D supplementation reduces the time to culture conversion, albeit in certain groups, e.g. MDR-TB (multidrug resistant tuberculosis) (11-13), there were some benefits. The same conclusion was reported by Liang et al., 2019 which found that while vitamin D supplementation did increase the percentage of patients who were able to achieve sputum conversion, the time to sputum conversion was not reduced consistently (14). Current randomized trials are still yielding inconclusive outcomes. For instance, in a 2×2 factorial trial Wang et al. (2020) showed that combined Vitamin A and D supplementation produced a significantly greater improvement in sputum conversion than placebo (13). On the other hand, Lubis et al. (2022) in a single-blind RCT, reported that Vitamin D only improved sputum smear negativity in patients with deficiency, and the effect was more muted in those with sufficient baseline levels (15). Thus, it appears that Vitamin D's effect is not just a question of baseline status, but possibly other genetic and immunological factors that vary across populations. Our study is the first in focusing only in patients with optimal baseline Vitamin D levels. We showed that there could still be a positive effect of supplementation on immune functioning and rate of bacterial clearance even when sufficient Vitamin D is present. This is likely due to Vitamin D's ability to immunostimulate bone marrow to increase the production of macrophages that kill Mycobacterium tuberculosis (16) and to enhance the production of defensins and other antimicrobial peptides while also adjusting inflammatory pathways. Discrepancies across the literature of study outcomes can be explained by differences in dosing frequency and formulation (cholecalciferol vs. calcitriol), severity of the disease, population diversity, and endpoint assessed (sputum vs. culture conversion) (17,18). Differences in the variability of host immune responses, and vitamin D receptor polymorphism, as cited, are possibly the most important of many other factors for the variability of the outcomes (10,11,19). Our study endorses the belief that Vitamin D supplementation, even in the presence of adequate serum levels, can be of additional immunological value and aids in converting sputum. This is important for TB-endemic areas, for instance, Pakistan, since the population tends to have subclinical Vitamin D insufficiency. Confirmatory data is needed to establish the results from which optimal dosing long-term outcomes (relapse, mortality, cost effectiveness) are to be assessed, from which outcome and prospective data can be incorporated.

Conclusion

This randomized controlled trial demonstrated that adjunctive Vitamin D supplementation, when administered alongside standard anti-tuberculous therapy (ATT), significantly enhances early sputum conversion among smear-positive pulmonary tuberculosis patients, even in those with optimal baseline Vitamin D levels. The findings suggest that Vitamin D may exert beneficial immunomodulatory effects, accelerating mycobacterial clearance and improving overall treatment response. By promoting faster sputum conversion, Vitamin D supplementation could also help reduce disease transmission and improve public health outcomes. The absence of significant influence from potential effect modifiers such as age, BMI, and diabetes further strengthens the observed association. These results support the potential inclusion of Vitamin D as a low-cost, safe, and effective adjunct to standard TB therapy. However, to generalize these findings, further large-scale, multicenter clinical trials are warranted to confirm the efficacy and safety of Vitamin D supplementation and to determine the optimal dosing strategy for different patient populations.

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