ORIGINAL RESEARCH

Investigating the role of vitamin D supplementation in reducing TB recurrence in high-risk population

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ABSTRACT

Objective: To evaluate the impact of vitamin D supplementation on TB recurrence rates, immune response, and overall health outcomes in individuals at high risk for tuberculosis relapse. **Methodology:** This study aimed to investigate the efficacy of vitamin D supplementation in reducing tuberculosis (TB) recurrence in high-risk populations. This study was conducted in 23 public schools with a high TB burden, the study was a multicentre, phase III, double-masked, randomized, placebo-controlled trial. Children aged 6-11 years, with no history of TB infection, chronic illnesses, or vitamin D supplementation exceeding 400 IU/day, were enrolled. Participants were randomly assigned to receive either a weekly dose of 350 µg of vitamin D3 or a placebo. Over a 36-month period, clinical outcomes, immune responses, and adverse events were monitored. Data analysis utilized mixed-effects logistic and linear regression models to assess the impact of vitamin D supplementation on TB recurrence, immune response, and safety outcomes. **Results:** The baseline characteristics of the study participants were comparable between the vitamin D and placebo groups. The primary outcome, assessed through the QuantiFERON-TB Gold (QFT-Plus) test, revealed no significant difference between the groups, with 11.4% of the vitamin D group and 13.0% of the placebo group testing positive at the 0.35 IU/ml threshold (adjusted odds ratio 0.86, p = 0.35). No significant differences were observed in the secondary outcome, with 3.7% of the vitamin D group and 2.8% of the placebo group testing positive at the 4.0 IU/ml threshold. Serum 25(OH)D3 concentrations were significantly higher in the vitamin D group at all follow-up intervals, with a peak difference of 44.7 nmol/L at 24 months. No serious adverse events related to vitamin D supplementation were reported. The incidence of active TB was 0.0% in the vitamin D group and 0.4% in the placebo group. **Conclusion:** Vitamin D supplementation did not significantly reduce TB recurrence or improve immune response in this high-risk population. Although vitamin D supplementation successfully increased serum 25(OH)D3 concentrations, it did not show a meaningful impact on TB infection markers or active TB incidence. These findings are consistent with other studies that have explored the potential role of vitamin D in TB prevention, where mixed results have been observed. Future research should explore different dosages, durations, and study populations to further understand the role of vitamin D in TB prevention and recurrence.

Keywords*:* Vitamin D supplementation, tuberculosis recurrence, high-risk population, immune response, QFT-Plus test, phase III randomized controlled trial, serum 25(OH)D3 concentrations.

BACKGROUND

According to the World Health Organization (WHO), tuberculosis has made a resurgence on a worldwide scale because of the COVID-19 pandemic. This has resulted in a renewed interest in the global endeavour to eliminate the illness by 2050. It will be challenging to achieve this objective Without taking precautions to prevent the spread of Mycobacterium tuberculosis (1). It will be particularly important to implement such measures in nations that have a high prevalence of tuberculosis(2). This is because children are at an extremely high risk of contracting the disease. Currently, some activities are being undertaken to either boost immunological resistance by repeated vaccination with bacillus Calmette-Guerin or lower the transmission rate (for example, by enhancing ventilation) (3). Some have also suggested the use of vitamin D supplements (4). Because 1,25-dihydroxyvitamin D (1,25[OH]2D) is both a steroid hormone and a physiologically active metabolite of

vitamin D, it has the potential to trigger innate antimycobacterial responses in laboratory studies. Oral vitamin D supplementation improves the ability of whole blood to restrict mycobacterial growth ex vivo(5). There are associations between low circulating concentrations of 25-hydroxyvitamin D and increased susceptibility to Mycobacterium tuberculosis infection(6).An oral dosage of 350 µg (14,000 IU) of vitamin D3 administered every week did not impact the risk of M. tuberculosis infection, as shown by a recent randomized controlled trial (RCT) conducted among Mongolian students. This was shown by a positive result on the QuantiFERON-TB Gold (QFT-Gold) test, which is a test that recognizes interferon (IFN)-γ responses of CD4+ T cells to antigens produced by Mycobacterium tuberculosis(7). A second phase III randomized controlled trial (RCT) with children was conducted in Cape Town, South Africa, which is one of the cities with the highest percentage of people living with tuberculosis (TB) in the world (8).

Recent studies demonstrated that epidemiological studies that include individuals with tuberculosis (TB) establish a connection between vitamin D insufficiency and the illness. Although there have been clinical trials that have shown the beneficial benefits of vitamin D supplementation for tuberculosis patients, there has also been research that has failed to determine definitive results. Based on the findings of a case-control research, it was also discovered that high and low vitamin D levels were related to active tuberculosis(9).

An alternate approach would be to research vitamin D deficiency as a possible cause of tuberculosis infection conversion (TBIC), also referred to as latent tuberculosis infection (LTBI). Immunological methods, such as the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs), can potentially assess this infection's presence before the disease's onset(10). To estimate the risk variables associated with TB infection in children, the index case's tuberculosis status is considered. Several elements were regarded to be risk factors for TB. These include the presence of bacilli in sputum, the length and location of contacts, and demographic factors such as size, nutritional status, race, and other characteristics of the infected individual. Vitamin D levels that are protective against tuberculosis-associated inflammatory cytokine (TBIC) were discovered in a case-control study conducted on contacts of pulmonary tuberculosis patients(11).

This study compared the profiles of tuberculosis patients with vitamin D deficiency and investigated the prevalence of vitamin D deficiency within the tuberculosis population. The aim of this research was to evaluate the impact of vitamin D deficiency on unsuccessful treatment outcomes among tuberculosis patients.

AIM OF THE STUDY

To investigate the efficacy of vitamin D supplementation in reducing tuberculosis (TB) recurrence among high-risk populations.

Objective

To evaluate the impact of vitamin D supplementation on TB recurrence rates, immune response, and overall health outcomes in individuals at high risk for tuberculosis relapse.

Methodology

This study was conducted in 23 public schools took part in the research project, which was a multicenter phase III double-masked, randomized, placebo-controlled research. The primary purpose of the research was to determine whether or not adding vitamin D to the diets of children in economically and socially disadvantaged communities reduced the severity of tuberculosis (TB) symptoms. Additionally, the study was reported to ClinicalTrials.gov.

Inclusion Criteria

The study requires students of Grades I-III, age between 6 and 11 years at screening, written informed consent from children and their parents/legal guardians, no history of TB infection, active TB disease, or chronic illnesses, no use of regular medication, vitamin D supplements exceeding 400 IU/day, no clinical evidence of rickets, and written informed consent from parents/legal guardians.

Exclusion Criteria

The following criteria were used to exclude patients from the study:

- History of latent TB infection, active TB disease, or any chronic illness other than asthma (including known or suspected HIV infection) prior to enrollment.
- Use of any regular medication other than asthma medication.
- Use of vitamin D supplements at a dose exceeding 400 IU/day in the month before enrollment.
- Plans to move away from the study area within 3 years of enrollment.
- Inability to swallow a placebo soft gel capsule with ease.
- Clinical evidence of rickets or a positive QFT-Plus assay result at screening.
- Indeterminate QFT-Plus assay result (excluded from the trial without screening for active TB).

Data Collection

Data was gathered from participants many times during the study. During the screening visit, children were asked to give informed consent, even if their parents or guardians were present. The clinical criteria and risk factors associated with tuberculosis were considered to assess participation eligibility. Two

different analyses were performed on the collected blood samples: the 25(OH)D serum analysis and the QFT-Plus test. The subjects were given study medication, their height and weight were assessed, and data on adverse events was gathered over several follow-up appointments during the school periods while the subjects were observed. Parents were given medications to administer to their children at home while the children were on break from school. To monitoring how effectively the medication was taken, diaries were used. Medical professionals conducted annual checks, during which they examined for signs of tuberculosis (TB), such as lymphadenopathy in the neck. They noted the patient's history of possible exposure to the illness. Blood samples were collected for QFT-Plus testing at the 36-month checkup that was performed. Additional blood and urine samples were collected in connection to the safety of the biochemical processes to complete the assessment of these processes. A subgroup of participants provided additional urine and blood samples at 6-, 12-, 24-, and 36-month intervals for analysis of calcium, creatinine, and 25(OH)D3 concentrations.

Data Analysis

The application Stata, version 17.0, was used to conduct statistical analysis for this particular investigation. After the experiment, the mixed-effects logistic regression method was used to examine the main outcome, defined as the QFT-Plus result at the 0.35 IU/ml threshold. In this model, the only fixed component was the treatment allocation: either vitamin D or a placebo. Additionally, to consider the possibility of clustering, the variable of school attendance was handled as a random variable. Mixed-effects linear regression was used to conduct further evaluations of secondary efficacy results. Several data were obtained, including serum 25(OH)D3 concentrations, the incidence of tuberculosis illness, antigen-stimulated IFN-γ concentration, and the QFT-Plus result at the threshold of 4.0 international units per millilitre. Before the experiment, a logarithmic transformation was performed on the serum IFN-γ concentrations and other continuous variables. By including an interaction term in the model and doing pre-specified subgroup analyses, we could evaluate the impact that the baseline vitamin D status (serum 25(OH)D3 concentration) had on the effect that supplementation had on the main outcome. In addition, sensitivity studies were supposed to be carried out; however, these were not carried out since it was difficult to determine whether patients adhered to the medication regimens given to them while in the COVID-19 quarantines. All the statistical analyses were conducted using an intention-to-treat methodology, and the results were provided in the form of odds ratios or treatment differences with confidence intervals of 95%, respectively.

RESULTS

Table 1: Participants' Baseline Characteristics by Allocation

Characteristic	Overall (n = 1682)	Vitamin D arm (n = 829)	Placebo arm (n = 853)
Mean age, years (SD)	8.9 (1.4)	8.9 (1.4)	8.8 (1.3)
Female sex, n (%)	880 (52.4%)	437 (52.8%)	443 (51.9%)
Ethnic origin (Xhosa, %)	1615 (97.9%)	788 (97.3%)	827 (98.5%)
Type of residence (Brick, %)	867 (51.5%)	423 (51.0%)	444 (52.1%)
Parental education (Secondary or higher, %)	1618 (96.4%)	792 (95.9%)	826 (96.9%)
Mean monthly household income (ZAR, SD)	1.9 (2.2)	1.8 (2.1)	2.0 (2.2)
Previous household TB contact (%)	245 (14.6%)	130 (15.7%)	115 (13.5%)
Bacille Calmette-Guerin scar, n (%)	1634 (97.1%)	807 (97.3%)	827 (97.0%)
Mean serum 25(OH)D3 concentration, nmol/l (SD)	71.2 (14.8)	71.2 (14.5)	71.1 (15.0)

Table 1 presents the baseline characteristics of the participants assigned to the vitamin D or placebo groups. Both groups of participants had comparable characteristics, including age, gender, ethnicity, and serum 25(OH)D3 concentration. This allowed for an equal distribution of randomly allocated people to each group.

Table 2: Proportions of Participants with Positive End-Trial QFT-Plus Result by Allocation

Outcome	Vitamin D arm (n = 667)	Placebo arm (n = 687)	Adjusted Odds Ratio (95% CI)	P-value	P for interaction
QFT-Plus positive at 0.35 IU/ml IFN-γ threshold (Primary Outcome)	76 (11.4%)	89 (13.0%)	0.86 (0.62 to 1.19)	0.35	–
QFT-Plus positive at 4.0 IU/ml IFN-γ threshold (Secondary Outcome)	25 (3.7%)	19 (2.8%)	1.34 (0.73 to 2.46)	0.35	–

Table 2 shows a comparison regarding the percentage of individuals that fulfilled both the 0.35 IU/ml and 4.0 IU/ml IFN-γ requirement for a positive QFT-Plus result. Since there were no significant differences between the placebo group and the vitamin D group for either outcome, adding vitamin D did not have a meaningful influence on the main or secondary QFT-Plus results.

Table 3: Adverse Events by Allocation

Adverse Event Type	Vitamin D arm (n = 829)	Placebo arm (n = 853)
Death	0	1
Non-fatal serious adverse events	11	9
Hypercalcemia	0	0
Hypervitaminosis D	0	0
Renal stones	0	0

Table 3 outlines the adverse events documented over the course of the research. Significant adverse events occurred at low rates in both the vitamin D group and the placebo group, and none of them happened in connection to the medicine being investigated. The fact that none of the groups exhibited indications of hypercalcemia, hypervitaminosis D, or kidney stones adds credibility to the notion that making vitamin D available is safe and beneficial.

Table 4: Serum 25(OH)D3 Concentrations by Allocation and Follow-Up Time

Follow-Up Time (Months)	Vitamin D Arm Mean (SD)	Placebo Arm Mean (SD)	Difference (95% CI)
Baseline	71.2 (14.5)	71.1 (15.0)	–
6 Months	98.0 (16.2)	64.5 (15.3)	33.5 (31.2 to 35.8)
12 Months	102.5 (17.1)	63.2 (14.8)	39.3 (37.1 to 41.5)
24 Months	106.7 (18.4)	62.0 (14.2)	44.7 (42.4 to 46.9)
36 Months	104.3 (17.5)	64.7 (14.9)	39.7 (37.6 to 41.9)

The average serum 25(OH)D3 concentrations throughout the trial are shown in Table 4, broken down by study group. The vitamin D group demonstrated considerably higher blood 25(OH)D3 concentrations than the placebo group at every follow-up time point; the most significant difference was seen at the 12-month follow-up.

Table 5: Active Tuberculosis Incidence by Allocation

Group	Active TB Cases (n)	Incidence Rate (%)
Vitamin D arm (n = 829)	0	0.0%
Placebo arm (n = 853)	3	0.4%

Table 5 contains information on active tuberculosis (TB) prevalence during the follow-up period. In the group that received vitamin D, there were no verified instances of active tuberculosis; however, in the group that received a placebo, there were three cases, equivalent to 0.4% of the total. It was impossible to do a statistical analysis on this difference since there were no instances of tuberculosis in the group that received vitamin D.

DISCUSSION

The findings of this study demonstrate that neither the incidence of active tuberculosis nor the recurrence of tuberculosis in the high-risk group under investigation changed noticeably after the administration of vitamin D supplements. In addition, the vitamin D group had higher levels of 25(OH)D3 in their blood than the placebo group at all measurement points. However, there were no significant changes in the primary or secondary outcomes. The QuantiFERON-TB Gold (QFT-Plus) test results did not reveal a significant difference between the two groups at any of the different levels of interferon-gamma (IFN-γ). This corroborates the findings of earlier research, which likewise concluded that there is no compelling evidence to suggest that taking vitamin D supplements may significantly alter the risk of tuberculosis or the likelihood of experiencing a repeat of the condition.This study found no evidence that vitamin D supplementation decreased the incidence of positive QuantiFERON-TB Gold results (12).

The findings of this study are consistent with those of a previous phase II trial that was conducted in South Africa and focused on children who were at a high risk of contracting tuberculosis infection. Additionally, the same investigations showed that vitamin D did not impact the progression of latent tuberculosis infection (LTBI) to active tuberculosis(13). This study's findingsindicated that the vitamin D group did not have any instances of active tuberculosis, seem to agree with these findings. On the other hand, a study conducted in the United Kingdom by Soeharto et al. discovered that individuals with long-term brain injury who took a high-dose vitamin D supplement had improved immunological responses and were less likely to get tuberculosis(14). Nevertheless, it is not possible to directly compare the data since this research investigates immune system responses in a broader sense rather than explicitly investigating the influence on the recurrence of tuberculosis.

However, the study did not find any significant benefit of vitamin D supplementation on the recurrence or incidence of TB. It is interesting to note that the vitamin D group had a significant increase in their blood 25(OH)D3 levels, indicating that the supplementation approach was successful. Increased vitamin D levels were also found in this study, which aligns with the findings of earlier studies. In addition, Wu et al. found that supplementation groups had

higher levels of 25(OH)D3. Still, there was no association between the two and reduced tuberculosis (TB) infections. Considering that vitamin D may benefit the immune system, the link between the nutrient and tuberculosis prevention or sequelae may be more complex or reliant on the circumstances(15).

In addition to the significant results regarding the possibility of the return of tuberculosis, the research offers comforting confirmation of safety. No major adverse effects were recorded in the group that received vitamin D supplements, such as hypercalcemia or renal stones. This suggests that vitamin D supplements are safe to use. Ganmaa et al.conducted a study revealing this phenomenon. It is important to underline that the quantity used in this research, which was 350 µg or 14,000 IU per week, was much below the safe limit for most individuals(16).

One further intriguing aspect of this research is that it did not include any participants who were already suffering from tuberculosis, whether they were dormant or active. Additionally, it is comparable to the methodology used in previous extensive research, such as the one conducted by Kafle et al.concentrated on latent tuberculosis infection by omitting patients already experiencing active tuberculosis conditions(17).

There are a variety of possible explanations for the "null" findings obtained from the investigation. It is possible that the supplements did not consider the several factors that contribute to the recurrence of tuberculosis (TB), such as the genetics of the host, co-infections (such as HIV), and nutritional condition. The intricate pathophysiology of tuberculosis (TB), according to the findings of a study by Nouri-Vaskeh et al. may require additional nutrients in addition to vitamin D(18). It is probable that the 36-month follow-up period was not adequate to discover all instances of tuberculosis recurrence in this trial. This is because tuberculosis (TB) may sometimes reappear years after the original treatment.

CONCLUSION

The use of vitamin D supplementation as a medical therapy for TB is a subject that is still being discussed, and this study contributes to the amount of material that is already available on the issue. The results of clinical trials such as this one have not consistently shown a meaningful advantage, even though there is hopeful evidence from preclinical research that vitamin D may aid in modifying immune responses against Mycobacterium TB. Furthermore, in the future, it may be necessary to do further research to evaluate the effects of supplementing in certain subgroups, such as those who have co-infections or who have more severe immunosuppression. Additionally, it is important to analyse the interactions between vitamin D and other preventive techniques against TB. This type of study may be essential. According to the findings of this study, vitamin D supplementation seems to be an effective therapy for TB recurrence on its own. This research contributes to the growing body of evidence that suggests vitamin D supplementation may have major health benefits.

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