The 4th International Conference on Community Medicine and Medical Sciences
Volume 2024
http://dx.doi.org/10.11594/nstp.2024.4405

NST Proceedings
OPEN ACCESS

Conference Paper

A Systematic Review: The Effectiveness of Vitamin D Supplementation on *Tuberculosis* Spondylitis

Aila Mustofa[1]*, Hamid Faqih Umam[2], David Noor Umam[3]

[1]General Practitioner, Indonesian Red Cross Surakarta, Indonesia
[2]General Practitioner, Roemani Muhammadiyah Hospital, Semarang, Indonesia
[3]Neurologist, Karanganyar Muhammadiyah Hospital, Lecturer at Universitas Muhammadiyah Karanganyar, Indonesia

**Corresponding author:*
E-mail:
ailamustofa@gmail.com

ABSTRACT

Introduction: Tuberculosis remains a major global health problem. About 50% of musculoskeletal tuberculosis involves the spine. Vitamin D deficiency is related to a higher risk of tuberculosis infection. Vitamin D has a potential benefit on the immune system during tuberculosis spondylitis. Methods: A systematic review was performed using PRISMA flowchart in five databases to identify articles until July 24th 2024. The risk of bias was evaluated by modified Jadad Scale. Results: Three articles using randomized controlled trials, with a total 162 patients. High-dose vitamin D supplementation (5.000IU and 10.000IU) showed significant efficacy in several indicators. Serum vitamin D levels increased to 38.49 ng/mL. There was an improvement in immune response (TLR2, TLR4) and a decrease in inflammatory markers (TGF-β1, IL-10, IL-17, IL-23, CRP, and ESR). High-dose vitamin D administration was shown to increase overall efficacy (95.65% vs. 80.43%, $p<0.05$), reduce pain, and improve spinal cord injury grade and activities of daily living. No difference in adverse events was observed in the intervention group. Conclusion: Vitamin D supplementation may improve the efficacy of tuberculosis spondylitis treatment. Further research is needed to determine the recommended dose and duration of supplementation in clinical practice.

Keywords: Vitamin D supplementation, tuberculosis spondylitis, immune response, clinical outcome

Introduction

Tuberculosis (TB) continues to be a major global health problem (Rajasa et al., 2018; Mancha et al., 2024). Extrapulmonary TB, specifically musculoskeletal TB, accounts for about 10% of TB cases (Rajasa et al., 2018). Tuberculosis spondylitis is the most prevalent type of skeletal TB and makes up approximately 50% of all cases (Rajasa et al., 2018; Arifin et al., 2023). Tuberculosis spondylitis is a chronic infection of Mycobacterium Tuberculosis affecting the spine and nearby structures, causing extensive tissue damage that can lead to disability and serious outcomes (Mancha et al., 2024). It is crucial to provide the correct treatment to prevent the most severe complications of tuberculosis spondylitis, such as neurological impairments and spinal deformities (Esteves et al., 2017).

The lack of vitamin D has consistently related to a higher susceptibility to Mycobacterium tuberculosis infection (Rajasa et al., 2018; Arifin et al., 2023). According to several studies, most patients with MTB infection were found to have a deficiency of vitamin D. Additionally, the severity of TB was observed to be inversely associated to the vitamin D levels (Wani et al., 2021). Vitamin D is known to be important in regulating immunity related to tuberculosis (Tang et al., 2017). Vitamin D is involved in supporting the immune system's defense against MTB through various mechanisms (Arifin

How to cite:
Mustofa, A., Umam, H. F., & Umam, D. N. (2024). A systematic review: The effectiveness of vitamin D supplementation on *Tuberculosis* Spondylitis. *The 4th International Conference on Community Medicine and Medical Sciences*. NST Proceedings. pages 26-32. doi: 10.11594/ nstp.2024.4405

et al., 2023). An increase in the immune system can be seen from indicators of inflammatory markers. In addition, clinical outcomes can be assessed. Vitamin D as a supplement may have a significant effect on the immune system in cases of tuberculosis spondylitis (Arifin et al., 2023).

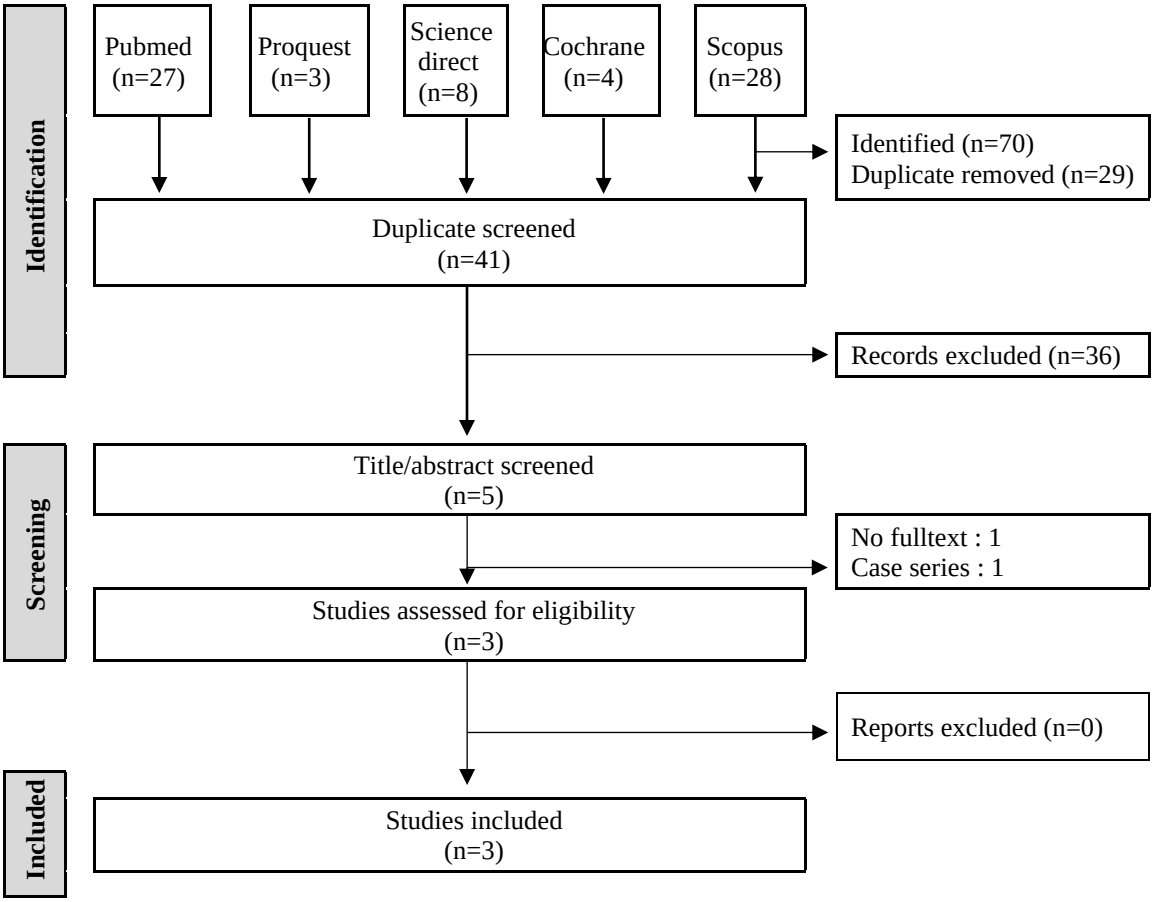

Figure 1. Search strategy flow

Material and Methods

Searching literature

Systematic searches were conducted using the PRISMA guidelines. The research question was formulated as follows:

- Population : Patients with a diagnosis of tuberculosis spondylitis.
- Intervention : Vitamin D supplementation combined with anti-tuberculous drugs
- Comparison : anti tuberculous treatment only
- Outcome : clinical outcome, laboratory indicator

A literature search was conducted using a combination of basic keywords: "Vitamin D supplementation" or "clinical outcome" or "immune response" combined with "tuberculosis spondylitis". The search was conducted on July 24th 2024 in five journal databases: PubMed, ProQuest, ScienceDirect, Scopus, and Cochrane Library. Inclusion criteria included articles published within the last 10 years, randomized control trial, case-control studies, cohort studies, and full text in analyses), editorials, conference abstracts, and case reports/series.

Table 1. Study characteristics

Study	Design	Inclusion	Age (years)	Outcome
Rajasa, 2018 Indonesia Sample: 34	Single-blind RCT **Dosage**: 800 IU/day **Follow up**: 2 months	-spinal TB on ATD -age 15–50 years; body mass index 15–25 kg/m2; and vitamin D concentration <30 ng/ml	control: 35.7 (±13.9) study: 33.6 (±12.4)	-**Vitamin D level (p <0.001)** before: 15.2 ± 7.7 ng/mL after: 28.8 ± 4.4 ng/mL -**CRP (p <0.001)** control: before vs after 5.7 (±6.2) mg/dl study: before vs after 21.3 (±10.2) mg/dl -**ESR (p =0.033)** control: before vs after 18.2 (±11.2) mm/hour study: before vs after 29.5 (±17.4) mm/hour
Yu, 2019 China Sample: 92	RCT **Dosage**: 2 capsules of oral vitamin D drops (NA doses) **Follow up**: 2 months	-diagnosed with spinal TB -patient without rheumatoid patient without TB and/or HIV	control: 67.41±8.43 study: 68.21±8.54	-**Clinical effectiveness (p=0.025)**: control vs study (80.43% vs 95.65 %) -**VAS score** control: 8.09±1.12 to 6.31±0.79 study: 8.15±1.10 to 4.08±0.68 -**Spinal cord injury grades** Control: before: class C (5), D (27), E (14) vs after: class C (1), D (20), E (16) Study: before: class C (3), D (27), E (16) vs after: class C (0), D (16), E (30); (p<0.05) -**Adverse reaction (p= 0.036):** control vs study (13% vs 5%) (p = 0.036) - **IL-1β (pg/mL)** control: 10.11±2.41 to 8.19±1.11 study: 10.18±2.39 to 4.90±0.92; p<0.05 -**IFN-γ serum level (pg/mL)** control: 51.82±11.70 to 44.20±9.79 study: 53.49±12.38 to 35.21±7.48; p<0.05 **Th17 cell-associated factors** -**IL-10 (pg/mL)** control: 34.88±5.69 to 24.79±23.19 study: 35.19±5.71 to 15.61±10.51; p<0.05 -**TGF-β1 (μg/L)** control: 80.11±10.22 to 56.10±24.41 study: 79.61±10.41 to 43.79±19.62; p<0.05 -**IL-17 (pg/mL)** control: 103.32±10.52 to 77.51±37.19 study: 102.59±10.41 to 45.61±36.78; p<0.05 -**IL-23 (pg/mL)**

To be continued…

				control: 752.16±101.35 to 482.36±283.55 study: 757.42±102.54 to 312.77±271.12; p<0.05
Arifin, 2023 Indonesia Sample: 36	RCT Control: 400 IU/day Study: 5.000, 10.000 IU/day **Follow up**: 4 and 8 weeks	-TB patient diagnosed with hematology MRI and GenExpert -Age 19-50 years	control: 30.9 ± 8.7 study: 5.000 IU: 42.0 ± 12.1 10.000 IU: 34.6 ± 14.5	-**Vitamin D level** (ng/mL) control: 28.38 ± 6.51 - 30.04 ± 4.15 ng/mL (p=0.786) study: 5.000 IU: NA level vitamin D (p= 0.01) and 10.000 IU: 27.91 ± 8.68 to 66.40 ± 4.89 ng/ml (p=0.001) -**TLR-2**: study groups increase to weeks 4 and 8 (p= 0.000) -**TLR-4**: study groups increase to weeks 4 and 8 (p= 0.000)

ATD: anti tuberculous drug; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IL: interleukin; IFN: interferon; Th: T helper; TGF: Transforming Growth Factor; TLR: toll-like receptor.

Data extraction and analysis

The following data were extracted from each selected study: author(s), publication year, country/city, design study, research year, sample size, mean age, inclusion criteria, exclusion criteria, dosage of supplementation, duration of follow up, follow up indicator, and statistical analysis. Detailed descriptions of the extracted data can be found in Table 1. Factors which have statistically significant difference in each article were considered as predictor variables.

Results and Discussion

Study selection

The systematic literature process is shown schematically in Figure 1. Initially, the search in PubMed, ProQuest, ScienceDirect, Scopus, and Cochrane Library yielded 70 articles. After excluding duplicates, 36 potential studies were identified. Five articles continued reading for abstract. One study without full text and one study with case series method.

Study characteristics

All studies had a randomized controlled trials, with a total 162 patients from different two countries. Two studies have similar average age. One study have elderly age. All three studies have same control group treatment, were given anti-tuberculous drug only. But study grup were given anti tuberculous drug and different variation dose of vitamin D. Only one study did not mention the number of doses of vitamin D administered.

Risk of bias

The risk of bias was assessed using the modified Jadad scale. The Jadad Scale consists of four items. Each item is scored on a scale, a total score ranging from 0 to 5. All studies are considered high quality (Table 2).

Table 2. Risk of bias

Study	Randomization	Concealment	Blinded	Withdraw /drop-out
Rajasa	1	1	1	1
Yu	1	1	1	1
Arifin	1	1	1	1

Effectiveness of supplementation

Trials varied in their indicators of effectiveness for vitamin D supplementation. Vitamin D concentration were found significant (p<0.001) different with t-paired test before (15.2 (±7.7) ng/mL) and after (28.8 (±4.4) ng/mL) treatment in study group (800IU of vitamin D (Rajasa et al., 2018). In study group with 5.000IU (p= 0.01) and 10.000IU (p= 0.001) of vitamin D showed significant increase from week 0 to weeks 4 and 8 of treatment (Arifin et al., 2018). There was significant decrease in CRP (p<0.001) and ESR (p<0.03) following 2 months of supplementing with vitamin D3. However, CRP (p = 0.328) or ESR (p = 0.895) levels did not show any correlation before and after taking vitamin D3 supplements (Rajasa et al., 2018). After the treatment, the study group patients showed a more significantly reduced in serum IL-1β and IFN-γ levels compared to the control group (Yu & Cailiang, 2021). In addition, the levels of TGF-β1, IL-10, IL-17, and IL-23 in study group were lower than their corresponding levels in the control group (p < 0.05) (Yu & Cailiang, 2021). TLR2 and TLR4 levels in the study group increased significantly from week 0 to weeks 4 and 8 of treatment (p < 0.05) (Arifin et al., 2023).

Clinical effectiveness of vitamin D supplementation assessed in four stages: cured, marked effective, effective, and ineffective. These four categories are summarized in a total effectiveness score, calculated in Eq 1, showed that higher in the study group (95.65 %) compared to the control group (80.43 %) (p=0.025) (Yu & Cailiang, 2021).

$$Total\ Effectiveness(\%) = \frac{(C + ME + E)}{Total\ case} x100\%$$

C: cured; *ME:* markedly effective; *E:* effective

Visual analogue scale (VAS) scores were rated on a scale of 0-10, with no pain scoring 0, mild pain scoring 1-4, moderate pain scoring 5-8, and severe pain scoring 9-10 (Yu & Cailiang, 2021). VAS scored was significantly (p<0.05) lower than pre-treatment values (8.15±1.10 to 4.08±0.68), but VAS scores were higher in control subjects (8.09±1.12 to 6.31±0.79) (Yu & Cailiang, 2021). Spinal cord injury grades based on Frankel grading, were improved in treatment group compared to the control group (p<0.05) (Yu & Cailiang, 2021).

Incidence of side effects were divided into gastrointestinal discomfort, lower extremities numbness, loss of vision, and tinnitus. The adverse events were lower in the treatment group (13.04%) compared to the control group (28.26%, p < 0.05) (Yu & Cailiang, 2021).

Bone tuberculosis most frequently affects the spine (Houston, A., & Macallan, 2014). Neurological complications, the most severe and feared symptoms of tuberculosis spondylitis, have been observed in 32% to 76% of cases. The specific neurological impairment is defined by the affected vertebrae, and if left untreated, it can advance to paraplegia or tetraplegia (Esteves, et al., 2017). The use of anti-tuberculous drugs to treat tuberculosis spondylitis is the primary method of treatment (Esteves, et al., 2017). Nevertheless, anti-tuberculous drugs might not reach minimum inhibitory concentrations in sclerotic bone lesions (Esteves, et al., 2017). Their effectiveness for treatment is also limited and they come with a wide range of side effects. In Yu et.al study, the overall efficacy of the treatment group that received ATD and vitamin D (95.65%) was significantly greater than the overall efficacy in the

control group (80.43%) (Yu & Cailiang, 2021). Adverse effect in the treatment group were significantly lower than in the control group (13.04% vs 28.26%) (Yu & Cailiang, 2021). In addition, the VAS score and the degree of spinal cord injury were significantly lower in the study group. Therefore, the use of vitamin D in combination with ATD is both safe and capable of suppressing the growth of tuberculosis, as well as reducing pain and spinal cord damage (Yu & Cailiang, 2021). Vitamin D might provide this beneficial outcome by suppressing the proliferation of bacilli by activating the body's cellular immunity system, thus enhancing the ability to resist Mycobacterium tuberculosis (Yu & Cailiang, 2021).

Vitamin D is recognized for versatile immunomodulatory molecule. Research has been shown to be involved in a potent innate immune reaction against several pathogens, including tuberculosis infection (Wani et al., 2021). To perform its required functions, the active form of vitamin D must bind to its receptor, and move into the nucleus. One of these functions involves boosting the production of cathelicidin, an essential molecule for fighting a range of bacterial and viral infections, especially those caused by MTB (Wani et al., 2021). Cathelicidin activity enhances macrophage activity by increasing phagocytic function against M. tuberculosis (Rajasa et al., 2018). Decreasing MTB colonies in the body reduces the inflammatory process by decreasing the synthesis of pro-inflammatory mediators, which are IL-6 and TNF-α (Rajasa et al., 2018). IL-6 and TNF- α, cytokines that stimulate liver hepatocyte to make CRP. CRP is an acute-phase protein released as an inflammatory response. In Rajasa et.al study showed that administration of vitamin D reduced CRP levels much more than ATD alone (Rajasa et al., 2018).

ESR is a laboratory measurement used to evaluate inflammatory activity in spinal tuberculosis infections (Rajasa et al., 2018). Although ESR is a nonspecific marker of inflammation, it is a simple measurement that can be checked in rural laboratories that lack equipment for more precise measurements. In Rajasa et.al study showed that administration of vitamin D reduced ESR levels much more than ATD alone (Rajasa et al., 2018).

Another proinflammatory factor is IL-1β, which involved in numerous the destruction of human tissue and the process of edema. IL-1β has the capacity to promote the growth and maturation of B lymphocytes and the production of immunoglobulins. IFN-γ is a lymphokine with broad immunomodulating activity that regulates immune responses through interfering with the transcription of immune-related genes. Th17 cytokines regulate the levels of TGF-β1, IL-10, IL-17, IL-23, and other factors in the immune response associated with TB. In addition, IL-10 is a multi-functional negative regulator that is released by macrophages, activated B cells and monocytes. TGF-β1 acts as a suppressor of polypeptide cell growth, binding to its receptor and controlling cellular processes through the mediation of the Smad3 signaling pathway. Additionally, it plays a role in inflammation. IL-17 is involved in defense against infection and is an early initiator of inflammatory responses induced by T Cells. A cytokine, IL-23, produce by activated macrophages and dendritic cells. It primarily affects Th17 cells, stimulating them to produce IL-17A, IL-17F, IL-22, and other molecules. In Yu et al. study, the combination of vitamin D and ATD showed a much greater reduction in IFN-γ, TGF-β1, IL-1β, IL-10, IL-17, and IL-23 than ATD alone (Yu, F., & Cailiang, 2021). Treatment involving both vitamin D and tuberculosis medications could potentially decrease suppressed immune system and inflammatory reactions.

Activating TLR2 and TLR4 signaling pathways at the same time leads in response to Mycobacterium tuberculosis and induces both apoptosis and necrosis. Mycobacterial are identified by TLR-2 and TLR-4 (Arifin et al., 2023; Wani et al., 2021). They have been implicated in TB susceptibility through interaction with toll-like interactive protein (TOLLIP). Their expression can be improved to resist infection increased with optimal vitamin D supplementation (Arifin et al., 2023).

Holick classifies 25(OH)D concentration deficit as: normal = 30–60, insufficient = 20–29, and deficient ≤ 20 ng/mL (Arifin et al., 2018). In Rajasa et al (2018) study, the intervention group had an improvement in mean 25(OH)D levels, but levels were still categorized as insufficient. Mean 25(OH)D concentration before treatment was 15.2 ng/mL, indicating deficiency, but after 800 IU vitamin D3 for

2 months, 25(OH)D concentration improved to 28.8 ng/mL (Arifin et al., 2018). But in Arifin et.al study, Vitamin D supplementation at 10,000 IU/day for 8 weeks can raise the levels of vitamin D above 50 ng/dl for optimal function as an immunomodulator. However, other doses of vitamin D did not exceed 50 ng/mL (Arifin et al., 2018).

Conclusion

Vitamin D supplementation shows significant and beneficial effects in patients with tuberculosis spondylitis. The combination of treatments promotes safety while also managing numerous inflammation factors, thereby reducing the inflammatory response. In addition, it improves the clinical condition of patients with tuberculosis spondylitis. More studies are required to establish the appropriate dose and duration for taking vitamin D supplementation in clinical practice.

References

Arifin, J., Massi, M. N., Biakto, K. T., Bukhari, A. et al. (2023). Randomized controlled trial of vitamin D supplementation on toll-like receptor-2 (tlr-2) and toll-like receptor-4 (tlr-4) in tuberculosis spondylitis patients. *J Orthop Surg Res., 18*(1), 983. https://doi.org/10.1186/s13018-023-04445-6.

Esteves, S., Catarino, I., Lopes, D., & Sousa, C. (2017). Spinal Tuberculosis: Rethinking an Old Disease. *J Spine, 06*(1), 1-12. https://doi.org/10.4172/2165-7939.1000358.

Houston, A., & Macallan, D. C. (2014). Extrapulmonary tuberculosis. *Medicine (United Kingdom), 42*, 18–22. https://doi.org/10.1016/j.mpmed.2013.10.008.

Mancha, D. G., Ode, M. B., Taiwo, O., Yilleng, S. B., Onche, I.I. (2024). An overview of *Tuberculous spondylitis* in a Tertiary Institution in North Central Nigeria (A 10 Year Retrospective Study). *International Journal of Clinical Studies and Medical Case Reports, 41*(1), 003. https://doi.org/10.46998/IJCMCR.2024.41.001003.

Rajasa, F., Rasyid, H. N., Tiksnadi, B., Ramdan, A., Ismiarto, Y., & Abtiza, R. (2018). Vitamin D3 as an anti tuberculosis supplement in spinal tuberculosis treatment. *Progress in Orthopedic Science, 4*(1), 1–6. https://doi.org/10.47363/POS/2018(4)131.

Tang, L., Liu, S., Bao, Y-C., et al. (2017). Study on the relationship between vitamin D deficiency and susceptibility to spinal tuberculosis. *International Journal of Surgery, 44,* 99–103. https://doi.org/10.1016/j.ijsu.2017.05.077.

Wani, B. A., Shehjar, F., Shah, S., Koul, A. et al. (2021). Role of genetic variants of Vitamin D receptor, Toll-like receptor 2 and Toll-like receptor 4 in extrapulmonary tuberculosis. *Microb Pathog., 156,* 104911. https://doi.org/10.1016/j.micpath.2021.104911.

Yu, F., & Cailiang, S. (2021). Effect of vitamin D combined with anti-tuberculosis drugs on serum IL-1β, IFN-γ and Th17 cell-associated cytokines for the management of spinal tuberculosis. *Tropical Journal of Pharmaceutical Research, 18,* 1141–1147. https://doi.org/10.4314/tjpr.v18i5.32.