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Impact of Vitamin D Supplementation in the Therapy of Tuberculosis

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Abstract
Ultraviolet B (UV-B) synthesis occurs when the skin is exposed to sunshine and produces vitamin D as a result. Additionally, nutritional supplements and diet can provide it. Animals are the primary source of vitamin D. Vitamin D has been identified as a risk factor for tuberculosis (TB) disease and infection. It is considered that vitamin D influences the release of antimicrobial peptides like cathelicidin in response to viral and bacterial stimuli, which is thought to affect both the innate and adaptive immune systems. This essay sought to provide an outline of vitamin D's role in the treatment of tuberculosis. For journal articles, reports, and reliable sources, several databases were searched to compile pertinent information. Additionally, search terms were utilised interchangeably to find pertinent materials. The majority of the literature revealed a connection between vitamin D levels and TB. Furthermore, research has indicated that certain vitamins, including Vitamins C and D, have antimycobacterial capabilities. Despite contradicting data about the relationship between Vitamin D Deficiency (VDD) and the risk of tuberculosis, vitamin D supplementation is still a viable strategy. The analysis of the impact of vitamin D supplementation as a potential therapeutic intervention for TB infection should pay more attention to exploring larger sample sizes and metabolite chemicals.
Keywords: Antimycobacterial, Mycobacterium tuberculosis, Tuberculosis and Vitamin D

INTRODUCTION

Due to their antioxidant, pro-oxidant, anti-inflammatory, and metabolic properties, vitamins are essential for many bodily processes (Patti *et al.*, 2021). According to Tessema *et al.* (2017). Vitamin D, a fat-soluble vitamin, has been shown to improve immunity against tuberculosis (TB), lessen the reactivation of latent TB, and lessen the severity of active TB disease. According to Tsounis *et al.* (2002), the vitamin D receptor (VDR) is essential for immunoregulatory processes that support liver homeostasis.

Although there is evidence linking vitamin D to the host immune response in TB, nothing is known about how vitamin D may affect non-tuberculous mycobacterial pulmonary disease (NTM-PD) (Oh *et al.*, 2019). According to research (Allegra *et al.*, 2017; Hong *et al.*, 2019), vitamin D levels are correlated with the degree of mycobactericidal activity. This suggests that vitamin D can boost phagocytosis by activating macrophages and reducing *Mycobacterium* TB intracellular growth.

Recent research has demonstrated the influence of different genes involved in vitamin D metabolism on immune system functions and the host's resistance to *M. tuberculosis* (Sadykov *et al.*, 2020). The risk and prognosis of TB are correlated with serum vitamin D concentrations and the methylation status of important genes in the vitamin D metabolic pathway (Wang *et al.*, 2018). Individual genetic differences relating to susceptibility and protection against TB may be revealed by genetic variants in VDR and CYP24A1 (Sadykov *et al.*, 2020).

Due to their antioxidant, pro-oxidant, anti-inflammatory, and metabolic properties, vitamins are essential for many bodily processes (Patti *et al.*, 2021). According to Allegra *et al.* (2017), single nucleotide polymorphisms in the VDR receptor also seem to affect how well treatments work. Additionally, vitamin D causes IL-1, which helps to resistance against TB, and interleukin (IL)-15 and IL-32 are involved in the

vitamin D-mediated defence mechanism against TB (Hong *et al.*, 2019).

The level of vitamin D affects the human cathelicidin LL-37, which possesses antibacterial and immunomodulatory effects (Acen *et al.*, 2021). According to research, a lack of vitamin D significantly increases the likelihood of acquiring active TB (Acen *et al.*, 2022). Similar to this, low vitamin D levels have been associated with a higher risk of contracting TB infection and illness (Acen *et al.*, 2021). It was discovered that people with low vitamin D levels had a five-fold increased risk of developing TB or chronic TB (Talat *et al.*, 2010). Vitamin D has been proven to have a preventive effect against TB disease, with patients with TB having greater rates of vitamin D insufficiency than healthy people (Acen *et al.*, 2021; Nouri-Vaskeh *et al.*, 2019). Higher vitamin D status may be linked to increased immune activity and less severe tissue damage, though this relationship may vary depending on the presence of co-morbidities like diabetes mellitus (Wang *et al.*, 2019). Vitamin D deficiency has been linked to a high prevalence in TB patients. A risk factor for TB infection and sickness has been discovered as low vitamin D levels (Acen *et al.*, 2021).

While some research has examined the link between a history of vitamin D insufficiency and the emergence of tuberculosis, the findings have been few and ambiguous (Aibana *et al.*, 2019; Gou *et al.*, 2018). Furthermore, neither demographic factors nor biochemical markers nor serum vitamin status have been consistently linked to TB treatment outcomes.

In this study, the impact of vitamin D supplementation on the treatment of tuberculosis infection was reviewed.

MATERIALS AND METHODS

Different databases were consulted for journal articles, reports, and reputable sources to gather relevant information. Also, keywords were interchangeably used in searching for relevant materials.

Essentials of Vitamin D

Regular supplementation of these micronutrients may be advantageous since they play important functions in maintaining the immune system's operation (Visser *et al.*, 2017). For *M. tuberculosis*, vitamins like biotin and thiamin are crucial for the development of infection (Tyagi *et al.*, 2017).

Vitamin D is essential for maintaining healthy bones because it helps the body absorb calcium from food (Elsori and Hammoud, 2018), but it also has the ability to lower child morbidity and death rates (Zisi *et al.*, 2019). When it comes to TB, combining different micronutrient supplements, such as zinc, may be more beneficial than relying simply on vitamin A supplements (Visser *et al.*, 2017). A few vitamins, including Vitamin C and Vitamin D, have also shown evidence of having antimycobacterial activities (Tyagi *et al.*, 2017). Vitamin D may be a useful, cost-effective, and safe supplemental therapy for a number of disorders due to the low frequency of side effects and its large safety margin. To determine its effectiveness under various circumstances, additional thorough investigations with sound design are required. It would be crucial to implement a global public health initiative that incorporates systematic food fortification with vitamin D to prevent severe deficiency as well as targeted vitamin D supplementation for particular at-risk groups (Amrein *et al.*, 2020).

Consequences of Vitamin D Deficiency

Alterations in vitamin levels are linked to mycobacterial illnesses (Oh *et al.*, 2019). Furthermore, inadequate dietary intake of micronutrients can impair adaptive immunity (Berger *et al.*, 2021). According to Elsori and Hammoud (2018), strict vegetarianism is the main cause of vitamin D insufficiency. The potential advantages of routine supplementing are highlighted by the crucial functions several micronutrients play in strengthening the immune system (Visser *et al.*, 2017).

Risk factors for Vitamin D Deficiency

Abubakar *et al.*, 2021 found several risk factors for vitamin D insufficiency. These include limiting sun exposure, having darker skin, using sunscreen frequently, covering up with clothing, and eating a diet low in fish and dairy items. These risk factors increase the likelihood of developing vitamin D insufficiency by decreasing vitamin D production or intake.

Risk Groups of Vitamin D Deficiency

Beyond certain risk populations, vitamin D insufficiency is extremely common worldwide. Adult vitamin D insufficiency is prevalent in parts of the world like the Middle East and Asia (Abubakar *et al.*, 2021). The risk of acquiring TB in those living with HIV is already increased by the presence of hypovitaminosis D (Musarurwa *et al.*, 2018).

While young children, pregnant women, older people, those living in institutions, and non-Western immigrants have historically been at risk for vitamin D insufficiency, new research has shown that teenagers and young adults are also at risk (Abubakar *et al.*, 2021). Therefore, for people in risk groups, it may be wise to consider

supplementing with moderate doses of vitamins C and D, as well as selenium (Se), zinc (Zn), and omega-3 polyunsaturated fatty acids (n-3 PUFA), during any restricted movement or lockdown (such as during the COVID-19 pandemic) in addition to maintaining a healthy and balanced diet (Berger *et al.*, 2021).

The potential of Vitamin D supplementation in the treatment of TB

Vitamin use in TB patients, including the use of vitamin D and vitamin E, is suggested and promoted by Patti *et al.* (2021). Vitamin E has shown promise in the management of TB due to its link with oxidative balance, while vitamin D has been demonstrated in laboratory experiments to inhibit the reproduction of *M. tuberculosis* (Patti *et al.*, 2021). By supplying nutritional support and interacting either directly or indirectly with the TB-causing bacteria, these vitamins may help treatment outcomes. To further bolster these suggestions, nonetheless, larger, more thorough experiments are required (Patti *et al.*, 2021). Further studies need to be done to look into the usage of vitamin D supplements for people receiving TB therapy and those who have latent TB infection (Talat *et al.*, 2010).

By stimulating macrophages, vitamin D has the power to improve phagocytosis and hence inhibit *M. tuberculosis* intracellular growth. Additionally, single nucleotide polymorphisms in the vitamin D receptor (VDR) gene may affect how well a medication works (Allegra *et al.*, 2017). The pharmacokinetics of TB medications may be impacted by genetic polymorphisms in drug transporters, transcriptional regulators, vitamin D metabolism-related enzymes, the VDR, and its pathway regulators (Thomas *et al.*, 2020).

Innovative tactics must be created to attack *M. tuberculosis* while taking the effectiveness of the used agents into account. According to Tyagi *et al.* (2017), vitamins may be effective tools for altering the biology and life cycle of *M. tuberculosis*.

Mechanisms by which vitamin D3 protects against and treats tuberculosis

The pathogenic bacterium *Mycobacterium tuberculosis* is the primary cause of tuberculosis, a fatal illness that affects people all over the world. Primarily infecting macrophages, *M. tuberculosis* prevents phagosomal maturation, autophagy, and apoptosis. The active metabolite of vitamin D, 1,25-dihydroxy vitamin D, has shown potential in increasing the immune response against M. tuberculosis, hence its use in TB treatment has been investigated (Wu *et al.*, 2022).

Unknown are the exact methods through which vitamin D3 both prevents and treats tuberculosis. The viability of THP-1 cells was assessed using MTT assays in this study, and it was discovered that vitamin D3 decreased viability in a dose- and time-dependent way. They used western blotting and RT-qPCR to examine autophagy-related elements in THP-1 cells infected with *M. tuberculosis*. As a result of the *M. tuberculosis* infection, the results showed that vitamin D3 greatly raised the expression of p62, LC3II/LC3I, Beclin-1, ATG-5, and AMPK, indicating the activation of cellular autophagy. A calcium concentration assay that was carried out by the researchers also provided evidence that vitamin D3 might encourage cellular autophagy by lowering calcium concentration (Wu *et al.*, 2022).

The researchers used Balb/c mice to further study the impact of vitamin D3 on *M. tuberculosis* infection. Pulmonary damage was determined by hematoxylin and Eosin (H & E) staining of lung tissue. The findings showed that vitamin D3 significantly lessened the cellular damage brought on by M. tuberculosis infection. This study's findings, which shed light on how vitamin D3 affects M. tuberculosis infection and help us understand its underlying mechanism for reducing and treating the inflammatory response linked to TB, suggest that vitamin D3 may activate cellular autophagy signals by regulating calcium concentration (Wu *et al.*, 2022).

Rifampicin, vitamin D and tuberculosis

SLCO1B1, ABCB1, PXR, and CAR, as well as the genes for metabolising enzymes CES1, CES2, and AADAC, the genes for the vitamin D receptor (VDR) and its pathway regulators VDR, CYP27B1, and CYP24A1, were targeted in a narrative review by Thomas *et al.* (2020) in order to find relevant literature examining the impact of genetic variations. The review emphasised that VDR polymorphisms and vitamin D insufficiency (VDD) have also been linked to TB. The pharmacokinetics of RF may therefore be affected by genetic polymorphisms in drug transporters, metabolising enzymes, and their transcriptional regulators, as well as VDR and its pathway regulators (Thomas *et al.*, 2020).

The research also found that there is no evidence at this time to indicate a link between RF plasma concentrations and genetic variations of ABCB1, PXR, CAR, CES1, and AADAC. To come to a firm conclusion, further thorough research is required to examine the relationship between RF pharmacokinetics and genetic variants of SLCO1B1, CES2, and genes involved in the

vitamin D pathway in many ethnic groups and bigger populations (Thomas *et al.*, 2020).

Serum Vitamin D Status

The activation of TB has long been linked to vitamin D insufficiency, commonly known as 25-hydroxycholecalciferol. Compared to healthy people, TB patients often have decreased serum vitamin D levels. It's interesting to note that sustained vitamin D deficiency can result from TB treatment. As a cofactor in the production of antimycobacterial activity, vitamin D has been shown in numerous studies to operate as a strong immunomodulator of innate immune responses (Talat *et al.*, 2010).

Vitamin D testing and supplementation have both significantly increased in recent years. The best way to supplement with vitamin D, as well as its amount and status, are still up for debate. This is due to the fact that extensive interventional studies, the majority of which were carried out in populations where vitamin D levels were already high, have not clearly shown any advantages (Amrein *et al.*, 2020). In a similar vein, baby vitamin D supplementation rates do not exceed recommended levels (Aul *et al.*, 2023). However, given that many studies did not meet the essential criteria of a nutritional intervention study, this discrepancy may be due to restrictions in trial design. These consist of populations with sufficient vitamin D levels, sizeable sample sizes, and consistent intervention techniques with regard to dosage and metabolites (Amrein *et al.*, 2020).

1-hydroxylase, an enzyme that changes 25(OH)D into its active form, 1,25(OH)2D, is crucially activated by vitamin D. The expression of cathelicidin, a microbicidal peptide effective *against M. tuberculosis*, results from this conversion. The enzyme has enough substrate at serum concentrations greater than 30 ng/mL. On the other hand, serum concentrations below 20 ng/mL may impede the innate immune response to *M. tuberculosis* that is triggered by macrophages. The disparities in TB susceptibility shown across various regional and ethnic communities could possibly be explained by these variations in serum vitamin D levels (Talat *et al.*, 2010).

According to the Endocrine Society's classification system, vitamin D levels below 20 ng/mL are considered inadequate, levels between 20 and 30 ng/mL are insufficient, levels between 30 and 150 ng/mL are sufficient, and levels above 150 ng/mL are a sign of hypervitaminosis D.

Deficiency was defined as less than 20.0 ng/mL, insufficiency as between 21 and 29 ng/mL, sufficiency as greater than 30 ng/mL, and severe deficiency as less than 10.0 ng/mL (Acen *et al.*, 2022).

A blood 25-hydroxyvitamin D [25(OH)D] level below 50 nmol/L or 20 ng/mL indicates a vitamin D deficiency and is indicative of adverse skeletal outcomes such as fractures and bone loss. Although some research points to the possible benefits of a higher threshold, the main treatment objective is to raise the 25(OH)D level above 50 nmol/L or 20 ng/mL. A 25(OH)D concentration below 30 nmol/L (or 12 ng/mL) indicates severe vitamin D insufficiency and is associated with an elevated risk of excess mortality, infections, and some other disorders. Therefore, wherever feasible, it is imperative to avoid severe insufficiency. In particular, for those who are seriously deficient, the evidence firmly supports the potential advantages of vitamin D in lowering mortality and preventing infections. It should be understood, therefore, that vitamin D is not a panacea and probably only works when there is a deficiency (Amrein *et al.*, 2020).

The ranges for total blood 25-hydroxyvitamin D concentrations indicating vitamin D status were confirmed as follows: deficiency was defined as less than 20 ng/mL (less than 50 nmol/L), suboptimal status as between 20 and 30 ng/mL (between 50 and 75 nmol/L), and optimal concentration as between 30 and 50 ng/mL (between 75 and 125 nmol/L) (Pudowski *et al.*, 2023).

CONCLUSION

Vitamin D supplementation remains a promising intervention despite conflicting reports on the association between Vitamin D Deficiency (VDD) and the risk of tuberculosis (TB). More focus should be tailored towards exploring a larger sample size and metabolite compounds in the analysis of the effect of vitamin D supplements as a potential therapeutic intervention for TB infection.

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