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Clinical efficacy of vitamin D supplementation on pulmonary TB patients: The evidence of clinical trials

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1. Dear Editor,

Tuberculosis (TB) is one of the most important infectious diseases and considered among the top 10 causes of death in the world. According to World Health Organization (WHO) report in 2020, about 10 million infected cases of TB and also 1.5 million death occurred form this disease in 2019 [1,2]. Moreover, about one fourth of infected patients by *Mycobacterium tuberculosis* (*Mtb*) are involved with more severe complications such as infection by drug-resistant TB (DR-TB) strains, co-infection with HIV virus, as well as latent TB (LTBI) infection. Although individuals affected by LTBI are asymptomatic and cannot infect others, but in general, some of them may develop to active-TB form that it is accounted as a concern for health services [3–5]. In addition, the standard treatment of TB is also a time consuming process and in some cases such as co-infection with HIV, DR-TB, and cases with side effects, therapeutic protocols may face with serious limitations. Therefore, it seems we will require to develop the novel therapeutic agents which reduce the course of treatment, and can cover the other problems in treating TB [5–7]. Vitamin D was first used by Williams in the beginning of 1849; he noticed that the fish liver oil improves the appetite and strength of the TB patients [8]. Rook et al. (1986) showed that calcitriol, the active biological form of Vitamin D, has *in vitro* anti-TB effects [9]. Based on the evidence, vitamin D influences the host immune system responses. It can activate the monocytes and lymphocytes of human through their vitamin D receptors (VDRs). For instance, this vitamin stimulates the physiological processes such as monocytes activities, restraining the proliferation of lymphocytes, stimulation of the immunoglobulin and cytokine production, stimulation of the reactive nitrogen and oxygen stress responses, restraining the matrix metalloproteinase activity, autophagy stimulation, and production of human antimicrobial peptides (AMPs) [10,11]. In recent studies, it has been demonstrated that the serum level of vitamin D has a significant relationship with susceptibility rate to TB [10–12]. Furthermore, it has been shown that the polymorphisms such as *TaqI* in the VDR gene also affect the development of TB [10]. Thus, it seems that vitamin D by improving the immune system responses causes the shorten course of TB treatment, increasing the intercellular elimination of *Mtb*, reducing transmissibility, and also improvement of the intensity and strength of infection by DR-TB strains [13].

Several clinical trials have so far been done about the effects of vitamin D on the treatment of TB, but some of which have shown controversial results. Moreover, the role of vitamin D supplement in the treatment of TB has not properly determined in the *meta*-analysis studies. The aim of this study was to evaluate the role of vitamin D on reducing the sputum conversion time in the patients with drug-susceptible TB and multi-drug resistant TB (MDR-TB). The polymorphism of *TaqI* can also modify the effect of vitamin D supplement on time conversion.

Using the key words “Tuberculosis” and “Vitamin D”, the clinical trial studies related to our study were searched from the clinical trial website (https://clinicaltrials.gov/). Then, the free access documents were retrieved for the clinical trial studies. The required information from these studies were extracted and listed in Table 1.

The Odds Ratio (OR) and Hazard Ratio (HR) indices at 95% confidence intervals were used to evaluate the relationship between the vitamin D supplementation as adjunctive therapy and the sputum conversion. Using OR the effect of polymorphism of *TaqI* gene on the time of sputum conversion was also measured. Pooling the data was done in the present study by use of the Comprehensive Meta-Analysis (CMA) software, version 2.2 (Biostat, Englewood, NJ). Based on Dersimonian and Laird method, the random effect models was used for the cases with high levels of heterogeneity (I^2 index > 25% and Cochran’s Q-test p-value < 0.05) [3].

Overall, eight studies that had been fulfilled between 2011 and 2018 were matched with our criteria studies. We evaluated the information about 1811 people, so that 34.29% of them were women and the rest were men. Also, the mean age of the patients was measured 31.6 ± 15. In the study by Ralph et al. (2013), they used of both L-arginine and vitamin D for some groups, but we omitted the information of L-arginine groups in order to merely to evaluate the pure effect

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Table 1
Characteristics of included studies.

Author	Publish year	Setting	Clinical trials register No.	Intervention vitamin D3	Dosage	Female/MaleAge	Statistics of studies			Refs.
							case	control	p-value	
Martineau	2011	UK	NCT00419068	vitamin D3 2.5 mg	2, 4 and 6 weeks	NA 30.6	36 (95% CI 31.8–40.2)	43.5 (95% CI 36.5–50.5)	HR: 1.39; 95% CI 0.90–2.16, P = 0.41	[10]
Daley	2015	India	NCT00366470	vitamin D3 2.5 mg	0, 2, 4, and 6 weeks	58/189 42.65	43·0 (33·3–52·8)	42·0 (33·9–50·1)	0·952	[12]
Mily	2015	Bangladesh	NCT01580007	vitamin D3 500 mg	Once daily for 2 months	23/19 27.4 ± 12	61.3% (38/62)	42.2% (27/64)	0.032	[14]
Salahuddin	2013	Saudi Arabia	NCT01130311	vitamin D3 600,000 IU	2 doses	118/141 28.05 ± 61	6.68 ± 2.04, 6.3–7.03	6.85 ± 2.50, 6.4–7.29	0.16	[15]
Tukvadze	2015	Georgia	NCT00918086	vitamin D3 1.25 mg	Thrice weekly for 8 week	72/127 33.25	29; 95% CI: 24, 36	27; 95% CI: 23, 36	HR: 0.86; 95% CI: 0.63, 1.18; P = 0.33	[16]
Bekele	2018	Ethiopia	NCT01698476	vitamin D3 5000 IU	FOR 16 weeks	147/201 30.47	1.07 0.43–2.65 P = 0.879	1.05 0.42–2.63 P = 0.904	NA	[17]
Ganmaa	2017	Mongolia	NCT01657656	vitamin D3 3.5 mg	four oral doses	134/256 33	NA	NA	Adjusted hazard ratio, 1.09; 95% confidence interval, 0.86–1.36; P = 0.48.	[18]
Ralph	2013	Indonesia	NCT00677339	vitamin D3 50,000 IU	Once daily for 4 weeks	69/131 27.5	59% (44/75)	65% (52/80)	Risk difference 7%, 95% CI 29 to 22%.	[19]

of vitamin D on TB.

Based on the primary statistical analysis, vitamin D supplementation increases the sputum smear and culture conversion (OR: 3.197; 2.39–4.26 with 95% CIs; I^2: 64.44; *Q* value: 11.24 and Egger's intercept: 1.81). However, the consumption of that had no impact on the time of sputum smear and culture conversion (HR: 1.05; 0.88–1.25 with 95% CIs; I^2: 38.11; *Q* value: 3.23; Eggers' intercept: 1.29). According to the secondary analysis, vitamin D had no impacts on the sputum conversion in the MDR-TB patients (OR: 0.91; 0.58–1.41 with 95% CIs; p-value: 0.69). In addition, we did not find a significant relationship between the effect of *Taql* gene polymorphism in adjunctive therapy of vitamin D and shortening the duration of sputum conversion (*tt* allele with OR: 1.12 and *p value*: 0.61; *Tt* allele with OR: 1.03 and *p value*: 0.86; *TT* allele with OR: 1.23 and *p value*: 0.31). Moreover, *Taql* polymorphism had no impacts on shortening the duration of sputum smear and culture conversion (HR: 1.43; 0.90–2.26 with 95% CIs; *p value*: 0.12). Regarding the statistical analysis, we also performed a supplementary analysis about the impact of vitamin D supplementation on the size of the lung cavity, total white blood cells (WBC) as well as deaths, although there was not found the significant relationship in this respect. For the three recent items, the statistical analysis results was OR: 0.92; *p value*: 0.49, OR: 1.18; *p value*: 0.145, and OR: 1.1; *p value*: 0.76 respectively. Vitamin D is one of the most well-known bioactive compounds that has an important effect on the reduction of pathogenesis of infectious diseases by modulating the immune system responses (Fig. 1).

By restraining the CD4 + T cell proliferation, inducing the IFN-γ, IL-2, and formation of VDR-RXR complex, vitamin D can shift the immune system response towards Th2/T regulatory (T reg) cells, and indeed effects on the final outcome of the infection by *Mtb* [20]. In the present study we demonstrated that vitamin D as adjunctive substance increases the sputum smear and culture conversion (OR: 3.19; *p value*: 0.01). However, based on our analysis, the consumption of vitamin D had no impact on the time of the sputum smear and culture conversion (HR: 1.05; p-value: 0.54). Furthermore, we observed no significant relationship between the vitamin D supplementation and sputum conversion in MDR-TB cases, total white blood cell counts, reduction of lung cavity size, death, and *Taql* polymorphism; previous studies had also controversial results. Jolliffe et al. (2019) showed that vitamin D supplementation can accelerate sputum smear conversion in the MDR-TB patients (aHR 1.15), but our findings were in contradiction with their results [21]. Wu et al. (2018) showed that vitamin D can increase the sputum smear and culture conversion (OR 1.21, *p value*: 0.007) and our results was also consistent with their results. However, Wu et al. stated that consuming vitamin D had a significant relationship with increasing the lymphocyte counts in the TB patients, but our findings was contradictory with the previous studies [22]. Wu et al. (2018) showed that vitamin D supplementation had no impact on the increasing of sputum conversion, but their results was not consistent with our results [22]. Nonetheless, the difference in the results could be due to the low sample size and limited studies. Although in the present study the existing clinical trials was evaluated up to April 2020, but we require more studies and more volunteers to evaluate the validity of the present study results.

In summary, we demonstrated that vitamin D supplementation increases the sputum smear and culture conversion in the TB patients. However, vitamin D has no impact on shortening the duration of sputum conversion in the TB patients. Regarding the present studies, it seems that vitamin D supplementation can increase the sputum conversion by improving the disinfecting activity of the macrophages. Hence, it can be concluded that vitamin D can be recommended for the adjunctive therapy in treating and prevention of TB, in combination with the anti-tuberculosis drugs and for the prophylactic aims.

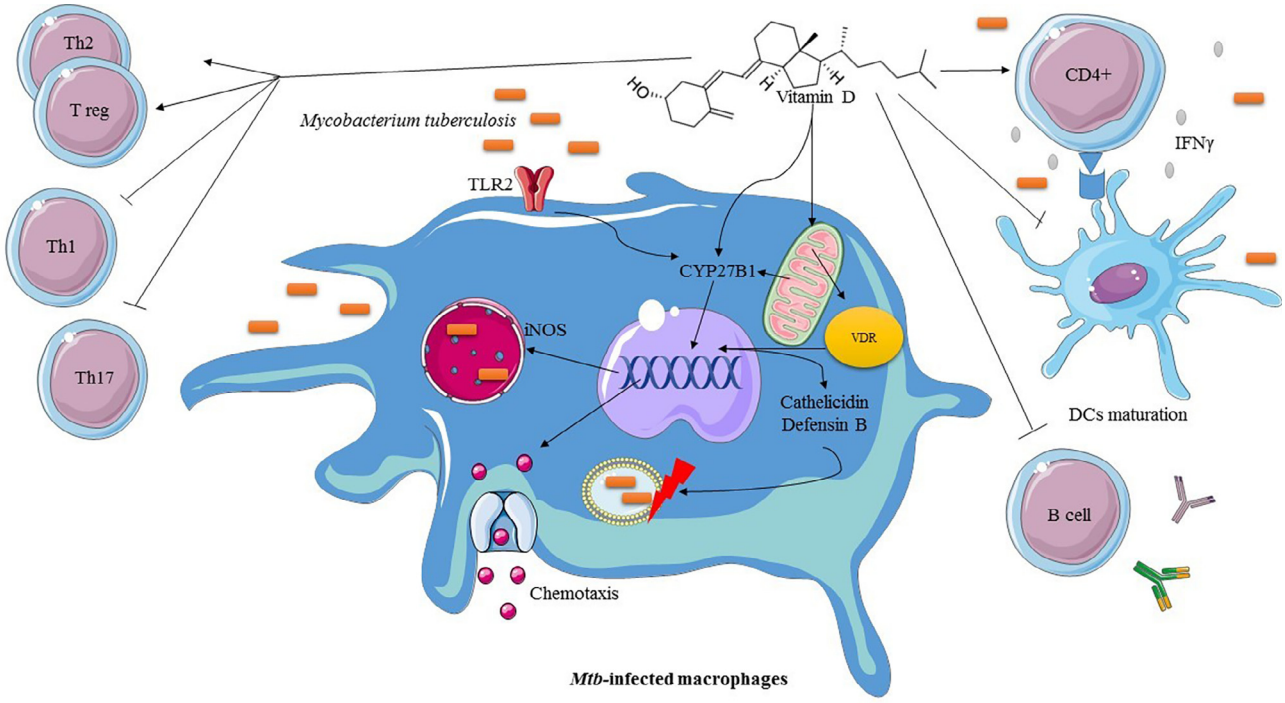

Fig. 1. The crucial role of vitamin D in the immunopathogenesis of TB. Vitamin D has immunomodulatory effects on the immune-system, so that it suppresses Th1, Th17, B cell as well as DCs maturation. However, it also stimulates the proliferation of T regulatory (T reg) cells, which in turn inhibit the excessive T cell-mediated immunity and tissue damage. In the other hand, it also has a specific receptor on the macrophages, vitamin D receptor (VDR). After the binding to the VDR, vitamin D triggers the processes such as the production of natural human antimicrobial peptides (AMPs), nitric oxide synthesis and chemotaxis to provoke immune response for clearance of *M. tuberculosis* (*Mtb*).

Ethical Statement

Ethical Statement is not applicable for this manuscript.

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