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Editorial

The role of vitamin D in tuberculosis☆

Vitamin D deficiency is associated with the risk of tuberculosis (TB) infection [1,2]. Vitamin D deficient individuals have a greater susceptibility to developing TB [3] and worse disease progression if infected with TB [4,5]. The likely mechanism through which vitamin D may prevent or limit infection by *Mycobacterium Tuberculosis* is through the binding of the bioactive form of vitamin D (1,25-dihydroxycholecalciferol) to the vitamin D receptor (VDR), a polymorphic nuclear receptor that regulates the expression of genes important for immune function and involved in cytokine production [6–8]. The VDR is present in immune cells [9,10] and bronchial and pulmonary epithelial cells [11,12], and is up-regulated following the ligation of specific toll-like receptors (TLRs) during an antimicrobial response [13,14]. Through this mechanism, calcitriol induces several endogenous antimicrobial peptides [15,16], specifically cathelicidin LL-37 and β defensin [13,16], and suppresses matrix metalloproteinase enzymes that degrade the pulmonary extracellular matrix [17].

Though vitamin D was used to treat TB during the pre-antibiotic era, trials in recent years have continued to assess its role in the treatment and prevention of TB. A systematic review published this month in the Journal of Clinical and Translational Endocrinology by Sutaria et al. [18] evaluated the results from 21 randomized, controlled trials in order to assess: the relationship between low vitamin D status and TB, the link between VDR polymorphisms and TB susceptibility, and the role of vitamin D supplementation in TB treatment and prevention. Sutaria et al. concluded that: 1) individuals with TB had lower vitamin D status (lower serum levels of 25(OH)D [19]) than healthy, age-matched, and sex-matched controls, 2) people with certain VDR polymorphisms (BsmI and FokI) had increased susceptibility to TB, and 3) TB patients receiving vitamin D supplementation had improved outcomes in a majority of studies [18].

Similar to Sutaria et al. [18], our recent systematic review regarding vitamin D supplementation in infectious disease [20] found 9 of 11 prospective, controlled trials in TB patients to have at least 1 positive outcome in response to vitamin D therapy. Vitamin D supplements promoted anti-mycobacterial activity [21], improved clinical outcomes (improved weight gain [22,23] and decreased tissue involvement on imaging studies [22,23]), increased sputum smear and culture conversion [24,25], reduced inflammation [26], and increased mediators of anti-microbial activity (cathelicidin LL-37 [27] and IFN-γ [22]). However, these results were not necessarily primary endpoints in their respective studies or applicable outside of specific subgroups. Furthermore, other studies had negative results for many of the same endpoints, including no change to clinical measures (X-ray involvement [23,24,28], clinical severity scores [29] and weight gain [29]), IFN-γ transcription [21] and sputum smear and culture conversion [25,28–30].

The inconsistent results in these studies make it difficult to draw a unifying conclusion on vitamin D in TB treatment. Many factors, including those inherent to the studies themselves, in addition to those that impact study participants' response to vitamin D and vitamin D status, may obscure a relationship between vitamin D and TB. Primarily, these trials are limited by their inability to evaluate vitamin D alone as treatment for TB, as it would be unethical to withhold established antibiotic therapy from study participants. In addition, the dose and duration of vitamin D treatment necessary to optimize infectious outcomes is currently unknown, leading to high variability between the dose (20,000 IU [27] to 1,200,000 IU [22] cumulative doses), dosing interval (days [23,24,27,31] to months [22,28,29]) and vitamin D formulation (1 study used vitamin D_2 [21] and 2 did not publish the formulation [23,24]). Some of these strategies may have been sub-optimal, such as daily dosing strategies (large clinical trials have shown poor adherence to daily doses [32,33]) and the use of vitamin D_2, which is less effective at increasing serum 25(OH)D than vitamin D_3 at similar doses [34,35].

Beyond the variability inherent to the studies themselves, there is a wide variation in individual responses to vitamin D supplementation on 25(OH)D concentration [36,37]. Since the anti-mycobacterial response mediated by TLRs in macrophages is strongly dependent on 25(OH)D concentration [13], characteristics that influence the change in vitamin D status following supplementation, including baseline 25-hydroxyvitamin D (25(OH)D) concentration [38] and genetic polymorphisms of the vitamin D binding protein (DBP) [39] and VDR [40], could also influence the effects of vitamin D supplementation on TB infection in certain individuals.

For one, baseline 25(OH)D concentration, the key measure of vitamin D status [19], is inversely linked to the response to vitamin D administration [35,41]; vitamin D sufficient individuals achieve a lesser increase in 25(OH)D concentration with supplementation compared to deficient individuals [38]. Individuals who are more vitamin D sufficient than others in a study population, due to variations in factors that impact vitamin D status (time outdoors [42], body habitus [43], skin pigment [44], etc.), may have a blunted vitamin D response and change to infectious outcomes in some studies. The implications of this observation were seen in Salahuddin et al. [22], where only the vitamin D deficient subset of study participants experienced significant increases in IFN-γ production following vitamin D administration. This may also explain the negative results in Wejse et al. [29], the only study with a mean baseline 25(OH)D concentration >30 ng/mL. Alternatively, as suggested by Heaney [45], a physiologic response following vitamin D supplementation would only occur if

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25(OH)D levels increase through the range at which the desired physiologic effects occur. Thus, studies may not demonstrate improvement following vitamin D supplementation if participants' baseline vitamin D status falls outside the range in which effects on infectious outcomes are seen.

The vitamin D binding protein (DBP) is another major determinant to the free and total circulating 25(OH)D concentration [46]; it binds 85–90% of the 25(OH)D in circulation [47], increases the half-life of 25(OH)D as a vitamin D reservoir in circulation, and aids in reabsorbing vitamin D filtered in the kidney [48,49]. The race- and genetic-dependent variations in the DBP [50,51] center around 2 single nucleotide polymorphisms (SNPs) in the globulin-complex (Gc) gene [52] that have different affinities for binding 25(OH)D [53]. Thus, certain variants of the DBP may prolong the half-life of vitamin D in circulation more than others [54] and play a role in preventing vitamin D deficiency [55]. Furthermore, studies suggest that free or bio-available 25(OH)D (vitamin D not bound to DBP) is more reflective of true vitamin D status than total 25(OH)D, the typical measure of vitamin D status [56]; bio-available 25(OH)D concentrations significantly correlate with bone mineral density [57,58] and parathyroid hormone levels [59] while total 25(OH)D does not [57–59]. Measuring bio-available 25(OH)D and evaluating DBP polymorphisms may thus be necessary to reassess vitamin D status following vitamin D administration in infectious disease. Although not extensively studied in infectious disease, 1 study found Gc genotype to be associated with susceptibility to TB [60] while 2 others found DBP variants to impact outcomes in rheumatic fever [61] and human immunodeficiency virus (HIV) [62]. While these observations may be due to the impact of DBP variants on vitamin D status, DBP also appears to have a direct impact immune function, attenuating the effect of complement factor C5a, a chemotactic protein [63], and stimulating macrophage activity [64].

Variants of the VDR have also been found to affect vitamin D status [46,65], in addition to susceptibility to TB [66–68]. The ethnicity- and geography-dependent susceptibility and resistance patterns to TB appear to be linked to the varying prevalence of these polymorphisms in different populations [18]. Though these polymorphisms have been analyzed in relatively few studies, including only one prospective trial of vitamin D administration in TB [25], the VDR polymorphism appears to affect the efficacy of the vitamin D administered; Martineau et al. [25] only observed a significantly accelerated sputum conversion rate in TB patients receiving vitamin D supplementation when participants were stratified based on genotype of the TaqI polymorphism. Thus, not accounting for VDR variations in other studies may have masked the impact of vitamin D on TB.

Overall, future research on vitamin D supplementation will likely need to account for factors that contribute to variations in response to vitamin D supplementation. Better assessment of vitamin D status by measuring bio-available or free vitamin D in addition to vitamin D binding protein may add more information in determining vitamin D status of subjects. Classification of subjects by genotype variations in the vitamin D axis would also be of interest. However, determining these genetic variants may currently be impractical for clinical care or research due to cost. Stratifying future study populations by characteristics such as race, age, health status, baseline vitamin D status, and skin pigment in order to create a cohort with a more homogenous response to vitamin D supplementation may be necessary in order to determine effective dosing strategies and to observe a clearer association between vitamin D and infectious diseases like TB.

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