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Review

Vitamin D status, receptor gene polymorphisms, and supplementation on tuberculosis: A systematic review of case-control studies and randomized controlled trials☆

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ABSTRACT

Objective: To investigate the impacts of vitamin D status, supplementation and vitamin D receptor (VDR) gene polymorphisms on tuberculosis (TB).
Methods: We conducted a systematic review of published studies pertaining to case–control and randomized-control trials from 2002 to 2014 using the PubMed database.
Results and conclusion: Individuals with TB have lower vitamin D status than healthy individuals. Some VDR gene polymorphisms are associated with increased susceptibility to TB while others may not. Supplementation with vitamin D leads to improved clinical outcomes. However, further studies with a larger patient population and different ethnicities are needed to confirm these effects.

Introduction

Tuberculosis (TB) remains a great burden throughout the world to this date. According to the latest World Health Organization data, an estimated 8.6 million individuals developed TB and 1.3 million died as a result of this disease in 2012. The majority of these cases occurred in South-East Asia (29%), Africa (27%), and the Western Pacific (17%). India and China accounted for 26% and 12% of the total cases, respectively. Furthermore, an estimated 1.1 million of the 8.6 million individuals who developed TB were also HIV-positive [1].

Vitamin D has been known to play an important role in bone health for almost a century [2]. However, the extra-skeletal roles of vitamin D have only received attention during the past two decades, which includes vitamin D's role in human innate immunity [3]. This particular role of vitamin D is especially important in the body's defense against tuberculosis through its action on enhancing macrophage-mediated eradication of *Mycobacterium tuberculosis* [4]. Vitamin D, either endogenously produced (vitamin D_3) or ingested (vitamin D_2 or vitamin D_3), must be activated in order to produce its effects (Figure 1) [5]. Upon entering the bloodstream, vitamin D is delivered to the liver, where it undergoes the first hydroxylation to become 25-hydroxyvitamin D (25(OH)D), the main circulating form of vitamin D. From the liver, the 25(OH)D travels to the kidney, where it undergoes another hydroxylation to become 1α,25-dihydroxyvitamin D (1α,25$(OH)_2$D), which is the active form. Upon undergoing the second hydroxylation, vitamin D is now able to regulate transcription of genes throughout the body. However, new evidence has been accumulated indicating that 25(OH)D and 1α,25$(OH)_2$D can be synthesized in tissues other than the liver and kidneys, respectively [5–7].

It has been shown that vitamin D deficiency [8] (serum 25(OH)D level <20 ng/mL or <50 nmol/L) and insufficiency [8] (serum 25(OH)D level <30 ng/mL or <75 nmol/L) are associated with a higher risk of active TB [9], suggesting that low serum 25(OH)D levels may also lead to prolonged clinical course of the disease if not corrected. Therefore, it is appropriate to surmise that individuals with higher levels of circulating 25(OH)D are associated with better

Abbreviations: TB, tuberculosis; 25(OH)D, 25-hydroxyvitamin D; 1α,25$(OH)_2$D, 1α,25-dihydroxyvitamin D; VDR, vitamin D receptor; WT homo, wild-type homozygous; HT, heterozygous; VR, variant recessive; TST, Tuberculin Skin Test.

Conflicts of interest: None declared.

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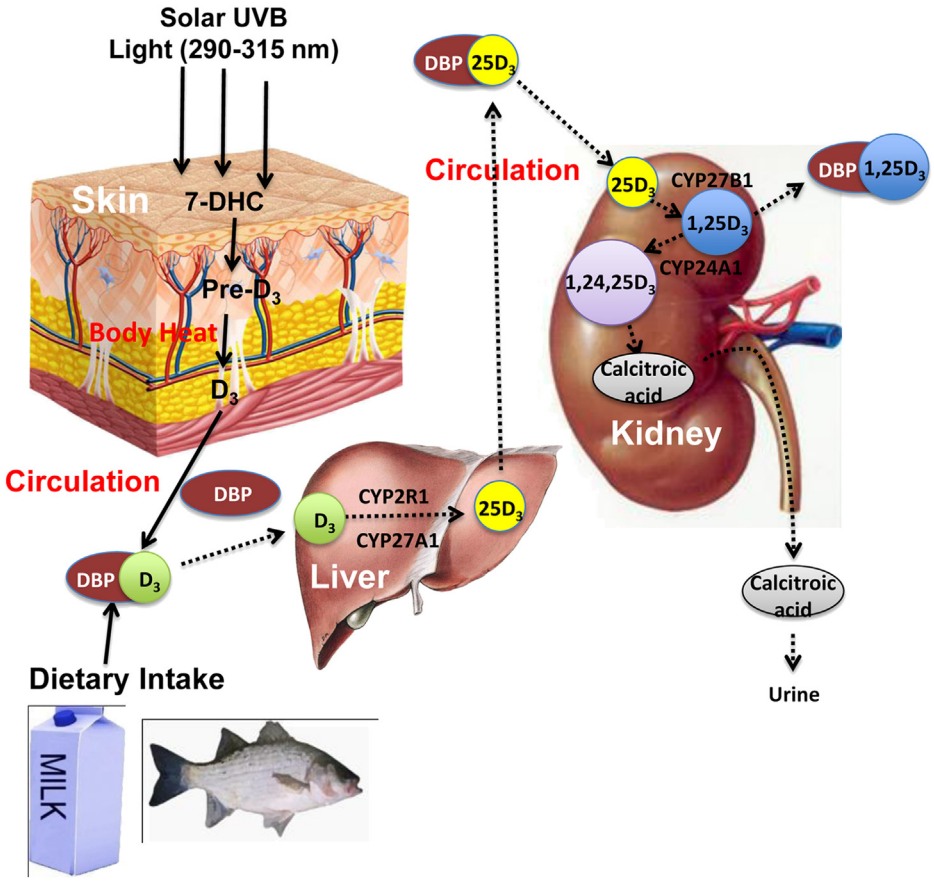

Figure 1. Photosynthesis and cytochrome P-450 enzyme-dependent metabolism of vitamin D_3. Humans receive most of their vitamin D requirement from the exposure of their skin to sunlight while a minor portion may obtained from dietary sources, such as fortified milk and oily fish. Upon exposure to ultraviolet B wavelengths between 290 and 315 nm, 7-dehydrocholecalciferol (7-DHC) in the skin is photolyzed to form a 9,10-seco-sterol pre-vitamin D_3 (Pre-D_3), which undergoes a heat-dependent isomerization to form vitamin D_3 (D_3). D_3 produced is specifically translocated by the vitamin D-binding protein (DBP) into circulation and then to the liver for hydroxylation at carbon-25 to form 25-hydroxyvitamin D_3 ($25D_3$) mainly by two cytochrome P-450 enzymes, CYP2R1 and CYP27A1. Synthesized 25D is then transported to the kidneys after binding to DBP in the bloodstream. In the kidneys, $25D_3$ is hydroxylated in the presence of CYP27B1 to 1α,25-dihydroxyvitamin D_3 ($1,25D_3$), the active form of vitamin D, which serves as a hormone to regulate a variety of cellular functions in other organs, or acts inside the kidneys in an autocrine and/or paracrine fashion. $1,25D_3$ is hydroxylated further by CYP24A1 at carbon-24 to form 1α,24,25-trihydroxyvitamin D_3 ($1,24,25D_3$). The hydroxylation at carbon-24 by CYP24A1 is the first step of 1,25D catabolism to terminate its actions, which leads to the formation of calcitroic acid, a water soluble metabolite, and excreted into the urine.

outcomes with regard to TB, as reported in a previously conducted systematic review and meta-analysis of seven observational studies [10].

Along those lines, it can be assumed that increasing vitamin D intake would help protect against TB, but in reality this is not always the case. Vitamin D mediates its effect on the innate immune system via the vitamin D receptor (VDR) [Figure 2]. Upon binding to $1\alpha,25(OH)_2D$, the active form of vitamin D, or its analogs, the VDR complex moves into the nucleus where it regulates expression of genes. Among its effects includes increased synthesis of components of the innate immune system, such as cathelicidin, which plays an important role against mycobacterial infections, as well as other antibacterial, antimycobacterial, and antiviral molecules [3,4]. Autophagy, the digestion of intracellular macromolecules and inclusions, is another important cellular function promoted by the activated VDR [3,4]. This is a particularly important function involved in clearance of intracellular pathogens, such as mycobacteria, as well as neoplastic cells. The activated VDR also plays a role in regulating the adaptive immune system by inhibiting lymphocyte proliferation and reducing production of pro-inflammatory cytokines to prevent excessive responses [11]. It has been previously shown that VDR gene polymorphisms exist [12], with some polymorphisms mediating stronger downstream effects than others. As a result, vitamin D's effect is dependent on the genotype of these receptors. As shown in several previous studies, certain VDR polymorphisms confer increased resistance to TB, while others make their hosts more susceptible [13,14].

Since TB has long been a burden throughout the world, many different treatments have been formulated and tested with varying results, including vitamin D. Several lines of evidence have led to the use of this seco-steroid. Starting back in 1848, physicians at the Royal Brompton Hospital in London reported that patients with consumption, an earlier term for TB, had a higher disease arrest (18% vs 5%) and survival (81% vs 67%) rate when cod liver oil was added to the standard therapy regimen [15]. This finding clearly suggested that vitamin D could be used in anti-TB therapy as it was well-known that cod liver oil contained high concentrations of vitamin D, and was the source where vitamin D was discovered and named by McCollum EV in 1922 [16]. Further implication of the usefulness of vitamin D in treating TB came from the studies using heliotherapy during the period between 1928 and 1929 by Howson [17], Mekie [18], and Rollier [19], and more recently by Hobday [20], Sabbatani [21], Willis et al. [22], and Ralph et al. [23]. The connection of sunlight exposure, vitamin D and chronic diseases has been extensively discussed [24]. After the discovery of vitamin D and after pure ergocalciferol (vitamin D_2) was available, a case report from 1947 notes its oral use in the successful treatment of a woman with cutaneous tuberculosis [25]. This highlights the fact that the