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Impact of vitamin D on infectious disease-tuberculosis-a review

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SUMMARY

Vitamin D, a fat soluble vitamin, is well known for calcium homeostasis. In recent years, many researchers have suggested that vitamin D performs multiple functions extending far beyond mineral homeostasis. The vitamin D synthesis machinery and related receptor have been reported in multiple tissues, where they play a key role in immune system modulation. Deficiency of vitamin D is not linked only with rickets or osteomalacia but with many other infectious and metabolic disorders. Emerging evidences suggest the relation of vitamin D deficiency in establishing tuberculosis. High prevalence of vitamin D deficiency in pulmonary TB patients indicates that vitamin D is a risk factor for the development of active tuberculosis. Therefore, maintaining vitamin D status in TB patients might be helpful to control tuberculosis. The level of vitamin can be maintained in reference limit by changing life style and use of multivitamin supplements. This review outlines the role of vitamin D in infectious diseases like tuberculosis and also effect of supplementation on treatment of TB; however, more studies are needed due to the clinical changes observed in patients with tuberculosis after vitamin D supplementation.

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Contents

1. Introduction

Vitamins are substances required for the good health but these are not synthesized in the human body. While cholecalciferol is called a vitamin, and it actually function as hormone. The discovery of vitamins is a breakthrough in the understanding the relationship between diseases and health [1]. Vitamin D also known as sun shine vitamin was first identified as a vitamin early in the 20th century. Discovery of vitamin D is linked with studies on rickets; in 1920's vitamin D was identified as a preventing agent against rickets [2]. Vitamin D is well known for calcium absorption and to maintain bone mineral dentistry. The importance of vitamin D for the human health and its potential beneficiary effects on the health have been established by a lot of research work in the past decade. From different epidemiological studies it has been evident that vitamin D plays a crucial role in several other physiological processes including cellular differentiation and proliferation, immune regulation, central nervous system function and cardiovascular health [3–5]. Beside its effect on calcium and phosphorus homeostasis vitamin D is also involved in providing immunity against microbial pathogens. Role of vitamin D in auto immune and metabolic disorders has also been established in many studies. Many research groups tried to establish the role of vitamin D in management and fighting against TB [6,7]. For this review article key words including vitamin D, tuberculosis, relationship of vitamin D with Tuberculosis, antimicrobial effect of vitamin D and guidelines for supplementation of vitamin D in Tb patients have been used from different data sources including google scholar, pub med and web of science.

2. Metabolism of vitamin D

Regardless of its source, either sunlight or diet it must undergo two hydroxylations, one in liver and one in kidney before it becomes active hormone. Vitamin D once in the body bind with vitamin D binding protein (VDBP) belongs to Gc family proteins and also known as Gc-globulin; these proteins bind with active and inactive vitamin D and transport it in circulation [8]. Inactive vitamin D or pre vitamin D3 with the help of DBP proteins first travels to liver where it undergo first hydroxylation by the cytochrome P450 enzyme vitamin D 25 hydroxylase (CYP2R1 and/or CYP27A1) to calcidol [9]. However, there are also some evidences of 25(OH)D extra hepatic hydroxylation. Calcidol or serum 25(OH)D is the major circulating form of vitamin D and have half-life of 2(OH) D is 15 days, serum 25(OH)D is the preferred form to measure vitamin D [9,10]. The

hydroxylation of 25(OH)D in liver is not regulated by the serum level of 25-hydroxylated vitamin D. The second hydroxylation occurs in kidneys, 25(OH)D travels to kidneys where it undergo second hydroxylation by the enzyme 25-hydroxyvitamin D 1-alpha-hydroxylase (25(OH)D-1αOHase or CYP27B1) [11]. Here the active hormonal form produced known as Calcitriol or 1,25(OH)D. The half-life of calcitriol is only 10–12 h much shorter than 25(OH)D [9,11]. Unlike liver hydroxylation the hydroxylation of 25(OH)D to its active form in kidneys is tightly regulated by calcium, parathyroid hormone, phosphorus and $1,25(OH)_2D$ levels [12]. Parathyroid hormone regulates synthesis of vitamin D that afterwards increases absorption of calcium from intestine for calcium homeostasis (Fig. 1). High levels of phosphate in blood cause down regulation of calcitriol. When phosphate levels are high, this causes synthesis of fibroblast growth factor-23 (FGF-23) in the bone, which inhibits synthesis of active vitamin D in kidneys [13]. In addition, 1,25(OH)2D itself regulate renal hydroxylation, the sufficient level of active metabolite induces the catabolic enzyme 1,25-dihydroxyvitamin D-24-hydroxylase (CYP24A1) that form 24,25-dihydroxy vitamin D in the kidney, further it is metabolized into inactive form calcitroic acid which is water-soluble and finally excreted by the kidney [12,13]. The 25(OH)D-1αOHase (CYP27B1) is not only present in renal tissue, this enzyme is also found in non-renal tissues including skin, brain, prostate, pancreas and macrophages, which result in some extent of extra renal activation of vitamin D. However regulation of non-renal synthesis is not well known.

Calcidol or 25(OH)D level is the major circulating form and 500–1000 times greater than $1,25(OH)_2D$ levels. Both metabolites once in circulation are mostly protein-bound. Predominantly 25(OH)D bound with vitamin D binding protein (VDB) and the small amount to albumin while a tiny amount of 25(OH)D is free, although the amount of free 25(OH)D varies but most of the studies suggest it is less than 1% [14–16].

2.1. Definition of vitamin D deficiency

At present there is no universal definition of vitamin D deficiency**.** Different studies used different cut off values of serum 25(OH)D to define vitamin D deficiency and insufficiency. In 2011, Endocrine Society Clinical Practice Guidelines states vitamin D deficiency when circulating 25(OH)D level is less than 50 nmol/l or 20 ng/ml (to convert from ng/ml to nmol/l, multiply by 2.49) [17]. According to a recent report regarding guidelines for vitamin D supplementation it is recommended to maintain level of 25(OH)D between 75 and 125 nmol/l for a healthy life. Daily dose of vitamin D range between 400 and 2000 IU/day is recommended for the pleotropic effects and the target concentration of vitamin D for this dose is 75 nmol/l. However, for bone centric guidelines recommended dose of vitamin D is 400–800 IU/day (age dependent) to achieve the target concentration 50 nmol/l [18]. However, in different cohort studies different definitions of vitamin D were used.

3. Role of vitamin D in public health

Vitamin D is traditionally known for bone mineralization but in last few years intensive research was done to explore other functions of vitamin D and D related metabolites. In human body most of the tissues other than liver and renal have receptors for 1,25(OH)D. A variety of cells also contain enzyme CYP27B1 that converts inactive major circulating metabolite into active form [11,19]. Among currently identified tissue and cells containing receptors for vitamin D are keratinocytes, osteoblast, active lymphocytes, β-islet cells, small intestine, prostate, colon, and most organs in the body, comprising brain, heart, skin, gonads, prostate and breast [20,21].

Macrophages and hematopoietic target cells can also synthesize $1,25(OH)_2D$ at inflammation site. Many epidemiological studies have shown inverse relation in vitamin D levels and incidence of various chronic and infectious diseases. Many researchers believe that reduced status of $1,25(OH)_2D$ in serum may be responsible for numerous chronic diseases, including autoimmune diseases, cancer, congestive heart failure, diabetes, hypertension and metabolic syndrome [22].

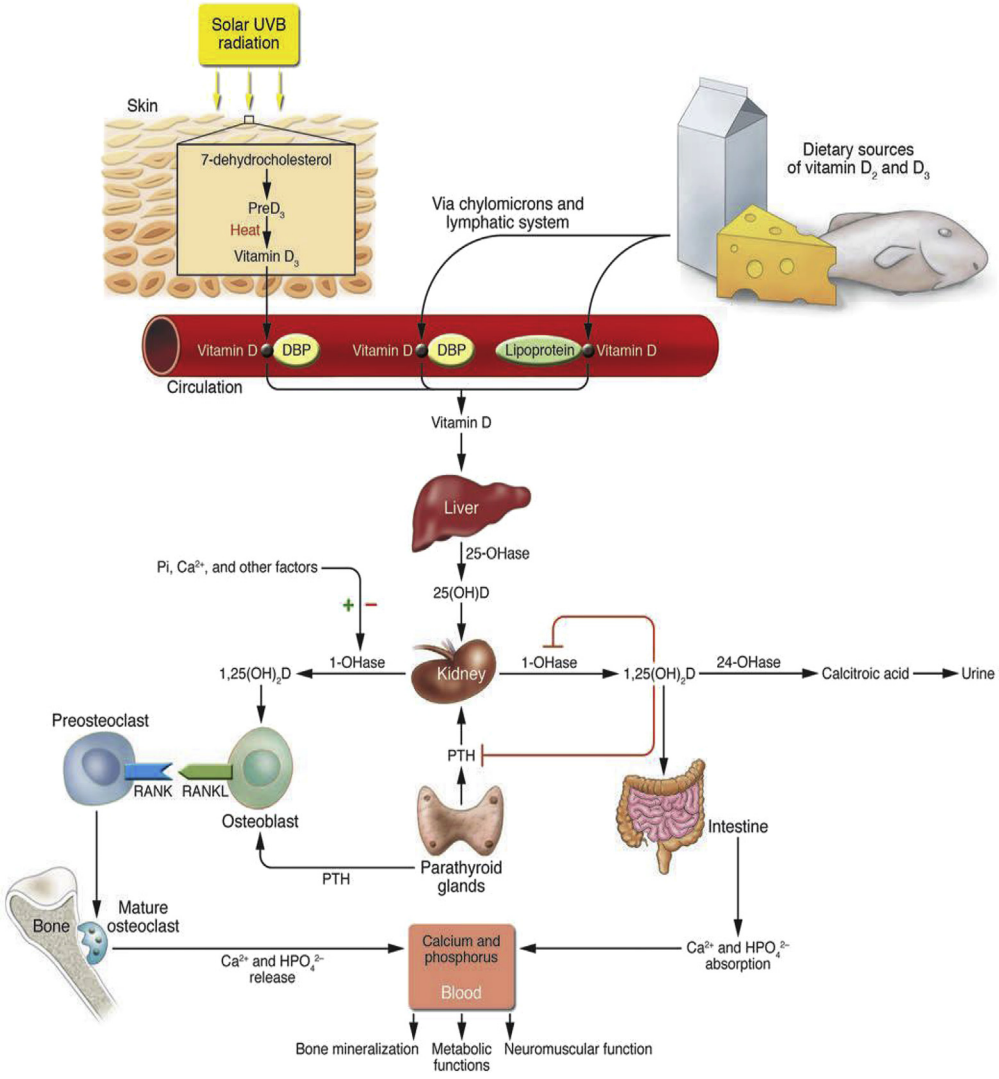

Fig. 1. Vitamin D synthesis and metabolism [17].

4. Vitamin D and infectious diseases

The relationship between reduced level of vitamin D and susceptibility to infectious agent is not new; it has been suggested many years before. The early observations were in rickets children who most likely experienced infections of the respiratory system called “rachitic lung” [23].

Few *in vitro* studies have also reported 5000 to 90,000 IU of vitamin D can inhibit growth of many important human pathogens like *Staphylococcus aureus*, *Streptococcus pyogenes*, *Klebsiella pneumonia* and *Escherichia coli*. In 1981 a British epidemiologist R.E. Hope–Simpson proposed some seasonal stimulus related with solar radiations which cause epidemic influenza [24]. Later Cannell and co-workers argue that association of vitamin D may be with common cold caused by rhinovirus and flu caused by influenza virus, they called it “Hope–Simpson stimulus” [25]. Furthermore Ginde and his colleagues found association of reduced levels of 25(OH)D in serum with high incidence of upper

respiratory tract infections [26]. Several other studies suggest that vitamin D associated with various infectious diseases for instance, tuberculosis, respiratory tract infections and influenza [27], chronic obstructive pulmonary disease [28], cystic fibrosis, sepsis and human immunodeficiency virus [29,30].

5. Tuberculosis: a global burden and impact on Pakistan

Tuberculosis is a global health problem present in all regions of world; it is the second leading infectious disease after HIV-AIDS that kills human, its being reported to cause more than two million deaths in a year. One third population across the world is likely to be infected with *Mycobacterium tuberculosis*. In 1997 WHO declared tuberculosis a global public health emergency. Since then, major efforts have been done to eradicate this disease. In 2013, almost 9 million people had TB and 1.5 million died from this disease. South-East Asia and Western Pacific Regions account more than half of the 9 million people who had TB, further one quarter was in the African Region, which also had the highest case notification rate and mortality due to TB.

Pakistan is a large and inhabited country where tuberculosis is a most important public health problem for a long time and a leading cause of morbidity. Unfortunately it has been the ignored in the past [31]. High rate awkwardly moved Pakistan from 8th to 5th rank in the list of 22 countries having the high burden of tuberculosis. Pakistan was ranked 8th in 2009 but now it is on 5th rank, indicating the high number of cases across the country [32].

In Pakistan incidence of drug resistant TB is also very high. Unfortunately Pakistan is at 4th rank in the list of high MDR-TB burden countries. In one report of WHO in 2010 it declared Pakistan alone contribute 69% of the MDR-TB in its region.

6. Vitamin D and tuberculosis

About 200 year ago, Champan first reported the administration of vitamin D content, cod liver oil in patients suffering with “Consumption” showed improved clinical outcome [33]. He also observed that patients supplemented with cod liver oil were exhibited most speedily, and showed noticeable improvement in appetite, general well-being and strength. He declared the cod liver oil the only remedy against tuberculosis or malady [34]. However, in this study no control group was observed and it was not confirmed the beneficiary effect of cod liver oil is due to its vitamin A content or vitamin D [34,35]. In 1859 the first sanatorium for TB patients was opened in Germany where patients infected with Mycobacterium were exposed to fresh air at high altitude in addition with good nutrients and advised to have rest [36]. Later heliotherapy (exposure of sunlight to enhance the synthesis of Vitamin D in the skin of TB patients) became a popular and common modality for the synthesis of Vitamin D [34]. The role of Vitamin D in the management of tuberculosis was then suggested by the Niels Ryberg Finsen who received Nobel Prize for Medicine in 1903. He showed short wave UV light (light from an arc lamp) was effective against cutaneous TB [37].

7. Vitamin D provides immunity against TB

First evidence of vitamin D providing immunity against *M. tuberculosis* was delivered in1986 by Rook and colleagues. They treated macrophages with 1,25D and found the growth rate of Mtb was reduced in macrophages treated with vitamin D [38]. The proliferation rate was further reduced after adding cytokine, IFN-γ, and CYP27B1 (stimulator of macrophage). In 2006, Liu and his colleagues stated in monocytes the expression of VDR and CYP27B1 has been increased by the Toll-like receptors 2/1 (TLR2/1) after sensing *M. tuberculosis* [39]. VDR is well known for trans activation of antimicrobial peptide called cathelicidin (LL37), transcriptional regulation of cathelicidin by active vitamin D has also been reported by others but Liu and co-workers showed the similar reaction of activation of antimicrobial peptide can also be regulated by intracarine activation of 25(OH)D. This power of intracrine activation by CYP27B1 was also achieved *in vivo*; from infected bovine mammary glands some infected cells were and expression of CYP27B1 was compared with other cells from a mock infection. High expression of CYP27B1 was observed in infected cells. In another study serum 25(OH)D was compared in samples of different donors having TB infection. It was observed individual's with lower level of

vitamin D also have lower induction of LL37 compared to those with sufficient level of vitamin D [40]. Similar findings were observed in serum samples before supplementation and after vitamin D supplementation. Cathelicidin or LL37 causes fusion of the phagolysosome, this fusion is necessary for the killing of *M. tuberculosis* [41] (Fig. 2).

VDR directly induce transcription of LL37 via VDRE (Vitamin D response element), VDRE is present in the promoter of the cathelicidin gene [42], but the activity of the VDR is not limited to the LL37, VDRE is also present in the promoter of γ-defensin 2 (DEFB4) [43]. This co-stimulatory mechanism activates NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). The induction of defensing protein has also been observed after the activation of NOD_2.

NOD_2 is an intracellular pathogen recognition receptor and is regulated in various cell types by 1,25D. The significance of this mechanism can be understand by the fact that ligand of this receptor (NOD_2) muramyl peptide is an important cell wall product in both gram positive and negative bacteria [43,44]. Therefore, it is possible that vitamin D can induce antibacterial response by many other routes.

Studies have also shown that $1,25(OH)_2D$ promotes autophagy in monocytes its response not only restricted to antibacterial proteins, but recent studies also indicate the role of vitamin D in promoting environment related to antibacterial activity. Vitamin D also generates reactive oxygen species (ROS) that have bactericidal effects. When monocytes were treated with *Mycobacterium* and vitamin D; they showed increased generation of ROS [45]. In mice, nitric oxide (NO) a well-known ROS is significant in fighting against bacteria, it is a thought that human may also share the similar kind of mechanism [46]. In another study, influence of vitamin D status on NO expression and killing of mycobacteria was established, when vitamin D deficient mice managed less well after infection with *Mycobacterium bovis* [47]. However, the exact proof of similar mechanism in humans is not obvious but in cultured monocytes $1,25(OH)_2D$ induced NO expression and suppress the proliferation rate of Mtb [46,47].

7.1. Prevalence of vitamin D deficiency in TB patients

Several studies in different populations have reported association of vitamin D deficiency and increased risk of tuberculosis. In a meta-analysis of Nnoahem and coworkers they concluded vitamin D deficiency is associated with high risk of tuberculosis [48]. Studies in Indian population revealed that

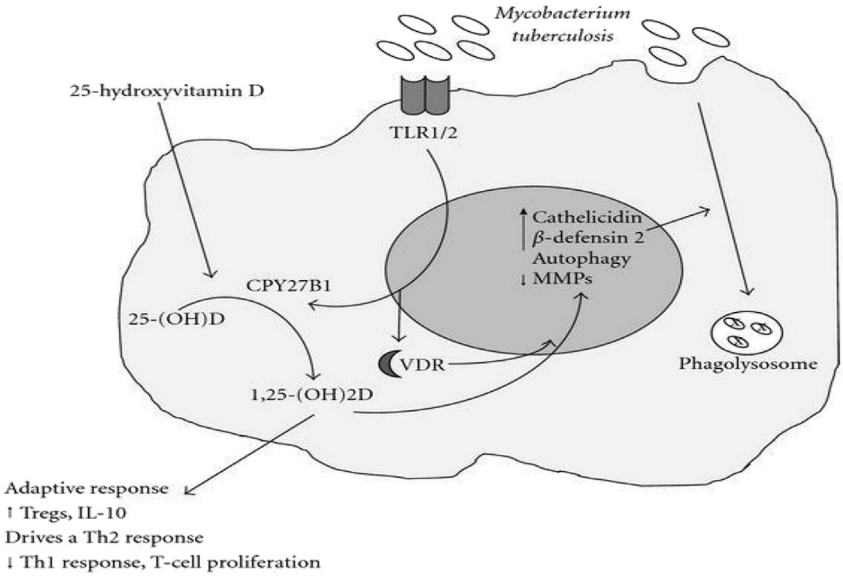

Fig. 2. Mechanisms for induction of vitamin D-mediated immunity against *Mycobacterium tuberculosis* [33].

lower level of vitamin D in Asian population has a role in high incidence of TB in this region [49]. Another study in Karachi (Pakistan) indicated low level of vitamin D in TB house hold contacts [6]. Other studies also supported vitamin D as a preventive agent against TB [7,48].

8. Vitamin D and polymorphism in its pathway

8.1. Vitamin D receptor (VDR)

Human vitamin D receptor is a nuclear hormone receptor encoded by the VDR gene located on chromosome 12q. It is the widely studied gene in vitamin D metabolism. VDR is a polymorphic gene and various SNPs have been reported. The most studied SNP in TB patients are Fok (rs2228570), Taq (rs731236), Bsm (rs1544410) and Apa1 (rs7975232). Many studies have been done to see the effect of any genetic variation in VDR gene on a person's susceptibility to tuberculosis; it was supposed that mutation in these four SNPs alter the effect of VDR that induce immune function. This hypothesis that genetic alteration of VDR is linked with TB infection was first studied by Bellamy and co-workers in 1999. In a case control study he established an association of Taq and tuberculosis in Gambian population. According to his study susceptibility of active TB is more in people with T allele [50]. Several other case control studies investigated association of polymorphism in VDR and susceptibility of tuberculosis. A meta-analysis of such studies reported association of Fok with tuberculosis; they suggest most people in Asia with ff genotype have more risk to develop TB infection however this risk of susceptibility of TB was not observed in Africans or Latin Americans. They also suggest recessive allele of Bsm is protective against TB [51]. Another meta-analysis in 2014 reported a potential impact of Vitamin D on TB, especially with regard to VDR polymorphism. They reported individuals with BsmI and FokI VDR polymorphisms showed higher odds of acquiring TB while those with the ApaI and TaqI VDR polymorphisms did not [52].

In contrast to numerous cross-sectional studies few cohort studies reported the influence of vitamin status and VDR polymorphism on anti-tuberculosis treatment. In another study it has been observed individual's with FF genotype of Fok and Tt genotype of Taq were fast respondent to anti-tuberculosis therapy and showed early sputum culture conversion [53], while these findings are inconsistent. Some other studies stated polymorphism in VDR genotype among TB patients have no effect sputum culture conversion time [51,53].

8.2. Vitamin D binding protein (VDB)

Vitamin D binding protein initially known as the group specific component (Gc-globulin) is highly expressed multifunctional protein encoded on chromosome 4. DBP has a molecular weight of 58 kDa and has multiple functions, physiological rage of VDB in plasma ranging from 300 to 600 μg/ml [6]. Once vitamin D and its metabolites are in circulation, it bound with DBP. This protein has high affinity with 25(OH)D and according to few reports approximately 99% of circulating 25(OH)D being bound with DBP. The half-life of DBP is short ranging from 2.5 to 3 days. The VDB gene is most widely studied gene in vitamin D metabolic pathway. More than 120 different alleles in human population have been identified in this gene. The two most studied SNPs in VDB are rs4588 and rs7466. Polymorphism in rs4588r results in a “C” to “A” that substitutes lysine (AAG) rather threonine (ACG). In rs7041 trans version of T to G results in glutamic acid (GAG) rather aspartic acid (ACG). There are three major electrophoretic protein variants in VDB based on these two SNPs. The three different isoforms of DBP arise as a result of polymorphism, are: group specific component 1 fast (Gc-1f), group specific component 1 slow (Gc-1s) and group specific component 2 (Gc12). These three different electrophoretic variations of DBP carry different combination of amino acid at these two SNPs (rs4588 and rs7041), GC-1f has threonine and aspartic acid (Thr-Asp); Gc1s has a threonine and glutamic acid (Thr-Glu) and finally Gc2 has lysine and aspartic acid (Lys-Asp), so six different diplotypes formed by these three proteins: 1f-1f, 1f-1s, 1s-1s, 1s-2, 1f-2, and 2-2.

Studies have indicated the effect of different genetic variants on binding affinity of 25(OH)D with DBP. It has been observed Gc1f have more affinity for 25(OH)D, Gc2 have the lowest affinity and Gc1s have intermediate affinity [51]. Arnaud and Constans demonstrated that the affinity of the Gc1f allele

was four times higher than that of the Gc2 allele and double that of the Gc1s allele [46]. Polymorphism of vitamin D binding protein and its influence on tuberculosis has been investigated in different population. No significant association between TB and DBP polymorphism was observed in Indian and Russian population. A study on Gujrati Asians living in London showed association between Gc2 allele and tuberculosis however this association depends upon vitamin D status. If serum vitamin D level is < 20 nmol/L this allele showed association suggesting intense vitamin D deficiency and presence of this allele may interact to increase the risk of developing of infection [54].

9. Vitamin D in prevention and treatment of TB

Role of vitamin D with tuberculosis is evident in many studies. However, confounding results are present. In last few years many studies based on clinical trials of adjunctive vitamin D have been done, some of them reported role of vitamin D is potent, however few of them reported null results. A meta-analysis reported no effect of vitamin D on the sputum culture time conversion though positive influence was observed in drug resistant patients of MTB for sputum culture conversion time [55] Observational studies in last 5–10 years strongly suggest relationship of profound vitamin D deficiency with susceptibility of tuberculosis and levels of vitamin D influencing sputum smear conversion time or sputum culture conversion time [56,57] On contrary, a systematic review in 2018 does not support the effect of vitamin D supplementation in pulmonary TB patients. Although vitamin D possess antibacterial effect against Mycobacterium but even then most of the clinical trials have negative results after vitamin D supplementation [58,59]. Another meta-analysis suggest similar results with no effect on sputum smear or sputum culture conversion time after supplementation but proportion of conversion of sputum conversion is enhanced by high levels of vitamin D [60].

In conclusion, a strong relationship is present between level of vitamin D and pulmonary TB. The effect of sunshine vitamin is somewhat ironic. Vitamin D with anti-mycobacterial activity can be helpful in fighting against MTB and MDR-TB. This vitamin, which can speed up the treatment duration of tuberculosis, is of renewed interest and has potential clinical importance. Further research to establish an adjuvant therapy after adjusting the proper dose to combat tuberculosis and investigation of vitamin D mechanism at molecular level is required.

Conflicts of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yclnex.2019.02.003.

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