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Review Article

Vitamin D and Tuberculosis Patients

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Abstract

Tuberculosis (TB) is a global health problem. According to WHO report 9.6 million people suffered from this disease all around the world in 2014. Although antibiotics in the treatment of TB have decreased death rate, the possibility of drug resistance in these patients has been increased due to prescribing errors and the long period of treatment. There is evidence of vitamin D deficiency in TB patients. The prominent role of vitamin D in the activity of the immune system is well documented. Since vitamin D plays a role through its receptor on nuclei of monocyte/macrophages, so plasma concentration of vitamin D on one hand and the role of these receptors on the other are the factors that influence on the person's ability to respond against TB by acting on host immune system. The studies have shown that using vitamin D supplement is a safe method that has had an important role in the acceleration of the improvement of the radiological outcomes and sputum smear/culture conversion. Taking vitamin D supplements in TB patients with lack of this vitamin could be critical.

Keywords: *Tuberculosis; Vitamin D; Drug Resistance; Smear; Culture*

Introduction

About one-third of the world population is infected with *Mycobacterium tuberculosis*, but only one-tenth of them show clinical symptoms. It is compared with HIV in mortality rate in the world [1]. In spite of the fact that new drugs were developed in the last sixty years; controlling TB is still a big challenge. Using multiple antibiotics could potentially create problems such as drug resistance, expensive treatments and side effects [2]. which encourage researchers to search for alternative remedies or use other auxiliary factors in the acceleration of treatment process to decrease drug resistance rates. In this field, the role of vitamin D is one of the most important factors in promoting host immune system [3] which has drawn the researchers' attention. The possibility of drug resistance in TB patients is very high because of the plurality of prescribed drugs (Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol), long treatment period (at least six months) or stopping treatment [4].

The active form of vitamin D (1, 25$(OH)_2$ vitamin D3) inhibits the intracellular growth of the bacteria, through inducing production of the antimicrobial peptide, cathelicidin, and helps to the autophagy of macrophages which have been contaminated with *M. tuberculosis* [5]. According to *in vitro* evidence, the active form of the vitamin D inhibits the bacteria replication within macrophages by stimulating the immune system [6]. In addition to plasma concentration of vitamin D, vitamin D receptor (VDR) gene polymorphisms affect receptor

activity and other following targets. Therefore, awareness of host genetic factors, especially polymorphisms in VDR gene has great importance in determining susceptibility or resistance of TB [7]. The aim of this study is investigating and reviewing existing information on the effect of plasma vitamin D concentration and its receptors on promoting the immune system of TB patients and the role of vitamin D in accelerating the improvement of TB patients for limiting bacteria transmission and clinical drug resistance.

Tuberculosis

TB is one of the worst infectious diseases in all around the world. According to a report from world health organization (WHO) 9.6 million TB cases were diagnosed in 2014 resulting in 1.5 million deaths [1]. This was mostly caused by *Mycobacterium tuberculosis* complex. TB mostly involves the lungs (pulmonary TB), however, other organs can be infected by this bacterium as well (extrapulmonary TB) [8]. TB is latent in approximately one-third of the world population having immune responses to bacteria antigen but only 10 percent of patients show clinical symptoms. Not only the bacteria but also other factors can cause this disease such as genetic factors, immunity system, nutrition, stress and life-style of the host [9,10]. At early stages of TB, symptoms like simple pulmonary infection, are not severe, so delays in diagnosis and treatment cause transmission of bacteria at this stage through coughing and sneezing [11]. There are many barriers to TB control and treatment such as drug plurality against TB, patients' mental tardiness because of the long period of drug use and continuation of it, lack of effective vaccination, the occurrence of resistant species, lack of awareness in transmission and disease progression [4].

Drug resistance in tuberculosis

Mismanagement of treatment such as inappropriate combinatorial drugs prescription, single drug treatment, incomplete treatment or in another word, not completing the course of prescribed drugs, and immunodeficiency problems are the main causes of drug resistance [12]. In this regarding, investigating the transmission process of drug-resistant strains, especially in immigrants from countries with high TB burden and researching on traditional treatments [13]. along with standard treatments can help us to eradicate the epidemic TB in the world. Also using supplements which are able to shorten the period of treatment, or at least decrease the power of transmission of this microorganism and improve the outcome of treatments can be effective.

Metabolism and physiological role of Vit D

Vitamin D is a fat-soluble secosteroid which is mainly synthesized in skin. The main part of this vitamin is synthesized by sunlight (UV-B) and some is provided through food [14].. Based on its receptor on macrophages nucleus, vitamin D is considered as a known human immune system modulator and so it can enhance cellular immune system [15]. Interactions between macrophages and *M. tuberculosis* antigens can cause the expression of 1- α- hydroxylase (CYP27B1), vitamin D receptors (VDR), and downstream targets of VDR such as cathelicidin, through activation of Toll-like receptor I &II [5]. 1-25-dihydroxy vitamin D (calcitriol) is able to promote innate immune system through inducing the production of cathelicidin and β-defensin2 as antimicrobial peptides. Reduction in the production of these peptides increases the susceptibility to infectious diseases such as TB [16]. LL-37 as the only member of the family of human cathelicidin, recruit monocytes, T cells, and neutrophils to the site of infection and has an immunomodulatory role [17]. Binding of this vitamin to VDR on monocytes increases the phagolysosome fusion and also activates nitrogen and oxygen mediators and antimicrobial peptides; this procedure can induce antimicrobial innate immune responses [18]. Calcitriol modulates adaptive responses directly via suppressing the Th1 by reduction of INF-γ, TNF-α, and IL-6 production and indirectly through reducing the expression of MHC II and IL-2 secretion by antigen presenting cells [19]. Also, calcitriol can play its role through the impact on the differentiation of T cells into regulatory T cells (Treg) or pro-inflammatory Th17 cells in adaptive immune system [20]. This vitamin is even able to increase the maturation of Th2 cells and also reinforces the producing of anti-inflammatory cytokines such as TGFβ1, IL-4, and IL-10 [21]. The proliferation of activated B cells is restricted by this vitamin and it results in the reduction of producing the immunoglobulins [22]. So, this vitamin has the power of suppressing the antigen-stimulated pro-inflammatory responses which are able to increase the mortality of patients with TB [23]. Based on the study conducted by Selvaraj., *et al.* [24] serum level of VDR protein significantly decreased in patients with pulmonary tuberculosis in comparison with normal cases and it was probably due to decrease in VDR gene expression in response to an increase in the

synthesis of 1,25-dihydroxy D [25]. Since cathelicidin is one of the direct targets of VDR, defects in VDR signaling can result in immune defects against *M. tuberculosis* and inflammation due to increase in inflammatory cytokines. Matrix metalloproteinases (MMPs), a family of zinc and calcium-dependent endopeptidases, regulate innate immune system responses by controlling the process of cytokines, chemokines, apoptosis and activating the antimicrobial peptides [26]. *M. tuberculosis* is able to induce expression of MMP-1, MMP-7 and MMP-10 genes in human macrophages and it can result in increased tissue damages [21]. It has been shown that circulating concentrations of MMP-9 are correlated with the severity of pulmonary TB [27]. Tissue inhibitors of MMPs (TIMP) restrict the activity of MMPs. TIMP-2 and TIMP-3 expression decreases in human macrophages and the expression of TIMP-1 is suppressed in pulmonary epithelial cells during infection by *M. tuberculosis* [28]. As it has been well documented, treatment of peripheral blood mononuclear cells by vitamin D results in attenuated expression of *M. tuberculosis* -induced MMPs such as MMP-7, MMP-9, and MMP-10 and on the other side increases the synthesis of TIMP-1 which has an important role in reducing the symptoms of disease and tissue damage caused by infection [21]. Thus, we can conclude that vitamin D leads to the activation of effective microbicidal mechanisms and on the other side, reduces the expression of inflammatory mediators with pathogenic effects [29]. Based on clinical observations, patients with low levels of 25-hydroxyvitamin D3 are more susceptible to tuberculosis and the risk of developing from infection phase to active disease is higher in these patients [30]. Therefore, vitamin D is able to prevent converting the latent TB to the active form of the disease and it can be used as prophylaxis in patients with latent TB [31].

Genetic determinants of susceptibility to TB

Vitamin D receptor (VDR) gene polymorphisms and tuberculosis

In addition to the serum level of vitamin D, the effective action of its receptors on the macrophages also plays a role as a component of the immune system regulator [15]. The biological activity of calcitriol in target cells is mediated through membrane vitamin D receptor (mVDR) or nuclear type (nVDR). Interaction with membrane types activates the intracellular signaling pathways, while connecting with nVDR regulates gene expression and microRNA [32]. The nVDR is genetically polymorphic. Four important gene polymorphisms (*Fok*I, *Bsm*I, *Apa*I, *Taq*I) have been documented for VDR gene. Polymorphisms in the 3' non-translated region (*Bsm*I, *Apa*I, and *Taq*I) is associated with stability of VDR mRNA, while polymorphism at translation initiation codon (*Fok*I) causes a three amino acids difference in the length of VDR and affects the final function of this protein [33]. Polymorphism of *Bsm*I (BB) and *Taq*I (tt) genotypes are probably involved in the regulation of protein expression of VDR [24]. *Taq*I (t) allele of VDR gene polymorphism leads to increased phagocytosis of *M. tuberculosis* in *in vitro* [34] and faster sputum culture conversion [35] in patients with Pulmonary TB. However, this association in South and West Asia has been in the form of increased risk of TB [36]. *Taq*I (T) allele leads to reduced production of tissue inhibitor metalloproteinase I (TIMP-I) that this decline in production is associated with an increase in the severity of the disease [37]. The allele of *Fok*I (f) of VDR gene polymorphisms leads to reduced transcriptional activity of VDR gene, reduced phagocytosis induced by calcitriol and, thus reduced sputum culture conversion in Pulmonary TB [34,35]. The results of a meta-analysis showed that having ff genotype compared with FF is considered to be a risk factor for TB among Asians. People with bb genotype had a lower risk for TB. On the other hand, no relationship was observed between VDR polymorphisms and susceptibility to TB among Africans and North Americas [38]. The results of another study of a series of 29 case-control studies, showed that *Fok*I (ff) significantly increases the risk of tuberculosis, while no relationship was observed between the other three polymorphisms with risk of tuberculosis. With respect to race, the heterozygous allele for *Bsm*I polymorphism and the homozygous allele for *Apa*I polymorphism caused a protective effect against TB in the European population [39]. The relationship between VDR gene polymorphisms and susceptibility or resistance to TB infection shows that the amount and type of impact can vary in different populations [36,39]. Moreover, a relationship has been reported between these polymorphisms and the development of multi-drug resistant in TB cases in northern India [40]. *Tak*I (tt) genotype protects Gambian population against TB infection [41]. Additionally, having Tt/TT genotype together with 25-hydroxyvitamin D deficiency in a population of Asians in South London is related to increased susceptibility to TB [42]. A recent study on the Paraguayans indigenous population showed that t allele protects people against

active disease but not against infection, while F allele was associated with a reduced risk of TB [43]. Another study refers to the role of tt genotype in increased susceptibility to TB and delays in the response to TB chemotherapy [44]. Although case-control analysis showed no relationship between VDR polymorphisms and pulmonary TB in the South African population, a cohort study on this population showed that *Apa*I (AA) and Tt/TT genotypes increase response to treatment. *Taq*I and *Fok*I genotypes of the VDR in patients with TB showed no difference in sputum culture conversion, but *Apa*I AA and *Taq*I TT/Tt genotypes compared with aa and tt genotypes had a faster time to sputum culture conversion [45]. According to results of a research in Peru, people with Tt genotype compared to those with TT genotype and people with FF genotype compared to those with non-FF genotypes showed a faster sputum culture conversion. In general, the likelihood of sputum culture conversion during TB treatment procedure was greater in Tt genotype than TT genotype which has been probably due to the effect of T allele on the inhibition of TIMP [35]. Heterozygous and homozygous recessive form of *Bsm*I was associated with an increased risk of tuberculosis in Asian and Middle Eastern population [46]. Although in our previous study [3] we showed that *Fok*I, *Bsm*I, *Apa*I and *Taq*I polymorphisms in VDR gene have no significant relationship with susceptibility to tuberculosis, the analysis of these polymorphisms based on plasma levels of vitamin D showed a significant relationship with regard to the *Fok*I-ff polymorphism. Thus, increasing the plasma levels of vitamin D in people with *Fok*I-ff genotype and low levels of vitamin D may protect them against tuberculosis. Differences between the results of VDR gene polymorphisms in various races and populations can probably be due to the plasma level of vitamin D which acts as compensation. The relationship between VDR polymorphisms and susceptibility to diseases such as TB can be regulated by vitamin D condition [47]. The use of higher doses of vitamin D and other vitamin D analogues in order to achieve better results in people with predisposing polymorphisms may lead to better outcomes.

Plasma levels of vitamin D after catching the TB disease

It is considered that there is a two way connection between plasma level of vitamin D and tuberculosis, This means that anti-TB drugs, such as isoniazid and rifampicin used in the treatment of TB, reduce the level of this vitamin in blood through various kind of mechanisms [48] and reduction of this vitamin in blood along with the immune system suppression results in intensification of the disease [49] The study on cultured THP-1 cells revealed that adding anti-TB drugs significantly reduced the expression of cathelicidin mRNA, which calcitriol was its trigger in treated macrophages. In addition, clinical studies on patients with TB who used 4 anti-TB standard drugs showed that there was a high prevalence of vitamin D deficiency in these patients [48]. Two major first-line drugs in the treatment of TB, isoniazid, and rifampin, and their influence on the content of vitamin D have been investigated. Isoniazid acts as an inhibitor of CYP450 and reduces both of vitamin D hydroxylation phases. This results in the reduction of the concentration of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D [50]. Rifampicin is a strong inducer of CYP3A4 which is a 24,25-hydroxylase of vitamin D and its activation results in inactivation of 25-hydroxyvitamin D [51]. However, the results also show that the concentrations of serum 25-hydroxyvitamin D during the first two months of treatment by anti-tuberculosis drugs have increased which is attributed to the improvement of patient's food diet due to the significant clinical improvement of patients in the first weeks of treatment. Another possible mechanism is the decrease of inflammatory stimuli during the process of starting of TB treatment, so 25-hydroxyvitamin D is less hydroxylated and serum level of this vitamin has increased [52]. It seems that the assessment of serum level of the vitamin D in TB patients at the first and also during the treatment process is essential.

Vitamin D as a supplement during TB treatment: from in vitro evidence to clinical studies

Most of the studies in this field have shown an inverse relationship between the concentration of 25-hydroxyvitamin D and the risk of active or latent TB [53]. Useful results obtained from *in vitro* studies on the immunomodulatory properties of vitamin D has created a great attention to the use of this vitamin as a supplement in the treatment of tuberculosis [54]. According to the animal model study [55] experimental bacterial burden induced by *M. tuberculosis* among mice with diet rich of vitamin D3 and the mice with a diet deficient of this vitamin was not significant. However, the inflammatory responses in the mice with diet rich of vitamin D were considerably weakened. It can be concluded that *in vivo* role of vitamin D is not to promote *M. tuberculosis* killing, but this vitamin suppress the immunopathol-

ogy created by the bacteria through hematopoietic cells. In other words, this vitamin as limiter of immunopathology associated with TB, protects the host. Related clinical studies (includes studies after year 1998) in which vitamin D had been prescribed as an adjunct therapy in patients with PTB are listed in table 1. According to a clinical trial on 96 patients with TB in the city of Ahvaz, Iran, performed in the years 2008 to 2009, in the intervention group, the patients received 800 IU daily vitamin D orally in addition to standard anti-TB drugs. Although the overall rate of improvement in the intervention group and the control group were not statistically different but increasing the serum level of vitamin D results in acceleration of TB bacilli clearance from the sputum of patients [56].

Reference; country; study design	Patients with TB	Dose of vitamin D	Adjunctive treatment	Therapeutic response	Adverse events
Morcos., *et al*. [60] 1998; Egypt; RCT	24 children	1000 IU vitamin D daily for 2 months	Isoniazid, rifampicin, and streptomycin	No significant changes in clinical response; radiological improvements	Not reported
Nursyam., *et al*.[57] 2006; Indonesia; RCT	67	250 µg vitamin D daily in the first six weeks	Anti TB drugs- not specified	Rapid radiological recovery; increased sputum smear conversion	Not reported
Wejse., *et al*. [66] 2009; Guinea-Bissau; RCT	365	Three doses of 100,000 IU vitD (total dose 300,000 IU)	Ethambutol, isoniazid, rifampicin, and pyrazinamide	No improvement in clinical outcome	Not reported
Alavi., *et al*. [56] 2010; Iran; RCT	96	800 IU daily vitamin D	Isoniazid, rifampicin, etanbutal, and pyrazinamide	Acceleration of TB bacilli clearance from the sputum of patients	Not reported
Martineau., *et al*. [53] 2011;UK; RCT	146	Four oral doses of 2.5 mg vitamin D3	Isoniazid, rifampicin, pyrazinamide, and ethambutol	Faster culture conversion in those with TaqI tt genotype	Eight serious adverse events in 7/70 and two adverse events in 2/70 who received at least one dose of vitamin D3; 3 patient discontinued vitamin D due to adverse events
Coussens., *et al*. [23] 2012; UK; RCT	95	2.5 mg doses of vitamin D (4 fortnightly doses) for 2 weeks	Anti TB drugs- not specified	Acceleration of sputum smear conversion; immunological impacts	Not reported
Salahuddin., *et al*. [64] 2013; Pakistan; RCT	259	600,000 IU of Intramuscular cholecalciferol for 2 doses one month apart	Isoniazid, rifampicin, ethambutol, and pyrazinamide	Greater weight gain and radiological improvements	Not reported
Ralph., *et al*. [58] 2013; Indonesia; RCT	200	50,000IU cholecalciferol 4 weekly	Rifampicin, isoniazid, pyrazinamide, and ethambutol	No effects on microbiological or clinical outcomes of PTB	Not reported
Mily., *et al*. [72] 2015; Bangladesh; RCT	288	5000 IU of vitD3 daily	Rifampicin, isoniazid, pyrazinamide, and ethambutol	Increased sputum culture conversion and clinical recovery	Not reported
Daley., *et al*. [73] 2015; India; RCT	247	Four doses of 2.5 mg	Anti TB drugs- not specified	No significant clinical outcome	Adverse events in 4/121
Tukvadze., *et al*. [74] 2015; Georgia; RCT	199	50,000 IUs (1.25 mg) thrice weekly for 8 wk and 50,000 IU every other week for 8 wk	Isoniazid, rifampicin, pyrazinamide, and ethambutol	Corrected vitamin D deficiency; no significant changes in clinical response	Not reported
Hassanein., *et al*. [65] 2016; Egypt; RCT	60	200,000 IU intramuscular vitamin D	Rifampicin, izoniazide, ethambutol, and pyrazinamide	Acceleration of sputum smear conversion; clinical improvements	Not reported

Table 1: *Clinical studies of Adjunctive Vitamin D in patients with PTB.*

In a study conducted in Jakarta [57] 250 μg vitamin D was prescribed daily in the first six weeks of treatment along with prescribed anti-TB drugs. In this study, rapid radiological recovery occurred in TB patients compared with placebo group that indicated the effect of this vitamin on the first group. Also, sputum smear conversion increased after 42 days (p = 0.002). Another similar study by Coussens., *et al.* [23] showed that the use of four 2.5 mg doses of vitamin D (four fortnightly doses), for 2 weeks along with anti-TB drugs in TB patients resulted in acceleration of sputum smear conversion. Also, it increased the number of lymphocytes induced by treatment and suppressed the response of inflammatory cytokines induced by *M. tuberculosis* antigens and decreased the number of monocytes [53].

Mean clinical outcome score did not show a significant difference between case and control group in treatment by supplementary 50,000IU cholecalciferol for 4 weeks along with anti-TB drugs; however, sputum smear conversion decreased from 69 to 59 percent in a group received vitamin D in comparison with the placebo group. Observed results probably were due to use of sub-therapeutic doses of vitamin D [58]. The other study conducted in Medwin hospital of Hyderabad in India on people with diabetes type II and TB showed that using 60,000IU vitamin D2 weekly and 1 gr calcium carbonate daily along with anti-TB drugs can reduce the time of sputum smear conversion from 8 weeks in placebo group to 6 week in group using vitamin D [59]. Although in a randomized clinical trial on 24 Egyptian children with tuberculosis [60] no significant changes in clinical response was found by administration of drugs such as isoniazid, rifampicin, and streptomycin in combination with a daily dose of oral vitamin D1000 IU, for 8 weeks between these trial groups, but rapid radiological improvement in these patients was recognized. Another clinical trial in Tanzania [61] showed that using multi-vitamin supplements including vitamin D reduced the mortality rate by 50% in patients affected by HIV and tuberculosis simultaneously during treatment procedure against tuberculosis. The use of 2.5 mg of oral vitamin D increased the innate responses to mycobacterial infection and patients with the lower baseline of vitamin D showed stronger *in vitro* effects after receiving ergocalciferol. Furthermore, this dose of vitamin D could recover the deficiencies of vitamin D in 6 weeks without causing hypocalcemia [62]. Also, similar results of lack of hypercalcemia were observed in a study recruited 23 patients with tuberculosis who used anti-tuberculosis drugs along with 5000 IU vitamin D2 for 10 weeks [63]. These may imply the safety of vitamin D consumption in the wide range of doses. In a study conducted [64]. on 259 Pakistanian patients with TB who were under treatment with anti-TB drugs 2 doses of 600,000 IU vitamin D administered intramuscularly resulted in accelerated clinical and radiological recovery in this group. IFN- secretion induced by *M. tuberculosis* increased following treatment with vitamin D supplementation in patients with vitamin D deficiency (< 20 ng/ml) in the beginning of treatment while this immune system improvement was not recognized in the patients with TB in the placebo group with vitamin D deficiency. The reason for lack of improvement in patients with vitamin D deficiency is attributed to the role of this metabolite in optimal activation of IFN- secretion. Also, the severity of disease in the treated group by vitamin D which was determined 12 months after treatment by chest radiography was lower compared to placebo group. Most recently Hassaneina., *et al.* [65] demonstrated that about 96% of patients with TB were vitamin D deficient in the beginning of the treatment with anti-TB drugs. Administration of single dose of 200,000IU vitamin D during treatment in a way that caused significant difference between concentration of this vitamin in the beginning of treatment and two months after beginning of treatment in patients with TB resulted in shortening the time of their sputum getting negative and acceleration of clinical improvement. Recently two randomized-controlled clinical trial conducted by Wejse [66] and Martineau [53] showed that after administration of three doses of 100,000IU vitamin D2 and four doses of 2.5 mg (400,000 IU) of 25- hydroxyvitamin D3 respectively, no significant difference in the rate of mortality and clinical result was recognized in comparison with placebo group. Wejse., *et al.* reported that serum level of 25-hydroxyvitamin D3 was not similar in the treatment and placebo group at the beginning of treatment and next months, and dosing regimen was shorter than to affect the serum concentration of this vitamin during follow up. Salahuddin., *et al*. [64] attributed the probable cause of the observed difference in response of 25-hydroxyvitamin D in their study compared with the results of the study conducted by Wejse, to the different baseline of 25-hydroxyvitamin D, polymorphisms of VDR and different doses of this metabolite. Although in the study by Martineau., *et al.* vitamin D didn't affect the sputum culture conversion in the study population, but in patients with tt genotype, the acceleration of this conversion was observed. It should be noted that based on numerous studies on different doses of this vitamin (calcitriol), it has been found that higher doses of this vitamin such as 250 μg daily instead of 125 μg had more influence on sputum smear conversion of TB patients [57,60,66]. The improvement of severe deficiency of vitamin D is effective in reducing the

risk of being infected by TB, but to eliminate the immunopathological effects, higher doses of this vitamin is needed [67]. Although there is not any defined program to correct vitamin D status, the study which was conducted in Medical Center of Boston University in united states on different populations including healthy, white, African-American, Hispanic, Asian and Native American adults showed that using more than 1000IU of vitamin D2 daily, as well as taking the same amount of D3, is able to maintain serum level of 5-hydroxyvitamin D [68]. Weekly program with higher doses of vitamin D can be a safe and effective method to accelerate improvement of plasma concentration of vitamin D [69]. According to a study on 120 children with latent TB it was found that using 25 hydroxyvitamin D3 (800 IU daily for 6 month) has resulted in 60 percent reduction in tuberculosis skin test conversion rate [70]. The inconsistency in the results of the use of vitamin D as a supplement along with anti-TB drugs in TB patients, despite of relative similarity in outcomes of the disease, is due to different reasons such as using different doses and duration of vitamin D supplementation, time intervals between doses and different measurement standards, the use of various forms of this vitamin, multiple follow up times, differences in the populations studied in terms of age, sex and race, the use of anti-retroviral drugs that reduces the absorption of vitamin D, genetic polymorphism of VDR, the baseline of 25-hydroxyvitamin D in serum and disorders in kidney or liver because these organs are vital for activation of vitamin D [71]. However, further studies are needed to optimize the dose and time periods of using this vitamin.

Conclusion

Considering the effects of vitamin D in enhancing the innate immune system and limiting the intracellular growth of *M. tuberculosis* and on the other hand, epidemiological studies about TB and the lack of vitamin D, have persuaded researchers to use of this vitamin as a supplement along with anti-TB drugs. Prescribing vitamin D as a supplement and safe method, in various forms along with anti-TB drugs, has had an important and dominant role in accelerating of radiological improvement and sputum smear/culture conversion, and these parameters are the critical points for recommending administration of this vitamin in the TB patients with vitamin D deficiency. Further studies on high-risk groups such as MDR-TB and XDR-TB is a recommended strategy as transmission of this infection to other people is a very critical issue.

Conflict of Interest

All authors declare that there is no conflict of interests.

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