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Research Article

Vitamin D and Tuberculosis in Children: A Review Vitamin D and Tuberculosis

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Abstract

Introduction: Despite the growing number of published studies, the role of vitamin D in the prevention or treatment of tuberculosis remains unclear.

Methodoloy: PubMed research for English articles published from 1915 to august 2013, using the terms "tuberculosis", "vitamin D", and "children".

Results: Current studies have shown relevant antimycobacterial immunostimulatory and immunosuppressive effects of vitamin D, but clinical trials of vitamin D supplementation in patients with active tuberculosis have produced contrast results. On the contrary, there are some evidences that vitamin D supplementation might represent a potential tool to prevent both infection and progression from latent to active tuberculosis. Only few studies evaluated this correlation in children.

Discussion: The potential link between tuberculosis and vitamin D levels is promising, because vitamin D supplementation of at-risk populations would be an affordable public health intervention, particularly in the light of the worldwide increase in tuberculosis notifications and drug-resistance. In this contest vitamin D might represent a new, affordable, easy to access and safe drug for the prevention and treatment ofTB. For all these reasons, well-done trials (focused on children, too)need to be considered a research priority, giventhepotentiallypublic health consequences of positive results.

Keywords: Tuberculosis; Vitamin D; Children; Review; Pediatric

Introduction

Traditionally, Tuberculosis (TB) has been classified as either latent infection or active disease. In recent years, this distinction has been questioned and the outcome of infection with *M tuberculosis* (Mtb) is now seen as a continuum ranging from asymptomatic to lethal disease [1-3]; (for clarity, in this review we still refer to latent TB infection (LTBI) and active TB).A number of factor are considered to influence the outcome of TB infection, such as Mtb virulence, infecting bacilli-load and the ability of the host (human) to control the invading bacilli. //In this last aspect, many factorsare currently under study for the development of new antimicrobial agents and adjunctive immunotherapies because they may positively or negatively influence the host-pathogen interaction, including: potential effect on T-helper-1 (Th1) antimycobacterial immune responses (eg, administration of interferon gamma) [4], upregulation of host innate (ie, macrophage) antimycobacterial immune responses (eg, vitamin D and nitric oxide) [5], decrease of immunopathology-mediated tissue damage because of excessive inflammatory responses (eg, corticosteroids) [6], and alteration of the metabolic shutdown state of TB bacilli to shift them out of a non-replicative, antibiotic-resistant state (eg, tumour necrosis factor α [TNFα] inhibitors) [7,8].There is hope that vitamin D might be implicated in some of these actions, posing promises on its use

as a potential adjunctive treatment in both active and latent TB [8] considering the necessity of new treatments due to rising drug resistance.In this review, we analyze current scientific literature to provide evidences about the relationship between vitamin D and TB, with a special focus on the pediatric population.

Methodology

We searched PubMed for articles published in English from 1915 to august 2013, using the search terms "tuberculosis", "vitamin D", and "children". We sourced further articles from personal databases and from references cited in papers identified through the research above.

Historical Aspects

The first clinical features of vitamin D deficiency have been described in 1651 [9]. In a chapter of the book, the authors described the autopsy of an infant with rickets that was really suggestive of TB mediastinal lymphdenopathy[10], suggesting a first potential association between vitamin D deficiency and TB.The earliest report of the benefits of vitamin D in TB patients published in 1848 describe disease arrest, weight gain and reduction in mortality in TB patients treated with cod liver oil compared to standard therapy alone [11].

In the 19th century, cod-liver oil was diffusely used in Europe to prevent childhood TB [12,13]. Although not a cure, a vitamin D related benefit in patients with TB was weight gain [13]. Nevertheless, the use of cod-liver oil in the treatment of TB fell during the early 20th century because of its unpleasant taste and the increased popularity of heliotherapy (sun exposure, introduced in the mid-1800s with the opening of a thermal treatment station in Slovenia [14] and phototherapy (exposure to an artificial light source) [8]. A great advance of exposure to sunlight as TB treatment was made by Finsen who used filtered sunlight in 1893 to treat cutaneous TB, and in 1901, created a carbon arc lamp that emitted (emitting) concentrated ultraviolet radiation–the first source of phototherapy [14]. For these discoveries, Finsen was awarded the Nobel Prize in Physiology and Medicine in 1903 [14]. In Italy, the San Camillo-Forlanini hospital, the historical sanatorium for the treatment of TB patients, was designated to provide with therapeutic fresh air and, more importantly, sunshineto sufferers.In the 1940s, several European physicians treated lupus vulgaris (cutaneous tuberculosis) with large doses of vitamin D2. Charpy, a French physician in 1945 reported successful results using the vitamin D2 to treat 20 patients with lupus vulgaris [15]. In London, a number of doctors had also widely used calciferol; they stated that their experience could "leave no room for doubt that calciferol in adequate dosage will cure a substantial proportion of cases of lupus"[10, 16].

The first reference of the successful treatment of pulmonary TB with vitamin D appeared in the Lancet in 1947 [17], but vitamin D was also used in the treatment of disseminated TB in 1948: a case report described success after oral administration of 100 000 IU cholecalciferol daily [18]. Nevertheless, despite these promising experiences, vitamin D was eventually replaced by antibiotics from the second half of the 20th century, until its recent return.

Biochemistry

Vitamins D2 and D3, which differ only by their side chains [19], have known physiological significance in humans, with both undergoing hydroxylation steps to become active hormones in calcium and phosphate metabolism [20].

The 2 forms of vitamin D can be obtained from the diet, but predominantly, vitamin D is obtained in the D3 form from the action of UV light on a vitamin D precursor in the skin [21]. Vitamin D3 undergoes two hydroxylation steps before becoming the active hormone: the first occurs in the liver and results in the production of 25-hydroxyvitamin D (25[OH]D) [22]; this form need to undergo a further hydroxylation step to become physiologically active in the form of 1-α,25-hydroxyvitamin D (1α,25[OH]2D) [23].

In the past, it had erroneously been assumed that this second hydroxylation was only performed in the kidneys; it is now clear that different cells, particularly innate immune cells (such as monocytes, macrophages and cerebral microglial cells) can produce active 1α,25[OH]2D [23]. Since the discovery of vitamin D receptors (VDRs) in macrophages, the role of 1α,25[OH]2D as an immune modulator has become increasingly apparent [24]. The actions of the hormone are mediated either through ligation with a nuclear VDR to regulate gene transcription, resulting in genomic responses, or via membrane rapid-response receptors [25]. Production of 1α,25[OH]2Din renal cells is under negative feedback control through induction by the hormone of 24-hydroxylase, which catabolizes25[OH]Das well as 1α,25[OH]2D. This feedback does not happen in macrophages, perhaps because macrophages express a splice variant of the 24-hydroxylase gene [26]. Thus, hypercalcemia is possible in granulomatous diseases that are characterized by macrophage activation, such as sarcoidosis and TB. This also means that hypercalcemia or also high levels of vitamin D, even if iatrogenic ally induced, does not inhibits the vitamin D effects on the immune system by a feedback process.

Vitamin D Measurement, Reference Ranges and Supplementation

Vitamin D status is calculated from the concentration of total 25[OH]D in serum. The methods used to detect this concentration, however, lack accuracy, reproducibility, and sensitivity [8]; for this reason, a vitamin D standardizationprogrammed is underway, using LC-MS/MS to standardize measurements of serum 25[OH]Dglobally [27]. In addition to drawbacks with measurement, there is no agreed consensus on the optimal level for vitamin D status in

adults and particularly in childhood [22,28-37]. In children, in fact, 25[OH]D levels below <25 nmol/L usually (but not always) manifest with clinical signs and symptoms of rickets [30]; however, children can be diagnosed with clinical rickets at higher 25[OH] D levels. Moreover, levels of 25[OH]D above the 25 nmol/L cut-offs may be associated with other poor health outcomes [38], such as upper respiratory tract infections [39] and bronchiolitis [40]. Therefore, whether the 25[OH]D concentrations regarded as sufficient for bone health are applicable to other vitamin D functions, such as immunity, remains unknown (Table 1)

25[OH]DConcentration	Vitamin Dstatus
<25 nmol/L	Deficient
25-50 nmol/L	Insufficient
50-75 nmol/L	Adequate
>75 nmol/L	Optimal

Table 1. Serum 25-hydroxyvitamin D (25[OH]D) classification in children.

$$1\ ng/ml = 2.5\ nmol/L$$

$$1\ \mu g = 2.5\ nmol/L$$

$$1\ \mu g = 40\ IU$$

shows most commonly used ranges for the definition of vitamin D cut-offs.

Strategies to optimize vitamin D status by oral intake in children and adults differ widely. The minimum vitamin D3 requirement is 400 IU/day across all ages [30,41], but treatment doses of 10000 IU daily, or up to 600 000 IU given as a one-off bolus in adults, have been proposed to treat deficiency in 2010 guidelines [21]. The US Endocrine Society proposes that infants and children aged 0-1 year require at least 400 IU per day of vitamin D and that children 1 year and older require at least 600 IU per day to maximize bone health [42]. In the UK and other European countries, vitamin D supplementation for all mothers of breastfed infants is recommended and in infants greater than 6 months who are taking less than 500 mL of formula milk per day [43]. US guidelines recommend, moreover, that supplementation directly to the breast fed (or partially breast fed) infant should commence in the first few days of life [21]. Nevertheless, compliance to these supplementation recommendations summarized in (Table 2).

Age group	Prevention	Treatment
Children 0-1 yrs-brest fed (exclusively)	400 IU per day	200,000 IU of vitamin D3 every 3 mo, 600,000 IU of vitamin D intramuscularly, repeat in 12 wk; 1000–2000 IU of vitamin D2 or vitamin D3/day with calcium supplementation
>6 mth who are taking < 500 mL of formulamilk/die	400 IU per day	As above
> 1 yr	600 IU per day	50,000 IU of vitamin D2 every wk for 8 wk
adults	400 IU per day	Depends on cause of deficiency

Table 2: Strategies to Prevent and Treat Vitamin D Deficiency, adapted from 44.

across countries remains poor [44]. Advances in the delivery of targeted drug systems have evolved to enable highly regulated site specific localization to subcellular organelles. Targeting therapeutics to individual intracellular compartments has resulted in benefits to therapies associated with these unique organelles. Endocytosis, a mechanism common to all cells in the body, internalizes macromolecules and retains them in transport vesicles which traffic along the endolysosomal scaffold. Targeting nanomedicine complexes to the endolysosomal pathway have serious potential for improving drug delivery for the treatment of lysosomal storage diseases, cancer, and Alzheimer's disease and, recently, also suggested for Vitamin D deficiency [45].

Immunomodulatory Effects Of 1α,25[OH]2D

1α,25[OH]2Dis known to have both immunosuppressive and immune stimulatory effects [46-50, 10]. Activation of macrophages via toll-like receptor [47] and interferon gamma [48], reversal of phagosome maturation arrest [49], and autophagy [48], which are all considered crucial components of the immune response to Mtb,require all the intervention of 1α,25[OH]2D.Contrastingly, 1α,25[OH]2D may also suppress the acquired immune response

by impairing clearance of Mtb through the downregulation of Th1 and Th17 cells-mediated responses, the generation of regulatory T cells [51], and by changing the balance in cytokine production towards an anti-inflammatory profile (down regulation of interleukin 6, TNFα, and interferon gamma) [52]. The T-cell suppression caused by 1α,25[OH]2D, combined with its immune-stimulatory effects, could be beneficial on one hand by mitigating immune-mediated tissue damage in active TB (as happens in TB meningitis (TBM)), on the other by promoting Mtbkilling through activated macrophage pathways.

Even though this in vitro role of 1α,25[OH]2D in pathophisiologic situations is well established, the effect of supplemental vitamin D on in-vivo immune responses to Mtbhas rarely been studied.Two studies have found contradictory results on the ability of vitamin D supplementation to enhance antimicrobial immunity measured by BCG-lux assay (a surrogate of innate immunity against Mtb, which measures the ability of whole blood to restrict bioluminescence of a reporter mycobacterium) [53] and interferon gamma secretion after stimulation of blood cells with mycobacterial antigens in vitro (acquired response) [54,55]. More recently, investigators have shown immunomodulatory effects of vitamin D therapy in 95 adult patients receiving antimicrobial therapy for pulmonary TB who were randomized to receive adjunctive high-dose vitamin D or placebo [56]. They found that Vitamin D hastened the resolution of Mtb antigenindependent and antigen-dependent hypercytokineaemia in pulmonary TB, in patients with both the ttTaqI polymorphism and with TT and Tt genotypes [57].

Vitamin D and TB: Observational Studies

To date, in-vivo studies in humans have been unable to clearly address whether vitamin D status affects susceptibility to TB infection, development of active disease from latency, or treatment response [8]. Moreover, most of described studies in current literature are cross-sectional and are therefore unable to determine whether low 25[OH]D levels are a result of, rather than a risk factor for, the disease process [8]. Already in 1985, Davies proposed that the increased rates of active TB in UK migrants from countries with a high incidence of LTBI coincided with the development of vitamin D deficiency, probably arising as a result of decreased sun exposure in the arrival country [58]. A meta-analysis of seven international studies has already showed that low 25[OH]D levels were associated with high active TB risk [10]. In particular, since Davies' observation, twelve case-control studies investigating the association between vitamin D status and susceptibility to active TB have been published. Of these, seven have reported a statistically significant association between vitamin D deficiency and susceptibility to active TB [59-65] three have reported a non-statistically significant trend towards such an association [66-68,10].In one study from Greenland [69], where consumption of sea mammal liver can produce high serum 25-hydroxyvitamin D concentrations, both high and low 25[OH]D concentrations were recorded in patients with TB compared with controls.Recently, a cross-sectional study in Malawi found that vitamin D deficiency is much more common in TB patients than non-TB patients, even when adjusted for other variables, suggesting that vitamin D deficiency may be associated with TB [70]. Low vitamin D levels have been recently described also in a young child with pulmonary and chest wall TB [71].

There is only one prospective study that provides evidence for the importance of vitamin D deficiency as an antecedent to development of active TB [72]. In this study, household contacts of TB patients in Pakistan (who did not receive preventive treatment) were followed up for up to 4 years. The risk of progression to active TB was higher among patients with the lowest25[OH]D concentrations. In particular, seven out of thirty contacts with baseline plasma 25[OH]D <17.5 nmol/l developed active TB during follow-up, compared with one of thirty-two with plasma 25[OH]D 17.5-33.5 nmol/l and none of thirty with plasma 25[OH]D >33.5 nmol/l. This association retained significance after adjustment for age and sex.Interesting findings have been recently described by Koh et al [73], who performed an ecological study that examined TB incidence in Birmingham from Dec 1981 to Nov 2009, using publicly-available data from statutory tuberculosis notifications, and related this to the seasons and hours of sunshine (UK Meteorological Office data). There were 9,739 TB cases over the study period, with a strong evidence for seasonality, with notifications being 24.1% higher in summer than winter (p,0.001). Winter dips in sunshine correlated with peaks in TB incidence six months later (4.7% increase in incidence for each 100 hour decrease in sunshine, p,0.001). Only 16% of total cases regarded children <18-year-old and a sub-group analyses for children was not performed. According to the authors, a potential mechanism for these associations included decreased vitamin D levels with consequent impaired host defense arising from reduced sunshine exposure in winter.

Similar findings have been found by Visser and colleagues[74], which retrospectively evaluated 189 consecutive children aged between 6 months and 13 years, diagnosed with 'definite' or 'probable' TBM at a tertiary teaching hospital in Cape Town (South Africa) between 2000 and 2005.A significant association was found between the monthly incidence rate of TBM and the number of hours of sunshine 3 months earlier (incidence rate ratioper 100 sunshine hours 0.69, 95% CI 0.54–0.88, P=0.002). This implies that a decrease of 100 sunshine hours/ month was associated with a 45.0% (=1/0.69) increase in TBM incidence 3 months later. Similar results were found for UVB radiation (IRR per 100 MED 0.75, 95% CI 0.61–0.91, P=0.003).While interesting and physiopathologically correct, these hypotheses should be confirmed by well-conducted done studies. Such a study should evaluate the rate of active TB development in patients with TB contacts, randomizing them to isoniazide (INH) plus placebo, INH

plus vitamin D, vitamin D plus placebo and no therapy.Obviously, such a study will be limitated by ethical issues, particularly in children.Importantly, none of the studies present in current English literature have evaluated this association in children with both active and latent TB (Table 3).

Study	Study design	Target	Findings	Comments
Morcos, 1998, [80]	25 mg vitamin D daily; placebo controlled trial	24 children aged 1.5-13 years of age with TB (13 extra thoracic, 7 intrathoracic, 4 mixed)	no statistically significant improvement on primary outcomes (body weight and resolution of symptoms)	Type of vitamin D (D2 v. D3) not reported
Nursyam, 2006 [78]	0.25 mg vitamin D per day for 6 weeks vs placebo (unclear if randomized)	Adults (range 15-59)	100% of vitamin D group had sputum conversion at 12 weeks after supplementation versus 76.7% of the placebo group	methodological problems (mode of tuberculosis diagnosis and randomization and masking processes not described). No children. Unknown whether differences at the end of therapy.
Martineau, 2007 [54]	100 000 IU cholecalciferol orally at 0, 2, 4, and 6 weeks vs placebo. Randomized, double blind, placebo controlled	Adult TB contacts	vitamin D had enhanced immunity to TB using the lux in vitro assays but did not affect IFNg production after ESAT-6/CFP-10 stimulation	No clinical effect evaluated. *No children included.*
Weise, 2009 [76]	100 000 IU cholecalciferol by injection at 0, 5, and 8 months vs placebo. Randomised, double blind, placebo controlled	Adult patients with pulmonary TB	No differences in clinical severity between groups and no differences in mortality 12 months later; non-significant reduction in 1-month smear positivity in the vitamin D group;	low vitamin D doses used; 60% of planned sample recruited; *no children evaluated*
Martineau, 2011 [77]	2.5mg vitamin D2 given at at 0, 2, 4, and 6 weeks vs placebo; Randomised, double blind, placebo controlled	Adult TB patients	Overall, no substantial benefi t from vitamin D; time to culture conversion was much faster in patients with TaqItt genotype of the TaqI VDR polymorphism	*No children evaluated*
Ganmaa, 2012 [81]	Randomized, double-blind, placebo-controlled study	Children (mean age 13 years)	Less (but not significant) TSTs conversion in children receiving vitamin D (P = 0.06), but almost all conversions occurred in those whose final vitamin D concentration remained <10 ng/mL (P = 0.05)	"booster phenomenon" for TSTs conversions? IGRAs not performed at follow up

Talat, 2012 [72]	Prospective observational study	Adults TB contacts	8/92 household contacts followed for 4 years developed tuberculosis, seven in the lowest, one in the middle, and none in the higher tertile of 25(OH)D; relative risk of progression to tuberculosis in lowest 25(OH)D group=5□1	Median 25(OH)D low overall; similar in patients with tuberculosis and contacts *No children evaluated*
Salahuddin, 2013 [79]	600,000 IU of im vitamin D3 for 2 doses vs placebo	Adult patients	After 12 weeks, the vitamin D supplemented arm demonstrated significantly greater mean weight gain, lesser residual disease by chest radiograph, >50% greater reduction in cavity size; increase in Mtb-induced IFN-g secretion; no statistically significant differences in sputum smear negativity and TB clinical score	authors unable to follow up patients to the end of treatment: are the benefits of vitamin D supplementation still evident at 6 months of therapy? *No children evaluated*
Koh, 2013 [73]	Observational study	Mainly adults (see comments)	TB notifications 24.1% higher in summer than winter (p,0.001).	Proposed mechanism: decreased vitamin D levels with consequent impaired host defence arising from reduced sunshine exposure in winter. Only 16% of total cases regarded children <18 year-old (age not specigied) and a sub-group analyses for children was not performed.
Visser, 2013 [74]	Observational study	189 children aged 6 months to 13 years	Significant association between the incidence rate of TBM and hours of sunshine 3 months earlier (IRR per 100 sunshine hours 0.69, 95% CI 0.54–0.88, P=0.002).	Retrospective study; information on vitamin D status or factors that might have influenced serum vitamin D levels (i.e. diet, body mass index, comorbidity, socio-economic status, personal exposure to sunlight).

Table 3. Summary of main studies on the association between vitamin D and Tuberculosis.

Vitamin D And TB: Clinical Trials

By contrast with the absence of prevention trials, administration of vitamin D in active disease has been widely reported.A review in 2006 of three trials and ten case series of treatment of patients with TB with vitamin D [8, 75] concluded that benefits were uncertain because the studies were of poor quality, often used vitamin D2, and did not examine the effect of vitamin D supplementation on outcomes.A number of trials have initially shown predominantly negative results, with only small effects (with unclear advantages in routine clinical practice) on composite clinical scores at 2-months of treatment and 12-month mortality [76] and time to culture negativity [77]. Nevertheless, the effects of 25-hydroxyvitamin D3 supplementation significantly improved sputum conversion rates in the subgroup of patients with the Taq1 25-hydroxyvitamin D VDR receptor polymorphism of the tt genotype [78]. Recent results showed more promising effects of vitamin D supplementation in TB than had previously been shown, such as substantial effects on clearance of acid-fast bacilli from sputum and radiographic improvement at 6 weeks [57,79], but no effect of the intervention was seen at 8 weeks in the first study.

Particular attention deserves the SUCCINT study which evaluated 250 adult patients randomized to receive either 600,000 IU of intramuscular vitamin D3 or placebo for 2 doses in adjunct to standard therapy and then assessed at 4, 8 and 12 weeks [79]. The

primary outcome variables were differences in weight gain and resolution of chest radiograph abnormalities. Secondary outcomes were differences in whole blood cell antigen-stimulated Interferon-gamma(IFN-g) responses, differences in sputum conversion rates and improvements in the TB score. After 12 weeks, the vitamin D supplemented arm demonstrated significantly greater mean weight gain (95% CI 1.99 - 3.23, p 0.009) and lesser residual disease by chest radiograph (p 0.004, 95% CI 0.15, 0.79) and 50% or greater reduction in cavity size (p 0.035); moreover, vitamin D supplementation led to significant increase in Mtb-induced IFN-g secretion in patients with baseline deficient 25-hydroxyvitamin D serum levels (p 0.021). On the contrary, there were no statistically significant differences in sputum smear negativity and TB clinical score. A limitation of this study is that the authors were unable to follow up patients to the end of treatment (6 months), therefore it is unknown whether the effects of vitamin D supplementation would be even more evident at 6 months and conversely or if the precocious differences seen at 12 weeks' therapy would not be seen at 6 months [80]. Moreover, the clinical advantage of faster chest X-ray improvements with no so much faster clinical improvement compared to the placebo group is questionable. A small placebo controlled trial on 24 children in Egypt reported no statistically significant improvement on primary outcomes (body weight and resolution of symptoms) after 25 µg vitamin D daily of oral vitamin D supplementation [80].

A pilot study in children (mean age 13 years) with latent TB suggested that it may still be a useful treatment for preventing progression to LTBI in endemic countries [81]. Ganmaa et al examined the effect of vitamin D supplementation (800 IU/day) on tuberculin skin test (TST) conversion. This double-blind, placebo-controlled study was conducted in 120 Mongol school children with mean baseline25[OH]D concentration was 7 ± 4 ng/mL(all with 25[OH]D < 25 ng/mL). At baseline, 16 children in the vitamin D group and 18 in the placebo group were TST positive (P = 0.7). Over 6 mo, TSTs converted to positive in 5 (11%) children receiving vitamin D compared with 11 (27%) receiving placebo (RR: 0.41; 95% CI: 0.16, 1.09; P = 0.06). Only one TST conversion occurred among those whose serum 25[OH]D concentration increased to >20 ng/mL, whereas 8 TST conversions occurred in those whose final 25[OH]D concentration remained <10 ng/mL (P = 0.05).Nevertheless, the high TST conversion rate may reflect a "booster phenomenon" observed after repeated TST, rather than acquisition of LTBI. Unfortunately, while interferon gamma release assay (IGRA) was performed at baseline in both groups, it was not performed at the end of follow up. This would have been an important data since a booster phenomenon with IGRAs has not yet described. Despite mentioned limitations, these findings appear particularly interesting (Table 3).

Conclusions

Despite a growing number of studies and ongoing researches on this topic, the role of vitamin D in the prevention or treatment of TB remains still unclear. Nevertheless, some evidence exists to suppose a correlation between vitamin D status and TB, but whether vitamin D is a key element couldplay a big roleto prevent the progression of latent to active TB or to treat either uncomplicated or complicated TB disease or simply as a potential important adjunctive therapy for the treatment of drug resistant TB needs to be clarified (Table 4).

Catergory	Current knowledge	Future perspectives
Vitamin D and Mtb immunology	Well characterized anti Mtbimmunostimulatory and immunosuppressive effects	Better clarification of anti-inflammatory role in Mtb infected tissues (potential steroid-like role in TB meningitis, but without side effects)
Vitamin D and Mtb immunology (in vivo)	Still inconclusive results; One study showed improved resolution of Mtb antigen–independent and antigen–dependent hypercytokineaemia in pulmonary TB	Better characterization on larger studies. Specific studies in young children.
Correlation between TB and vitamin D (observational studies)	Strong seasonality of TB disease (major after months of low sun exposure); Very low levels in LTBI and active TB patients.	Need for studies in children; Clarification whether low vitamin D levels are a predisposition to or a consequence of LTBI/ active TB
Vitamin D and LTBI	Low levels in LTBI patients. Small studies suggest a predisposition to acquire LTBI in high TB burden countries, also in children	Large, randomized, double-blinded, placebo-controlled, observational studies in high TB burden countries to evaluate TSTs/IGRAs conversions according to vitamin D status (potential affordable public health intervention, even in low income countries, for the prevention of LTBI)

From LTBI to active TB	higher risk of progression among patients with the lowest vitamin D concentrations	Larger studies need to confirm this important finding (potential affordable public health intervention, even in low income countries, for the prevention of LTBI). Specific studies designed for children
Vitamin D and uncomplicated TB (children)	Lack of studies. Probably not important due to good response to standard therapy in uncomplicated, drug resistant TB	Need for studies that address clinical, radiological and immunological differences between vitamin D and placebo groups at the end of 6 months therapy
Vitamin D and uncomplicated TB (adults)	Inconclusive results with short follow up. Probably not important due to good response to standard therapy in uncomplicated, drug resistant TB	Need for studies that address clinical, radiological and immunological differences between vitamin D and placebo groups at the end of 6 months therapy
Vitamin D and complicated TB (both children and adults)	Lack of studies. Potential important topic (e.g, anti-inflammatory steroid-like role in TBM, without side effects)	Randomized, double-blind, placebo controlled studies in extra-pulmonary TB (e.g. TBM)
Vitamin D and drug resistant TB (both children and adults)	Lack of studies. Potential important topic (e.g, lack of new drugs, side effects of new drugs)	Randomized, double-blind, placebo controlled studies in pulmonary and extra-pulmonary drug resistant TB

Table 4. Summary of current evidences and future researches needed on the link between TB and vitamin D.

summarizes current knowledge on the relationship between vitamin D and TB and shows future research questions that need to be answered in order to clarify the potential important role in TB prevention and treatment.Although methodological challenges of conducting such studies are great [82], we strongly support the need for these studies, which are certainly fundable and feasible. For example, the use of diagnostic test for latent TB to asses T cell response to Mtb might be influenced by Vit D status.

The potential link between TB and vitamin D levels is promising, as prevention strategy because vitamin D supplementation of at-risk populations could be a plausible and affordable public health intervention even in low income countries. Moreover, due to the growing number of TB also in high income countries [83] and the increase of drug resistant TB cases worldwide, vitamin D might represent a new, affordable, easy to access and safe drug for the treatment of complicated and drug resistant TB.Even though the questions seem far to be answered, the light is just at the end of the tunnel. The same light that could help future generations to go through a TB-free world and that deserve to be reached.

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