pagepress

Vitamin D and tuberculosis in children: a role in the prevention or treatment of the disease?

Danilo Buonsenso[1,2,3#], Davide Pata[4#], Arianna Turriziani Colonna[4], Vittoria Ferrari[4], Gilda Salerno[4], Piero Valentini[1,4]

[1]Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario "Agostino Gemelli", Rome; [2]Department of Basic Biotechnological Sciences, Intensive and Perioperative Clinics, Catholic University of the Sacred Heart, Rome; [3]Center for Global Health Research and Studies, Catholic University of Sacred Heart, Rome; [4]Institute of Pediatrics, Catholic University of Sacred Heart, Rome, Italy

[#]These authors contributed equally

Abstract

Despite the growing number of published studies, the role of vitamin D in the prevention or treatment of tuberculosis remains unclear. In this review we analyze current scientific literature to provide evidence about the relationship between vitamin D and TB, with a special focus on the pediatric population. While *in vitro* studies have shown relevant antimycobacterial immune-stimulatory and immunosuppressive effects of vitamin D, this has not panned out *in vivo* with active TB. On the contrary, there is some evidence that this tool could work as prevention – both against TB infection as well as progression from latent to active infection. However, only a few studies have evaluated this correlation in children. The potential link between tuberculosis and vitamin D levels is promising. If effective, vitamin D supplementation of at-risk populations would be an affordable public health intervention, particularly in light of the worldwide increase in identified TB cases and drug-resistance. Vitamin D might represent a new, affordable, safe and easy to access drug for the prevention and treatment of TB. For stronger evidence, considering the features of infection (relative low incidence of reactivation of latent infection in immunocompetent patients) we need clinical trials with large numbers of participants conducted in endemic regions with a prolonged follow-up time.

Correspondence: Davide Pata, Catholic University of Sacred Heart, Largo Francesco Vito 8, 00168 Rome, Italy.
Tel. +39.06.30154390.
E-mail: davide.pata01@gmail.com

Key words: Tuberculosis; vitamin D; prevention TB; pediatric TB.

Contributions: DB, DP, PV, contribution to concept and design of the paper; DB, DP, manuscript drafting; ATC, GS, data collection. All authors contributed to manuscript revision, read, and approved the submitted version, and agreed to be accountable for all aspects of the work.

Conflicts of interest: The authors declare no competing interests.

Ethics approval and consent to participate: not applicable

Received for publication: 6 October 2021.
Accepted for publication: 24 March 2022.

Licensee PAGEPress, Italy
Monaldi Archives for Chest Disease 2022; 92:2112
doi: 10.4081/monaldi.2022.2112

Introduction

Tuberculosis (TB) is distinguished into latent infection and active disease. However, the latest evidence overcomes this separation, and the spectrum of *Mycobacterium tuberculosis* (Mtb) infection encompasses a variety of conditions, from asymptomatic to fatal disease [1-4].

Several factors are believed to influence the clinical manifestations of TB infection, such as bacterial load, virulence, and host immune response.

Many processes are currently being studied for the development of new therapies capable of influencing the evolution from latent infection to active disease. New strategies are represented by enhancement of T-helper-1 (Th1) antimycobacterial immune responses [5], upregulation of innate immunity against mycobacteria (e.g., nitric oxide or vitamin D) [6], inhibition of inflammatory tissue-damaging immune responses (e.g., corticosteroids) [7], and metabolic shutdown of TB bacilli to a non-replicative state with increased sensitivity to antibiotic therapy (e.g., tumor necrosis factor α [TNFα] inhibitors) [8,9].

We performed this review of the current scientific literature in order to analyze the connection between vitamin D and pediatric TB infection.

Methods

We conducted a narrative non-systematic review of PubMed and Medline of English articles published from 1945 to 2020. The search MeSH terms were Tuberculosis AND Vitamin D AND children. We decided to exclude every manuscript that did not address our question. We organized the search and the description of the study results in the following sections: historical aspects, biochemistry, immunomodulatory effects, observational studies and clinical trials.

Historical aspects

The role of vitamin D in the host-pathogen interaction has been suggested in a series of studies, having a promising use in both active and latent TB [9-22]. The first clinical features of rickets were described in 1651 [23]: the autopsy of a child performed by the authors revealed the presence of TB mediastinal lymphadenopathy [24], describing a potential relationship between vitamin D deficiency and TB.

The first study regarding the advantages of vitamin D in TB patients was made in 1848: in addition to anti-tuberculosis therapy, patients were treated with cod liver oil, rich in vitamin D. They demonstrated weight gain, disease arrest, and a reduction in mortality compared to controls [25]; as a result, during the 19th century in Europe, children took cod liver oil to prevent tuberculosis [26,27].However, due to its unpleasant taste, cod liver oil was subsequently replaced by natural (heliotherapy) or artificial (phototherapy) exposure to sunlight [28].

Further advances in the use of heliotherapy for TB treatment were carried out by Finsen: in 1893 he treated cutaneous TB with filtered sunlight and, in 1903, he was awarded the Nobel Prize in Physiology and Medicine for his findings [28].

In 1934, the Carlo Forlanini hospital was inaugurated in Italy, a sanatorium for the treatment of TB patients which exploited also alternative techniques, as sun exposure and therapeutic fresh air [29]. In 1945, Charpy successfully treated lupus vulgaris (cutaneous tuberculosis) with vitamin D_2 [30]. Subsequently, vitamin D was used with success for the treatment of pulmonary TB [31] and disseminated TB [32].

Biochemistry

Vitamins D_2 and D_3, distinguished by their side chains [33], are involved in the metabolism of calcium and phosphate [34]. They can be acquired with food, but vitamin D_3 is mainly synthesized in the skin by the reaction of a precursor with UVB radiation [35]. Subsequently, vitamin D_3 must be converted into an active hormone: initially 25-hydroxyvitamin D (25[OH]D) [36] is formed in the liver, then it is converted into the active form 1-α,25-hydroxyvitamin D (1α,25[OH]$_2$D) with a second hydroxylation reaction [37]. This second reaction is carried out in the kidney, but recent evidence showed that this conversion may also occur in innate immune cells (such as monocytes and macrophages). Furthermore, via binding to a vitamin D receptor (VDR) exposed on macrophages, 1α,25[OH]2D is able to regulate gene transcription and play an immunomodulatory role [38-41].

Immunomodulatory effects of 1α,25[OH]2D

1α,25[OH]2D is able to stimulate the immune response both positively and negatively [42-46].

Among the processes involved in the immune response to Mtb are included: differentiation of monocytes, activation of macrophages *via* toll-like receptors [42], phagocytosis [43], maturation of phagolysosome [44], production of anti-microbial peptides (cathelicidin, ß-defensin 2, hepcidin). Each one of these needs the intervention of 1α,25[OH]2D. Moreover, Salamon et al. found that vitamin D3 can interfere with lipid metabolism in infected cells to the detriment of Mtb growth [47]. However, 1α,25[OH]2D is able to depress the immune response through the production of anti-inflammatory cytokines, the downregulation of Th1- and Th17-mediated responses, and the stimulation of regulatory T cells [48].

Afsal *et al*. showed that 1,25-(OH)2D3 can reduce the share of cytolytic molecules ($p<0.05$), decreasing inflammation and consequent tissue damage of the adaptive immune response [49].

This effect could be useful in TB meningitis (TBM), where immune-mediated damage occurs, while the killing of Mtb is promoted thanks to the immunostimulatory effect of the vitamin and the activation of macrophages [50]. The dynamic immunomodulatory effects of vitamin D_3 have also been recently confirmed by Gough and colleagues [51].

Although several manuscripts analyzed the role of 1α,25[OH]2D *in vitro*, studies investigating its effect on the immune response to Mtb *in vivo* are rare. Two studies examined the consequences of vitamin D supplementation on the innate and adaptive immune response to Mtb infection but obtained contradictory results [52-54]. Coussens *et al*. randomized 95 adult patients on anti-tuberculosis therapy for pulmonary TB to high-dose vitamin D or placebo [55]. In their study, the authors highlighted that the vitamin D group showed a more radical resolution of the antigen-dependent and independent cytokine storm in patients with TT and Tt genotypes and with the tt TaqI polymorphism [56].Recently, Reeme *et al*. performed an in vivo model (C3HeB/FeJ mice) in which dietary vitamin D supplementation attenuated advanced-stage Mtb-related disease, while not influencing bacilli load [57].

Vitamin D and TB: observational studies

Based on the *in vivo* studies available to date, it is unclear whether vitamin D levels could lead to susceptibility to TB infection, transition from latent infection to active disease, or treatment efficacy. Furthermore, most of the available studies are retrospective, thus unable to determine whether low levels of the vitamin are the result of or a contributing cause to TB infection [9-21].

First Davies *et al.* observed increased rates of active disease associated with low vitamin D levels in British immigrants, possibly due to less sunlight exposure [58]. In 2008 Nnoaham *et al.* performed a meta-analysis that correlated a high risk of active TB with low vitamin D levels [59]. In addition, Zeng e*t al*. reported in a meta-analysis of 15 studies that 25(OH)D levels below 25 nmol/L were associated with an increased risk of active TB [60]. Recently, Gou *et al*. confirmed, in a meta-analysis including 10 studies, the association between vitamin D deficiency and pediatric TB (OR, 1.78; 95% CI, 1.30-2.44; $p<0.05$) [61]. Consequently, starting with Davies' observation, several studies

were published evaluating the association between vitamin D concentration and active TB. Many of these manuscripts linked vitamin D deficiency to the onset of active TB [62-69], while 3 studies found no statistically significant association [11,70-72]. For example, in Greenland, where the assumption of marine mammalian liver, rich in 25-hydroxyvitamin D, is widespread, both high and low levels of 25[OH]D were reported in patients with TB compared with controls [72]. In Malawi, low vitamin D values were more frequently observed in TB patients with respect to controls, suggesting that vitamin D deficiency may be related to TB susceptibility [73]. In a recent paper we observed low levels of vitamin D in an infant with pulmonary and chest wall tuberculosis [74]. Talat *et al*. followed up the family contacts of patients with TB in Pakistan without subjecting them to a preventive treatment [75]. They observed that the risk of progression to active TB was higher among patients with concentrations of 25[OH]D <17.5 nmol/L (7 of 30 total patients with active TB), while no contact with 25[OH]D >33.5 nmol/L developed the disease. In a similar cross-sectional study conducted in Indonesia on a population of 178 under-five children with history of close TB contact, Yani at al. observed a significant association of latent TB with vitamin D status, exclusively in children less than 1 year of age [76]. Koh *et al*. [77], comparing the notifications of tuberculosis and the data from the UK Meteorological Office, carried out a study with the aim of evaluating the incidence of tuberculosis in Birmingham from December 1981 to November 2009. In particular, the authors noted the presence of a seasonality, with an increase of cases in summer rather than winter (p=0.001). Although a subgroup analysis was not performed for the pediatric population, they hypothesized that reduced sun exposure during the winter season (with a relative drop in vitamin D levels) altered the immune response and caused an increase in cases during the following summer. Similar findings were described in Israel during a 10-year study from 2001 to 2011 [78]. Visser and colleagues [79] retrospectively studied children with “definite” or “probable” TB in South Africa. The authors observed that a 100-hours decrease per month in the exposure to sunlight was associated with a 45% increase in the incidence of TB 3 months later (0.69, 95% CI 0.54-0.88, p=0.002). None of the various studies in the literature has ever evaluated these aspects prospectively. Indeed, these different hypotheses should be confirmed by studies considering the onset of active TB in close contacts randomized to isoniazid (INH) plus vitamin D, INH plus placebo, or vitamin D plus placebo. However, ethical issues, especially in children, hinder the attainment of this research. Gupta *et al*. underlined an association between low vitamin D levels and variants in Toll-like receptor genes significantly influencing the risk of tuberculosis in HIV infected or exposed infants, demonstrating the importance of genetic host variants [80] (Table 1).

Vitamin D and TB: clinical trials

Unlike prevention studies, vitamin D therapy in active TB has been extensively investigated [81-83]. In 2006 Martineau performed a review of the literature regarding the administration of vitamin D in adults with TB [9,84]. However, he reported inconclusive results: the studies were heterogeneous, with small sample sizes and sub-optimal therapeutic doses. Some trials described predominantly negative results, with limited benefits in routine clinical practice with regard to composite clinical scores, mortality [84] and time to culture negativity (85). Instead, a trial showed advantages in the subgroup with the Taq1 25-hydroxyvitamin D VDR receptor polymorphism of the tt genotype, with a faster rate of sputum negativization in patients treated with the vitamin [86]. More recent studies reported better results on vitamin D supplementation than in the past, as regards sputum negativization and the improvement of the radiological picture at 6 weeks [44,87].

The SUCCINT study analyzed 250 adult patients randomized to receive vitamin D or placebo in addition to anti-tuberculosis therapy [88]. At the 12-week follow-up, the treated arm reported a major weight gain (95% CI 1.99 - 3.23, p=0.009), an improvement in the radiographic picture (p=0.004, 95% CI 0.15 - 0.79) and an increase in IFN-γ production compared to patients with low baseline vitamin D values (p=0.021). Instead, the two study groups did not show significant differences in sputum negativization and clinical TB score. However, a main limitation of this study is the lack of follow-up until the end of anti-TB therapy (6 months), thus not being able to exclude whether the effects of vitamin D supplementation could be greater at 6 months or if the differences reported at 12 weeks were only transient [88]. A small placebo-controlled trial of 24 children did not describe any significant effect on the primary outcomes with oral vitamin D supplementation [89].

Ganmaa *et al*. studied the consequences of vitamin D therapy on the conversion of the tuberculin skin test (TST). They performed a double-blind, placebo-controlled trial of 120 children with low vitamin D values in Mongolia [90]. The authors reported a higher conversion rate of TST in the control arm than in the treatment group; however, this may be the result of a «booster phenomenon» after repeated TST, rather than the acquisition of LTBI (the interferon gamma release assay (IGRA) was not performed at the end of the follow-up). A recent clinical trial by Khandelwal *et al*. analyzed 266 children with intra-thoracic tuberculosis (140 children received vitamin D supplementation, while others did not). Patients who did not demonstrate sputum conversion after intensive treatment had significantly lower Vitamin D levels than others. Despite the limitations of the study (healthy controls not involved, small number of children with poor outcome), the number of children involved in this clinical trial is interesting [91,92] (Table 1).

Vitamin D, TB and microbiota

Mtb is able to remain in a latent state in the human body, resulting in the development of an active disease after many years. Granuloma development in TB involves the interaction between several elements. A recent paper showed that the lung microbiota is among the factors that could influence its formation. Furthermore, vitamin D is able to modulate both the host immune response and the intestinal and lung microbiome. Consequently, the interaction between these three elements – microbiome, granuloma and vitamin D – might be able to determine the evolution of the infection [93].

Conclusions

Vitamin D is a micronutrient that, in addition to the effects on bone metabolism, is able to influence the host defense and inflammation. Theoretically, its deficiency can be associated with lung diseases, including TB. Furthermore, due to the increased incidence of both TB cases worldwide [94] and drug-resistant Mtb, a great deal of interest has arisen in the use of vitamin D.

Table 1. Main evidence of the existing literature.

Authors	Study design	Participants	Main findings	Comments
Davies, 1985 [58]	Observational study	/	Increased rates of active disease with low vitamin D levels	Review of the existing literature
Nnoaham *et al.*, 2008 [59]	Systematic review and meta-analysis	7 studies included; adult population	High risk of active TB with low vitamin D levels	No normal distribution and commonvariance
Zeng *et al.*, 2015 [60]	Meta-analysis	11 studies involving adults, 2 children and 2 both	25(OH)D levels below 25 nmol/L were associated with an increased risk of active TB	High heterogeneity
Gou *et al.*, 2018 [61]	Meta-analysis	10 studies in children	Association between vitamin D deficiency and pediatric TB	Small number of subjects; observational studies included; heterogeneity
Nielsen *et al.*, 2010 [72]	Case-control study	216 adults included: mean age 39 years	Both high and low levels of 25 [OH]D were reported in patients with TB compared with controls	Retrospective design; limited number of participants with active-TB
Mastala *et al.*, 2013 [73]	Cross-sectional sample	157 adult patients	Low vitamin D values were more frequently observed in TB patients	No control healthy group
Talat *et al.*, 2010 [75]	Cohort follow-up study	128 (44 children and 84 adults)	The risk of progression to active TB was higher among patients with concentrations of 25[OH]D <17.5 nmol/L	Small number of participants; no information about diet or sunlight
Yani *et al.*, 2017 [76]	Cross-sectional study	178 children <5 years	Association of latent TB with vitamin D status	No data about risk factors for TB or low vitamin D
Koh *et al.*, 2013 [77]	Ecological study	9739 cases (children and adults)	Notifications of TB higher in summer than winter	Reduced sun exposure during the winter season, caused an increase in cases during the following summer; no information about socioeconomic status
Gray *et al.*, 2012 [79]	Retrospective study	328 children (median age 7.8 years)	Decreased sunlight exposure was associated with an increased incidence of TB	Retrospective nature, no IGRA testing
Gupta *et al.*, 2016 [80]	Case-cohort study	466 infants (mean age 7.59 months)	Low vitamin D levels and variants in Toll-like receptor genes increase the risk of TB in HIV infected or exposed infants	Low breastfed children
Martineau *et al.*, 2006 [84]	Narrative review	3 RCT and 10 case series (one study with only children, while two with only adults)	Review of 3 clinical trials and 10 case series with vitamin D as treatment	Inconclusive results
Wejse *et al.*, 2009 [85]	Double-blind, randomized, placebo-controlled trial	365 adult patients	Vitamin D does not improve clinical outcome among patients with TB	Possible dose insufficient
Martineau *et al.*, 2011 [86]	Randomized Controlled Trial	126 adult patients (median age 30.7 years)	Faster rate of sputum negativization with the tt genotype of the Taq1 VDR polymorphism	Suspected incomplete adherence to therapy; short follow-up
SUCCINT study, 2013 [88]	Clinical trial	259 adult patients (mean age 27.8 years)	The treated arm reported a major weight gain, an improvement in the radiographic picture and an increase in IFN-γ production	There were not differences in sputum negativization and clinical TB score; lack of follow-up until the end of anti-TB therapy
Morcos *et al.*, 1998 [89]	Placebo-controlled trial	24 children	Clinical improvement in the treatment group	Small study; no significant effect on the primary outcomes
Ganmaa *et al.*, 2012 [90]	Double-blind, placebo-controlled trial	120 children (mean age 13 years)	Higher conversion rate of TST in the control arm than in the treatment group	Probable «booster phenomenon» after repeated TST
Khandelwal *et al.*, 2014 [91]	Clinical trial	266 children (mean age 106.9 months)	Patients without sputum conversion after treatment had significantly lower Vitamin D levels	No healthy controls, small number of children with poor outcome. High number of children involved

In fact, it could represent a new, cheap, safe and easily accessible drug for the prevention and treatment of tuberculosis. Since numerous studies were performed with ambiguous results, we carried out this review of the existing literature with the aim of clarifying its usefulness in the field of TB. Although in vitro studies have shown significant antimycobacterial effects of vitamin D, this has not been confirmed in vivo. Regarding prevention, based on the available manuscripts, it is unclear whether vitamin D levels may influence susceptibility to TB infection or the transition from latent infection to active disease. On the other hand, older studies on its use in anti-TB therapy described predominantly negative results. More recent manuscripts showed encouraging results, especially as regards the time of sputum negativization. However, the results are not conclusive and heterogeneous. To date, the correlation between TB and vitamin D levels requires further research. For stronger evidence, considering the characteristics of the infection (low incidence of latent infection reactivation in immunocompetent patients) we need clinical trials with large numbers of participants conducted in endemic regions with a prolonged follow-up time.

References

1. Young DB, Gideon HP, Wilkinson RJ. Eliminating latent tuberculosis. Trends Microbiol 2009;17:183-8.
2. Barry CE 3rd, Boshoff HI, Dartois V, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol 2009;7:845-55.
3. Gideon HP, Flynn JL. Latent tuberculosis: what the host "sees"? Immunol Res 2011;50:202-12.
4. Mtei L, Matee M, Herfort O, et al. High rates of clinical and subclinical tuberculosis among IV-infected ambulatory subjects in Tanzania. Clin Infect Dis 2005;40:1500-7.
5. Reljic R. IFN-gamma therapy of tuberculosis and related infections. J Interferon Cytokine Res 2007;27:353-64.
6. Ralph AP, Kelly PM, Anstey NM. L-arginine and vitamin D: novel adjunctive immunotherapies in tuberculosis. Trends Microbiol 2008;16:336-44.
7. Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev 2008;(1):CD002244.
8. Skerry C, Harper J, Klunk M, et al. Adjunctive TNF inhibition with standard treatment enhances bacterial clearance in a murine model of necrotic TB granulomas. PLoS One 2012;7:e39680.
9. Ralph AP, Lucas RM, Norval M. Vitamin D and solar ultraviolet radiation in the risk and treatment of tuberculosis. Lancet Infect Dis 2013;13:77-88. Erratum in: Lancet Infect Dis 2013;13:106. Erratum in: Lancet Infect Dis 2013;13:192.
10. Williams B, Williams AJ, Anderson ST. Vitamin D deficiency and insufficiency in children with tuberculosis. Pediatr Infect Dis J 2008;27:941-2.
11. Torun E, Cakir E, Aktas EC, et al. Intracellular cytokine and cathelicidin secretion from monocytes and neutrophils in childhood tuberculosis. Pediatr Infect Dis J 2014;33:224-6.
12. Mily A, Rekha RS, Kamal SM, et al. Significant effects of oral phenylbutyrate and vitamin D3 adjunctive therapy in pulmonary tuberculosis: A randomized controlled trial. PLoS One 2015;10:e0138340.
13. Tukvadze N, Sanikidze E, Kipiani M, et al. High-dose vitamin D3 in adults with pulmonary tuberculosis: a double-blind randomized controlled trial. Am J Clin Nutr 2015;102:1059-69.
14. Ustianowski A, Shaffer R, Collin S, Wilkinson RJ, Davidson RN. Prevalence and associations of vitamin D deficiency in foreign-born persons with tuberculosis in London. J Infect 2005;50:432-7.
15. Arnedo-Pena A, Juan-Cerdán JV, Romeu-Garcia A, et al. Latent tuberculosis infection, tuberculin skin test and vitamin D status in contacts of tuberculosis patients: a cross-sectional and case-control study. BMC Infect Dis 2011;11:349.
16. Desai NS, Tukvadze N, Frediani JK, et al. Effects of sunlight and diet on vitamin D status of pulmonary tuberculosis patients in Tbilisi, Georgia. Nutrition 2012;28:362-6.
17. Srinivasan A, Syal K, Banerjee D, et al. Low plasma levels of cholecalciferol and 13-cis-retinoic acid in tuberculosis: implications in host-based chemotherapy. Nutrition 2013;29:1245-51.
18. Mehta S, Mugusi FM, Bosch RJ, et al.. Vitamin D status and TB treatment outcomes in adult patients in Tanzania: a cohort study. BMJ Open 2013;3:e003703.
19. Sudfeld CR, Giovannucci EL, Isanaka S, et al. Vitamin D status and incidence of pulmonary tuberculosis, opportunistic infections, and wasting among HIV-infected Tanzanian adults initiating antiretroviral therapy. J Infect Dis 2013;207:378-85.
20. Kibirige D, Mutebi E, Ssekitoleko R, et al. Vitamin D deficiency among adult patients with tuberculosis: a cross sectional study from a national referral hospital in Uganda. BMC Res Notes 2013;6:293.
21. Joshi L, Ponnana M, Penmetsa SR, et al. Serum vitamin D levels and VDR polymorphisms (BsmI and FokI) in patients and their household contacts susceptible to tuberculosis. Scand J Immunol 2014;79:113-9.
22. Huaman MA, Sterling TR, Shepherd BE, Fiske CT. 25-Hydroxyvitamin D levels after recovery from tuberculosis: insights into pathogenesis. Tuberculosis (Edinb) 2014;94:51-4.
23. Glisson F, Bate G, Regemorter A. A treatise of the rickets: being a disease common to children. London: P. Cole; 1651.
24. Martineau AR. Old wine in new bottles: vitamin D in the treatment and prevention of tuberculosis. Proc Nutr Soc 2012;71:84-9.
25. Green M. Cod liver oil and tuberculosis. BMJ 2011;343:d7505.
26. Grad R. Cod and the consumptive: a brief history of cod-liver oil in the treatment of pulmonary tuberculosis. Pharm Hist 2004;46:106-20.
27. DeLuca HF. Vitamin D: Historical overview. Vitam Horm 2016;100:1-20.
28. Roelandts R. The history of phototherapy: something new under the sun? J Am Acad Dermatol 2002;46:926-30.
29. Venanzetti M. [Anch'io fui studente al Forlanini. Una giornata con il suo fondatore tra segreti e curiosità].[Book in Italian]. Rome: Scienze e lettere; 2012.
30. Charpy J. [Clinical research on psoriasis therapy].[Article in French]. Ann Dermatol Syphiligr (Paris) 1945;5:227.
31. Phelan JJ. Calciferol in pulmonary tuberculosis. Lancet 1947;1:764.
32. Ellman P, Anderson KH. Calciferol in tuberculous peritonitis with disseminated tuberculosis. Br Med J 1948;1:394.
33. Okamura WH, Midland MM, Hammond MW, et al. Chemistry and conformation of vitamin D molecules. J Steroid Biochem Mol Biol 1995;53:603-13.
34. Zhang R, Naughton DP. Vitamin D in health and disease: current perspectives. Nutr J 2010;9:65.
35. Wagner CL, Greer FR, American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D

deficiency in infants, children, and adolescents. Pediatrics 2008;122:1142-52. Erratum in: Pediatrics 2009;123:197.
36. Mimouni FB, Shamir R. Vitamin D requirements in the first year of life. Curr Opin Clin Nutr Metab Care 2009;12:287-92.
37. Battersby AJ, Kampmann B, Burl S. Vitamin D in early childhood and the effect on immunity to Mycobacterium tuberculosis. Clin Dev Immunol 2012;2012:430972.
38. White JH. Vitamin D metabolism and signaling in the immune system. Rev Endocr Metab Disord 2012;13:21-9.
39. Norman AW, Mizwicki MT, Norman DP. Steroid-hormone rapid actions, membrane receptors and a conformational ensemble model. Nat Rev Drug Discov 2004;3:27-41.
40. Ariganjoye R. Pediatric hypovitaminosis D: Molecular perspectives and clinical implications. Glob Pediatr Health 2017;4:2333794X16685504.
41. Ren S, Nguyen L, Wu S, et al. Alternative splicing of vitamin D-24-hydroxylase: a novel mechanism for the regulation of extrarenal 1,25-dihydroxyvitamin D synthesis. J Biol Chem 2005;280:20604-11.
42. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311:1770-3.
43. Fabri M, Stenger S, Shin DM, et al. Vitamin D is required for IFN-gamma-mediated antimicrobial activity of human macrophages. Sci Transl Med 2011;3:104ra102.
44. Hmama Z, Sendide K, Talal A, et al Quantitative analysis of phagolysosome fusion in intact cells: inhibition by mycobacterial lipoarabinomannan and rescue by an 1alpha,25-dihydroxyvitamin D3-phosphoinositide 3-kinase pathway. J Cell Sci 2004;117:2131-40.
45. Coussens A, Timms PM, Boucher BJ, et al. 1alpha,25-dihydroxyvitamin D3 inhibits matrix metalloproteinases induced by Mycobacterium tuberculosis infection. Immunology 2009;127:539-48..
46. Vidyarani M, Selvaraj P, Jawahar MS, Narayanan PR. 1, 25 Dihydroxyvitamin D3 modulated cytokine response in pulmonary tuberculosis. Cytokine 2007;40:128-34.
47. Salamon H, Bruiners N, Lakehal K, et al. Cutting edge: Vitamin D regulates lipid metabolism in Mycobacterium tuberculosis infection. J Immunol 2014;193:30-4.
48. Looman KIM, Jansen MAE, Voortman T, et al. The role of vitamin D on circulating memory T cells in children: The Generation R study. Pediatr Allergy Immunol 2017;28:579-87.
49. Afsal K, Selvaraj P, Harishankar M. 1, 25-dihydroxyvitamin D3 downregulates cytotoxic effector response in pulmonary tuberculosis. Int Immunopharmacol 2018;62:251-60.
50. Facchini L, Venturini E, Galli L, et al. Vitamin D and tuberculosis: a review on a hot topic. J Chemother 2015;27:128-38.
51. Gough ME, Graviss EA, May EE. The dynamic immunomodulatory effects of vitamin D3 during Mycobacterium infection. Innate Immun 2017;23:506-23.
52. Kampmann B, Gaora PO, Snewin VA, et al. Evaluation of human antimycobacterial immunity using recombinant reporter mycobacteria. J Infect Dis 2000;182:895-901.
53. Martineau AR, Wilkinson RJ, Wilkinson KA, et al. A single dose of vitamin D enhances immunity to mycobacteria. Am J Respir Crit Care Med 2007;176:208-13.
54. Yesudian PD, Berry JL, Wiles S, et al. The effect of ultraviolet B-induced vitamin D levels on host resistance to Mycobacterium tuberculosis: a pilot study in immigrant Asian adults living in the United Kingdom. Photodermatol Photoimmunol Photomed 2008;24:97-8.
55. Coussens AK, Wilkinson RJ, Hanifa Y, et al. Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment. Proc Natl Acad Sci USA 2012;109:15449-54.
56. Lalvani A, Connell DW. Dissecting the immunological, antimicrobial and clinical effects of vitamin D therapy in tuberculosis. Pathog Glob Health 2012;106:378-9.
57. Reeme AE, Robinson RT. Dietary vitamin D3 suppresses pulmonary immunopathology associated with late-stage tuberculosis in C3HeB/FeJ mice. J Immunol 2016;196:1293-304.
58. Davies PD. A possible link between vitamin D deficiency and impaired host defence to Mycobacterium tuberculosis. Tubercle 1985;66:301-6.
59. Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. Int J Epidemiol 2008;37:113-9.
60. Zeng J, Wu G, Yang W, et al. A serum vitamin D level <25nmol/l pose high tuberculosis risk: a meta-analysis. PLoS One 2015;10:e0126014.
61. Gou X, Pan L, Tang F, et al. The association between vitamin D status and tuberculosis in children: A meta-analysis. Medicine (Baltimore) 2018;97:e12179.
62. Davies PD, Church HA, Brown RC, Woodhead JS. Raised serum calcium in tuberculosis patients in Africa. Eur J Respir Dis 1987;71:341-4.
63. Davies PD, Church HA, Bovornkitti S. Altered vitamin D homeostasis in tuberculosis. Int Med Thailand 1988;4:45-47.
64. Wilkinson RJ, Llewelyn M, Toossi Z, et al. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. Lancet 2000;355618-21.
65. Sasidharan PK, Rajeev E, Vijayakumari V. Tuberculosis and vitamin D deficiency. J Assoc Physicians India 2002;50:554-8.
66. Sita-Lumsden A, Lapthorn G, Swaminathan R, Milburn HJ. Reactivation of tuberculosis and vitamin D deficiency: the contribution of diet and exposure to sunlight. Thorax 2007;62:1003-7.
67. Gibney KB, MacGregor L, Leder K, et al. Vitamin D deficiency is associated with tuberculosis and latent tuberculosis infection in immigrants from sub-Saharan Africa. Clin Infect Dis 2008;46:443-6.
68. Ho-Pham LT, Nguyen ND, Nguyen TT, et al. Association between vitamin D insufficiency and tuberculosis in a Vietnamese population. BMC Infect Dis 2010;10:306.
69. Grange JM, Davies PD, Brown RC, et al. A study of vitamin D levels in Indonesian patients with untreated pulmonary tuberculosis. Tubercle 1985;66:187-91.
70. Chan TY, Poon P, Pang J, et al. A study of calcium and vitamin D metabolism in Chinese patients with pulmonary tuberculosis. J Trop Med Hyg 1994;97:26-30.
71. Martineau AR, Leandro AC, Anderson ST, et al. Association between Gc genotype and susceptibility to TB is dependent on vitamin D status. Eur Respir J 2010;35:1106-12.
72. Nielsen NO, Skifte T, Andersson M, et al. Both high and low serum vitamin D concentrations are associated with tuberculosis: a case-control study in Greenland. Br J Nutr 2010;104:1487-91.
73. Mastala Y, Nyangulu P, Banda RV, et al. Vitamin D deficiency in medical patients at a central hospital in Malawi: a comparison with TB patients from a previous study. PLoS One 2013;8:e59017.
74. Buonsenso D, Focarelli B, Scalzone M, et al. Chest wall TB and low 25-hidroxy-vitamin D levels in a 15-month-old girl. Ital J Pediatr 2012;38:12.
75. Talat N, Perry S, Parsonnet J, et al. Vitamin d deficiency and

tuberculosis progression. Emerg Infect Dis 2010;16:853-5.
76. Yani FF, Lipoeto NI, Supriyatno B, et al. Vitamin D status in under-five children with a history of close tuberculosis contact in Padang, West Sumatra. Asia Pac J Clin Nutr 2017;26:S68-72.
77. Koh GC, Hawthorne G, Turner AM, et al. Tuberculosis incidence correlates with sunshine: an ecological 28-year time series study. PLoS One 2013;8:e57752.
78. Margalit I, Block C, Mor Z. Seasonality of tuberculosis in Israel, 2001-2011. Int J Tuberc Lung Dis 2016;20:1588-93.
79. Gray K, Wood N, Gunasekera H, et al. Vitamin d and tuberculosis status in refugee children. Pediatr Infect Dis J 2012;31:521-3.
80. Gupta A, Montepiedra G, Gupte A, et al. Low vitamin-D levels combined with PKP3-SIGIRR-TMEM16J host variants is associated with tuberculosis and death in HIV-infected and -exposed infants. PLoS One 2016;11:e0148649.
81. Walker VP, Modlin RL. The vitamin D connection to pediatric infections and immune function. Pediatr Res 2009;65:106R-113.
82. Yamshchikov AV, Kurbatova EV, Kumari M, et al. Vitamin D status and antimicrobial peptide cathelicidin (LL-37) concentrations in patients with active pulmonary tuberculosis. Am J Clin Nutr 2010;92:603-11.
83. Iftikhar R, Kamran SM, Qadir A, et al. Vitamin D deficiency in patients with tuberculosis. J Coll Physicians Surg Pak 2013;23:780-3.
84. Martineau AR, Honecker FU, Wilkinson RJ, Griffiths CJ. Vitamin D in the treatment of pulmonary tuberculosis. J Steroid Biochem Mol Biol 2007;103:793-8.
85. Wejse C, Gomes VF, Rabna P, et al. Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2009;179:843-50.
86. Martineau AR, Timms PM, Bothamley GH, et al. High-dose vitamin D(3) during intensive-phase antimicrobial treatment of pulmonary tuberculosis: a double-blind randomised controlled trial. Lancet 2011;377:242-50.
87. Nursyam EW, Amin Z, Rumende CM. The effect of vitamin D as supplementary treatment in patients with moderately advanced pulmonary tuberculous lesion. Acta Med Indones 2006;38:3-5.
88. Salahuddin N, Ali F, Hasan Z, et al. Vitamin D accelerates clinical recovery from tuberculosis: results of the SUCCINCT Study [Supplementary Cholecalciferol in recovery from tuberculosis]. A randomized, placebo-controlled, clinical trial of vitamin D supplementation in patients with pulmonary tuberculosis'. BMC Infect Dis 2013;13:22.
89. Morcos MM, Gabr AA, Samuel S, et al. Vitamin D administration to tuberculous children and its value. Boll Chim Farm 1998;137:157-64.
90. Ganmaa D, Giovannucci E, Bloom BR, et al. Vitamin D, tuberculin skin test conversion, and latent tuberculosis in Mongolian school-age children: a randomized, double-blind, placebo-controlled feasibility trial. Am J Clin Nutr 2012;96:391-6.
91. Khandelwal D, Gupta N, Mukherjee A, et al. Vitamin D levels in Indian children with intrathoracic tuberculosis. Indian J Med Res 2014;140:531-7.
92. Mukherjee A, Saini S, Kabra SK, et al. Effect of micronutrient deficiency on QuantiFERON-TB Gold In-Tube test and tuberculin skin test in diagnosis of childhood intrathoracic tuberculosis. Eur J Clin Nutr 2014;68:38-42.
93. Balcells ME, Yokobori N, Hong BY, et al. The lung microbiome, vitamin D, and the tuberculous granuloma: A balance triangle. Microb Pathog 2019;131:158-63.
94. Buonsenso D, Lancella L, Delogu G, et al. A twenty-year retrospective study of pediatric tuberculosis in two tertiary hospitals in Rome. Pediatr Infect Dis J 2012;31:1022-6.