# Vitamin D and tuberculosis*

## Vitamina D e tuberculose

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## SUMMARY

**BACKGROUND AND OBJECTIVES**: The vitamin can be obtained from certain foods or through the exposition to solar light. It works together the parathyroid hormone to keep the sanguineous calcium levels, but it has an interesting participation in immunologic mechanisms of regulation, mainly of the infectious illnesses, being present in the history of the tuberculosis for a long time. The aim of this study is to revise what has been published, on the role of vitamin D in the tuberculosis physiopathology.
**CONTENTS**: This review deals with immunological mechanisms in tuberculosis infection, the involvement of vitamin D in this mechanisms and what is its applicability in clinical practice for the treatment of tuberculosis.
**CONCLUSION**: Vitamin D can be beneficial as adjuvant therapy in the treatment of tuberculosis. It would be appealing, in a country with our features, that a greater interest in the study of this topic occurred.
**Keywords**: Calciferol, Calcitrol, Tuberculosis, Vitamin D.

## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: A vitamina pode ser obtida dos alimentos ou através da exposição à luz solar. Trabalha junto com o hormônio paratireoideano para manter os níveis de cálcio sanguíneo, mas tem uma interessante participação em mecanismos de regulação imunológicos, principalmente das doenças infecciosas, estando presente na história da tuberculose há muito tempo. O objetivo deste estudo foi revisar o do que já foi publicado, sobre o papel da vitamina D na fisiopatologia da tuberculose.
**CONTEÚDO**: Esta revisão trata sobre mecanismos imunológicos na infecção por tuberculose, o envolvimento da vitamina D nesses mecanismos e qual a sua aplicabilidade na prática médica para o tratamento da tuberculose.
**CONCLUSÃO**: A vitamina D pode ser benéfica como terapia adjuvante no tratamento da tuberculose. Seria atraente, em um país com características climáticas e econômicas como o Brasil, que ocorresse um interesse maior no estudo desse tema.
**Descritores**: Calciferol, Calcitrol, Tuberculose, Vitamina D.

## INTRODUCTION

The most known role of vitamin D is the calcium regulation, but this vitamin-hormone has also gained importance in medicine due to its interesting participation in immunological regulation mechanisms, mainly those of infectious diseases. For many decades[1], even in the pre-antibiotic[2-4] era and before the cod liver oil was used, the vitamin D has been prescribed in the treatment of tuberculosis, associated with exposure to sun light[5].
Early studies have mentioned the importance of the vitamin D in the monocyte activity against mycobacterial infections, and latter ones have shown that the vitamin helps against the infection through the induction of catelicidine peptidium, which has microbicidal activity ,in macrophages.
But, is vitamin D really important in the susceptibility, prophylaxis, or treatment of tuberculosis infection?
In this article, some of what has been published about the subject of the vitamin D and its role in the physiopathology of tuberculosis is reviewed, as well as its clinical implementation and usages.

## CHEMICAL ASPECTS, SOURCES, PHYSIOLOGICAL NEED OF VITAMIN D

The vitamin D is a secosteroid hormone. Its structure is very similar to those of steroids if not for the fact that two carbon atoms rings of the usual four, are not joint, as observable in figure 1.
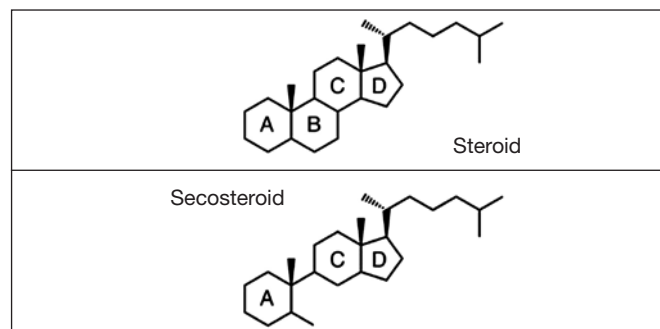
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Figure 1 - Schematic of molecular structure of steroids and secosteroids.

It can be obtained from food as vitamin $D_3$ (colecalciferol), vitamin $D_2$ (ergocalciferol) and the ergosterol, a molecule derived from the plants' sterol. Its unique structure causes it and its metabolites to be susceptible to oxidation, conformational changes induced by ultraviolet rays and free radicals.

The second process for the body to obtain vitamin D is the exposure to the sunlight. The UVB rays (290-315nm) go through the skin and cause the photolysis of the pro-vitamin $D_3$ (7- dihidrocolesterol) to pre-vitamin $D_3$[6,7]. Once formed, the pre-vitamin suffers a thermal isomeration and transforms into the vitamin $D_3$. When the vitamin D enters the circulation, both from intestinal absorption or from the skin, it links with the D Binding Protein (DBP), a globular protein of 58 KDa[8].

The first step on the metabolic activation of the vitamin D is the enzymatic catalisation of an OH from the carbon 25 to generate the 25- hydroxivitamin D [25(OH)D], the circulant form of the vitamin D. This process takes place in the liver[9,10].

The 25(OH)D enters the circulation and binds strongly to the DBP[11]. Only small quantities of 25(OH)D are now free and capable of intramembranous diffusion to exert their biological function.

The conversion of 25(OH)D into 1,25 dihydroxivitamin D[1,25 $(OH)_2D$],the calcitrol, is made by the enzyme 1α-hydroxilasis and occurs mainly in the kidneys, even though it has been related to happen in other parts of the body, including the brain[12-16].

The half-life of the 25(OH)D in the circulation is about 2-3 weeks (17 days) and for that reason is a good indicator of the level of vitamin D in the body.

The 1,25 $(OH)_2D$ or calcitrol is considered the hormonal form of vitamin D, and is a more active form. It, together with the parathyroid hormone, keeps the calcium levels in the blood, raises the absorption of calcium by the intestine, reduces the calcium elimination through urine and prevents loss of calcium from the bones. Various studies have shown that a single dose of full-body exposition to sunlight or UVB rays capable of producing soft erithema is the equivalent to an oral dose of 250-625 ug (10.000-25.000 UI) of vitamin D[18-21].

For individuals with dark skin the exposure needed is 10 times longer, the reason is the melanin in the skin, which competes for the UVB photons and diminishes the efficiency of the process over the pre-vitamin[22,23].

According to the 2011 directive of "Endocrine Society"[24], newborn and children under 1 year old need at least 400 UI/day of vitamin D to grow with bone health. Children over 1 year old need 600 UI/day but 1000 UI/day may be required to elevate the blood level of 25(OH)D consistently over 30 ng/mL.

Adults aged between 19 and 70 need 600 UI/day to maximize bone health and muscle function, over the age of 70, 800 UI/day are needed. To obtain 25(OH)D levels of over 30 ng/mL in the adult cases can take, in the least, 1.500 – 2.000 UI/day. The recommended level of the vitamin D for children and adults is between 40 and 60 ng/mL. Pregnant and lactating women need a minimal of 600 UI/day and 1500 UI/day to keep levels of 25(OH)D over 30 ng/mL.

Obese people or under anticonvulsive, glucocorticoids, antifungals (as cetoconazol) or AIDS medicines need 2 to 3 times more vitamin D to fulfill their physiological needs.

Directives recommend that, for individuals deficient of the vitamin, higher levels may be necessary to correct, treat and prevent the condition (2.000 UI/day for children under 1 year old, 4.000 UI/day for those between 1 and 18 years, and up to 10.000 UI/day for adults). Both vitamin $D_2$ and $D_3$ are good to fight the deficiency.

Overdose of vitamin D could induce toxicity, that causes: loss of appetite, nausea and vomiting, fatigue, muscle weakness, polyuria, polydipsia, nocturia, hypercalcemia, nervousness and tremors, increase of blood pressure, acute or chronic renal failure, and differents levels of hyperphostatemia[25,26].

No case of hypervitaminosis D caused by exposure to sunlight has been related[27]. The pre-vitamin D during a long exposure to UVB rays is photolysed mainly into a biologically inactive isomer, the lumisterol[28]. Once formed it remains in a quasi-photostationary state and only 10-15% of the provitamin are converted. On the other hand, the colecalciferol is sensitive to the radiation of UVB rays and converts to: 5,6 trans-colecalciferol, supersterol and supersterol II[29].

## ABOUT TUBERCULOSIS

Tuberculosis is one of the deadliest human diseases. According to the World health Organization (WHO), 9.400.000 new cases and 1.700.000 deaths caused by the disease in 2009. The risk grows with the spread of the AIDS and new mycobacteria resistant to the medicines used[30]. A third of the world population, around 2 billion people, is already infected. The majority do not develop the disease, despite the resilience of the pathogen, explaining the survival of this micro-organism. Less than 10% of the infected develop the disease, but when not treated it is fatal in 50% of the cases.

Only five bacillus of *Mycobacterium tuberculosis* (Mtb) are needed to infect humans[31], even so, only aerosol particles are small enough to reach the alveolar space(< 5-10 μm) and are considered infectious.

After the inhalation of the aerosols, the Mtb is phagocyted by the alveolar macrophages, starting an immunological response by the host, with the participation of a series of innate and acquired defense mechanisms.

### The role of the vitamin D in the response to the *Mycobacterium tuberculosis*

The immune response acquired to the mycobacterium is well stablished with the importance of TH1/IFN-y[32].

The Mtb survives inside the phagosome during its initial state of maturation, keeping it from fusing with lysosomes[33,34-36].

In the phagosome, it has easy access to iron molecules needed by the host for various defense mechanisms[37] and is able to promote its own intracellular survival[38].

Even so, some phagosomes manage to evolve to their final maturing stage, but those active macrophages can fail to eradicate the Mtb[39], that survives in a latent stage with poor metabolic activity, without producing illness.

There is, whatsoever, a risk that this situation changes and leads to the posterior development of the disease.

The antigens from Mtb inside phagosome were exposed to the surface of the macrophage linked to Major Histocompatibility Complex II. Those stimulate CD4 Lymphocytes, also known as T Helper-1, potent producers of gamma-interferon (INF-y).

The INF-y is a central factor in the activation of mycobactericidal properties in the macrophages and is considered crucial in the pro-

tection against tuberculosis. Despite residing in the macrophage, the Mtb is also capable of stimulating CD8+ cells restricted to class I MHC. The CD8+ cells, similarly to CD4+, can produce INF-y, but their primary function is the death of the target cell by lysis[39].

The innate immunological response to the Mtb involves a series of recognition macrophages receptors, the pattern recognition receptors (PRRs), such as the Toll-like receptors (TLRs)[40] and other non-TRLs as the NOD-like receptors (Nucleotide Oligomerization Domain Like Receptors) and C-type lectin[41].

The innate response is the first defense of the host. The recognition of the micobacteria by the PRRs induces genes expression of defense substances. Among the products of those genes, the vitamin D receptor (VDR) and the Cyp27b1 seem to be induced by the link of the type 2 TRL receptor of macrophages with mycobacterial antigens.

The Cyp27b1 is a 25-hidroxivitamin D 1-$\alpha$-hydroxilasis that catalyses 25 (OH)D into 1,25 (OH)$_2$D or calcitrol[42].

The complex formed by the link between VDR and 1,25 (OH)$_2$D provokes, in the macrophage, the expression of the catelicidine peptide[43], which is very important in the mycobactericidal activity in macrophages.

The catelicidine mediates the immune response to the Mtb[44,45] and induces the autophagy in macrophages and monocytes[46].

Studies also show that mutations and polymorphisms in the genes related to immunity lead to susceptibility to the infection by Mtb, as in the polymorphisms of VDR[47].

That way the vitamin D modulates the activity monocyte-macrophage and has an important role in the innate immunity of the host to tuberculosis, since the macrophage is a crucial element in the pathogenesis of this infection.

## Correlation between vitamin D and tuberculosis treatment: bibliographical revision

There are many works about vitamin D supplementation and correction of deficiencies in the treatment and prophylaxis of tuberculosis[47-58].

Martineau and col[59] have demonstrated that a single dose of ergocalciferol "in vivo" has benefical effects in the overall blood to inhibit the "in vitro" growth of mycobacteria.

Morcos and col[60] have demonstrated faster resolution of the tuberculosis symptoms and gain of weight in children treated with daily doses of vitamin D as complement to the standard treatment for 2 months.

Nursyam et al.[61] have observed the reduction of six weeks in the time of conversion of sputum (the culture become negative) of a group treated with the standard therapy and 100.000 UI/day of vitamin D, against the group treated solely with the conventional therapy.

In 2008, Nnoaham and Kelechi[62] published a meta analysis that reviewed 151 articles published between 1980 and 2006, identified through Medline. This review was restricted to articles and researches that compared blood levels of vitamin D in patients with tuberculosis, not necessarily under treatment, with a control group of healthy individuals. It excluded data in which patients had vegetarian diets or were bearers of other commorbities, revisions and correspondences, the ones which related vitamin D to ethnic group and the ones that had no control individuals. Seven (7) articles involving 531 participants were left.

In the end, the conclusion was that low levels of vitamin D are associated with a high risk of active tuberculosis, but more studies were needed to establish more firmly the basis of that association. In 2009, a randomized study conducted by Wejse[63] observed no difference between the group that received the vitamin and the one that received the placebo. This study caused a great impact and served as a warning that the effects of vitamin D can be modest and that future studies must be led with caution. It is discussed, though, if the dosage and interval between the vitamin D applied were sufficient for positive results, since the blood concentrations of vitamin D were not different between the 2 groups studied[64].

Another review of randomized and controlled studies made in 2009 searched for standing ground for the treatment and prevention of infectious diseases with vitamin D. This review reinforced the conclusion that more rigorous studies are still needed to evaluate the relationship between vitamin D and the immune response to viral and bacterial infections.

In 2010, a new article about new anti-tuberculosis drugs being developed[66] as a measure against the association of HIV and tuberculosis and the emergence of new multi-resistant isolates of Mtb. This review explains that the deficiency of vitamin D is a risk for the contraction of tuberculosis. It also refers to the genetic differences in the VDR and the susceptibility to tuberculosis[47,67,68].

That same year, Martineau, in a multicentre study that involved brazilian patients and researchers[69], studied the genotypic variant Gc of the vitamin D binding protein (DBP), that has a different affinity to the vitamin D metabolites, and verified if this genotype is associated with susceptibility to tuberculosis.

The Gc1F (F=faster) and the Gc1S (S=slow) variants have greater affinity to the 25(OH)D than the Gc2[70].

It was observed that the Gc2/2 genotype was strongly associated with the susceptibility to active tuberculosis in the group of Asian patients from Gujarati (originary from the United Kingdom) when compared to the Gc1/1 genotype. This association only happent when the blood concentration of 25(OH)D was < 20 nmol/L (8 ng/mL), and not with values ≥ 20 nmol/L.

No association between the Gc genotype and tuberculosis was observed in other ethnic groups studied (Brazilians and south Africans). Authors discussed this result, refering that it has already been demonstrated that individuals with the skin very pigmented have higher frequency of the 1F[71] allele and would have a benefit in survival due to the smaller penetration of the UVB rays in their skins. January 2011 Martineau published[72] a new controlled study in which the administration of 4 doses of 2,5 mg(100.000 UI) of vitamin D raised the blood concentration of 25(OH)D in patients under the intensive treatment for tuberculosis. The vitamin did not reduce the sputum conversion time in all the patients, but accelerated significantly the conversion in participants presenting the Taql genotype of the vitamin D receptor. The VDRs occur as genetic variants or polymorphisms[73]. The Talq and Fokl variants were also studied.

The presence of the allele t of the Taql polymorphism of VDR is related to the phagocytosis of Mtb induced by calcitrol "in vitro"[74] and a 10 times faster sputum conversion in patients with pulmonary tuberculosis[75]. On the contrary, the f allele of the Fokl polymorphism of VDR is related to the reduction of the transcriptional activity[76], reduction in the phagocytosis induced by calcitrol[74] and decrease of culture sputum conversion speed[75].

## CONCLUSION

It is known that vitamin D deficiency has been raising in the last decades. As the majority of the circulating 25(OH)D is derived from exposure to sunlight, the deficiency is attributed to the indoors lifestyle, old age, avoidance of sunlight, sunlight protectors, the reduction of vitamin D bearing foods and the increase in obesity, for the adipose tissue absorbs the vitamin[16,77].

Generally speaking, the vitamin D seems to be benefic as an adjuvant therapy in the treatment of tuberculosis.

The main limitation about its applicability is the lack of randomized clinical works on the subject. Future clinical studies will have to consider: dosage; ethnic group; geographical location; age; HIV associated pathologies; the use of antiretroviral or antituberculosis therapies that reduce the absorption of vitamin D[62,78]; BBP and VDR genetic variants; and toxicity.

The variables are many. In face of the facts here exposed it would seem the vitamin D can be beneficial as an adjuvant therapy in the tuberculosis treatment.

It would be interesting for a country such as Brazil further research on the subject, most importantly to make the correlation between patients with vitamin D deficiency and patients infected by Mtb and its communicants. Actually, the value of the procedures table of the Unified Health System (Sistema Único de Saúde) (http://sigtap.datasus.gov.br) of the 25(OH)D dosage is R$ 15,24. The blood dosage of calcium and phosphorus cost R$ 1,85 each and the cost of colecalciferol manipulation is low.

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