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Review article
Pregledni članak

THE HEALTH BENEFITS OF VITAMIN D RELEVANT FOR TUBERCULOSIS

ZDRAVSTVENI ZNAČAJ VITAMINA D U TUBERKULOZI

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Summary

Vitamin D has an important role in numerous physiological functions. Vitamin D receptors are characterized by polymorphisms and presence in different tissues including a number of cells of the immune system. The role of vitamin D as a biological inhibitor of inflammatory hyperactivity is of particular importance. Hypovitaminosis D has been associated with many serious chronic diseases, such as autoimmune, infectious and cardiovascular diseases as well as some types of cancer. Vitamin D has an influence on the immune response to tuberculosis. Calcitriol (1,25-dihydroxycholecalciferol), the major active form of vitamin D, has shown *in vitro* activity against *Mycobacterium tuberculosis*. It has been found that susceptibility to chronic mycobacterial infections is strongly correlated with a low vitamin D intake and particular VDR alleles. Vitamin D deficiency might predispose the individuals infected with *Mycobacterium tuberculosis* to develop tuberculosis. Calcitriol binds to vitamin D receptors and modulates immune responses by regulating the transcription of genes responsive to vitamin D. Faster conversion of sputum mycobacterial culture in patients with pulmonary tuberculosis is associated with being a carrier of the *t* allele of the *Taq*I vitamin D receptor polymorphism. On the contrary, slower sputum culture conversion in pulmonary tuberculosis has been found in the carriers of the *f* allele of the *FokI* vitamin D receptor polymorphism. The results of *in vitro* studies, clinical research and population studies indicated that vitamin D

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Kratak sadržaj

Vitamin D ima značajnu ulogu u velikom broju fizioloških funkcija, posebno kao biološki inhibitor inflamatorne hiperreaktivnosti. Hipovitaminoza je povezana sa mnogim hroničnim oboljenjima, uključujući autoimune, infektivne, kardiovaskularne bolesti i neke vrste tumora. Vitamin D utiče na imuni odgovor kod tuberkuloze, te nedostatak vitamina D može biti značajan faktor rizika za nastanak tuberkuloze među osobama koje su inficirane *Mycobacteriumom tuberculosis*. Postoji jaka povezanost između nedostatka vitamina D u ishrani i prisustva određenog VDR alela, i podložnosti mikobakterijskoj infekciji. Pokazano je da kalcitriol, glavni aktivni oblik vitamina D (1,25-dihidroksiholekalciferol) ima *in vitro* antimikobakterijsku aktivnost. Receptori za vitamin D su polimorfni i prisutni su u različitim tkivima, uključujući i ćelije imunog sistema. Kalcitriol se vezuje za odgovarajuće receptore za vitamin D, modulira imunološki odgovor i reguliše transkripciju gena koji zavise od vitamina D. Brža konverzija kulture mikobakterija iz sputuma kod pacijenata sa plućnom tuberkulozom ukazuje na nosioce *t* alela polimorfizma *TaqI* receptora za vitamin D. Suprotno tome, sporija konverzija kulture mikobakterija iz sputuma u plućnoj tuberkulozi povezuje se sa nosiocima *f* alela polimorfizma *FokI* receptora za vitamin D. Rezultati bazičnih naučnih i kliničkih istraživanja i populacionih studija sugerišu da nedostatak vitamina D može predstavljati značajan rizik za nastanak tuberkuloze. Vitamin D je jeftin, lako

List of abbreviations: Vitamin D receptor (VDR), United States (US), systemic lupus erythematosus (SLE), *Mycobacterium tuberculosis* (MBT), parathyroid hormone (PTH).

deficiency might be a strong risk factor for developing TB. Vitamin D is an inexpensive, easily accessible vitamin, relevant for the prevention of tuberculosis. In addition, vitamin D could contribute to the success of tuberculosis treatment.

Keywords: vitamin D, calcitriol, vitamin D deficiency, tuberculosis, tuberculosis treatment

dostupan vitamin, važan za prevenciju tuberkuloze. Pored toga, vitamin D može doprineti uspehu lečenja tuberkuloze.

Ključne reči: vitamin D, kalcitriol, deficit vitamina D, tuberkuloza, tretman tuberkuloze

Introduction

Tuberculosis is a highly prevalent disease worldwide. In 2008, there were globally 9.4 million cases of tuberculosis and 1.8 million deaths from this disease (1). Hypovitaminosis D has been associated with many serious chronic diseases, such as autoimmune and cardiovascular diseases, deadly cancers, as well as infectious diseases including tuberculosis (2). Vitamin D interacts with the immune system and influences the immune response to tuberculosis. Increased risk of tuberculosis has been found in different vitamin D-deficient populations. Genetic polymorphism of the gene responsible for coding the VDR has been associated with host susceptibility to developing active tuberculosis (3).

Sources and Metabolism of Vitamin D

Vitamin D is mainly naturally produced in the skin exposed to ultraviolet radiation. Therefore, vitamin D deficiency is usually found in inhabitants of the countries with a lack of ultraviolet light during the winter months. In these countries, the main sources of vitamin D are food and dietary supplements (4). Wild salmon, sardines, herring and mackerel, fish liver oil, goat milk and eggs are foodstuff rich in vitamin D (2). Both exogenous and endogenous vitamin D are metabolized in the liver to 25-hydroxyvitamin D (25(OH)D), the major circulating form of vitamin D (5, 6). After additional hydroxylation within the kidney, 25(OH)D forms the biologically active form of vitamin D, 1,25 dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), also called dihydroxycholecalciferol or calcitriol. Calcitriol, an active form of vitamin D, is a lipid soluble hormone that interacts with VDRs in target tissues (2).

Definition of Vitamin D Sufficiency

Based on the Institute of Medicine's (US) committee recommendations from 2010, the levels of vitamin D are considered sufficient for adults and children when 25-hydroxyvitamin D serum concentration is 50 nmol/L or higher (6). Vitamin D deficiency, insufficiency, and sufficiency are defined by the experts as <50, 52 to 72, and >75 nmol/L serum levels, respectively. A minimum of 1000 IU of vitamin D_2 or vitamin D_3 is needed daily to provide vitamin D sufficiency in inadequate conditions for cutaneous production of vitamin D_3, such as lack of ultraviolet exposure or when a sunscreen is used. For bone health, it is best when vitamin D levels are at 90–100 nmol/L (36–40 nmol/L). It is considered that 75 nmol/L is the low limit of vitamin D necessary for maintaining healthy bones (7). When 25(OH)D levels are >75 nmol/L, parathyroid hormone levels begin to reach their peak and intestinal calcium absorption in adults is maximized (6).

There is increasing evidence of vitamin D deficiency in some populations. In the Serbian population, only 8% of individuals have sufficient 25(OH)D concentrations (>75 nmol/L), while about two thirds (68.5%) are vitamin D deficient (25(OH)D <50 nmol/L) (7–9).

The Health Benefits of Vitamin D

Vitamin D has an important role in numerous physiological functions. Parathyroid hormone (PTH) and calcitriol have a key role in bone formation and resorption, the two processes crucial for maintaining calcium homeostasis in the body (10).

Vitamin D inhibits inflammatory hyperactivity. It has been found that inhabitants of northern regions have a relatively high prevalence of multiple sclerosis and inflammatory bowel disease due to the lack of sunlight (11). Additionally, vitamin D deficiency is linked to many other autoimmune diseases including type one diabetes mellitus, rheumatoid arthritis, and SLE (10). Also, the majority of the analyzed patients with multisystem sarcoidosis had vitamin D deficiency (12).

In vitro studies have shown that calcitriol acts against MBT. Calcitriol induces the antimycobacterial peptide cathelicidin. Cathelicidin is involved as the first line of defense in the prevention of infections caused by mycobacteria, including tuberculosis (14). Vitamin D receptors (VDR) are expressed on antigen-presenting cells and activated lymphocytes. VDR control the immune response by regulating the transcription of genes responsive to vitamin D. Calcitriol modulates the host response to mycobacterial infection by induction of reactive nitrogen, and oxygen intermediates suppression of matrix metalloproteinase enzymes implicated in the pathogenesis of pulmonary cavitation (13).

In vitro and *in vivo* studies have demonstrated that calcitriol in humans has profound antitumor activity in leukemia, squamous cell carcinoma, and prostate, breast, and colon cancer. Calcitriol has antiproliferative effects on multiple tissues by regulating cell proliferation, differentiation and apoptosis (15). It is estimated that the risk for developing colorectal, breast, and prostate cancer could be reduced by 30 to 50% by either increasing vitamin D intake (at least 1000 IU/d) or increasing sun exposure to raise the blood levels of vitamin D to 25(OH)D >75 nmol/L. It has been suggested that women with vitamin D deficiency are at increased risk for developing colorectal cancer of 253%. On the contrary, in women whose four-year intake of vitamin D_3 is 1500 mg/day calcium and 1100 IU/day vitamin D_3, risk for developing cancer is reduced by >60% (16).

Vitamin D as a Modulator of the Immune System

Vitamin D has an important role in the immune response. It participates in the genetic regulation of cytokine production, and has direct effects on T and B cells as well as their responses to activation. It has been shown that vitamin D in B cells inhibits antibody secretion and autoantibody production. Calcitriol inhibits proliferation of T lymphocytes. Vitamin D has immunomodulatory effects on various cells of the immune system, such as inflammatory dendritic cells, T cells, B cells, plasma cells, macrophages, and antigen-presenting cells (APC), as well as inhibitory effects on the secretion of interleukins. It has been found that vitamin D promotes the induction of monocytic differentiation to macrophages and modulates macrophage responses by preventing them from releasing inflammatory cytokines and chemokines. Dendritic cells play a central role in regulating immune activation. Besides being targets for calcitriol immune cells (particularly activated macrophages and dendritic cells), dendritic cells express 1α hydroxylase (the vitamin D-activating enzyme). This enzyme is required for the conversion of vitamin D_3 to calcitriol (the metabolically active form of vitamin D). The 1α-hydroxylase present in immune cells is identical to the renal enzyme. However, the regulation of its expression and activity is different. While the extrarenal regulation of hydroxylase is determined by local factors, such as the production of cytokines and growth factors, and by the levels of 25(OH)D, the regulation of renal 1-α-hydroxylase depends on the ingestion of calcium and phosphate, circulating levels of $1.25(OH)_2D_3$ metabolites, and PTH. It has been shown that vitamin D in B cells inhibits antibody secretion and autoantibody production (10).

Vitamin D and Susceptibility to Chronic Mycobacterial Infections

Hayes et al. (17) have found that poor vitamin D intake and particular VDR alleles are strongly associated with the susceptibility to chronic mycobacterial infections. Calcitriol is an immunomodulator that modulates both innate and adaptive immune responses (18) and plays a relevant role in the immune response to *M. tuberculosis*. Vitamin D functions in the immune system are numerous: it increases chemotaxis and phagocytosis of monocytes, macrophages and dendritic cells; is involved in regulation of the differentiation and activation of CD4 lymphocytes; increase in the number and function of regulatory T cells, reduction in the production of cytokines, interferon-g, IL-2, and TNF-α by Th1 cells, and stimulation of the function of Th2 helper cells; inhibition of the production of IL-17 by Th1 cells (18). Vitamin D influences formation of the phagolysosome and production of LL-37, the antimicrobial peptide which has a direct bactericidal activity and an immune-regulating function. The biological mechanisms underlying the modulation of the immune system by vitamin D are still being studied (19, 20). However, two possible mechanisms have emerged as the most likely. It appears that, in infected macrophages, 1,25-dihydroxyvitamin D3 reduces the viability of MBT by enhancing the fusion of the phagosome and lysosome. In the presence of 1,25-dihydroxyvitamin D3, the capacity of MBT to prevent macrophage maturation and formation of the phagolysosome is completely reversed. The pathways which are used for the promotion of the vitamin D-induced phagolysosome formation are independent of the classical interferon-gamma (IFN-gamma)-dependent macrophage activation and involve the products of phosphatidylinositol-3-kinases (PI3K), which help in regulation of the transport of endosomes to lysosomes (21). In addition, calcitriol may enhance the production of LL-37. LL-37 is a peptide of the cathelicidin family which has been identified in human alveolar macrophages, lymphocytes, neutrophils, and epithelial cells (19, 22). In addition to having microbicidal activity for MBT, LL-37 also modulates the immune response by attracting monocytes, T cells, and neutrophils to the site of infection. LL-37 induction by calcitriol may play a role in the host's defense against TB infection. The presence of calcitriol in neutrophils and macrophages upregulates the hCAP-18 gene that codes for LL-37 in a dose-dependent manner. Serum levels of vitamin D greater than 75 nmol/L provide an adequate macrophage-initiated innate immune response to MBT. However, immune response may be impaired when serum levels of vitamin D are lower than 50 nmol/L (23).

The vitamin D receptor is characterized by polymorphism and presence in different tissues including numerous cells of the immune system. Calcitriol binds to vitamin D receptors and regulates the transcription of genes which are responsive to vitamin D. Patients with pulmonary tuberculosis who are carriers of the *t* allele of the *Taq*I vitamin D receptor polymorphism have more rapid conversion of sputum culture. On the contrary, being a carrier of the *f* allele of the *Fok*I vitamin D receptor polymorphism has been associated with a reduction in transcriptional activity, reduction of calcitriol-induced phagocytosis, and a slower sputum culture conversion in pulmonary tuberculosis (24, 25).

Vitamin D Supplementation

Based on the results of *in vitro* studies, clinical research and population studies, vitamin D could play an important role in the treatment of tuberculosis. Vitamin D requirements in adults differ widely, depending on whether physiological replacement or pharmacological dosing is desired and which treatment is preferred (daily or intermittent bolus). The minimum vitamin D requirement is 400 IU/day at all ages. According to the 2010 guidelines, doses of 1000 IU daily, or up to 600 000 IU given as a one-off bolus in adults, have been recommended for the treatment of vitamin D deficiency (6). The dose of vitamin D depends on the indication.

Vitamin D supplementation may be beneficial in patients suffering from autoimmune disorders such as multiple sclerosis and diabetes type one (10). However, vitamin D supplementation during TB treatment remains controversial. A few studies have reported clinical improvement in pulmonary TB (15, 24) and one study reported no effect (16). Martineu et al. (24) have indicated that tuberculosis can be cured faster with high doses of vitamin D. They administered vitamin D3 in doses of 2–5 mg four times during the treatment (at the beginning of the treatment and every 14 days after starting standard tuberculosis treatment).

Comparative Analysis of Vitamin D Status

Vitamin D deficiency might predispose individuals infected with MBT to develop tuberculosis. A study conducted in Pakistan found that 79% of people who developed tuberculosis had vitamin D deficiency. Risk that healthy people infected with TB through household contacts could develop TB was dependent on the severity of vitamin D deficiency (26). Meta-analysis of 7 case-control studies conducted in different ethnic populations (including the Indian population) showed that 70% of healthy controls had higher vitamin D levels compared to untreated TB patients (27). These results are in concordance with the data from studies from Australia which analyzed African immigrants. It has been found that lower mean levels of vitamin D were associated with high probability of latent, current, or past TB infection (28).

A cross-sectional study conducted in Tanzania among the patients with tuberculosis showed that mean levels of vitamin D were lower in patients with culture-positive tuberculosis compared to patients with culture-negative tuberculosis (29). Monahan and Clarke's meta-analysis of the studies published between 1980 and 2006 analyzed the association between low serum vitamin D and risk of active tuberculosis in humans. Low serum levels of vitamin D were associated with a higher risk of active tuberculosis. Susceptibility to develop disease after being infected with MBT and response to the treatment of tuberculosis are influenced by host genetic polymorphisms in the VDR gene and other genes involved with vitamin D metabolism and function (4, 27, 30). The conversion of culture tests was significantly faster in TB patients with the *tt* or *FF* VDR genotypes than in patients with the *TT/Tt* and the *Ff/ff* VDR genotypes. The results of a multicenter randomized controlled trial conducted among 146 patients (62 assigned to 2.5 mg vitamin D3, 64 assigned to placebo) with smear-positive pulmonary tuberculosis revealed that vitamin D did not significantly affect time of sputum conversion from positive to negative in the whole study population (median time was 36.0 days in the intervention group and 43.5 days in the placebo group; p=0.14). However, vitamin D significantly accelerated the conversion of sputum culture in participants with the *TT* genotype of the *TaqI* vitamin D receptor polymorphism (24).

Conclusion

Vitamin D deficiency has been associated with host susceptibility to developing active tuberculosis. As vitamin D deficiency could increase the susceptibility of individuals to develop tuberculosis, vitamin D supplementation could play an important role in the prevention of this disease. In addition, vitamin D supplementation may contribute to tuberculosis treatment success.

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Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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