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REVIEW / DERLEME

Tuberculosis and vitamin D

Tüberküloz ve D vitamini

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ABSTRACT

Tuberculosis (TB) is still highly prevalent world-wide accounting for over one million deaths annually. Especially the multi drug-resistant *Mycobacterium tuberculosis* necessitates the development of new agents to enhance the response to antimicrobial therapy for active TB. In the pre-antibiotic era, vitamin D was used to treat TB. However, after the development of antituberculosis agents, it lost its importance. Recently, its active metabolite, 1,25-dihydoxyvitamin D, was shown to enhance the immune response to mycobacteria. Vitamin D does not have a direct killing effect but 1,25-dihydoxyvitamin D, is a modulater of the immune system. The synthesis of 1,25-dihydroxyvitamin D promotes the production of endogen defensin and cathelicidin. These products have a direct lethal effect on bacteria and intracellular microorganisms like *M.tuberculosis*.

In this review, the role of vitamin D in host resistance to *M.tuberculosis* infection and its effect for supplementation therapy is discussed.

Keywords: Tuberculosis, Vitamin D, 1,25-dihydoxyvitamin D, Immune response, Defensin, Cathelicidin

ÖZET

Tüberküloz, hala tüm dünyada yılda bir milyondan fazla kişinin ölümüne yol açan en yaygın hastalıklardan biridir. Özellikle çoklu ilaca dirençli *Mycobacterium tuberculosis* enfeksiyonlarında antimikrobiyal tedavi cevabını arttırmak için yeni ajanların gelişimine ihtiyaç duyulmaktadır. Antibiyotik öncesi dönemde tüberküloz tedavisinde kullanılan D vitamini, antitüberküloz ilaçların gelişimiyle önemini yitirmiştir. Son zamanlarda D vitamini aktif metaboliti, 1,25-dihydroxyvitamin D'nin mikobakterilerde bağışık yanıtı arttırdığı bilinmektedir. D vitamininin direkt öldürücü etkisi yoktur, ancak 1,25-dihydoxyvitamin D, bağışık yanıt üzerinde modülator görevi yapar. 1,25-dihydroxyvitamin D sentezi endojen defensin ve katelisidin sentezini arttırır. Bu ürünlerin bakterilere ve *M.tuberculosis* gibi hücre içi yerleşimli mikroorganizmalara direkt ölümcül etkileri vardır.

Bu derlemede, D vitamininin, *M.tuberculosis* enfeksiyonunda konak direncindeki rolü ve destek tedavisi ile ilgili etkileri tartışılmıştır.

Anahtar Kelimeler: Tüberküloz, D Vitamini, 1,25-dihydoxyvitamin D, Bağışık yanıt, Defensin, Katelisidin

Introduction

Tuberculosis (TB) is still a global health problem. In 2012, there were an estimated 8.6 million new cases of TB and 1.3 million people died from TB [1]. The resistant *M.tuberculosis* represents a threat that calls for new approaches in therapy of active TB infections.

An association between infection and nutritional rickets, the prototypical disorder of vitamin D deficiency, has its origins in observations from the 17th to 19th centuries. Vitamin D was accepted as very important for the prevention of infectious diseases in the pre-antibiotic area. The first clinical use of cod liver oil, rich of vitamin D for the treatment of tuberculosis was in 1849. Later, before the use of effective antimicrobial therapy, high doses of vitamin D3 were a choice for skin and pulmonary TB [2]. There were rachitis outbreaks between 1650 and 1930 in Britain and in other North European countries and Robert Koch thought that an infectious agent was the primary etiologic factor of rickets [3]. In

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1903, Dr. Niels Finsen won the Nobel prize for introducing the use of ultraviolet radiation on the skin of tuberculosis patients for the treatment of tuberculous skin lesions [4]. Purified and crystalized vitamin D2, was used in the treatment of TB in 1931 [5]. However, from the mid 1950s antituberculosis drugs took the place of vitamin D.

Recently, many studies about the effect of vitamin D on the immune system have established a relation between hypovitaminosis of vitamin D and host immune reactions to TB infections. In this review, the relation between TB and hypovitaminosis of vitamin D and also the role of vitamin D supplies in the prevention and treatment of TB, especially those caused by multi drug resistant (MDR) strains, is evaluated.

Vitamin D:Endocrine metabolism

Vitamin D is an essential micronutrient. Although vitamin D is commonly called a vitamin, it is synthesized in the body therefore it is also called a hormone. It is composed of sterol and vitamin D can be ingested in the form of vitamin D3 or vitamin D2 (ergocalciferol). Vitamin D2 is derived by irradiation of the fungal steroid ergosterol. Vitamin D3 (specifically cholecalciferol) produces 1,25-dihydroxyvitamin D (1,25-(OH)2D) from cholesterol by the action of the 25-hydroxylase enzyme under adequate sun exposure. Finally, 25-hydroxyvitamin D is transformed by the enzyme 25-hydroxyvitamin D-1-α-hydroxylase (CYP27B1) into 1,25-(OH)2D, the active form of vitamin D. 7-dehydrocholesterol, in the stratum basale and stratum spinosum of the skin, is transformed into cholecalciferol by ultraviolet B (UVB). Classical effects of vitamin D are on bone and calcium metabolism, however, non-classical effects of vitamin D are getting more attention recently [6].

Vitamin D:Immunologic effects

The first reports on extra renal production of vitamin D was provided when high levels of active vitamin D were obtained in patients with TB and sarcoidosis in the 1980s. Later it was explained that skin, breast, prostate, lung and brain can also produce vitamin D. Non-classical effects can be categorised as; 1. regulation of immune functions, 2. regulation of cell proliferation, 3. regulation of hormone secretion.

Regulation of immune functions is based mainly on the presence of vitamin D receptors (VDRs) in activated human inflammatory cells. Activated human inflammatory cells, like macrophages, can produce active metabolites of vitamin 1,25-(OH)2D which inhibit T cell proliferation [7, 8].

Innate Immunity

Innate immunity is based on the activation of toll-like receptors (TLRs), present in both inflammatory cells (polymorphonuclear cells, monocytes, and macrophages) and in epithelial cells of the epidermis, gingiva, intestine, vagina, bladder, and lungs. When TLRs are stimulated by an antimicrobial peptide of a micro-organism, macrophages take in 25-hydroxyvitamin D from the extracellular fluid by endocytosis. The macrophages synthesize 1,25 (OH)2D and this binds to VDR. Activation of VDR increases the production of endogen defensin and cathelicidin. These products have a direct lethal effect on bacteria [7,8].

Adaptive Immunity

Vitamin D exerts an inhibitory effect on adaptive immunity. It inhibits the differentiation of B cells to plasma cells and immunglobulin production as well. It also inhibits T lymphocyte proliferation. T lymphocytes stimulated by antigen can direct the immune response to Th1 or Th2 according to the expressed cytokines. 1,25(OH)2D inhibits T cell proliferation, in particular that of the Th1 cells capable of producing IFN-γ and IL-2 and activating macrophages and Th17 cells capable of producing IL17 and IL22. In contrast IL-4, IL-5, and IL10 production is increased, shifting the balance to a Th2 cell phenotype. Dendritic antigen-presenting cells (APC) contain VDR. Mature APC cells are affective for the production of Th1 and proinflammatory cytokines; IL- 12. 1,25(OH)2D reduces the maturation of dendritic cells and the antigen presenting capability. IL-12 decreases and IL-10 increases (anti-inflammatory cytokines) [7,8]. The ability of 1,25(OH)2D to suppress the adaptive immune system is beneficial for conditions in which the immune system is directed to Th2 [8].

Vitamin D:Pathogenesis of TB

An increased incidence of infectious diseases has been associated with vitamin D deficiency [1]. Anti-mycobacterial activity depends on the immune response of macrophages, T lymphocytes and cytokines. Alveolar macrophages are the first step in the defense mechanism against *M. tuberculosis* infections. In 2006, Liu and colleagues proved that *M. tuberculosis* sensing by the toll-like receptor 2/1 (TLR2/1) complex increases expression of VDRs and CYP27B1 in monocytes [9].

The synthesis of 1,25-(OH)2D promotes VDR-mediated transactivation of the antimicrobial peptide cathelicidin. Especially, LL-37 from the family of cathelicidins, an antimicrobial peptid is increased [10,11]. Cathelicidins can be present in many different species of mammals, however LL-37 is the only cathelicidin in humans. It is present in alveolar macrophages, lymphocytes, neutrophils, and epithelial cells. The increase in the production of cathelicidin can cause killing of intracellular *M. tuberculosis.*

In some studies, it has been reported that, 1,25-(OH)2 D3 increases cell protection, by limiting the growth of bacilli in monocytes and macrophages [12]. Another study, has shown that *M. tuberculosis* causes cell damage by superoxide degration [13]. Pathogens living in macrophages, and that inhibit phagosome-lyzosome fusions can live in macrophages. The crucial role played by vitamin D in the immune response to *M. tuberculosis* consists of promoting phagolysosome formation as well as the production of the LL-37.

In 2006, Liu demonstrated that transcriptional regulation of cathelicidin can be mediated by activation of 1,25-(OH)2D. Stimulation of TLR receptors and of the C type lectin receptor, Dectin-1, in macrophages by microbial products results in increased conversion from the inactive 25-hydroxyvitamin D to the active 1,25-(OH)2D [14, 15]. According to Adams and colleagues, one consequence of TLR activation is the production of defensin-2 and of cathelicidin: these two antimicrobical peptides are strongly up-regulated by 1,25-(OH)2D. While the production of IL-6, TNFα and interferon-γ (IFNγ) decreases, IL-10 increases. These low

levels of proinflammatory cytokines, cause TLR 2, 4 and Dectin-1 transcription and VDR inhibition [16,17].

Epidemiologic data have identified hypovitaminosis of vitamin D as an important factor in TB prevelance and sensitivity to the active disease [18-20]. Therefore, vitamin D supplementation may represent a new strategy for prevention of TB and for the shortening of TB treatments in the face of growing drug resistance.

Wilkinson compared the levels of serum 25-hydroxyvitamin D in Indians living in London with active TB infections (n:126) with levels in a healthy control group (n:116). In this study, the serum levels of vitamin D3 were found to be as low as 81.7% in the active TB group and 36.2% in the control group. Hypovitaminosis of vitamin D and TB infection has also a strong relation in African immigrants. Serum levels of 25-hydroxyvitamin D3 are below 25 nmol/L in 78% and 33% of active and latent TB patients respectively [21].

In a study, from Turkey, the role of 25-hydroxyvitamin D in the pathogenesis of TB was investigated by determining serum levels in patients with active pulmonary TB. In these patients, serum levels of 25-hydroxyvitamin D were 3 fold lower than those in a healthy control group ($p<0.001$) [22]. Therefore, it was reported that the decreased 25-hydroxyvitamin D concentrations in patients with active TB could be the cause of active infection.

Vitamin D: TB Treatment

Besides the effects of vitamin D3 in modifying the immune system, therapeutic role raise some important questions. Prospective studies with vitamin D3 have been done on treatment of multidrug-resistant TB [22]. In a study from Indonesia, pulmonary TB patients (n:34) treated with anti TB drugs and with vitamin D3 were compared with patients (n:33) who had been treated only with anti TB drugs and placebo in terms of sputum conversion (Change of ARB positivity to ARB negativity), and radiological improvement. The sputum conversion was 100% in the vitamin D-supplemented group whereas it was 77% in the placebo group. The percentage of radiological improvement on x-ray images showed improvement in 87.5% of the vitamin D group and in 65% of the placebo group [20]. In another study from the USA, a black woman with pulmonary TB was treated with directly observed therapy (DOT)(INH,RP,PRZ,ETB) for the first 4 months, after diagnosis. At the end of this period, it was discovered that weight loss and culture positivity continued and this was accepted as a treatment failure. Since at that time the serum 25-hydroxyvitamin D3 level was found to be low (7ng/ml), therapy was supplemented with vitamin D and radiological healing and culture negativity was demonstrated at the end of 12 months [24]. In a multi center study from Pakistan, 259 pulmonary TB patients, were evaluated to determine whether vitamin D supplementation could influence recovery. Supplementation with high doses of vitamin D accelerated clinical and radiographic improvement in all TB patients. These results suggest a therapeutic role for vitamin D in the treatment of TB [25].

Conclusions

Although the host immune system quickly responds to the presence of *M. tuberculosis*, bacilli can develop several ways to escape. Vitamin D by both inhibiting phagolysosome fusion and producing the antimicrobial peptide LL-37, plays a role in the immune response to *M. tuberculosis*. Vitamin D supplementation could be a low-cost, practical method to protect groups of people with a high incidence of TB and for people undergoing treatment for TB and those with latent TB infection.

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