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The role of vitamin D in immunoadjuvant therapy for tuberculosis depending on the HIV status of patients

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ABSTRACT

Search queries were conducted in the PubMed and eLIBRARY.ru databases using keywords, including publications from 2018–2024. A review of the literature on vitamin D deficiency in patients with tuberculosis (TB), human immunodeficiency virus (HIV), and TB/HIV combination is presented, which revealed heterogeneous prevalence. The roles of vitamin D in the body immune response to TB are shown depending on the presence of HIV infection. The data on the therapeutic use of single and prolonged administration of vitamin D at various doses in adjuvant TB therapy are presented. The prospects for the use of vitamin D in the combined treatment of TB patients are outlined depending on the HIV status, especially with multidrug-resistant pathogens requiring study in Russian clinical trials.

Keywords: tuberculosis, HIV, immunity, vitamin D, adjuvant immunotherapy, host therapy

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Роль витамина D в иммуноадъювантной терапии туберкулеза в зависимости от ВИЧ-статуса пациентов

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РЕЗЮМЕ

В базах данных PubMed и eLIBRARY.RU по ключевым словам были проведены поисковые запросы, включающие публикации за 2018–2024 гг. Представлен анализ литературы о дефиците витамина D у больных при туберкулезе (ТБ), вирусе иммунодефицита человека (ВИЧ), в сочетании ТБ и ВИЧ, который выявил неоднородную распространенность. Показана роль витамина D в иммунологическом ответе организма при ТБ в зависимости от наличия ВИЧ-инфекции. Приведены данные терапевтического при-

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менения в качестве адьюванта к химиотерапии туберкулеза витамина D в различных дозировках в однократном и пролонгированном введении. Обозначены перспективы использования витамина D в комбинированном лечении больных ТБ в зависимости от ВИЧ-статуса, особенно со множественной лекарственной устойчивостью возбудителя, требующие изучения в российских клинических исследованиях.

Ключевые слова: туберкулез, ВИЧ, иммунитет, витамин D, адъювантная иммунотерапия, терапия хозяина

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

In the Russian Federation, there are three key factors significantly influencing further epidemiological situation associated with tuberculosis. The first factor is a high level of multidrug resistance (MDR) of the causative agent of the disease. Currently, every third patient with newly diagnosed respiratory tuberculosis is infected with Mycobacterium tuberculosis (MBT) that is resistant to at least rifampicin. On the whole, Russia has not seen significant changes in the detection rate of such cases recently. However, in Siberian regions, such as the Kemerovo, Tomsk, and Novosibirsk regions, a steady increase in the detection rate has been noted since 2019, exceeding the national value of the parameter [1].

The second problem is associated with a large number of patients with human immunodeficiency virus (HIV) and tuberculosis (TB). In these regions, despite the overall decrease in the proportion of HIV-infected individuals among the population, the incidence of TB and HIV infection is high. In 2023, it was 48.7, 43.2, and 35.8 cases per 100,000 population, respectively [2, 3]. The third aspect is insufficient effectiveness of anti-TB therapy, which is also related to the above two circumstances. Currently, Russia has not achieved the values for the effectiveness of TB treatment recommended by the World Health Organization, especially in treatment regimens for patients with multidrug- / extensively drug-resistant MBT.

Therefore, in addition to introducing new anti-TBs drugs into clinical practice, methods of immune-mediated therapeutic strategies are being actively developed. Their candidates and technologies will not only enhance the potential of etiological treatment but also have immunomodulatory effects [4, 5].

In this regard, the aim of this work was to summarize current data on the role of vitamin D in the immunological response to TB infection, as well as the results of its use as adjuvant therapy in patients with TB, HIV infection, and TB / HIV. The research involved the analysis of scientific papers published in English and Russian. Search queries were conducted in the PubMed and eLIBRARY.ru databases using the following keywords in English: tuberculosis, HIV, immunity, vitamin D, adjuvant immunotherapy, host therapy. The search was mainly limited to the time frame of 2018–2024.

At the initial stage of the analysis, current data on the role of vitamin D in protecting the body from infectious agents, including TB and HIV infection, were identified. At the second stage, following the results of systematic reviews and meta-analyses, information on vitamin D levels in patients with TB and TB/HIV was updated. In the third phase of the study, individual publications were analyzed, which represented randomized controlled trials on vitamin D levels compared to healthy controls, depending on patients' age, localization of the process, disease duration, MBT sensitivity to anti-TB drugs, and the presence of HIV infection.

THE EFFECT OF VITAMIN D ON MECHANISMS OF NONSPECIFIC AND SPECIFIC BODY DEFENSE AGAINST INFECTIOUS AGENTS

Table 1 presents the main immunomodulatory properties of vitamin D, summarized in recent scientific reviews [6–10]. In the human body, vitamin D is obtained through foods or produced in the skin under sunlight exposure. Ultraviolet radiation induces the conversion of 7-dehydrocholesterol into previtamin D3, which is then transformed into vitamin D3 or cholecalciferol. In the liver, vitamin D3 undergoes 25-hydroxylation to form 25-hydroxyvitamin D (25(OH)D), calcidiol, the primary circulating form of vitamin D, a prohormone without inherent hormonal activity. Subsequently, most of the 25(OH)D is converted in the kidneys by 1-α-hydroxylase into the bioactive hormonal form 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) under strict regulation by parathyroid hormone, calcium, and phosphorus levels. In this activated state, vitamin D not only exerts classical endocrine effects, controlling calcium metabolism in blood serum and bone tissue, but also affects the immune system, whose effector cells (monocytes, macrophages, dendritic cells, T- and B lymphocytes) possess vitamin D receptors (VDR).

To date, compelling evidence has been obtained regarding the regulation of 1,25(OH)2D3 innate immune responses in the antimicrobial and antiviral defense of the human body, whose target genes *CYP24A1* and *CYP27B1* induce the expression of genes encoding antimicrobial peptides (AMP), β-defensin 2, and hepcidin. Among these, human cationic antimicrobial protein cathelicidin (hCAP18/LL-37) activates not only the signaling pathways for recognizing and binding to scavenger receptors on the cell surface of pathogens but also induces chemotaxis of neutrophils, monocytes, macrophages, and T cells to the site of infection, facilitating the removal of various pathogens by triggering endocytosis, apoptosis, and autophagy of infected cells. Calcitriol directly affects processes in adaptive immunity, regulates the division of T lymphocytes, slows down the transformation of precursor B cells into plasma cells, inhibits the production of interleukins (IL) and costimulatory molecules associated with Th1 cells, and promotes the production of cytokines associated with the Th2 response [6–10].

Table 1

The Role of Vitamin D in Protecting the Body Against Infectious Agents

Immune components, cells	Mechanism, effect
Nonspecific immunity	
Dendritic cells (DC)	Modulation of DC towards a less mature and more tolerant phenotype with changes in both morphology (more adhesive spindle-shaped cells) and production of cytokines and surface markers; decreased expression of the major histocompatibility complex (MHC) II, differentiation cluster (CD80), costimulatory molecules (CD86) and adhesion molecules (CD54), as well as increased expression of chemokine receptors (CCR5), antigen uptake (DEC205), costimulatory protein of antigen-presenting cells (CD40), mature macrophage molecules (F4/80).
Macrophages, monocytes	Acceleration of monocyte maturation into macrophages, enhancement of infected macrophage function through activation of a number of adaptor proteins and kinases that participate in the induction of key antimicrobial factors: CYP24A1, CYP27B1, (CAMP/LL37), DEFB2/DEFB4/HBD2; stimulation of autophagy and autophagosome activity.
Cytokine modulation	Suppression of lipopolysaccharide-mediated production of proinflammatory ILs in monocytes and production of IL-2, IL-6, IL-9, IL-17, IL-21, TNFα, induction of transcription of the gene encoding IL-1β, activation of the receptor activator of nuclear factor kappa-B ligand (RANKL) and cyclooxygenase-2 (COX 2), enhancement of expression of the anti-inflammatory cytokine IL-10 in natural killer cells (NK cells) and Th2 cells, which leads to inhibition of IL-12 and IL-23 production and reduction of IFNγ expression.
Specific immunity	
T lymphocytes	Suppression of T lymphocyte proliferation; reduced activation of T lymphocytes by B lymphocytes through decreased expression of costimulatory molecules (CD860) and increased expression of the differentiation cluster (CD74).
Th1 and Th2 cells	Shifting the balance towards the Th2 cell phenotype and inhibition of Th1 cells by reducing the proliferation of autoreactive T lymphocytes, increasing the level of regulatory T cells (Treg), inducing IL-10 and apoptosis of autoreactive T lymphocytes.
B lymphocytes and plasma cells	Suppression of plasma cell formation by differentiating mature B cells (through modulation of CD40 and nuclear transcription factor (NF-κB)), induction of apoptosis of activated B lymphocytes.

In TB, elements of the MBT cell wall are recognized by Toll-like receptors (TLRs), subtypes of which are stimulated by bacterial ligands. TLR2 together with TLR1 detect antigens of the TB cell wall, mediated through TLR4, which are activated by the 38-kDa MBT antigen. Through the 19-kDa bacterial lipopolysaccharide of the MBT cell membrane, macrophages are stimulated, where 25(OH)

D is converted into an active metabolite through hydroxylation and binds to VDR whose signal passes into the nucleus. This increases gene transcription for hCAP18/LL-37, and cathelicidin and other AMPs are formed [9, 10]. Digestive capacity is enhanced, apoptosis is enhanced, and the antimycobacterial and antiviral potential of infected macrophages is realized, as cathelicidin affects retrovirus replication in HIV infection [11]. Additionally, 25(OH)D increases the level of cytokines (IL-4, 5, 6, 10, 18, INFγ), enhancing both cellular and antibody-mediated immune responses. At the same time, the influence of vitamin D on the expression, secretion, and activity of a number of matrix metalloproteinases (MMPs) has been proven. 25(OH)D reduces the expression of MMP-7, MMP-9, and MMP-10 in human peripheral blood monocytes and increases the expression of tissue MMP inhibitor (TIMP-1), which helps reduce the severity of pulmonary parenchyma destruction and the formation of cavitation during TB inflammation [12].

VITAMIN D DEFICIENCY IN PATIENTS WITH TUBERCULOSIS AND HIV INFECTION

Recent scientific research continues to actively explore the relationship between the detected vitamin D deficiency in TB. The conflicting results of vitamin D levels determined in systematic reviews are explained by the population/genetic/racial characteristics of patients, differing in territorial affiliation, duration of exposure and intensity of natural ultraviolet radiation, standard of living and socio-economic status, as well as age, gender, nutrition, and the presence of concomitant pathology, primarily liver-related one [13–15].

Vitamin D deficiency can also be caused by congenital anomalies in vitamin D metabolism associated with mutations in the cytochrome P450 system (CYP3A4, CYP24A1), which lead to dysregulation of the activity of 24-, 25-, 1α-hydroxylase enzymes that accelerate its inactivation and excretion, as well as mutations in vitamin D receptors leading to the development of target organ resistance [16]. It has been proven that taking certain medications, such as thiazide diuretics, phenytoin, phenobarbital, carbamazepine, and theophylline, affects vitamin D metabolism. Among anti-TB drugs, isoniazid induces the cytochrome P450 enzyme system, thereby changing the level of 25-hydroxylases and 1-hydroxylases, while rifampicin activates CYP3A4 [9, 17]. Among antiviral drugs used to treat HIV-infected patients, efavirenz alters vitamin D levels and induces CYP24A1 enzymes that promote the breakdown of 25(OH)D and active vitamin D 1,25(OH)2D3 into inactive water-soluble metabolites [18].

Until 2024, optimal vitamin D concentrations in blood serum were recognized as values ranging from 30 to 100 ng / ml (75–250 nmol / l). Insufficiency was recognized at 20–30 ng / ml (50–75 nmol / l), and deficiency was noted at < 20 ng / ml (< 50 nmol / l). Currently, clinical guidelines from global endocrinology experts have determined that vitamin D deficiency in the human body, which should be artificially replenished, needs to be re-evaluated [19]. This is especially important considering the growing evidence of the role of vitamin D in innate immunity against infections, diabetes mellitus, cancer, autoimmune, cardiovascular, and other diseases.

In this regard, scientific publications of randomized controlled trials (RCTs) of recent years deserve consideration, including data on vitamin D levels in the blood serum of patients with TB of various localizations, comparable in age and gender with healthy controls (Table 2). Unfortunately, there is no current comparative analysis of 25(OH)D content in the blood serum in the Russian cohort of patients. During the specified period, only values for children and adolescents with TB were published [20, 21]. The study by L.V. Panova deserves attention, where out of 75 patients under the age of 18 years, 49.3% had a concentration of 25(OH)D in the blood serum of less than 10 ng / ml, and significant differences were found in the level of 25(OH) D in the groups of newly diagnosed patients and those with repeat admissions: 13.10 ± 1.04 ng / ml and 8.74 ± 1.07 ng / ml, respectively.

Table 2

Vitamin D Levels in the Blood Serum of Patients with Tuberculosis (according to Case – Control Studies, 2018–2024)

Country	Sample (*n*), TB / HC	Age (years), men / women	Tuberculosis localization, *n*	$M \pm m$ or Me (Q_1; Q_3), ng / ml	Year, reference
Russia	75, 75 / no HC	TB – up to 17, 29/46	PTB, 75	13.10 ± 1.04 (newly detected TB) 8.74 ± 1.07 (TB relapse)	2024, [20]
Russia	31, 31 / no HC	TB – up to 14, 13/18	PTB, 31	14.60 ± 1.30	2024, [21]

End of table 2

Country	Sample (n), TB / HC	Age (years), men / women	Tuberculosis localization, n	$M \pm m$ or Me (Q_1; Q_3), ng / ml	Year, reference
India	116, 58/58	TB – 50, 31/27 HC – 49, 32/26	PTB, 29 EPTB , 29	PTB – 15.30 (8.63, 23.47) EPTB – 13.40 (8.47, 25.72) HC – 19.08 (13.92, 26.17)	2024, [16]
India	400, 200/200	TB – 32, 130/70 HC – 33, 120/80	PTB, 122 EPTB, 78	PTB – 18.02 ± 7.58 EPTB – 17.26 ± 6.58 HIV (-) – 17.65 ± 7.26 HIV (+) – 17.48 ± 7.13 DS-TB – 17.82 ± 7.36 MDR-TB – 17.25 ± 6.50 HC – 32.34 ± 13.79	2024, [22]
Egypt	89, 47/42	TB – 32, 25/22 HC – 31, 22/20	PTB, 47	TB – 17.1 ± 5.5 HC – 51.8 ± 27.3	2024, [23]
Uganda	95, 78/22	TB – 28, 37/46 HC – 28, 9/13	PTB, 78	TB – 17 (12.6, 21.4) LTB – 23 (16, 29.2) HC – 22 (16.7, 27.8)	2022, [24]
India	100, 50/50	All over 18 years, TB – 88/12 HC – 88/12	PTB, 50	TB – 19 (7.75, 27.25) HC – 25 (19.75, 32.00)	2021, [25]
Peru	889, 180/709	TB – over 25 years 50.6%, 94/86 HC – over 25 years 49.5%, 366/343	PTB, 180	TB – 21.5 (17.1, 25.6) HC – 21.9 (44.5-67.1)	2019, [13]
Brazil	72 24/48	TB – 32, 24/0 HC – 33, 48/0	PTB, 24	TB – 27.7 ± 7.85 HC – 37.1 ± 8.94	2018, [26]

Note. TB / HC – tuberculosis / healthy controls, PTB – pulmonary tuberculosis, EPTB – extrapulmonary tuberculosis, LTB – latent tuberculosis infection, DS-TB – drug-susceptible tuberculosis, MDR-TB multidrug-resistant tuberculosis.

Recent studies from Asia and Africa have demonstrated vitamin D deficiency in adult TB patients, and that characteristics of the disease (localization, drug sensitivity of MBT, presence of HIV) do not affect its concentration [16, 22]. In these studies, vitamin D deficiency was considered as a predisposing factor for the development of TB, as its insufficiency was recorded in patients at the initiation of anti-TB treatment. A case-control study from India showed that the prevalence of vitamin D insufficiency in TB patients according to accepted criteria was 68.9% compared to 51.7% in the control group, with medians of 14.35 ng / ml (8.65, 25.48) and 19.08 ng / ml (13.92, 26.17), respectively [16]. In another study from the same country, the concentration of 25(OH)D in pulmonary tuberculosis (PTB) was slightly higher (18.02 ng / ml) and did not change significantly in patients with extrapulmonary TB (EPTB), in TB patients with cooccurring HIV, and in patients with drug-resistant TB. Similar data were presented by scientists from African countries.

On the contrary, research results from South America (Brazil, Peru) did not reveal vitamin D insufficiency, medians of 25(OH)D in TB patients exceeded 20 ng / ml and were comparable to values in people with latent tuberculosis infection (LTB) and patients who had disease progression. Researchers from European countries indicated a range of vitamin D close to normal (from 20 to 30 ng / ml) in TB patients with its associations with the disease, its spread (tuberculosis of multiple localizations), and comorbid HIV [27].

A notable randomized clinical trial from India compared the concentrations of vitamin D, calcium, and parathyroid hormone in the blood serum of patients with PTB not only with healthy controls but also depending on MBT sensitivity to anti-TB drugs. Randomization in the study groups excluded patients with concomitant pathology of the liver, kidneys, heart, gastrointestinal tract, and as well as with HIV infection. For the first time in such studies, the dietary and insolation characteristics of patients were determined in parallel. The results of the trial convincingly demonstrated that patients with MDR-TB had lower baseline concentrations of vitamin D in their blood serum than patients with DS-TB and controls. At the same time, vitamin D consumption through food had a greater impact on its level than weekly exposure to sunlight [28].

In HIV-infected patients, a similar situation was observed in cohort studies with gender-, age-, and residence-matched controls. Only studies from China, India, and the United States recorded vitamin D levels below 20 ng / ml (15.93 (13.92, 17.94) ng / ml, 19.7 (17.64, 21.76) ng / ml, and 19.09 (13.43, 24.750) ng / ml, respectively). In other countries, according to systematic reviews and meta-analyses, these values in HIV-infected individuals did not significantly differ from the controls [29]. Despite this, a relationship was found between vitamin D deficiency and the risk of disease progression to the stage of acquired immunodeficiency syndrome and all-cause mortality, as vitamin D deficiency prevalence reached 85% [18]. Meanwhile, inflammatory processes characteristic of HIV infection and immune system activation, leading to increased levels of IL-6 and TNFα and impaired renal 1α-hydroxylase activity, exacerbate vitamin D insufficiency in patients with TB/HIV co-infection [30].

ADJUVANT VITAMIN D THERAPY FOR TUBERCULOSIS AND HIV INFECTION

In clinical phthisiology practice, increasing evidence is accumulating about the positive effects of combination treatment. In studies of patients with TB undergoing chemotherapy with vitamin D administration (total dose of 600,000 IU), positive clinical and radiological dynamics are demonstrated in the form of weight gain in patients, reduced intoxication, cough, and normalization of hematological parameters, as well as a pronounced decline of infiltrative and destructive processes in the lungs compared to the control group [31, 32]. This applies to both adults and children (1,000 IU / day) [33, 34]. There is evidence that a single administration of vitamin D at a dose of 200,000 IU during PTB treatment leads to reduction of sputum conversion time compared to the group receiving only standard anti-TB treatment [35].

In patients with type 2 diabetes mellitus and PTB, a negative acid-fast bacillus smear was obtained after 6 weeks of anti-TB treatment and vitamin D intake (total of 60,000 IU per week) compared to 8 weeks of conventional treatment in the control group [36]. In some studies, vitamin D administration regimens were prolonged. A relatively similar positive effect was achieved after daily intake of vitamin D at a dose of 10,000 IU (250 μg / day) for 6 weeks for PTB and oral administration of 50,000 IU once a week for 6 weeks (total of 300,000 IU) with a maintenance dose of 1,000 IU per day for 3 months of treatment for EPTB [37].

The largest (*n* = 4,000) double-blind, placebo-controlled study assessing the impact of combining vitamin D and antiretroviral therapy on the development of TB and mortality in adult HIV-infected patients was conducted in Tanzania [38]. Antiviral treatment and oral administration of four doses of vitamin D (50,000 IU) once a week with a prolonged administration of 2,000 IU per day did not affect mortality and did not increase patient one-year survival compared to patients in the placebo control group. Later, a comprehensive systematic review and meta-analysis including 14 studies formulated the same conclusions [39]. Additionally, scientists did not find the expected positive effect on the number of CD4+ cells in microliters of peripheral blood and viral load. Similarly, in TB, as well as in TB/HIV co-infection, mortality and recurrence rates did not differ in comparison groups depending on patients' vitamin D intake. No effect of vitamin D intake on sputum conversion time was found, either by smear microscopy or culture.

Thus, based on the published research, no statistical differences have been found in the effectiveness of TB treatment, including cooccurring HIV / TB treatment, in patient groups depending on vitamin D intake. The noted positive clinical effects of combined anti-TB treatment with vitamin D intake, such as faster reduction of intoxication symptoms, normalization of acute-phase proteins in peripheral blood, and impact on destructive processes in the lungs, require further study.

CONCLUSION

In the global medical community, research focused on developing host-directed therapy has intensified [4, 5, 39, 40]. Today's challenges for phthisiology require not only progress in creating new anti-TB drugs and repurposing existing medicinal compounds but also re-engineering of multifunctional personalized immunotherapy. Immune activators or suppressors based on chemical compounds, drugs with immunomodulatory properties, interleukins, granulocyte-macrophage colony-stimulating factor, cell therapy based on allogeneic immune effector cells, as well as new drugs obtained through nano- and biotechnologies, can make an effective contribution to schemes for combined anti-TB therapy aimed primarily at reducing treatment duration and increasing safety and clinical effectiveness.

Stimulation of receptor-induced expression of antimicrobial peptides, induction of autophagy, as well as regulation of proinflammatory cytokine secretion and modulation of matrix metalloproteinase production comprise the potential of immunoadjuvant therapy for TB patients using vitamin D. Currently, due to the lack of data, Russian specialists have not reached a consensus regarding the use of vitamin D in chemotherapy regimens (standard / individual), age categories of patients (newly diagnosed / relapse / chronic course), localization of the process, as well as comorbid HIV. Therefore, initiating clinical trials on the use of vitamin D in TB and HIV infection, taking into account individual patient characteristics, is a pressing issue for developing clinical guidelines.

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