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# Clinical and Morphological Features of Vitamin D in the Formation of Anti-Infectious Immunity

**Xalimova Yulduz Salokhiddinovna**

Department of Clinical Sciences, Asian International University, Bukhara, Uzbekistan

**ABSTRACT**

The review article provides up-to-date data on the immunotropic and anti-infectious effects of vitamin D, the role of vitamin D deficiency in the pathogenesis of certain infections, and target levels of 25(OH)D sufficient to prevent and reduce the severity of infectious diseases of various etiologies. The assessment of the availability of laboratory diagnostics of vitamin D deficiency and deficiency in the conditions of the Central Asian megalopolis was carried out, the authors' opinion on the optimal methods for determining the status of vitamin D for a practitioner was presented.

***KEYWORDS:*** *vitamin D deficiency and insufficiency, antiinfectious immunity, immunoanalysis, ImmunoChem luminescence analysis.*

The prevalence of vitamin D deficiency and insufficiency, according to large population studies, in some countries reaches 80% among men and women. The main function of vitamin D is the regulation of calcium homeostasis; other biological effects include the regulation of rapid proliferation and differentiation of several cell populations, including keratinocytes, endothelial cells, osteoblasts and lymphocytes. In vitro and in vivo experiments revealed a significant effect of vitamin D metabolites on immunogenesis.

The aim of the work is, based on the analysis of domestic and foreign literature, to clarify the target levels of 25(OH)D sufficient for the prevention and reduction of the severity of infectious diseases of various etiologies, to identify the optimal method, from the point of view of a practitioner, for determining the status of vitamin D and to assess the availability of laboratory diagnostics of vitamin D deficiency and deficiency

**The immunomodulatory effect of vitamin D**

The main circulating precursor of active vitamin D molecules is 25(OH)-vitamin D (25-D). The biologically active form — 1,25 (OH)- vitamin D (1,25-D) is formed under the influence of the enzyme 25-hydroxy-vitamin-D-1-α-hydroxylase (CYP27B1) in the kidneys. The action of the active metabolite 1,25-D is realized through cytoplasmic and membrane receptors for vitamin D (VDR) [1, 2]. Previously, it was believed that the role of vitamin D was limited mainly by the regulation of calcium metabolism, but further study showed its versatility.

The importance of vitamin D metabolites in the regulation of both the innate and adaptive immune systems has been demonstrated by a number of effects [3-14]:

- expression of VDR not only in epithelial cells (EC) of barrier tissues and renal tubules and hepatocytes, but also in almost all cells of the immune system (CIS);
- wide extracellular and intracellular expression of CYP27B1 upon activation of CIS, in particular by monocytes (MC), macrophages (MF), dendritic cells (DC). Activation of these cells is mediated mainly through Toll-like receptors (TLRs);
- antigen-presenting cells (APC) independently metabolize 25-D to active 1,25-D, which modulates the epigenome of immune cells, especially monocytes, during the meeting with the antigen and differentiation of the innate immune system;
- stimulation of human MF through activation of TLR1/ TLR2/TLR4 leads to induction of VDR and CYP27B1 expression and enhanced endogenous production of 1,25-D from circulating 25-D, and the degree of induction of VDR expression depends on the level of 25-D in serum (dose—dependent effect); - treatment of human MC and MF 1,25-D inhibits synthesis TLR2/TLR4, depending on exposure and dose, 1,25-D, which blocks inflammatory and autoimmune reactions mediated by type 1 (Th1) T-helper cells and reduces the possibility of pathogen penetration into the cell. In contrast, in EC, 1,25-D increases TLR2 expression and enhances vitamin D signaling by inducing VDR and CYP27B expression (positive feedback loop). A large amount of TLR allows you to bind more pathogens at the stage of primary antigen penetration;
- 1,25-D plays a direct antimicrobial role due to the induction of antimicrobial peptides (AMP) cathelicidin and difensins in MC, MF and neutrophils;
- 1,25-D regulates cytokine expression by enhancing the synthesis of chemokines/cytokines, dose-dependently reducing the level of some pro-inflammatory and increasing the expression of anti-inflammatory cytokines;
- 1,25-D modulates tolerant DCS towards a less mature and more tolerant phenotype with reduced expression of the main histocompatibility complex type II, costimulating molecules CD80 and CD86, adhesion molecules CD54;
- high levels of 1,25-D increase the number and/or function of circulating CD4+ CD25+Tcl current (T-reg) due to induction of the clone-specific transcription factor FOXP3 (anti-inflammatory polarization of lymphocytes). T-reg controls allo- and auto-immune T-cell responses by synthesizing anti-inflammatory cytokines (IL-10, transforming growth factor-β (TGF-β)) and releasing granzymes and perforins. Through the expression of inhibitory coreceptors such as CTLA-4, T-reg prevent antigen presentation and initiation of an inflammatory response.

Thus, there is indisputable evidence of a significant and dose-dependent immunomodulatory, mainly anti-inflammatory, effect of vitamin D metabolites. *The role of vitamin D in the development of infectious and infectious-inflammatory diseases*

The introduction of 1,25-D using animal models of human diseases successfully treats a number of conditions, including autoimmune retinitis, acute colitis, diabetes, arthritis, experimental allergic encephalitis, asthma. Rodent models have shown a correlation between therapeutic efficacy, an increased amount of T-reg and the expression of anti-inflammatory cytokines IL-10, TGF-β and CTLA-4. However, human clinical studies have demonstrated much less convincing changes in the amount and function of T-reg compared to experimental models [2, 13].

This may be due to a number of factors:

- insufficient doses and/or duration of treatment;
- genetic factors (polymorphism) and/or a variety of environmental factors in the human population;
- differences in the methods of measuring the number and location of T-reg;
- the vitamin D preparations used. The active metabolite 1,25—D was used in animal studies.

In human studies, colecalciferol was used, the activation of which requires a complex pathway involving liver and kidney hydroxylases, and their expression and activity may vary from one subject to another or systematically decrease after taking D3. Epidemiological data link vitamin D deficiency with an increased risk of infectious and inflammatory diseases: acute respiratory tract infections, pulmonary tuberculosis, inflammatory bowel diseases. An association has been demonstrated between low 25-D levels and adverse outcomes (both in morbidity and mortality) in severe infectious and immuno-mediated diseases. It is possible that in some cases a low level of 25-D is a marker or even a consequence rather than a cause of the disease [15-22].

**Herpes is a viral infection.**

The effect of antimicrobial peptides associated with vitamin D on herpesviruses is described. For example, cathelicidin reduced the titer level of herpes type 1 virus in patients with keratoconjunctivitis. In patients with chronic kidney disease, the risk of reactivation of herpes zoster was significantly lower in those receiving vitamin D supplements, and the risk of infection was lower in subjects with higher or normal serum vitamin D levels [23].

**Hepatitis C virus.**

In patients infected with hepatitis C virus, serum vitamin D levels were inversely proportional to the degree of liver inflammation and the stage of fibrosis. At the same time, a meta-analysis of clinical trials did not reveal a protective effect from taking vitamin D [14, 27, 28].

**The flu virus.**

The most important antiviral effect is the stimulated 1,25-D production of AMP: defensins and cathelicidin [2, 4, 8, 29]. The level of cathelicidin depended on the serum level of 25-D: for optimal induction of cathelicidin mRNA, a level of at least 30 ng/ml was required, and a higher level of 40 ng/ml was not more effective.

**The target level of vitamin D in the human body**

The analysis of numerous clinical data allows us to state with a high degree of confidence that for the normal functioning of the human musculoskeletal system, the target concentration levels of 25-D in the blood should be considered a level exceeding 30 ng/ml. During pregnancy, as well as for the implementation of pleiotropic effects of vitamin D, a level exceeding 40 ng/ml should be considered optimal [1]. The protective effect was observed in those patients who received vitamin D daily or weekly without additional bolus, unlike those who received one or more bolus doses. The positive effects were inversely correlated with the baseline level of 25-D in the blood: the lower the level of vitamin D in the blood before the start of treatment, the stronger the effect. The optimal dose of the vitamin preparation varied from 1000 to 4000 IU/day of colecalciferol [8, 29]. The degree of protection against infections increased as vitamin D levels increased. It was noted that the level of 25-D, equal to 38 ng/ml, is sufficient to reduce the risk of ARVI. Other authors suggest maintaining serum vitamin 25-D levels of at least 30 ng/ml or in the range of 40-60 ng/ml [1, 2, 35, 40]. In the study of seasonal fluctuations in vitamin D levels, no connection was noted with a seasonal increase in the incidence of SARS. No stable association was found between vitamin D levels and serological response to the flu vaccine [29].

*Laboratory diagnosis of vitamin D* deficiency Until the last decade, the diagnosis of vitamin D deficiency was carried out based on indirect signs, for example, a decrease in the concentration of calcium in the blood due to the lack of available laboratory analysis methods.

Thus, numerous evidences of the immunomodulatory and protective effects of vitamin D and data on the significant prevalence of its deficiency and/or insufficiency dictate the need to determine the level of 25-D in the blood in real clinical practice. The target levels of 25-D concentration in the blood should be considered a level exceeding 30 ng/ml. During pregnancy, as well as for the implementation of pleiotropic effects of vitamin D, a level exceeding 40 ng /ml should be considered optimal. The degree of protection against infections increased as vitamin D levels increased. It was noted that the level of 25-D, equal to 38 ng/ml, is sufficient to reduce the risk of ARVI. In this regard, modern methods for determining vitamin D levels should be implemented faster by health care organizers for use in clinical practice within the framework of the compulsory health insurance system of the population, subject to the use of standardized techniques and certified equipment. This will automatically lead to a reduction in the cost of test systems, a transition from analysis accessible to a few to widespread implementation in our country, and will contribute to the preservation of the health of the entire population.

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