Vitamin D as a Prevention Factor in Acute Respiratory Infections

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Abstract

Respiratory diseases are commonly found in children with a vitamin D deficiency. These diseases are caused by a combination of processes resulting from the lack of vitamin D, beginning with poor rib mineralization and thoracic deformations, followed by decreased resistance to infections and delayed differentiation of some pulmonary cell types. The main arguments for the immunomodulatory properties of $1.25(OH)_2D_3$ are: 1) the detection of fermented 25(OH) D-1α-hydroxylase and VDR in immune system cells, 2) the prevention of autoimmune diseases in laboratory animals with the aid of hormone D and its analogues, 3) VDR activation by hormone-D, hindering gene activity and cellular immunity factors such as interleukin 2 (IL-2), coloniostimulator factor granulocyte-macrophage (FCS-GM), and γ-interferon (γ - IFN).

Key words: respiratory tract infections, children, vitamin D.

Витамин D как фактор профилактики острых респираторных инфекций

Респираторные заболевания часто встречаются у детей с дефицитом витамина D. Они представляют собой сочетание процессов, которые, в свою очередь, вызваны недостаточностью витамина Д: деффективная минерализации реберного каркаса грудной клетки, а также низкая сопротивляемость инфекциям и задержка дифференциации некоторых типов легочных клеток. Главными аргументами в пользу иммуномодулирующих свойств 1α25(OH)2D3 выступают: 1) обнаружение ферментера 25(OH)D-1α-гидроксилазы и рецепторов к витамину D (РВД) в клетках иммунной системы; 2) предотвращение с помощью гормона D и его аналогов аутоиммунных заболеваний у лабораторных животных; 3) активация гормоном D РВД затормаживает активность генов и клеточных факторов иммунитета, таких как интерлейкин-2 (ИЛ-2), гранулоцитарно-макрофагальный колониестимулирующий фактор (ГМ-КСФ), γ-интерферон (γ - ИНФ).

Ключевые слова: респираторные инфекции, дети, витамин D.

Respiratory diseases are common in children with vitamin D deficiency. They result from a combination of processes caused by the lack of vitamin D: beginning with poor rib mineralization and thoracic deformations, and followed by decreased resistance to infections and delayed differentiation of some pulmonary cell types. The basis of $1.25(OH)_2D_3$ effect on the immune system is represented by its impact on white blood cells growth and differentiation [1-5]. Many years ago it was established that the development of carential rickets is accompanied by a decreased immune response and a high rate of pulmonary diseases [6, 7]. Scientific evidence-based explanations of this phenomenon have started to be given only recently [8, 9, 10, 11-14].

Some studies have established that the number of hematopoietic stem cells in the bone marrow of vitamin D-loaded and depleted rats was twice as low as in the vitamin D-deficient group [1]. These data suggest that vitamin D is essential for stem-cell differentiation during embryonic development. Vitamin D deficiency in chickens is manifested by a functional decrease in B and T lymphocytes and monocytes' activity. Protein $1.25(OH)_2D_3$ receptors have been found in thymus lymphocytes [15], in pulmonary monocyte-macrophage series cells [16], in bone marrow cells, in activated monocytes-macrophages and in lymphocytes. $1.25(OH)_2D_3$ regulates the proliferation, differentiation and function of myeloid cells through the VDR.

Extensive in vitro studies have analyzed the effects of $1.25(OH)_2D_3$ in human HL-60 leukemic cells. These cells express a large number of receptors to $1.25(OH)_2D_3$ (more than 4 000 copies in one cell). It was proven that the hormone stimulates rapid maturation of macrophages-like cells [17]. This process is accompanied by an inhibition of cell proliferation and by the amplification of phagocytic activity. The stimulation of macrophages differentiation under the influence of $1.25(OH)_2D_3$ is observed in vivo in rats [2]. 1.25–dihydroxivitamin D3 increases the number of alveolar macrophages both by directly influencing the processes of precursor cells differentiation, and by stimulating the development of splenic cells. The cultures of splenic cells show that approximately 90% of cells 3 days after 1.25–dihydroxivitamin D3 administration transform into macrophages with a degree of maturation directly correlated to the hormone dose.

Aside from being target cells for $1.25(OH)_2D_3$, macrophages express 25(OH)D-1-hydroxylase activity. Macrophages from pulmonary alveoli in humans produce 3H – $1.25(OH)_2D_3$ when cultivated with a 3H – $25OHD_3$ marked substrate [4]. The activity of 1-hydroxylase increases rapidly under the influence of interferon and is in direct relation with its dose. Both an increase in the number of macrophages and in their antibacterial function occur, representing an important therapeutic factor. This mechanism encountered locally in macrophages helps the $1.25(OH)_2D_3$ enhance the human monocyte/macrophage capacity to inhibit the growth of tuberculosis mycobacteria in vitro [18]. In addition, activated T-lymphocytes from patients with tuberculosis contribute to the local production of $1.25\text{-}(OH)_2D_3$ [19]. This explains in part the well-known examples of the beneficial effects of vitamin D3 in the treatment of tuberculosis as well as the hypercalcemia encountered in 10%-20% of the patients with tuberculosis or granulomatous diseases such as sarcoidosis.

Interleukin 2, the production of which is controlled by $1.25(OH)_2D_3$, modulates the transformation of macrophages in mononuclear giant cells – osteoclasts [2]. This transformation is accompanied by the loss of receptors for $1.25(OH)_2D_3$. Thus, the receptor disappears completely in the last stage of monocyte-macrophage-osteoclast cell line differentiation, and $1.25(OH)_2D_3$ looses its influence on osteoclasts [20].

1.25(OH)2D promotes the differentiation of hematopoietic and monocyte-macrophages cell lines. The first experiments carried out in 1983-1984 have shown its positive effect on differentiation of promyelocytic leukemic cell lines (HL-60 line) into macrophage type cells. These in vitro results have since been amply confirmed and extended to the identification of multiple effects on the normal lines of circulating monocytes-macrophages. Thus, 1.25(OH)2D promotes monocytes differentiation into macrophages and the fusion of these cells to give rise to multinucleated cells. It controls the proliferation and recruitment of these cells in regulating lymphocyte and monocyte production of growth factors, such as IL-3 and GM-CSF. Finally, it increases the ability of adhesion, phagocytosis, bactericidal activity and antitumoral cytotoxicity of these cells.

Inversely, 1.25(OH)2D appears to be able to play an immunosuppressive role. It first decreases the ability of monocytes-macrophages to activate T cells. This effect requires the presence of IL-4, and has at least three known effects. Vitamin D inhibits the differentiation and maturation of dendritic cells of a monocytic origin into antigen presenting cells. It increases the ability of spontaneous mature cells apoptosis. Finally, it decreases the expression of HLA class II and protein B7.2 molecules by these cells, a costimulator of major histocompatibility complexes recognition by T lymphocytes. It also decreases the secretion of IL-12 by antigen presenting cells, which is a Th1 cells activating cytokine. These effects lead to the recruitment of less responding, less specific and less gamma-interferon secreting T cells.

1.25(OH)2D also directly acts on lymphocytes by decreasing the production of immunoglobulins by B cells, by reducing the proliferation of CD4+ and CD8+ T lymphocytes, by reducing the production and function of cytotoxic killer cells ("Natural Killer" NK, and Cytotoxic T lymphocytes, CTL), and by modulating the immunosuppressive activity of T lymphocytes. In regards to T cells, its action is exerted preferentially on Th1 helper cells and mainly on their ability to secrete IL-2 and gamma-interferon, which decreases.

Chronic administration of 1.25(OH)2D and of some analogs decreases the level of circulating IL-2 and IgG immunoglobulins without modifying the number and repartition of circulating lymphocytes subtypes, or of leukocytes and platelets.

The clinical observations of an altered resistance to infectious disorders in carential rickets have been reported long before the modern conception of rickets physiopathology and vitamin D metabolites action was defined [18]. The main arguments are the increased receptivity to acute respiratory infections in breastfed infants with rickets, the permanent identification of pathological manifestations of rickets in children who have died within the first year of life, and the lower values of these indices if specific ante- and postnatal preventive measures with adequate doses of vitamin D have been undertaken.

Clinical epidemiology in frequently ill children from the Republic of Moldova has demonstrated the presence of rickets in all these children. The majority of children with signs of rickets had frequent episodes of acute respiratory diseases and relapsing forms of pneumonia with a subacute evolution. The description of the flourishing rickets includes data on a reduced resistance to infections, possible association with carential anemia, as well as the notion of rachitic lung. The term "rachitic lung" includes a group of anatomic and functional changes related to rickets, which aggravate dyspnea in respiratory pathologies following intrication of infectious and rachitic factors. Rickets has a primordial mechanical action, impairing the respiratory dynamics, while the osseous factor (extreme softening of costal arches, with rib cupping and flaring, forming the "rachitic rosary"), as well as the muscular factor (rachitic muscular hypotony) impair the respiratory kinetics. Rachitic bronchomalacia and reduced resistance to infections are additional pathological conditions characteristic of rachitic lung. Vitamin D deficiency and hypocalcaemia are accompanied by a significant decrease in sialic acids level, which inhibit the neuraminidase of bacterial and viral agents; it is also manifested through an impaired monocyte/macrophage activity, phagocytosis, pinocytosis, membrane channels function following a reduced activity of 3.5-cAMP [12, 13].

Thus $1.25\text{-}(OH)_2D_3$ acts as one of the main regulators of calcium metabolism both at the cellular level and in the body as a whole, having a severe impact on an infant's immune system strengthening against infectious agents, and, specifically, against acute respiratory infections.

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Manuscript received December 30, 2009; manuscript revised March 22, 2010