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VITAMIN D DEFICIENCY AND POSSIBLE SEQUELAE

Medical Science

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KEYWORDS:

Vitamin D belongs to the group of fat-soluble secosteroids. Found in 1782 and isolated not until the early 1920s, it was chemically characterized in 1931. In recent years, more emphasis has been given on the three mechanisms of action of vitamin D: endocrine (regulating the calcium absorption), autocrine/paracrine (facilitating the gene expression) and immune (activation of macrocytes and other cells) (1-5).

Five types of vitamin D are known: D1, D2, D3, D4 and D5. For the human body, most important are vitamin D3 (also known as cholecalciferol) and vitamin D2 (ergocalciferol) (1, 3, 6). The main source of vitamin D - about 90%, comes from its synthesis in the skin upon exposure to ultraviolet B radiation (UVB, 295-310 nm). The absorption of UV radiation depends on the location, time of day, season, use of a protective cream, etc. Vitamin D3 is synthesized in the subdermal (basal corneous and spinous corneous) layers under the action of UVB radiation. There, 7-dehydrocholesterol is converted into provitamin D3. The latter is isomerized and converted to vitamin D3 (cholecalciferol) under the influence of the body temperature. Upon UVB exposure of about 30 minutes only, 7-dehydrocholesterol is synthesized in large quantities (from 10,000 to 20,000 IU) (2, 6, 7). Cholecalciferol and ergocalciferol can be obtained from the diet or by supplementation. Very few types of food, however, are a good source of vitamin D and its intake with food is about 10%. Such food includes mostly oily fish (including salmon, sardine, cod, tuna, plaice), liver, milk, cheese, egg yolk, certain nuts, etc.

Vitamin D, obtained via UVB radiation or from the diet, is biologically inert. From the skin and intestines, it enters the lymph and after then, the venous circulation. There it binds specific proteins (85-90%) and albumin (10-15%), while less than 1% remains free. Proteins transport D2 and D3 and their metabolites to the cells and tissues. Circulating D2 and D3 enter the liver. There, these are hydroxylated by 25-hydroxylases to 25-hydroxy vitamin D (25OHD), also known as 25-hydroxycholecalciferol or **calcidiol**. This is the main circulating metabolite of vitamin D. Its half-life is 2-3 weeks. The level of calcidiol is an indicator of the vitamin D status in the body. Once entered the kidneys, calcidiol is hydroxylated by 1α-hydroxylase (CYP27B1) in the biologically active form of vitamin D, namely 1,25-dihydroxy vitamin D (1,25(OH)2D3 or 1,25(OH)2D), also known as **calcitriol**. After the final step of conversion into the kidneys, calcitriol is released into the circulatory system (1, 3, 7, 8). Vitamin D can also be converted to the active form outside the kidneys – in the prostate, breasts, colon, brain, pancreas, macrophages and others. Calcitriol is significantly more effective than vitamin D2. It is transported to the cells of various organs, where impacts the biological processes through activation of vitamin D receptors. There are data, obtained from several organs and systems, which show that vitamin D3 has autocrine (vitamin D3 activity occurs from 1,25D, synthesized within these cells) and/or paracrine action (i.e. 1,25D is synthesized in one cell type and is acting in adjacent cells). The highest concentration of calcidiol is in the plasma (20-150 nmol/L or 8-60 ng/mL), but its highest pool is in the adipose tissue and muscles. The catabolic enzyme 24-hydroxylase (CYP24A1) is responsible for the conversion of calcidiol and mainly, of calcitriol to inactive, soluble metabolites. The latter are eliminated via the bile in the feces and a very small part, in the urine (15, 17).

Vitamin D has been shown to have a role in gene expression (12, 15). In the past decade, studies were focused on the vitamin D receptors (VDRs) (1, 3, 9, 10, 11). VDRs belong to the family of nuclear hormonal receptors. It was found that almost any tissue and cell type in the body have receptors for vitamin D. These were found in the adrenal glands, parathyroid glands, the heart, placenta, pituitary gland, ovaries, testicles, mammary glands, skin, hepatocytes, biliary cells, promyelocytes, thymus, nervous tissue, lymphocytes, and large intestine. In these organs and tissues, 1α-hydroxylase - an indicator for the local production of 1,25(OH)2D – was also detected. The discovery of the receptors showed that cellular activities of vitamin D are carried out by genomic regulation (10, 11, 12). After entering the cell and undergoing intracellular conversion, calcitriol binds the nuclear VDRs. Subsequently, the complex VDR-ligand forms heterodimers. In combination with transcription factors and regulatory proteins, this complex activates or inhibits the transcription of a variety of genes. In addition to regulating gene transcription, VDRs also participate in non-transcription cellular reactions. Most of these biological effects of vitamin D are enabled by the nuclear VDRs. Vitamin D regulates the cell cycle - by binding its receptor, it impacts the cells of the immune, nervous and cardiovascular systems, etc. (10, 12, 13, 14). Moreover, it has anti-inflammatory, anti-apoptotic and anti-fibrotic effects. VDRs are expressed in almost all cells and vitamin D regulates approximately 3 - 5% of human genes, through its endocrine effects. VDRs are nuclear ligand-dependent transcription factors, which in a complex with the hormonally active calcitriol, regulate the expression of more than 900 genes. The effect of calcitriol-VDR complex on signaling of the immune system and its relation to various inflammatory diseases was also found (14, 15, 16).

Some organs form locally calcidiol with cell-specific actions - proliferation, differentiation and immune regulation (8, 12). Calcitriol, synthesized via a peripheral autocrine pathway (in various peripheral, non-renal tissues), serves as an important component in the signaling cascades for gene transcription. By binding intracellular VDRs in those tissues, calcitriol may regulate cell proliferation and differentiation, inflammation, immune and endocrine systems, including insulin resistance and lipid metabolism. The discovery of this non-classical pathway revealed a new concept for managing nutritional vitamin D deficiency, considering the potential role of D hypovitaminosis in a number of chronic diseases, such as diabetes, chronic kidney disease, infectious processes, hypertension, cardiovascular disease and other (1, 6, 7, 15, 16).

Endocrine function of vitamin D is associated with the absorption of minerals (calcium, phosphorus, magnesium, zinc) and the balance of their concentrations. Calcitriol increases the blood level of calcium (Ca^{2+}) by intensifying its absorption from the intestines and possibly, its release from the bones. Only a few years ago, vitamin D was known as "the vitamin of bones." It supports the required, balanced concentrations of serum calcium and phosphorus, so necessary for the bone mineralization and remodeling by osteoblasts and osteoclasts (17, 18, 19). In recent years, vitamin D deficiency was found to increase the risk for the development of various diseases:

cardiovascular, skeletomuscular, autoimmune (type 1 diabetes, rheumatoid arthritis, multiple sclerosis, etc.), infectious and others (20, 21, 22). Regarding bones, the classic targets of vitamin D are mesenchymal stem cells, early and late osteoblasts, and osteocytes. There are new data on the biological and clinical importance of the steroid hormone 1α, 25-dihydroxy vitamin D3 [1α, 25(OH) 2D3] and its receptor for bone health. Together with calcium, it prevents the elderly from osteopenia and osteoporosis (21, 22, 23, 24). Parathyroid hormone (PTH) is also significant for maintaining normal serum calcium and phosphorus concentrations. It is regulated by calcitriol and serum calcium, as there is a feedback between serum calcidiol and the PTH, to a certain level of the first. The activity of the renal enzyme 1α-hydroxylase (CYP27B1) is under the control of the plasma parathyroid hormone and fibroblast growth factor 23 (FGF23) in response to serum calcium and phosphorus. Hypophosphatemia also promotes the synthesis of the enzyme 1α-hydroxylase and increases calcitriol. The latter stimulates the intestinal absorption of calcium and phosphorus, and together with the PTH, increases the distal tubular reabsorption of calcium. Calcitriol deficiency leads to secondary hyperthyroidism. The 25ON2D3 promotes hyperplasia of the parathyroid gland and abnormal expression of VDRs in the gland. The final result is an increase of the serum PTH and abnormal calcium and phosphorus balance.

Vitamin D3 was identified in 1919 as a crucial factor in the development of rachitis. While rachitis in children shows reduction, osteopenia and osteoporosis tend to increase. Osteopenia is determined as a reduced bone mineral density, with T-score between -1.0 and -2.5 (3, 5). It is an early, preceding stage of the development of osteoporosis, which means "porous bones" (21, 24). Our bones are strongest around the age of 30 years. After then, they start to lose their density. They become thinner with aging because the cells are reabsorbed by the body more quickly than new bone tissue is formed. So, the bones lose minerals, mass and structure, which makes them weaker and prone to breakage. Osteoporosis is a skeletal disorder, characterized by compromised bone strength, decreased bone mineral density and factors predisposing to a risk of fracturing. The small bone size, unfavorable architecture (for example, increased length of the femoral neck), cortical porosity, compromised quality of bone materials and reduced viability of osteocytes are factors that contribute to reduced strength. The following regulatory factors play an important role: 1α, 25 (OH)2D3; parathyroid hormone that stimulates the production of renal 1,25 (OH)2D3; fetal growth factor 23; and serum calcium and phosphate concentrations (4, 12, 18, 23). The diagnosis of osteoporosis or the risk assessment of its development in the future is built on imaging studies, such as dual energy X-ray absorptiometry and quantitative computed tomography. Osteopenia and/or osteoporosis develop slowly. Women are 4 times more prone to osteopenia and osteoporosis than men. This is because of women's lower peak bone density and loss of bone mass, associated with hormonal changes during the menopause (loss of estrogen).

Vitamin D has also a definite role in **immune system functions** (Figure 1) (11, 12, 13, 14). VDRs are widely distributed in many immune cells, such as macrophages, dendritic cells, T- and B-cells (9, 14, 26). All these cells are able to synthesize calcitriol. Vitamin D binds the receptors in the immunologically active cells, including helper T-cells. Upon activation of vitamin D receptors, Th2 response occurs that leads to reduction of presented inflammation. Vitamin D activates also the cathelicidins, which are antimicrobial peptides (9, 12, 14, 27). Cathelicidins have been found in the lysosomes of macrophages, polymorphonuclear leukocytes and keratinocytes. Defensins belong also to antimicrobial peptides. Cathelicidin peptides have been found in many cells, including epithelial cells and macrophages, following activation by bacteria, viruses, fungi or vitamin D. Thus, vitamin D inhibits the development of certain diseases - experimental autoimmune encephalomyelitis, thyroiditis, type 1 and type 2 diabetes, systemic lupus erythematosus, rheumatoid arthritis, etc. One of the functions of vitamin D is to promote the differentiation of monocytes, dendritic cells and lymphocytes (12, 25, 26). These cells are the first line of defense of the non-specific immune system and play an important role in infection control. The effect of vitamin D on the immune system may be due to paracrine and autocrine feedback mechanism, thereby reducing the inflammatory response. The differentiation of active CD4 + T cells modifies and the inhibitory function of T-cells increases. Vitamin D promotes also the differentiation of monocytes into mature macrophages, by inducing p21. Through the transcription factor C/EBP or CCAAT, vitamin D provides the macrophages with antibacterial, antiviral and antitumor activities. Vitamin D can modulate the innate and adaptive immune responses. Vitamin D deficiency is associated with an increased autoimmunity and increased susceptibility to infections. Patients with vitamin D deficiency suffer from recurrent infections (4, 12, 25, 28). Calcitriol improves the host defense against bacterial infections. Furthermore, there may be a difference between the local and plasma levels of calcitriol. The extrarenal enzyme 1-α-hydroxylase in macrophages differs from the renal hydroxylase, since it is not regulated by the PTH. The serum concentration of the vitamin may be induced by cytokines, such as IFN-γ, IL-1 or TNF-α. The vitamin D-VDR complex suppresses the development of *Mycobacterium tuberculose* by inhibiting the synthesis of IL-12 and γ-interferon, and the Th1 immune responses (12, 25, 28). Serum calcidiol concentrations are significantly lower in patients with tuberculosis than in controls. Vitamin D deficiency is associated with increased incidence of respiratory diseases, influenza, cystic fibrosis, interstitial lung disease, chronic obstructive pulmonary disease, etc. This is associated with vitamin D effects on cells of the immune system. It inhibits B-cell proliferation, B-cell differentiation and the secretion of immunoglobulins (4, 25). Vitamin D further inhibits the proliferation of T-cells and leads to a change from Th1 to Th2 phenotype. It also affects T-cell maturation and facilitates the induction of T-regulatory cells. These effects lead to reduced production of inflammatory cytokines (IL-17, IL-21) and increased production of anti-inflammatory cytokines, such as IL-10. In addition to modulating innate immune cells, vitamin D promotes in a tolerogenic manner the immunological status (Figure 2).

This overview presents in brief the main functions of vitamin D in terms of endocrinology, genetics and immunology, and the possible role of vitamin D in the pathogenesis of various diseases.

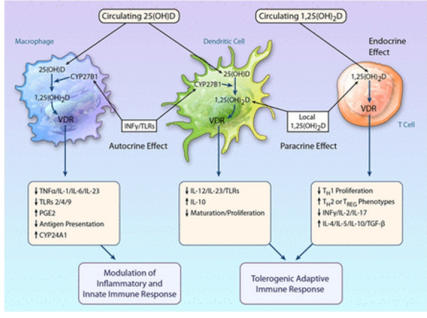

Figure 1. Schematic representation of vitamin D metabolites and immune modulation: endocrine, paracrine and autocrine responses (by Norman, N 2)

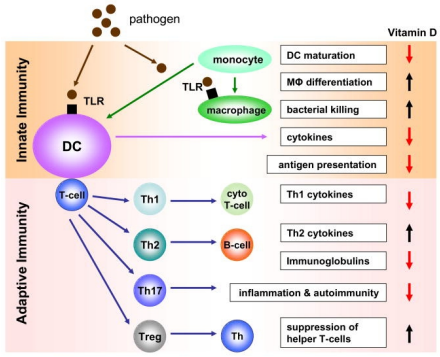

Figure 2. Effects of vitamin D on innate and adaptive immunity (by Hewison, N 2)

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