ISSN 2181-3187

# CLINICAL FEATURES OF VITAMIN D EFFECTS ON BONE METABOLISM

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**Resume**. The problem of vitamin D deficiency is currently of particular importance, since, according to numerous studies, hypovitaminosis D is present in almost 1/3 of the world's population. The article presents epidemiological data on the availability of cholecalciferol in children of various age groups, and defines modern approaches to assessing the content of vitamin D in the body. Special attention is paid to the ideas about the metabolism and biological functions of vitamin D, which consist not only in its positive effect on the state of bone tissue, but also in many extra-skeletal biological effects.

**Keywords**: vitamin D, bone metabolism, extra-skeletal effects of vitamin D, vitamin D deficiency.

It has been proven that the importance of vitamin D for the human body lies not only in its effect on the formation of the bone system, but also in many extra-skeletal effects of cholecalciferol. According to modern concepts, vitamin D deficiency is associated with an increased risk of diabetes mellitus, hypertension, heart failure, peripheral artery disease, acute myocardial infarction, various forms of cancer, autoimmune and inflammatory diseases, decreased immune defenses and increased mortality. The problem of vitamin D deficiency is one of the most urgent, since, according to the results of numerous studies, its deficiency is registered in half of the world's population. That is why there is a growing interest in quantifying and understanding the mechanisms of vitamin D metabolism in the human body [1]. During sun exposure, 7-dehydrocholesterol (7-DHC) is converted into provitamin D3 (PRED3) in human skin. As a result of thermal exposure, provitamin is converted into vitamin D3 (colecalciferol). Vitamin D2 (ergocalciferol) enters the body with food. Cholecalciferol can also come with food if it is enriched in foods, or if it is part of biologically active food additives. Both vitamins (D3 and D2) differ slightly in chemical structure and have similar metabolic stages. Vitamin D is not considered biologically active until it undergoes 2 enzymatic hydroxylation reactions.

The first occurs in the liver with the participation of the enzyme 25-hydroxylase (cytochrome P450 2R1, CYP2R1), which promotes the formation of 25-hydroxyvitamin D — 25(OH)D. The second stage of vitamin D activation occurs in the kidneys. In conditions of calcium and phosphorus deficiency under the influence

ISSN 2181-3187

of 1-hydroxylase (CYP27B1), 25(OH)D is converted to the biologically active hormone calcitriol (1,25-dihydroxyvitamin D, 1,25(OH)2D). 1,25(OH)2D interacts with the vitamin D receptor (VDR) in the small intestine, enhancing intestinal absorption of calcium, and osteoblast receptors, regulating phosphoric calcium metabolism. At normal or elevated concentrations of calcium and phosphorus in the blood serum, the activity of the enzyme 24-hydroxylase (SUR24A1) increases, under the action of which an alternative metabolite 25(OH) is formedD — 24.25(OH)2D, which ensures the fixation of calcium and phosphorus in bone tissue [2-4]. The biological effects of 1,25(OH)2D are classified into classical, regulating phosphorus-calcium homeostasis in the body, and non-classical, which include functions unrelated to calcium metabolism [4, 5]. The main effect of vitamin D is its effect on the balance of serum calcium and phosphates. This is of paramount importance for the normal mineralization of bone tissue, muscle contraction, nerve conduction and many other cellular functions. The main regulators of calcium and phosphorus metabolism, along with the active metabolite of vitamin D, are parathyroid hormone (PTH) and calcitonin, the targets of which are bone tissue, kidneys and intestines. The signal for an increase in the intensity of PTH secretion is a decrease in the concentration of ionized calcium in blood plasma and interstitial fluid associated with vitamin D deficiency, limited intake or loss of calcium ions through the kidneys. Changes in the extracellular concentration of ionized calcium are recorded by membrane Ca++ receptors, which are present in all cells, but are especially densely localized in the parathyroid glands and kidneys, in the ascending part of the Henle loop. Stimulation of these receptors is accompanied by an increase in the level of PTH secretion, which increases the intake of calcium into the bloodstream for 30-60 minutes due to three effects:

• increased bone resorption;

• slowing down the excretion of calcium in the urine (by direct activation of reabsorption in the distal tubules of the nephron);

• increased absorption of calcium in the small intestine (mediated by calcitriol, whose synthesis in the kidneys increases under the influence of PTH in conditions of hypocalcemia). PTH has the opposite effect on the content of phosphates in the blood: by suppressing tubular reabsorption, it increases the excretion of phosphates in the urine, thereby reducing their level in the blood. It should be noted that PTH provides rapid (emergency) regulation of calcium homeostasis, while constant regulation occurs with the help of vitamin D metabolites. The antagonist of PTH is calcitonin, secreted with cells of the thyroid gland and carotid bodies. Under its influence, calcium reabsorption in the renal tubules decreases and bone mineralization processes increase. The value of calcitonin increases dramatically during periods of increased calcium demand (during intensive growth, pregnancy, lactation), when it significantly inhibits bone resorption. These conditions are characterized simultaneously by an increase in

ISSN 2181-3187

serum levels of 1,25(OH)2D3 (calcitriol) and increased absorption of calcium in the intestine. Calcitriol increases the resorption of calcium from the skeleton, leading to osteomalacia and osteopenia. However, calcitonin inhibits this process through the action of 1,25(OH)2D3, mainly on intestinal cells, where the production of calcium-binding proteins increases [4]. While maintaining calcium homeostasis and normal bone structure is generally considered to be the main biological effect of 1.25(OH)2D, modern research has shown that vitamin D performs many other important functions in the human body. Receptors sensitive to the effects of 1,25(OH)2D are found in most cells of the body, which confirms the presence of vitamin D in a large number of biological functions. The studied effects include participation in the regulation of cell proliferation and differentiation processes, and the effect on hormone secretion. It is also found that 1.25(OH)2D can be synthesized not only in the kidneys, but also in cells of the pancreas, vascular endothelium, stomach, epidermis, colon, immune system, as well as macrophages and placenta, which indicates the presence of para- and autocrine function in cholecalciferol [5-7]. 25(OH)D is the only metabolite of vitamin D that is used to determine its content in the body. Despite the fact that 1.25(OH)2D is a biologically active form of vitamin D, it cannot be considered as an ideal measure for determining the status of vitamin D, given the complex mechanisms of regulation of the synthesis of this metabolite in the body [2, 8]. As soon as vitamin D deficiency develops in the body, there is a decrease in intestinal absorption of calcium, which leads to a temporary decrease in its serum level. This is a signal to increase the secretion of PTH. PTH regulates calcium metabolism by increasing its tubular reabsorption, increasing mineral mobilization from skeletal bones, and increasing renal synthesis of 1,25(OH)2D. Thus, by increasing the concentration of PTH, the level of 1.25(OH)2D will be normal or elevated and uninformative for reliably determining the status of vitamin D in the body. In addition, the half-life is 1.25(OH)2D is only 4-6 hours, and the number of circulating molecules of this metabolite is 1000 times less than 25(OH)D [9]. The determination of the amount of 1.25(OH)2D makes sense only for the diagnosis of a number of hereditary and acquired disorders of calcium metabolism resulting from the pathology of the renal stage of calcitriol synthesis [10]. Most experts currently agree that vitamin D deficiency can be talked about at a concentration of 25(OH)D in the blood serum is less than 20 ng/ml, its insufficient content is indicated when the content of the metabolite is in the range of 21-29 ng/ml. The target concentration of vitamin D in the blood serum for adequate provision of all biological functions in the human body should correspond to a level of more than 30 ng/ml. The concentration of vitamin D in the blood above 150-200 ng/ml is considered excessive. Intoxication is characterized by the development of hypercalcemia, hypercalciuria and often hyperphosphatemia [11-15]. Vitamin D deficiency in the body can have various clinical signs. In young children, exo- or endogenous cholecalciferol deficiency is

ISSN 2181-3187

manifested by the development of rickets. Taking into account the two main ways of vitamin D intake into the body, its deficiency can occur either in conditions of inadequately low synthesis in the skin under the influence of sunlight, or with insufficient intake from food or vitamin preparations. The only additional source of vitamin D in breastfed infants is the mother's milk. However, the content of cholecalciferol in women's milk ranges from 15 to 100 IU / l, which cannot satisfy the need for it in a growing child. In addition, the vitamin D content in breast milk depends on the availability of it to a woman during pregnancy. Thus, epidemiological studies carried out in Europe and North America have shown that the active fortification of food products has led to a significant decrease in the incidence of rickets in children. However, the disease continues to be registered among children of immigrants from the Middle East, India, Pakistan, as well as in African-American infants. The main factors determining the high incidence of rickets in these population groups are skin pigmentation, insufficient exposure of mothers to the sun due to national peculiarities of clothing and behavior, as well as prolonged natural feeding, in which the child is deficient in vitamin D due to its low content in mother's milk [16]. In conditions of vitamin D deficiency, calcitriol synthesis decreases, resulting in a decrease in calcium absorption in the intestine. Hypocalcemia, which develops at the same time, activates the synthesis of PTH. In conditions of secondary hyperparathyroidism, bone resorption increases in order to maintain normocalcemia, as well as reabsorption of calcium in the kidneys and excretion of phosphates increases (Fig. 3). Increased absorption of calcium in the intestine is temporary, since this process is carried out through activation of parathyroid synthesis of 1,25(OH)2D3 in the kidneys, however, in conditions of deficiency of the initial substrate (25(OH)D3) the calcitriol formation process will also be disrupted [3, 4]. Calcium, phosphate deficiency and increased bone resorption in conditions of secondary hyperparathyroidism are key pathogenetic factors in the formation of bone changes typical of rickets. In the distal parts of the growth zones in rickets, significant changes are noted, expressed in the inability of the newly formed osteoid to adequately mineralize. Proliferation and hypertrophy of cartilage cells lead to the proliferation of metaphysical plates, which is characterized by deformations of the skull bones typical of rickets, the appearance of "rickety rosaries". Thus, under conditions of hypovitaminosis D in the structure of bone metabolism, there is a predominance of resorption processes over bone neoplasm, leading to the deposition of osteoid in the absence of its adequate mineralization. With a persistent deficiency of vitamin D, the bones of the skeleton lose their strength and undergo deformation due to muscle contraction and the gravity of their own body. Insufficient vitamin D supply has a negative effect on the condition of bones in adolescents. Impaired accumulation of peak bone mass in childhood is an important risk factor for the development of osteoporosis in the future [17, 18]. Currently, an increasing number of studies indicate

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the role of vitamin D deficiency in the development of chronic diseases of the cardiovascular system, diabetes, and oncopathology. However, most of the evidence base is based on epidemiological studies in adults. Much less is known about the effect of vitamin D deficiency on the development of chronic pathology in children and adolescents. Vitamin D deficiency increases the risk of developing autoimmune diseases. It is known that longer sun exposure in childhood and early adolescence is associated with a reduced risk of developing multiple sclerosis [19]. Vitamin D supplements may have a protective role in relation to the development of type 1 diabetes mellitus. This was proved by observational studies, which revealed an almost 30% reduction in the risk of this pathology in children who received vitamin D in early childhood [24]. It is known that antiepileptic drugs, being powerful inducers of liver enzymes, accelerate the metabolism of vitamin D and disrupt the normal process of bone mineralization.

Infectious diseases remain one of the main causes of morbidity and mortality in children in all countries of the world [29]. Currently, there is evidence that 1.25(OH)2D regulates the effectiveness of the immune response and has an anti-inflammatory effect. Several recent epidemiological studies have established a link between vitamin D deficiency in the body and the incidence of respiratory infections among children.

Although the peak incidence of viral infections, especially in the pediatric population, usually occurs in the winter months, when the skin synthesis of vitamin D is insufficient, there is evidence that individuals with a level of 25(OH)D below 10 ng/ml have a higher risk of developing an upper respiratory tract infection, regardless of the season of the year [34]. One study showed that the level of 25(OH)D was lower in children with bronchiolitis or pneumonia admitted to the pediatric intensive care unit than in healthy children of the control group or in children with pneumonia who did not need therapy in intensive care [35].

There is evidence that the low content of 25(OH)D in umbilical cord blood has a strong inverse correlation with the number of acute respiratory infections in the first 3 months of a child's life, as well as with the incidence of respiratory syncytial viral infection in the first year of life [38]. The physiological need for vitamin D for children and adults is 10 mcg/day (400 IU/day), for people over 60 years of age — 15 mcg/day (600 IU/day) [39]. Very few foods contain vitamin D. One of its richest sources is fatty fish (salmon, tuna, mackerel). A small amount of vitamin D is present in beef liver, cheese and egg yolks. Vitamin D in these products is presented in the form of the metabolite 25(OH)D3. Vitamin D2 is available in varying amounts in mushrooms. There are also vitamin D-enriched foods on the market (milk, yoghurts, baby food). There are 2 forms of biologically active vitamin D supplements in products — D2 (ergocalciferol) and D3 (cholecalciferol), which differ in chemical structure. Vitamin D2 is produced by UV irradiation of ergosterol in yeast fungi, and vitamin D3 is

ISSN 2181-3187

produced by irradiation of 7-dehydrocholesterol from lanolin [1]. Vitamins D2 and D3 are traditionally considered equivalent, since the main stages of their metabolism and therapeutic efficacy are largely similar. A guaranteed way to provide vitamin D to young children in conditions of insufficient insolation and difficulty correcting the diet due to products rich in cholecalciferol is the additional administration of vitamin D preparations in a daily dose of 500-1000 IU, depending on the nature of feeding, health status and the presence of risk factors for rickets and osteopenia. It should be noted that aqueous forms, unlike oil forms, are better absorbed in the presence of concomitant pathology in the child:

• impaired intestinal absorption in the small intestine (food allergy, exudative enteropathy, celiac disease);

• cholestasis syndrome;

• exocrine insufficiency of the pancreas (relative — reactive pancreatitis, syndrome of excessive growth of microbial flora in the small intestine; absolute — cystic fibrosis, Schwachman–Diamond syndrome);

• Crohn's disease, ulcerative colitis, etc. Current and future research into the effects of vitamin D will contribute to a better understanding of its role in ensuring optimal functioning of the human body. Screening and elimination of vitamin D deficiency in children and adolescents can not only improve the condition of the bone system, but also reduce the risk of developing many chronic diseases.

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