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CAUSES, CONSEQUENCES, AND TREATMENT OF VITAMIN D DEFICIENCY IN HUMANS

Marko Koprivica[1], Svetlana Kasikovic-Lecic[1,2]
[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia
[2]Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia

УЗРОЦИ, ПОСЛЕДИЦЕ И ЛЕЧЕЊЕ НЕДОСТАТКА ВИТАМИНА Д КОД ЉУДИ

Марко Копривица[1], Светлана Кашиковић-Лечић[1,2]
[1]Универзитет у Новом Саду, Медицински факултет, Нови Сад
[2]Институт за плућне болести Војводине, Сремска Каменица

ABSTRACT

This group of vitamins consists of vitamin D2 and vitamin D3, which are synthesized in the body of some invertebrates and plants, but also in the human body. Ultraviolet rays cause vitamin D to integrate under the skin. The vitamin is transported via specific proteins to all parts of the body, where it performs numerous roles. The low level of vitamin D in blood is a current public health problem. Vitamin D deficiency is especially pronounced among the elderly and obese. Currently, vitamin D deficiency is associated with an increase in bone and cardiovascular diseases, diabetes, malignant, autoimmune and allergies diseases. That is why it is extremely essential to establish and correct the deficiency of this vitamin in a timely manner. Compensation can be done partly through food, but also through oral supplements, and in more severe cases, by intramuscular administration of vitamins.

Key words: *vitamin D; risk factors; vitamin D deficiency.*

САЖЕТАК

Ову групу витамина чине витамин Д2 и витамин Д3, који се синтетишу у организму неких бескичмењака и биљака, али и у људском организму. Ултраљубичасти зраци узрокују да се витамин Д интегрише испод коже. Витамин се преко специфичних протеина преноси у све делове тела, где обавља бројне улоге. Низак ниво витамина Д у крви актуелни је проблем јавног здравља. Недостатак витамина Д посебно је изражен код старијих и гојазних особа. Тренутно је недостатак витамина Д повезан с порастом коштаних и кардиоваскуларних болести, дијабетеса, малигних, аутоимуних и алергијских болести. Због тога је изузетно важно благовремено утврдити и исправити недостатак овог витамина. Компензација се може вршити делимично храном, али и оралним суплементима, а у тежим случајевима и интрамускуларном применом витамина.

Кључне речи: *витамин Д; фактори ризика; дефицијенција витамина Д.*

INTRODUCTION

Vitamin D is the only vitamin that is also a hormone. It belongs to the group of lipo-soluble vitamins. For humans, the two most important forms of vitamin D are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) (1). These forms are synthesized after exposure to ultraviolet radiation. Vitamin D2 is created in the body of some invertebrates and fungi, while vitamin D3 is produced in the body of vertebrates (2). Formation of endogenous vitamin D starts in the skin. The Epidermal and dermis cells contain 7-dehydrocholesterol (7-DHC). Ultraviolet rays (UV) at a wavelength of 280-315 nm result in 7-DHC absorbing photons and converting into previtamin D3. Cholecalciferol is formed after significant isomerizations, (3, 4). Prolonged sunlight effect results in the formation of vitamin D, which reaches its plateau, so only 10%-15% of the initial doses of 7-DHC are converted into previtamin D, while the rest is due to later photoisomerization, transforms into two biologically inactive forms – lumisterol and tachysterol (5). The synthesis of vitamin D in the skin is limited by numerous factors such as skin pigmentation, age, length of exposure to solar radiation, and air quality (6). The study performed in the USA showed that protecting from the sun and wearing special clothes significantly reduce the synthesis of vitamin D. Contrary to these results, the use of creams with a high protection factor has no effect on the synthesis of vitamin D (7).

The process of hydroxylation of cholecalciferol and ergocalciferol takes place in the liver with the help of the D-25-hydroxylase enzyme, which produces 25(OH)D (calcidiol). The newly created product enters the kidneys where, with the help of the enzyme 25(OH)D-1 hydroxylase (CYP27B1), undergoes hydroxylation once again, forming the metabolically active form of vitamin D-1,25(OH)2D – calcitriol. Extrarenal conversion of calcidiol into calcitriol appears in muscle, colon, prostate, and pancreatic cells. "Ectopic" sites of conversion are usually sufficient to satisfy local needs for this hormone (3, 4). The active form of vitamin D binds to some proteins

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Marko Koprivica,
University of Novi Sad, Faculty of Medicine, Novi Sad,
Phone: +381 63 770 32 38,
E-mail: markokoprivica@uns.ac.rs

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and via blood enters different types of tissues where it performs its function. Upon arrival in certain tissues, vitamin D is separated from DBP and is taken into cells using the vitamin D receptor (VDR) (3, 4).

Daily needs

Daily requirements for vitamin D depend primarily on age. In the period after birth until the completion of the first year of life, the daily needs are 400 IJ of vitamin D (10 μg per day) (8). After this period, during the entire childhood until the age of 70, the daily needs for vitamin D are 600 IJ (15 μg per day) (8). Even during pregnancy and breastfeeding, these needs remain the same as for the rest of the population. After 70 years of life, the need for vitamin D increases when it amounts to 800 IJ (20 μg per day) (8). The Society of Endocrinologists advises 400 to 1000 (IU) per day for babies up to one year, 600 to 1000 IU are advised for children aged 1 to 18 years, while for all adults this ranges from 1000 to 2000 IU (9).

Risk factors

Some risk factors for the low level of vitamin D are dark complexion, chronic renal insufficiency, long-term immobilization, existence of some diseases (malabsorption syndromes - Crohn's disease, cystic fibrosis, severe liver diseases), taking certain drugs (rifampicin, anticonvulsants, thiazides, corticosteroids), taking substances that hinder the absorption of vitamin D (mineral oils, cholestyramine, laxatives) (10). Furthermore, excess body weight can contribute to a relatively low level of vitamin D in the serum, due to its distribution and storage in fatty tissue (11). The low level of vitamin D is a consequence of insufficient vitamin intake through food or due to insufficient sun exposure (12).

Vitamin D deficiency caused by the use of corticosteroids

Vitamin D deficiency is especially observed in patients who are on corticosteroid therapy. These drugs increase the excretion of calcium by kidneys and reduce its absorption in the intestines. At the same time, corticosteroids stimulate bone resorption and reduce its renewal, which results in the reduction of bone mass and increases the risk of pathological fractures (13). Research has also shown that steroids enhance the action of hydroxylase, which also minimises the level of vitamin D in the body (14). A large NHANES cross-sectional study performed in the USA showcased that the frequency of vitamin D deficiency was 11% among people who used steroids compared to 5% among people who did not use steroid drugs (15).

MANIFESTATIONS OF VITAMIN D DEFICIENCY

The effect of vitamin D on gastrointestinal and endocrine systems

In cells of the gastrointestinal tract, calcitriol increases calcium and phosphorus uptake. Beside calcitriol, the metabolism of these electrolytes is controlled by parathyroid hormone (PTH). The enzyme which converts 25 (OH) D into calcitriol is stimulated by parathyroid hormone. Enzyme activity influences an increase in the concentration of calcitriol. Likewise, calcitriol suppresses PTH activity, inhibits parathyroid cell proliferation and their secretion (3).

Effect on bone tissue

On bone tissue cells, calcitriol also acts together with PTH to regulate bone metabolism. VDR receptors located on osteoblasts allow the entry of calcitriol into bone cells where this vitamin acts by enhancing the expression of certain genes, especially genes that participate in receptor activation for nuclear factor κB ligand (RANKL) (16). RANKL then binds to receptors located on monocyte cell lineage and thus promotes their aggregation, formation and maturation of osteoclasts. Mature osteoclasts release numerous enzymes including collagenases and hydrochloric acid and lead to the degradation of collagen and stimulate the release of calcium and phosphorus into the bloodstream (16). Vitamin D deficiency has consequences for almost all organs and organ systems. Vitamin D deficiency leads to disturbances in calcium and phosphorus metabolism and bone metabolism. Reduced concentrations of this vitamin cause a decrease in the absorption of calcium and phosphorus in the interstitial tract (17). The resulting secondary hyperparathyroidism aims to maintain normal serum calcium concentrations by mobilizing calcium from bone and increasing renal phosphorus excretion. This process leads to a generalized decrease in bone density and the development of osteopenia and osteoporosis. Increased renal excretion of phosphorus causes hypophosphatemia, which further impairs bone mineralization. In children, the lack of vitamin D will manifest itself in the skeletal system as rickets, while in adults, osteomalacia will occur, with consequent pains occurring in the bones and muscles and an increased tendency to develop pathological fractures (10).

Effect on immune system

It is known that vitamin D stimulates innate and modulates acquired immunity (18). Vitamin D increases the number of certain peptides, such as cathelicidin (ll-37) in the cells of the respiratory system, which has the ability

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to destabilise bacterial membranes. (19). The low level of vitamin D contributes to higher risk of respiratory infections (20, 21, 22). Vitamin D insufficiency is also related to an increased risk of infection caused by the SARS-CoV-2 virus (23). There is a correlation between vitamin D insufficiency and dysregulated cytokine release, which leads to complications in COVID-19 patients (20, 24-26). The level of vitamin D in blood is considered a biological indicator of the outcome of the COVID-19 infection (27). A low serum level of vitamin D can adversely affect the clinical picture because the vitamin D initially controls viral replication and later regulates the hyperinflammatory response (24). Most immune cells possess very high levels of receptors for vitamin D. Vitamin D functions as a transcription factor, when vitamin D binds to receptors, then the given receptors are activated and modulate the response of cells infected with viruses (28). Surfactant is synthesized by alveolar type 2 cells which are stimulated by vitamin D. The lack of vitamin D affects the level of surfactant which can be decreased and result in a higher risk of COVID-19 infection (20). Vitamin D participates in the modulation of the immune response and its deficiency is highly correlated with the occurrence of autoimmune diseases. (29). Vitamin D deficiency is also associated with the development of sarcoidosis and other autoimmune diseases (30).

Effect on the occurrence of malignant diseases

Vitamin D insufficiency correlates with some types of cancer (31, 32). It has been found that a large number of people with melanoma have vitamin D insufficiency or deficiency (33). Low levels of vitamin D have also been recorded in people with thyroid cancer (34). In women with breast cancer and vitamin D deficiency, the malignant disease shows a significantly faster progression and a lower survival rate compared to women with preserved vitamin D levels (35). A prospective study conducted in Japan showed that during a 15-year follow-up, the incidence of breast cancer and hepatic cancer was higher in women with low concentrations of vitamin D (36).

Anticancer effect

There are numerous preclinical data that link vitamin D with the control of the cell cycle (37). The antitumor effect of vitamin D is reflected in the inhibition of proliferation and differentiation of cancerous cells (38). Liposoluble vitamin A also has antitumor effects (39). The antitumor effect of vitamin D is reflected in the inhibition of proliferation and differentiation of cancerous cells. This role of vitamin D is thought to be accomplished in several ways. Stimulation of the cell cycle and proliferation of cancerous cells are promoted by the action of cyclin-dependent kinases. These enzymes are regulated by numerous proteins, the most important of which are inhibitors of cyclin-dependent kinases. Vitamin D achieves its role by inducing cell growth arrest by regulating the transcription of genes that encode inhibitors of cyclin-dependent kinases, increasing their expression (38). This theory is supported by a study by Hager et al., in which calcitriol stimulated the expression of p21 and p27 genes, as well as hypophosphorylation of the Rb protein, which led to a halt in the G0/G1 phase of the cell cycle (40). Another mechanism by which calcitriol achieves its anticancer effect is the antiproliferative influence it has in the Wnt-b-catenin pathway. In normal cells, the activation of this pathway induces the expression of genes involved in the control of the cell cycle (38). Another way in which vitamin D exerts its antitumor effect is the regulation of pro- and antiapoptotic factors. Vitamin D also participates in the inhibition of telomerase activity (38).

Effect on the cardiovascular system

Previous research has shown that maintaining adequate concentrations of vitamin D in the body is extremely important for the proper functioning of the cardiovascular system. High levels of parathyroid hormone (PTH) are strongly associated with increased blood pressure. Calcitriol, however, can decrease blood pressure by reducing PTH levels. (41). One research shows that calcitriol leads to a decrease in the production of renin (42). Research conducted on mice showed that calcitriol works directly on sarcomeres, regulating their contractions, which supports the fact that there is a correlation between this vitamin and cardiovascular diseases (43).

Effect on insulin secretion and blood glucose regulation

The effect of vitamin D on beta cells of the pancreas is reflected in the increased stimulation of these cells to secrete insulin. On the peripheral tissues, vitamin D leads to an increased sensitivity of cells to insulin, which encourages the uptake of glucose into the tissues. This is also an indirect effect that reduces the risk of cardiovascular diseases that occur as a result of high concentrations of glucose in the blood (41). In a study conducted by Maestroet and associates it had been shown that calcitriol can trigger the transcription of the gene for the human insulin receptor on promonocyte cells (44).

Although the biological mechanisms that link the development of diabetes with vitamin D deficiency are poorly understood, it is believed that the lack of this vitamin increases the risk of developing diabetes mellitus type 2 by increasing the concentration of glucose in the blood, and has a direct effect on the beta cells of the pancreas and therefore on insulin secretion (45). Reduced

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concentrations of vitamin D reduce the sensitivity of peripheral tissues to insulin and lead to the development of insulin resistance. At the same time, hyperglycemia has a stimulating effect on pancreatic cells, increasing insulin production and promoting hyperinsulinism (46). Vitamin D deficiency affects the reduced regulation of calcium and reactive oxygen radicals that stimulate beta cells of the pancreas to produce insulin. Over time, excessive activation of cells leads to the exhaustion of cellular mechanisms and the occurrence of cell death (47).

DIAGNOSIS OF VITAMIN D DEFICIENCY

Vitamin D deficiency can be determined by determining the concentration of calcitriol using the radioimmunoassay method. Based on the obtained values, the result is interpreted as:

- vitamin D insufficiency (20-29 μg/L),
- mild vitamin D deficiency (10-19 μg/L),
- moderate vitamin D deficiency (<9 μg/L) i
- severe vitamin D deficiency (<5 μg/L) (10).

In parallel with determining the level of vitamin D in the blood, the concentration of PTH and ionized calcium is also determined. In case of vitamin D deficiency, PTH values are usually elevated (10).

VITAMIN D SUPPLEMENTATION

Recommendations are to maintain serum vitamin D concentrations >30 μg/L both in the general population and in individuals with risk factors (1). After starting treatment, it is advised not to check blood vitamin D control values for the first three months, which allows adequate and stable concentrations of this vitamin to be established in the body. After reaching the desired vitamin D concentrations, further tests and checks are not necessary, unless the risk factors for the occurrence of deficiency do not change. Frequent monitoring is necessary in persons with malabsorption syndrome who require high-dose therapy (1, 46). Supplementation of vitamin D is recommended for all persons with a proven deficiency of vitamin D. Vitamin D supplementation is subject to numerous factors ranging from age, body weight, deficiency of the vitamin in blood, and also the manner of dressing (48).Treatment is carried out using oral preparations or in the form of intramsicular injections, depending on the degree of deficiency. In persons with a mild form of vitamin D deficiency, the treatment is carried out with the use of oral preparations of vitamin D, that is, with the use of cholecalciferol in a dose of 1000-2000 IU per day. In people with a moderate form of deficiency, treatment is carried out with slightly higher oral doses of cholecalciferol 3000-5000 IU daily for 6 to 12 weeks or intramuscular administration of ergocalciferol in a dose of 50000 IU once a month for 6 months. In people with severe deficiency, treatment involves intramuscular injections of high-dose ergocalciferol, 50,000 IU, once a week for four weeks. Following this initial phase, the treatment regimen continues with the patient receiving one dose per month for a period of 3-6 months. (10). According to data from the literature, some doctors reported the administration of 28,000 IU per week and from 50,000 IU per month in patients with COVID-19 infection (49). Vitamin D can also reduce the production of inflammatory cytokinins such as: IL-6, IL-8, IL-12, IL-17 and thus prevents the progression of inflammation and damage to other organs (49). Toxicity may manifest itself in the form of various symptoms, including polyuria and irregular heart rhythm. The occurrence of these symptoms directly correlates with the consumption of high doses of this vitamin, with toxic effects manifesting at threshold doses ranging from 10,000 to 40,000 international units per day. (50). An overdose of vitamin D can result in elevated calcium levels in the body, increased calcium excretion, and the deposition of calcium in soft tissues (51).

CONCLUSION

Vitamin D aids in the maintenance of numerous functions in the human body. It should be emphasized that vitamin D deficiency is very dangerous because it can result in many diseases as specified in this paper. The level of deficiency will determine the severity of clinical picture and the rate of disease occurrence. This is a significant public health issue therefore it is essential to intake optimal vitamin D doses. Supplementation should be recommended by experts who know the patient's clinical picture as well as the vitamin D deficiency level.

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