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The role of vitamin D in the human body and the influence of vitamin D on the proliferation of cancer cells

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ABSTRACT

The publication focuses on the presentation of the role of vitamin D3 in the human body. The content contains important information on the influence of vitamin D3 on the course of Covid-19 disease caused by the Sars-Cov-19 virus. Cholecalciferol has been studied for years. Its basic functions include the regulation of bone mineral metabolism and calcium-phosphorus metabolism. In addition, the publication characterizes the course of vitamin D3 synthesis and presents the important role of vitamin D3 in the body. Additionally, the currently conducted research in terms of anti-cancer properties of selected vitamin D3 analogues was described.

Key words: Covid-19; Human physiology; cancer; Vitamin D

INTRODUCTION:

Vitamin D was discovered in 1919 by the English scientist Edward Mellanby. In later years, it was shown that this vitamin exists in two chemical forms, namely as ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃). In the first form, this vitamin occurs in the organisms of plants and fungi, and the second is in animal organisms [Napiórkowska, Franek 2009].

The term "vitamin D" refers to the group of secosteroid hormones, but most often it refers to two of them: ergocalciferol (or vitamin D₂) and cholecalciferol (D₃). These compounds differ in the presence of one methyl group. Ergocalciferol is synthesized by plants and fungi (which can be a source of vitamin D from the diet), and cholecalciferol is formed in the skin under the influence of ultraviolet B radiation (UVB) and is absorbed with food of animal origin (mainly fish). [Napiórkowska, Franek 2009].

Cholecalciferol is synthesized in the body in two ways. It is most effective through peel synthesis (about 80% of the vitamin D in the body is produced this way). The second way to synthesize a vitamin is to take it with food (the remaining 20%). Under the influence of UVB radiation on keranocytes in the skin, a cascade of reactions is triggered, which leads to the production of a hormonally active form of vitamin D. of cholesterol metabolite into pre-vitamin, which isomerizes to cholecalcephore [Napiórkowska, Franek 2009, Pełczyńska et al., 2005]. It has been proved that the highest intensity of the precursor synthesis occurs at UVB radiation with a wavelength of 297 nm. The intensity drops to a minimum at 320 nm [Oleđzka 2013]. Other factors influencing the synthesis of pre-vitamin are: seasons of the year, latitude and the degree of sunlight. Factors adversely affecting the synthesis of vitamin D are UVA radiation, which is used in tanning salons, and a large amount of adipose tissue [Dittfeld et al. 2014].

Vitamin D activation occurs in two steps. The first of these occurs in the liver, where the reaction is catalyzed by the enzyme calcidiol 25-hydroxylase. Cholecalciferol is hydrolyzed to 25-hydroxycholecalciferol. This is followed by the transport of 25-OH-D to the kidneys, where the second stage of 25-hydroxycholecalciferol biosynthesis takes place. Under the influence of the enzyme calcidiol 24-hydrolase, 25-OH-D is secondly hydroxylated, resulting in the metabolically active 1,25-dihydroxycalcitriol. 25-hydroxycholecalciferol and 1,25-dihydroxycalcitriol can be converted to an inactive form, calcitic acid, which is

eliminated in the bile. This reaction is also catalyzed by the enzyme calcidiol 24-hydroxylase. [Napiórkowska, Franek 2009, Pełczyńska i wsp., 2005, Murray 2006].

Ergocalciferol is hydrolyzed to 1,25-dihydroxyergocalciferol. The activated vitamin is transported through the circulatory or lymphatic system in a form associated with nuclear vitamin D receptors (VDR). Vitamin D hydroxylation also occurs in the prostate gland, mammary glands, large intestine, lungs, pancreatic islet β cells, monocytes and parathyroid cells. In the kidneys, 25-OH-D₃ is reabsorbed, but sometimes it is secreted extrally, locally, but only to target cells with the nuclear receptor (VDR) [Napiórkowska, Franek 2009, Pełczyńska et al., 2005, Murray 2006] e.g. to the heart muscle, smooth muscles, B and T lymphocytes, endocrine glands, brain [Napiórkowska, Franek 2009, Karczmarewicz et al. 2012]. In endothelial cells, smooth muscle cells of blood vessels and active macrophages, the peripheral 1α -hydroxylase enzyme is active, which converts 25-OH-D to the form of active vitamin D [Karczmarewicz et al. 2012].

DESCRIPTION OF THE STATE OF KNOWLEDGE

Vitamin d metabolism

The cytochrome P-450 enzymes are involved in the metabolism of vitamin D. The transformation into the active form is due to CYP2R1 and CYP27A1 (25-hydroxylase) in the liver and CYP27B1 in the kidney [Sang-Min Jeon and Eun-Ae Shin 2018]. Enzymes of this origin need additional elements to function properly. For mitochondrial CYPs, these are electron transport proteins containing ferredoxin and ferredoxin reductase, and for microsomal CYPs, cytochrome P450 NADPH reductase [Glenville Jones et al. 2014].

There is reason to believe that CYP2R1 is the major enzyme that hydrolyzes the vitamin D carbon bond (though not the only one). Patients with a mutation that caused this protein to be inactive showed a 25 (OH) D deficiency, which resulted in vitamin DD-dependent rickets. Studies in mice have shown that serum 25 (OH) D levels can be as much as 50% lower compared to individuals with properly functioning protein, without mutation [Sylvia Christako et al. 2015]. Both vitamin D₃ and D₂ can be a product for CYP2R1, it hydrolyzes them to the same degree, which is not characteristic of other 25-hydroxylases [Robert C. Tuckey et al. 2019].

Genome changes at the sites responsible for the synthesis of CYP2R1 and CYP27A1 showed no relationship between the synthesis of CYP27A1 and the level of 25 (OH) D in the serum. Further research is needed to confirm the role of CYP27A1 as a catalyst for the

formation of 25 (OH) D. However, the activity of CYP27A1 in the synthesis of other, indirect metabolites of vitamin D, not related to the main pathway of metabolism of this substance cannot be ruled out [Robert C. Tuckey et al. 2019].

CYP27B1 is calcidiol D-1 α -hydrolase. It is responsible for the formation of 1,25- (OH)₂-D, the active form of vitamin D, in all tissues where this synthesis takes place. No other compound was found involved in this reaction. CYP27B1 is expressed in many types of cells, mainly in the kidneys, but also in the placenta or macrophages, to a much lesser extent in epithelial cells of the skin, lungs, intestines, breast and many others [Daniel D. Bikle 2014]. This enzyme is involved in the metabolism of vitamins D3 and D2 to the same extent. Malfunctioning CYP27B1 is the cause of vitamin D type 1-dependent rickets. In addition, studies in mice show that deficiency of this enzyme can reduce the number of CD4 + and CD8 + lymphocytes [Glennville Jones et al. 2014]. The level of this enzyme is hormonally regulated by parathyroid hormone (stimulation of synthesis) and FGF23 (inhibition). In addition, a high level of 1.25 (OH)₂ D also reduces the synthesis of CYP27B1 [Robert C. Tuckey et al. 2019].

CYP24A1 is responsible for the regulation of calcidiol and calcitriol levels, which is a binding hydrolase at carbon 24 and 23 of vitamin D3 and vitamin D2. It is present in all cells with the VDR nuclear receptor, in the highest concentration in the kidney [Sylvia Christako et al. 2015]. This enzyme catalyzes all steps in the synthesis of calcitriol acid and thus inactivation of vitamin D. Research shows that deficiency of this enzyme can result in hypercalcemia. Additionally, due to the possibility of carbon hydrolysis, 23 is responsible for the formation of 1.25 (OH)₂ D-26.23 lactone, and (when the substrate is 25 (OH)₂ D) 25 (OH)₂ D-26.23 lactone [Glennville Jones et al. 2014]. The analyzes suggest that in humans the 24-hydrolysis pathway of vitamin D3 occurs much more frequently [Robert C. Tuckey et al. 2019].

CYP11A1, whose main role is to catalyze the reactions leading to the formation of steroid hormone precursors from cholesterol, also participates in the transformation of vitamin D. This enzyme synthesizes vitamin D metabolites due to its ability to hydrolyze the bond at carbon 20 and 22 [Sang-Min Jeon and Eun-Ae Shin 2018]. These metabolites are biologically active. This enzyme catalyzes reactions with vitamin D3 and D2. The main products of these reactions are 20 (OH) D (has an activity similar to 1,25 (OH)₂ D), 22 (OH) D and 17 (OH) D, which can be further transformed by CYP11A1 at 17.20 (OH)₂ D; 20.22 (OH)₂ D; 20.23 (OH)₂ D; 17, 20, 23 (OH)₃ D [Robert C. Tuckey et al. 2019]; [Sang-Min Jeon and Eun-Ae Shin

2018]. The presence of CYP11A1 has been demonstrated in such tissues as skin, placenta, and intestine. It has been proven that the metabolites formed with this enzyme inhibit DNA damage caused by UV radiation. All synthesized substances can be further transformed by the enzymes CYP27B1, CYP27A1, and CYP24A1 - respectively 1C hydrolase, 25,26C hydrolase, 24,25C hydrolase. The existence of over 50 metabolites of vitamin D has been shown [Federica Saponaro et al. 2020].

The effect of vitamin D on the human body

Vitamin D is not an active compound - it occurs in the body as a prohormone. Its active form is 1,25 (OH) 2D (calcitriol). It is involved in calcium metabolism together with parathyroid hormone and in phosphate metabolism together with the fibroblast growth factor 23. The parathyroid glands release parathyroid hormone when plasma calcium levels are too low, unlike calcitriol, which is synthesized by 24-hydrolase at high calcium concentrations. blood (feedback) [Murray 2006, Karczmarewicz et al. 2012]. Vitamin D induces the synthesis of calcium-binding protein, which results in an increase in its resorption in the distal renal tubules and its absorption in the small intestine. All these processes are used to maintain adequate calcemia. In turn, the appropriate phosphatemia is maintained by the FGF-23 hormone secreted by osteocytes at too high a plasma concentration of both phosphorus and 1,25 (OH) 2D. It cooperates with the Klotho protein regulating its expression, in addition, the FGF-23 receptor can bind to it in the distal renal tubules, which results in a reduction of phosphate resorption (and lowering the concentration of 1,25 (OH) 2D). This protein also influences the activity of potential-dependent calcium ion transport channels (including the V-type vanilloid receptor), which means that it also plays a role in maintaining calcemia [Karczmarewicz et al. 2012].

Calcitriol is one of the factors influencing the functioning of the cell, regulating its most important stages of life, such as growth, division and death. It has been proven to act inductively on the process of programmed cell death and regulate its activity. It is determined by the ability of vitamin D and its analogues to regulate genes responsible for apoptosis, ie bcl-2, kethepsin B, bax, TRPM-2 / clusters [Pełczyńska et al. 2005]. This leads to a reduction in the intensity of apoptosis. Additionally, calcitriol is responsible for inhibiting proliferation and ending the cell cycle (proteins responsible for the initiation of the S phase are not

phosphorylated). Moreover, it regulates the expression of genes responsible for cell growth and cell differentiation processes.

The presence of vitamin D has an undeniable effect on our immunity. It inhibits the proliferation of T and B lymphocytes. Calcitriol prefers the synthesis of Th2-type cytokines over Th1-type cytokines by T-lymphocytes. Due to the ability to regulate IL-17 secretion, receptor mechanisms and action on Treg lymphocytes, it can alleviate the course of autoimmune diseases such as type I diabetes or sclerosis. Moreover, vitamin D affects the activity of B lymphocytes, inhibiting the activity of plasma cells and the synthesis of memory cells, and activating the functions of monocytes and macrophages [Dittfeld et al. 2014].

The most frequently mentioned role of vitamin D is its influence on bone mineralization. Calcitriol regulates the correct content of calcium and phosphorus in both bones and blood. The body maintains adequate calcemia due to the action of 1,25 (OH) 2D on osteoblasts (osteogenic cells - which build up calcium phosphate in the bone to maintain their proper density) and on osteoclasts (osteoclast cells - releasing calcium from the bone into the blood when the concentration of calcium in the plasma is too low) [Konturek 2003]. Appropriate concentrations of these minerals and active vitamin D counteract the emergence and progression of skeletal diseases. With proper calcium intake, a dose of 1600 mg per day should not be exceeded. It is difficult to overdose vitamin D, the problem is rather deficiencies, however, studies show that when the dose exceeds 10,000 mg / day for several days or when a dose of more than 150 mg / cm³ is taken once), it has a detrimental effect on the body [Olędzka 2013].

Research shows that blood levels of calcidiol correlate inversely with renin levels, suggesting a role for vitamin D in regulating blood pressure. In patients with arterial hypertension and heart anemia, vitamin D supplementation brings beneficial effects [Dittfeld et al. 2014].

Effect of vitamin D and its analogues on cancer cells

Vitamin D, along with other fat-soluble vitamins, is called an antioxidant vitamin when it affects cancer cells. It is known to have pro-apoptotic and antiproliferative properties, but it is mainly used in combination therapy and is administered in small doses [Kulik-Kupka K. et al. 2016]. The effect of calcitriol and its analogues on cancer cells is currently being investigated. The model object of in vitro research is the human promyelocytic leukemia HL-

60 cell line on which derivative compounds with vitamin D activity are tested and the human colon cancer cell line on which the vitamin D analogue ZK156718 is tested. The goal of all analogues is to inhibit the proliferation of cancer cells with greater efficiency compared to biological vitamin D. Some studies indicate that the use of the analog is also used. 1,25-dihydroxy-16-ene-23-yne-vitamins in vivo enables the inhibition of tumor cell differentiation with the beneficial effect of prolonged life in mice. In the case of studies on tumor growth inhibition, the 22-oxa-1,25- (OH) 2D3 analogue and the EB 1089 analogue, which effectively inhibits the angiogenesis process within the tumor, leading to necrosis of cancer cells [Pełczyńska et al. 2005], are tested. It has been shown that vitamin D has an inhibitory effect on 17 different cancers, the studies are largely based on cancer of the breast, ovary, uterus, prostate, esophagus, stomach, colon, anus, kidney, bladder and lymphoma [Dittfeld et al. 2014].

One of the factors causing cancer is the effect of reactive oxygen species on healthy cells in organs or skin. During oxygen stress, which results from an antioxidant imbalance, i.e. when the systems of removing oxygen free radicals fail, ROS accumulates in the tissues, which may induce neoplastic changes and may reduce cellular sensitivity to the taken anti-cancer drugs. The excess of ROS contributes to the stimulation of cell division and the formation of mutations not only in the nuclear genome, but also in the mitochondrial genome, which in turn leads to genome instability, which may affect the functioning of important organs or even switch off the activity of important enzymatic proteins in the fat or metabolic pathway. carbohydrates thus contributing to the emergence of acquired diseases, eg type 2 diabetes, atherosclerosis or obesity. [Kulik-Kupka K. et al. 2016]

It is well known that low vitamin D levels are associated with an increased risk of any type of cancer and decreased survival, mainly due to increased severity of symptoms and metastatic potential of tumors. Clinical studies suggest that vitamin D supplementation is significantly associated with increased overall survival and a lower risk of recurrence of myeloid, but not lymphoid, neoplasms in transplant recipients. A possible relationship between vitamin D and the immune regulation of the tumor microenvironment was also discussed. It is well known that vitamin D modulates the immune response by inactivating the cellular signaling pathway dependent on the nuclear transcription factor NF- κ B. In the tumor stroma, the secretion of cytokines and prostaglandins is necessary for the proliferation of neoplastic cells, but vitamin D, by regulating the cell signaling pathway dependent on the

nuclear transcription factor NFκB and cyclooxygenase 2 (COX-2), can reduce their secretion. [Żmijewski M.A. 2019]

Although no detailed studies have found an association between menopause and breast cancer risk, it is known that two things occur at this stage in a woman's life. One is weight gain in adults and obesity, which promotes an increase in circulating estrogen and is associated with an increased risk of hormone-dependent breast cancer. Vitamin D supplementation may reduce the risk of breast cancer in these women as it may reduce the expression of estrogen receptors and weaken the synthesis and signaling of these hormones. [De La Puente-Yague M. et al. 2018]

As with many other tumors (e.g., large intestine, breast, lung, and non-Hodgkin's lymphoma), studies have found a higher risk of prostate cancer or fatal prostate cancer in men living in northern latitudes, and a greater overall risk of prostate cancer and / or poor prognosis among men with an estimated low vitamin D intake. One of the most convincing cases of the link between vitamin D and prostate cancer comes from studies of African-American men. In these men, 25 (OH) D₃ levels are often low (mainly due to the effect of skin pigmentation reducing intradermal vitamin D synthesis) and the risk of prostate cancer and mortality is clearly higher than in Caucasian men. Although this relationship has been described many times, the mechanisms behind this link are unclear. [Trump D. L., Aragon-Ching J.B. 2018]

Studies show a relationship between the life expectancy of cancer patients and the latitude in which they live. People who settled around high geographical regions of the colon, prostate or pancreatic cancer [Kulik-Kupka K. et al. 2016].

Vitamin D3 in the course of COVID-19

The COVID-19 pandemic caused by the SARS-CoV-2 virus has had a negative impact on humanity as a whole, but countries in the northern hemisphere have suffered the most. Due to the massiveness of the pandemic, many scientists began to look for the causes. The areas most affected by the pandemic appear to coincide with the pattern of seasonal vitamin D₃ deficiency. This resulted in enormous interest in vitamin D₃, it was hypothesized that its deficiency increases the likelihood of a more severe course of COVID-19.

According to the conducted research [G. Davies et al.], The greatest outbreaks of the disease, along with the enormous mortality, occur above + 30 ° N latitude in the northern

hemisphere, while outbreaks in the tropics and southern hemisphere have a much lower mortality. In the southern hemisphere, the mortality rate is 0.2% per million inhabitants, and in areas between 30 ° and 55 °, the mortality rate is between 3% and 37% per million inhabitants. However, not all countries that do not suffer from seasonal vitamin D3 deficiencies, such as Spain and Italy, have higher mortality rates than countries in the north. One hypothesis is that the elderly are deficient in vitamin D3, which disrupts cytokine synthesis, resulting in severe COVID-19 transition and death. And a study by the University of Granada on 200 participants showed that vitamin D supplementation (a dose of 25,000 UI), especially in patients with vitamin D hypovitaminosis, can reduce symptoms caused by the Sars-COV-2 virus.

Unfortunately, due to the short period of the research and the small groups of volunteers on whom it was conducted, it is not possible to precisely determine whether the course of SARS-COV-2 infection is influenced by vitamin D or some other, yet unknown factor.

CONCLUSION

Vitamin D has many important functions in the human body. The most famous function among humans is the regulation of calcium and phosphate metabolism, and the association of vitamin D deficiency with rickets. To perform this function, it works with the kidneys, parotids, bones, calcitriol, PTH, 1,25-D and the FGH-23 factor. Vitamin D in the activated form also affects such cellular processes as: proliferation, apoptosis, the cell cycle, cell differentiation and regulation of gene expression. Due to the regulation of many cellular processes, vitamin D is being studied for its effect on the proliferation of cancer cells in the human body. This can be seen in studies where people living in higher latitudes have lower plasma levels of vitamin D, which increases the likelihood of developing diseases such as: bowel, pancreatic and prostate cancers; COVID-19; diabetes; atherosclerosis; obesity. This is due to the fact that most vitamin D is synthesized by the body under the influence of sunlight, and only a small part is supplied to the body with food. Additionally, vitamin D has many intermediate metabolites whose properties and functions are not yet fully understood.

Vitamin D is the subject of much research and scientific observation, and it also affects other diseases and pathogens not listed in this article. Due to its abilities, it can have a huge impact on modern oncology and as a substance used in the prevention of chronic diseases, and in the

future we can expect even greater interest of scientists and the rest of the society in this unusual vitamin.

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