VITAMIN D3 –
the process of synthesis, metabolism, mechanism of action and pleiotropic effect

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ABSTRACT

Vitamin D3 is a steroid hormone produced in the skin under the influence of UV radiation. It is a vitamin discovered in the 20th century and constantly rediscovered. Over the last few decades, numerous scientists conducting research on vitamin D3 have shown its increasing impact on the proper functioning of the human body. This work will present the process of synthesis, metabolism, mechanism of action of vitamin D3, as well as its pleiotropic effect. In preparation for this review mostly publications from the last 20 years were selected, but older, highly valued publications were not excluded.

Keywords: vitamin D, vitamin D synthesis, vitamin D metabolism, vitamin D deficiency, pleiotropic effect of vitamin D, vitamin D3 supplementation, cancer, breast cancer, colon cancer, immune system, cardiovascular system, skeletal system, nervous system, multiple sclerosis, ischemic stroke, neurodegenerative diseases, vascular dementia, Parkinson's disease

Introduction

1,25(OH)2D3 is the active form of vitamin D3, necessary to maintain proper calcium and phosphate homeostasis. In terms of its chemical structure, it is similar to hormones such as estrogens and testosterone.

The problem of vitamin D3 deficiency is constantly observed in developing countries. Living indoors, eating highly processed food, avoiding the sun or comorbidities may lead to significant deficits. Persistent low levels of vitamin D3 are correlated with low levels of calcium in the blood. The consequence of this is the possible development of rickets in children like and osteoporosis in adults. However, the effect of vitamin D, apart from the obvious impact on the

proper functioning of the skeletal system, turns out to have an actual impact on the functioning of numerous systems constituting one whole, which is the human body. Therefore, research increasingly shows the real need for vitamin D supplementation.

PRODUCTION AND METABOLISM OF VITAMIN D3

Cholecalciferol is synthesized in the skin under the influence of sunlight from 7-dehydrocholesterol. Under the influence of UVB light of the appropriate wavelength i.e. 280-320 nm, previtamin D3 is produced. The form isomerizes to cholecalciferol in a thermosensitive process. The resulting cholecalciferol undergoes further transformations. 25-hydroxylation, 1α-hydroxylation and 24-hydroxylation are the main stages of vitamin D metabolism. These processes are carried out by cytochrome P450 oxidases, which are present both in the mitochondrion and the endoplasmic reticulum. The electron donor in the mitochondria is ferredoxin and ferredoxin reductase, while in the endoplasmic reticulum it is NADPH (nicotinamide adenine dinucleotide phosphate) (1). The first hydroxylation takes place in the liver and leads to the formation of the 25OH2D3 form. It occurs due to the presence of mitochondrial 25-hydroxylase, which is CYP27A1. It is the main enzyme that regulates the level of 25OH2D3 in tissues and blood serum (1). The second hydroxylation takes place in the kidneys, the source of which is 1,25(OH)2D3. Only CYP27B1 has 1α-hydroxylase activity. This enzyme is regulated by parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23) and 1,25(OH)2D3. When the concentration of calcium in the blood serum is increased, the secretion of parathyroid hormone is inhibited, and thus CYP27B1 is inhibited. However, when the concentration of phosphates in the blood serum remains elevated, fibroblast growth factor 23 (FGF 23) is stimulated and secreted (98). FGF23 transmits a signal through its own receptors in the presence of the Klotho coreceptor and leads to the activation of mitogen-activated kinases (MAPK) (1). CYP24A1 is induced and inhibition of CYP27B1. This action causes suppression and leads to 1,25(OH)2D3 catabolism (6). It has been observed that high FGF23 levels, leading to 1,25(OH)2D3 suppression, occur in genetically determined diseases, such as X-linked hypophosphatemic rickets or autosomal dominant hypophosphatemic rickets (143-145). In the case of the former, increased FGF23 activity leads to excessive loss of phosphates by the kidneys. High levels of FGF23 have also been described in cancer and chronic kidney disease (6). CYP27B1 can also be inhibited directly by 1,25(OH)2D3 by affecting vitamin D receptors (VDR) (1). Another factor that influences CYP27B1 is calcitonin. It is a hormone produced by the thyroid gland and, like parathyroid hormone, is responsible for the proper maintenance of calcium and phosphate metabolism. It is secreted when the calcium concentration in the blood is high, and its secretion is inhibited when the calcium concentration is low (6). The conducted research has shown that during lactation there is an increase in the secretion of 1,25(OH)2D3 and calcitonin, which affects the transcription of CYP27B1 (5). High prolactin concentration during lactation stimulates CYP27B1 (6).

vITAMIN D3 RECEPTORS AND MECHANISM OF ACTION 1,25(OH)2D3

VDR (vitamin D receptor) belongs to nuclear receptors, the human genes of which are located on chromosome 12. The human VDR protein consists of 427 amino acids. It contains 8 coding exons and 6 or more non-coding exons. It has two ends: NH2 and COOH. At the NH2 end there is a DNA-binding domain, and at the COOH end there is a ligand-binding domain. When 1,25(OH)2D3 binds, VDR heterodimerizes with RXR and a conformational change occurs. This connection determines the correct expression of genes. Steroid receptor activators (SRC-1,2,3) and p160 coactivators bind to the VDR domain. The p160 coactivator then enables the

formation of a multi-subunit complex due to the activation of the CBP/p300 coactivators. Changes occur within chromatin as a result of methylation and acetylation processes. The combination of VDR with transcription factors leads to the formation of a pre-initiation complex. The participation of RNA polymerase II, a multi-protein complex and a mediator, is necessary (6). Mutations may occur within the ligand-binding domain as well as within the DNA-binding domain. Such cases have been described in hereditary vitamin D-resistant rickets (HVDRR) (6).

24- HYDROKSYLAZA

The enzyme 24-hydroxylase also participates in the metabolism of vitamin D. CYP24A1 has both 23-hydroxylase and 24-hydroxylase activity. In case of mutations in CYP24A1, the concentration of 24,25(OH)2D decreases, but the concentration of 1,25(OH)2D remains normal or higher (4). It has been observed that such a mutation occurs in children with idiopathic hypercalcemia, which results in an increase in the concentration of calcium in the blood, i.e. hypercalcemia; an increase in the concentration of calcium in the urine, i.e. hypercalciuria, as well as a decrease in the concentration of parathyroid hormone. It has been shown that the main function of CYP24A1 is to maintain normal concentrations of 1,25(OH)2D and 25OHD so that toxic levels are not reached (1).

CHARACTER D2

Vitamin D, in addition to possible supplementation, can be obtained from food as ergocalciferol. It is particularly present in products such as fatty fish and dairy products. Similarly to vitamin D3, it is metabolized to 25-hydroxyvitamin D (25OHD) in the liver and to 1,25-dihydroxyvitamin D (1,25(OH)2D3) in the kidneys. The structure of ergocalciferol differs from the D3 form. It has a double bond between C22 and C23 and a methyl group at C24 in the side chain. Therefore, this form has lower affinity for vitamin D binding protein (DBP). Therefore, it is removed from the blood faster. This results in difficult conversion to 25-hydroxyvitamin D. Therefore, supplementation with D2 relative to D3 turns out to be ineffective when not used daily. However, when comparing the 1,25(OH)2D2 and 1,25(OH)2D3 forms, the affinity for the vitamin D receptor (VDR - vitamin D receptor) is comparable in both cases (12).

VITAMIN D3 SUPPLEMENTATION

Data indicate that 1 in 8 Europeans are at risk of vitamin D deficiency, defining deficiency as a 25(OH)D concentration below 30 nmol/l (99). The trend of deficiency is estimated to increase to as much as 28–65% for ethnic minorities in Northern Europe (99). It has been observed that there are common factors that increase the incidence of vitamin D deficiency. Certainly, such predictive factors include leading a closed lifestyle, older age, higher BMI, stimulants (tobacco), lack of supplementation of other vitamins, including vitamin D, and calcium. (100). Attention has also been paid to other factors leading to limited availability of vitamin D, including developing inflammation (101), fat malabsorption syndromes, nephrotic syndrome and various drug interactions that change metabolism and absorption (101).

To initiate vitamin D supplementation, it is necessary to determine the initial concentration of 25(OH)D in blood serum. To achieve a beneficial therapeutic effect, it is also important to determine the target value (107).

Table 1. 25(OH)D concentrations in blood serum for Poland (135), global (136) and Central Europe (137).

	Recommendation for Poland 2009, (135)	**Global Recommendation 2016, (136)**	**Recommendation for Central Europe 2016, (137)**
Optimal concentration	children and youth: 20–60 ng/ml adults and seniors: 30–80 ng/ml	>20 ng/ml	>30–50 ng/ml
suboptimal concentration	**not defined**	12–20 ng/ml	>20–30 ng/ml
deficit	<10 ng/ml	<12 ng/ml	0–20 ng/ml
toxic concentration	**not defined**	>100 ng/ml	>100 ng/ml

a Other data indicate a toxic dose above 150 nmol/l (129).
b Other data indicate a toxic dose above 250 nmol/l (122).

Table 2. Recommended daily doses of vitamin D supplementation depending on age for Poland (135), global (136) and Central Europe (137).

	Recommendation for Poland 2009, (135)	**Global Recommendation 2016, (136)**	**Recommendation for Central Europe 2016, (137)**
0- 6 month of life	400 IU/day	400 IU/ day	400 IU/ day
6- 12 month of life	400 IU/ day	400 IU/ day	400–600 IU/ day
2-18 years	400 IU/day	600 IU/ day	600–1000 IU/ day
>18 years	800–1000 IU/ day	600 IU/ day	800–2000 IU/ day
pregnancy and lactation	800–1000 IU/ day	600 IU/ day	1500–2000 IU/ day

Table 3. Indications for vitamin D supplementation at a dose of 800–1000 IU/day (104).

people with limited sun exposure • people with insufficient supply of vitamin D • elderly people at risk of falls • people at risk of osteoporosis • patients treated for osteoporosis • patients with fragile fractures • obese patients • patients with malabsorption syndrome • patients after bariatric surgery • patients treated with glucocorticoids • patients treated with anticonvulsants

Table 4. Indications for vitamin D supplementation at a loading dose of 25,000 or 50,000 IU/weekfor a period of 4–6 weeks (104).

• people with low levels of 25(OH)D • patients after bariatric surgery • patients with malabsorption syndrome • patients with severe obesity

PLEIOTROPIC EFFECT OF VITAMIN D3

CANCER

Research shows that 1,25(OH)2D3 slows down the development of cancer. Calcitriol and its analogues inhibit the growth of cancer cells by stopping the cell cycle in the G0/G1 phase and then cell differentiation (13).

Cancer cells obtain energy from the ongoing aerobic glycolysis and obtain intermediates for the synthesis of amino acids and fatty acids (19). 1,25(OH)2D3 reduces glycolysis. It leads to reduced conversion of glucose to acetyl-coA and oxaloacetate, and consequently to reduced activity of the Krebs cycle (6). It has been shown that the active form of vitamin D has antiproliferative effects, induces apoptosis, influences the ongoing inflammatory process, affects cellular metabolism, and inhibits angiogenesis and metastasis (14). The anticancer effect of 1,25(OH)2D3 requires the presence of VDR receptors on the surface of cancer cells. The presence of VDR next to estrogen and androgen receptors, as well as its greater expression, gives a better prognosis and prolongs overall survival (6). Chronic inflammation may be a factor in the development of cancer. It has been shown that 1,25(OH)2D3, an immunosuppressant, reduces the activity of cyclooxygenase-2 and increases the activity of 15-hydroxyprostaglandin dehydrogenase, which reduces the synthesis of prostaglandins (11,12). In vivo studies have shown that mice transplanted with cancer cells and fed a diet low in 25(OH)D experienced significant tumor growth (20,21,22). Other studies have shown that the lack of VDR receptors in mice leads to increased carcinogenesis after exposure to carcinogenic products(23). Two groups of mice that had or did not have the VDR receptor were compared. In the group without the VDR receptor, it was shown that the tumor grows larger compared to the group that had the VDR receptor (24). It has been reported that the level of β-catenin/TCF increases, and calcitriol does not transfer B-catenin to the plasma membrane and does not inhibit transcription (24). In other studies on rodents with colon cancer, it was shown that the supply of 25(OH)D to the body contributes to the reduction of tumor mass. Supplementation with 5000 IU of vitamin D3/kg is as effective as 1,25(OH)2D3 in breast and prostate cancer (25). In turn, other studies (26,27) showed that treatment with 1,25(OH)2D3 or vitamin D3 analogues increases the response to chemotherapy. This makes it possible to use lower doses of chemotherapy and thus reduce side effects thanks to combined treatment. Vitamin D supplementation may influence cancer progression, but has no direct effect on carcinogenesis (6). Prospective studies have shown that in the group with a higher level of 25(OH)D in blood serum, the risk of developing colorectal cancer is 30-40% lower than in the group with the lowest level of 25(OH)D in blood serum (28). However, in the case of other cancers, such as bladder, prostate or skin cancer, no relationship between the level of 25(OH)D and the risk of cancer development has been demonstrated (29,30,31). Most randomized studies using vitamin D supplements showed a relationship between supplementation and mortality, but no relationship between supplementation and the occurrence of cancer (32-35)

BREAST CANCER

One of the most common cancers in women is breast cancer. An increasing tendency in its incidence is observed from year to year. In addition to genetic factors that play a significant role in the occurrence of breast cancer, attention is also paid to factors such as an active lifestyle, diet and ionizing radiation. Some studies have shown that nutrition may influence

approximately 35% of breast cancer cases (125). Therefore, increasing the amount of fiber in the diet, supplementing vitamins or limiting the consumption of alcohol and red meat may protect against the development of cancer (126). Numerous evidence points to a linear cause-and-effect relationship between vitamin D concentration and the risk of cancer development (127,128), and the demonstration that enzymes that are present in the kidney are present in breast epithelial cells makes a vitamin D-breast cancer relationship seem likely. (126). 1a hydroxylase (CYP27B1) is present in mammary gland cells, converting 25OHD into 1,25OH2D. Locally generated calcitriol has an autocrine and paracrine effect, which protects against neoplastic transformation (126).

The expression of VDR receptors determines the proper functioning and development of the mammary glands during puberty, pregnancy and the stage of breast involution (126). 1,25(OH2)D3 is a VDR agonist and reduces the expression of estrogen receptors (126). In vitro, 25OHD at a concentration of 35–100 nM inhibits the growth of mammary gland cells. However, at higher concentrations it protects MCF-12F cells against hypoxia and oxidative stress. 25OHD has been shown to prevent the formation of pre-cancerous lesions by protecting against chemical carcinogens (126). Various preclinical, experimental and observational studies have shown that calcitriol inhibits angiogenesis and cell proliferation and induces apoptosis and cell differentiation. A meta- analysis showed that the relationship between 1,25(OH2)D3 and breast cancer is inversely proportional (130). It has been observed that interruption of a given stage of vitamin D synthesis and metabolism may induce the development of breast cancer (131). Through epigenetic mechanisms, the expression of CYP27B1, CYP24A1, VDR and megalin is altered (126). Other analyzes aimed at demonstrating the relationship between menopause and the risk of breast cancer still turn out to be insufficient. However, it has been observed that during this period women gain weight and increase the level of estrogen in the blood serum. This is an unfavorable phenomenon because it may contribute to the development of hormone-dependent breast cancer (132,133,134). Therefore, vitamin D supplementation appears to be promising due to its effect on reducing estrogen receptor expression (126).

COLON INTESTINE CANCER

One of the most common malignant tumors in Europe is colorectal cancer. Data show that up to 85% of all colorectal cancer cases originate from adenomas (141). The disease is more and more common in people over 50 years of age, in those who smoke cigarettes, lead an inactive lifestyle, are obese and abuse alcohol. The genetic component also plays an important role in the occurrence of colorectal cancer. Therefore, numerous studies are being conducted that would present groundbreaking results on how to prevent and inhibit the development of colorectal cancer. Therefore, vitamin D and its anti-cancer effect were taken under the microscope. The anticancer effect of calcitriol includes, among others: on inhibition of cell proliferation, inhibition of angiogenesis, induction of epithelial cell differentiation or induction of apoptosis. A prospective study, which included 16,818 participants in the United States, showed that the relationship between mortality from colorectal cancer and the level of 25(OH)D is inversely

proportional (139). Another case-control study confirmed this relationship (140). A meta-analysis of 35 independent studies also showed this pattern (138). Although numerous genetic and molecular studies have shown that vitamin D protects against colorectal cancer, the number of studies carried out is still insufficient. Test results showing loss of VDR expression and changes in CYP27B1 and CYP24A1 in colorectal cancer show that vitamin D both prevents and/or treats the early stages of this cancer (142).

IMMUNE SYSTEM

1,25(OH)2D3 influences the regulation of innate and acquired immunity. It stimulates the congenital form and inhibits the acquired form (36). It contributes to a decrease in the secretion of pro-inflammatory cytokines: IL-1, IL-2, IL-6, IL-12, IFN-γ, TNF-α, TNF-β and to an increase in the production of anti-inflammatory cytokines: IL-4, IL-5 and IL-10. It inhibits the formation of the NFAT/AP-1 complex and thus inhibits IL-2 transcription. Moreover, it has been shown to have an inhibitory effect on the Th9 and Th17 lymphocytes they secrete, respectively

IL-9 and IL-17.

1,25(OH)2D3 acts on dendritic cells and blocks their maturation. It leads to reduced expression of MHC class II, CD40, CD80 and CD86 molecules as well as IL12/IL10 (38,39). In vivo studies show that in mice NOD dendritic cells under the influence of 1,25(OH)2D3 can migrate and inhibit T cell proliferation (40). Increasing glycolysis and oxidative phosphorylation, through changes in metabolic pathways, lead to changes in the phenotype of dendritic cells (41). In vivo studies on mouse models have shown that 1,25(OH)2D3 can protect against the development of autoimmune diseases, such as inflammatory bowel disease (IBD) or autoimmune encephalomyelitis (EAE) (41). In experimentally induced colitis, it was observed that the use of 1,25(OH)2D3 inhibits Th1 and Th17 lymphocytes, reduces inflammation and leads to the induction of T reg lymphocytes (43,44). In autoimmune encephalomyelitis, 1,25(OH)2D3 inhibits IL-12 and IL-17 (37). To reduce paralysis in EAE, it has been observed that the combination of vitamin D at a dose of 20 IU/g diet with IFN-β is significantly more effective than the use of vitamin D or IFN-β alone (37). Therefore, patients with multiple sclerosis (MS) are often treated with a combination of vitamin D and IFN-β. Research shows that 1,25(OH)2D3 has a protective effect on the course of autoimmune diseases, but the benefits of vitamin D supplementation and its analogues remain unknown.

CARDIOVASCULAR SYSTEM

Epidemiological studies show that the frequency of cardiovascular events increases in winter and with distance from the equator. Due to presented epidemiological data and studies carried out on mice, interest in vitamin D is constantly growing. In studies on animal models, 1,25(OH)2D3 treatment was introduced in rats with chronic arterial hypertension, cardiac hypertrophy and congestive heart failure. This study showed that vitamin D supplementation led to a reduction in cardiac hypertrophy, especially in those rats on a high-sodium diet (45). It has been shown that this vitamin has a direct effect on the

renin-angiotensin-aldosterone (RAA) system. VDR signaling affects both the vascular endothelium and the heart, but full understanding requires further research. A study conducted by Giovannucci E et al. (46) showed that the incidence of myocardial infarction is higher in people with reduced 25(OH)D3 levels. The study involved 18,000 men who were health care workers (46). It was reported that in men with a 25(OH)D3 level < 15 ng/ml, the incidence of myocardial infarction was as much as 2.42 times higher than in men with a level above 30 ng/ml (46). In another study, it was observed that patients who underwent coronary angiography and had a 25(OH)D3 level <8 ng/ml had a higher cardiovascular mortality than patients with a 25(OH)D3 level > 28 ng/ml (47).

Skeletal system

Studies showing the relationship between reduced 25(OH)D3 levels and a greater risk of fractures are still controversial. Therefore, numerous attempts are made to demonstrate this relationship. A prospective study (105) involved a group of 1,662 men aged 70-97 years living in Australia. There were 123 fractures recorded throughout the study, after taking into account bone mineral density, sun exposure and physical activity. It has been observed over approximately 4 years that in patients with 25(OH)D3 levels above 72 nmol/l or below 36 nmol/l, fractures are more common. It has been shown that both too low and too high a concentration of vitamin D3 may be harmful to health (105). A study conducted by Atteritano et al. (51) showed an association between low levels of vitamin D3 in blood serum and greater susceptibility to fractures in HIV-positive patients with brittle bones. It has been observed that they suffer from vertebral fractures more often, which may also be related to vitamin D deficiency (51). Another study, however, presented completely opposite results to those discussed above. The use of cholecalciferol at a dose of 100,000 IU/month for a period of 2.5–4.2 years does not prevent falls or fractures (106). Although a Cochrane systematic review (108) indicates that falls cannot be prevented by vitamin D supplementation in the general population, other meta-analyses indicate that maintaining the baseline vitamin D level below 75 nmol/l in 90% of the population reduces the risk of falls by 15 % (109). Randomized controlled clinical trials examining the effect of vitamin D on reducing the risk of falls confirmed its positive effect. The study concerned participants who achieved normal 25(OH)D levels during treatment and/or had 25(OH)D deficiency in blood serum (110-114). However, other randomized studies did not show this relationship - a reduction in the number of falls after 25(OH)D supplementation. It was concluded that these data may be due to the fact that the specific population studied had high vitamin D levels at the beginning of the study (115-119) or too high a dose of vitamin D was administered (115, 120,121).

The link between vitamin D supplementation and osteoarthritis is still a matter of debate. Observational studies have shown that there is no such relationship in patients whose average 25(OH)D level was above 50 nmol/l (123).

Another study of 2,756 women and men whose average age was 74.2 years noted that those who had the lowest 25(OH)D values had a higher risk of developing osteoarthritis (124). Despite some inconsistencies, it has been shown that vitamin D supplementation together with calcium has a beneficial effect on possible fractures, including hip fractures. The greatest benefit from supplementation may be obtained by adults with a vitamin D deficiency of less than 50 nmol/l, in order to achieve a 25(OH)D level in the range of 50-100 nmol/l (104). However, reaching 25(OH)D levels above 100 nmol/l may have a negative impact, increasingthe risk of fractures (104).

NERVOUS SYSTEM

Due to the presence of vitamin D3 receptors (VDR) in the thalamus, hypothalamus and hippocampus, more and more researchers decide to conduct research on the effect of vitamin D3 in various neurological conditions. 1,25(OH)2D3 has been shown to influence neuronal maturation and differentiation (53). Moreover, it regulates the synthesis of serotonin, dopamine, gamma-aminobutyric acid (GABA) and acetylcholine (54,55,56). Many studies have shown that it activates the remyelination process. It contributes to the removal of myelin debris and activation of microglia (59).

MULTIPLE SCLEROSIS

In multiple sclerosis (MS), an autoimmune disease, nerve tissue is damaged. It has been shown that vitamin D3 deficiency is an important risk factor for the development of MS, and maintaining a normal level of vitamin D3 in blood serum may reduce the risk of MS. Cohort studies including 187,000 women showed a relationship between the supply of vitamin D3 from diet or supplementation and the risk of developing MS (60). Women who consumed about 700 IU/day had a lower risk of developing multiple sclerosis by 33% compared to women whose vitamin D3 intake was lower than the stated value. However, women who used supplementation of approximately 400 IU/day had a 41% reduced risk of developing MS compared to those women who did not use supplementation (60). Prospective study from 2012. (61) confirmed that vitamin D3 levels >30 ng/ml are associated with a lower risk of developing MS. Studies have shown that vitamin D3 supplementation brings numerous benefits to MS patients. However, there is a real need for further research randomized to clearly determine whether it is possible to use this vitamin as a gold standard in the treatment of multiple sclerosis. Moreover, the concept of "sufficient" vitamin D3 levels is still controversial. According to the Institute of Medicine (IOM), the level of 25(OH2)D3 should be >20 ng/ml (50 nmol/L) (63). However, the Endocrine Society states that this value should be approximately 30 ng/ml (75 nmol/l) (63). Other researchers, based on experimental studies, state that the level of 25(OH2)D3 should be in the range of 30-50 ng/ml, because then it has immunomodulatory activity. In the case of patients with CIS (clinically isolated syndrome), multiple sclerosis and 25(OH2)D3 level <20 ng/ml, supplementation with ergocalciferol is necessary. The recommended dose is 50,000 IU/week for a period of eight weeks to achieve a value of > 30 ng/dl in blood serum. In maintenance supplementation, cholecalciferol is administered at a dose of 1000 to 2000 IU/day to replenish the deficiencies (62). Other authors indicate that most patients should supplement 2000-5000 IU/day to maintain the 25(OH2)D3 level in the range of 40-60 ng/ml (63).

ISCHEMIC STROKE

Ischemic stroke is a disease of heterogeneous etiology, which is influenced by both modifiable factors, such as smoking or physical inactivity, and non-modifiable factors, such as genetics, gender or age. It has been shown that vitamin D3 deficiency is associated with a greater risk of developing ischemic stroke, and if it occurs, it increases the severity of the disease and complicates post-stroke recovery. Studies (64,65) have shown a relationship between low 25(OH)D levels and a higher risk of ischemic stroke depending on age, gender and race. There was no association between reduced 25(OH)D levels and a higher risk of ischemic stroke in blacks compared to whites. The relationship between vitamin D3 and ischemic stroke may result with an inhibitory effect on the development of thrombosis. However, vitamin D3 may contribute to the development of hemorrhagic stroke (52).

A study conducted by Manouchehri et al. (66) showed that vitamin D deficiency increases the risk of ischemic stroke by almost 7 times compared to the control group. Researchers reported a 4.37-fold increase in the risk of small- vessel ischemic stroke and a 13-fold increase in the risk of large-vessel ischemic stroke (66). It has been described that vitamin D3 and B12 deficiency and hyperhomocysteinemia intensify the course of the first ischemic stroke. Therefore, great attention is paid to the determination of these parameters as part of primary and secondary prevention (52).

Patients with lower 25(OH)D levels have been shown to have greater disability in the initial phase of stroke (65). And immobilized patients have lower levels of 25(OH)D in blood serum compared to those who are physically active outdoors and synthesize vitamin D3 from UV radiation (52). The role of vitamin D3 in the pathophysiology of ischemic stroke is to inhibit the release of pro-inflammatory cytokines, such as TNF-α, IL-6, IL-12, IFN-γ, which may intensify atherosclerotic changes in vessels and influence the instability of atherosclerotic plaque (67,68). In addition, cholecalciferol inhibits the synthesis of prostaglandins and reduces the expression of nuclear factor kappa B - NF-κB (69,70). The conducted research and collected data indicatea relationship between the level of vitamin D3 and ischemic stroke.

NEURODEGENERATIVE DISEASES

Degenerative diseases are chronic diseases leading to the death of nerve cells. These include Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. It has been show that there is a relationship between altered expression of VDR (vitamin D receptor) and lower use of vitamin D in nerve cells, and thus greater susceptibility to neuronal degeneration (71). Vitamin D induces phagocytosis of amyloid beta protein due to the presence of macrophages (72,73) and reduces inflammation caused by amyloid deposition (56). In cultured astrocytes after vitamin D administration, it was observed that the level of mRNA coding for TNF-alpha and GM-CSF was reduced (56). Moreover, it has been reported to have neuroprotective effects by protecting against glutamate toxicity (74). Vitamin D3 inhibits the synthesis of nitric oxide synthase and regulates gamma-glutamyltranspeptidase, which participates in glutathione metabolism (75). It reduces the hyperphosphorylation of tau protein, which progresses with age, and stimulates the activity of protein phosphatase 2A (76). In a population group of people suffering from mild cognitive impairment, low levels of vitamin D concentration in blood serum have been reported (77). A 7-year study of older women showed that greater vitamin D

supplementation led to a reduced risk of developing Alzheimer's disease (78,79). Despite the provided data from molecular analyzes and conducted studies, vitamin D supplementation and its impact remain unclear and require further observations and clinical practice. Answers to many questions are needed to explain the possibility of using therapy to prevent the development of the most common neurodegenerative disease - Alzheimer's disease (52).

VASCULAR DEMENTIA

Studies link vitamin D deficiency with an increased risk of diabetes, congestive heart failure, hypertension, stroke (80), as well as vascular dementia and small vessel disease (81,82). A diet rich in vitamin D has an anti-lymphoproliferative effect on the vascular endothelium and protects against the effects of inflammatory cytokines (83,84). It regulates the function of voltage-sensitive L-type calcium channels and the expression of 36 proteins and 74 genes related to the development of the cytoskeleton (85,86). Various studies show a relationship between vitamin D deficiency and dementia. They indicate the antioxidant effect of vitamin D and protection against free oxygen radicals (ROS) and regulation of vessels to maintain proper cerebral circulation (82,45). Studies have shown that in small vessel disease there is an increase in reactive oxygen species and hyperexpression of NOX 2 and NOX 4 isoforms (87,88). Free oxygen radicals cause cell damage and induce apoptosis. Chung et al. (82) showed that vitamin D deficiency leads to microbleeds in the white matter and hyperintense lesions. Moretti et al. (89) presented the hypothesis that in the case of small vessel disease, which involves changes in cerebral blood flow and neuromuscular disorders, vitamin D may play a significant role. It has been shown to regulate the neuromuscular junction system and influence the release of glutamate. It inhibits the influx of calcium and thus regulates the synthesis of nitric oxide, which activates phospholipase A2 and influences further cascades of prostaglandin metabolism. It also increases the synthesis of vasoactive intestinal polypeptide (VIP) and acetylcholine (52). Therefore, vitamin D deficiency may disrupt neurovascular coupling, nitric oxide synthesis or smooth muscle control, and thus increase the development of small vessel diseases (52). However, the number of studies on the issue of vitamin D supplementation in vascular dementia is still insufficient.

PARKINSON'S DISEASE

Parkinson's disease is the second most common degenerative disease of the nervous system in older people. Patients with this disease struggle with slow movement (bradykinesia), increased muscle tension, resting tremor and posture disorders on a daily basis. The relationship between vitamin D and Parkinson's disease appears to be significant in numerous considerations. It has been noted that poly[ADP-ribose] polymerase 1 (PARP1) is overexpressed in the substantia nigra in Parkinson's patients (90). Calcitriol, through mechanisms related to the reduction of microglial activation, may contribute to the regulation of PARP1 expression (91). In another mechanism, it has been observed that heme oxygenase is overexpressed in damaged dopaminergic neurons in patients with Parkinson's disease and in the substantia nigra of the brain (92,94). However, in healthy people, the expression of this protein is limited only to neuroglia (93). In this case, the role of vitamin D appears to be unpredictable in delaying the action of heme oxygenase and in influencing glial immunoreactivity (95). The Sp1 gene, which is a transcription factor, also draws attention. It is responsible for the expression of the dopamine receptor gene and the dopamine transporter gene (96,97). It has been shown that VDR affects the regulation of Sp1 gene expression and the relationship between Sp1 and vitamin D results from different binding sites of transcription factors.

CONCLUSIONS

More and more research draws attention to vitamin D as necessary for the proper functioning of the immune, cardiovascular, skeletal and nervous systems. Its deficiency has been reported in numerous diseases, which proves its real impact on the brain, bones, heart and vessels. In vivo, in vitro and human studies confirm these assumptions. Vitamin D supplementation can have many benefits and be a cheap and safe method. However, the issues of vitamin D supplementation and its clinical benefits remain unclear. Prescribing doses higher than recommended by guidelines still raises controversy and concerns about its potential toxicity. Therefore, it is necessary to continue randomized trials, paying attention to vitamin D supplementation with calcium. Great hopes are placed on vitamin D and its real impact on the course of the disease and mitigating its effects. And although meta-analyses indicate that vitamin D does not reduce the incidence of diseases, including cancer, it does influence mortality. Therefore, there is a need for further research at the molecular level and clinical trials in patients with neurodegenerative, cancer, cardiovascular and immune disorders.

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