EFFECTS OF VITAMIN D DEFICIENCY ON THE CARDIOVASCULAR SYSTEM

Abstract. Vitamin D deficiency occurs in 30-50% of the world's population [1]. Vitamin D deficiency increases in proportion to distance from the equator, which explains the increased filtration of UV rays. [2]. It causes rickets, osteoporosis, osteomalacia, but also cardiovascular disease. The Russian and foreign studies presented in this review indicate that moderate and severe vitamin D deficiency is a risk factor for the development of cardiovascular diseases. [3]. A decrease in vitamin D levels is a risk factor for cardiovascular pathology: arterial hypertension (AH), dyslipidemia, diabetes mellitus (DM), myocardial fibrosis and a predictor of adverse cardiovascular events - strokes and heart attacks. Vitamin D has a vasoprotective effect, reducing endothelial dysfunction, has a positive effect on blood pressure, reduces the risk of left ventricular hypertrophy and atherosclerosis, slows down vascular remodeling and myocardial fibrosis, reduces insulin resistance, and affects the course of inflammatory processes [4].

Keywords: vitamin D deficiency, 25(OH)D, 1,25(OH)2D, cardiology, arterial hypertension, atherosclerosis, disturbance of heart rate, congestive heart failure.

Vitamin D is fat-soluble and was discovered over 90 years ago when scientists discovered that fish oil could treat rickets. Vitamin D enters the body with food, but the amount of food in which it is contained is very limited. But this is not the only way for vitamin D to enter the body - it can be synthesized under the influence of UV rays in the skin. To convert to the active form, vitamin D needs to undergo two hydroxylation processes: the first stage occurs in the liver and vitamin D is converted into 25 (OH) D (25-hydroxyvitamin D) (calcidiol), then the second stage of
hydroxylation in the kidneys - the active form of vitamin D is formed - 1,25 (OH) 2D (1,25-dihydroxyvitamin D).

The spectrum of action of vitamin D is not limited only to the control of calcium-phosphorus metabolism, it also affects the development of cardiovascular diseases. This was confirmed in the large-scale Framingham Offspring Study, which lasted more than 5 years. It was shown that the incidence of cardiovascular events (ischemia, heart attacks, strokes) was 33% higher in the group of patients with vitamin D deficiency, and a direct correlation was shown with the level of vitamin D and the presence of arterial hypertension [5].

Vitamin D affects not only the course and prognosis of chronic diseases, but also acute conditions. Among patients admitted to intensive care units (ICUs), 40-70% have vitamin D deficiency. A systematic review of 14 studies (involving 9715 ICU patients) found that vitamin D deficiency was associated with higher mortality. The review also concluded that vitamin D deficiency may be a predictor of adverse health outcomes among ICU patients [6].

According to the results of another large study, it was found that in patients with low-normal levels of 25 (OH) D (<37.5 nmol / L), compared with patients with sufficient levels (≥75 nmol / L), the risk of MI increased by more than 2 times [7].

Based on the above studies, vitamin D deficiency is one of the risk factors for the development or worsening of the course of cardiovascular diseases. Next, the effect of vitamin D deficiency on specific cardiovascular pathologies will be discussed.

**Vitamin D deficiency and the development of atherosclerosis**

The development of atherosclerosis is a serious risk factor for adverse cardiovascular outcomes, but despite the extensive number of clinical studies, its pathogenesis is still not fully understood.

The main regulator of vascular homeostasis is the endothelium. As a result of endothelial dysfunction, inflammatory reactions occur that can lead to smooth muscle proliferation, thrombogenesis and contribute to the development of atherosclerosis. Vitamin D plays a protective role and reduces the risk of atherosclerosis by: decreasing platelet adhesion and aggregation, decreasing
oxidative stress, increasing NO production, suppressing the release of proinflammatory cytokines and inhibiting smooth muscle fiber proliferation [3].

The rigidity of the vascular wall is an important factor in the development of atherosclerosis. According to research data, patients with a 25 (OH) D level less than 20 ng / ml have an increased pulse wave velocity in the aorta> 9 m / s (N = 4-6 m / s), while an increase in the pulse wave velocity has a direct correlation with an increase in the risk of developing atherosclerosis. This study concluded that the lower the level of vitamin D, the more stiffness of the arteries, while maintaining the level of vitamin D in the reference interval contributes to a 2-fold reduction in the risk of atherosclerosis [8]. One of the probable mechanisms of pathogenesis is the positive effect of the active metabolite of vitamin D - 1,25 (OH) 2D. It reduces the deposition of mineral deposits on the endothelium by regulating the serum calcium and phosphorus levels.

Inflammatory reactions play one of the main roles in the development of atherosclerosis. The most widely studied markers of vascular inflammation are C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α). A large body of research suggests that vitamin D levels can inhibit TNF-α release, and vitamin D levels are inversely related to serum CRP levels. In addition, a high level of vitamin D is reliably associated with high concentrations of interleukin-10, which has a cardioprotective effect, suppressing the production of proinflammatory cytokines [9].

Statins are the main component of atherosclerosis therapy. There are publications recommending co-administration of vitamin D with statins. Vitamin D inhibits HMG-CoA reductase, an enzyme that plays a key role in the development of atherosclerosis, thereby enhancing the therapeutic effect of statins.

**Vitamin D deficiency and the development of hypertension**

The relationship between vitamin D deficiency and the development of arterial hypertension has been discussed since the end of the last century. The first study to reveal their relationship - Rostand in 1979, showed that the risk of developing hypertension is higher in people with vitamin D deficiency (living further from the equator). A study on the study of ultraviolet radiation (UVR) also confirmed the
effect of UVR on blood pressure (BP). After exposure to ultraviolet irradiation, a moderate, statistically significant decrease in systolic blood pressure was observed [10].

There are several mechanisms of action of vitamin D on blood pressure. An important component in the control of blood pressure, water-salt metabolism and vascular tone is the renin-angiotensin-aldosterone system (RAAS). According to recent studies, the active metabolite of vitamin D – 1,25 (OH) D is involved in the regulation of the RAAS, suppressing the expression of the renin gene. This effect has been proven in a study in rodents: inhibition of the synthesis of 1,25 (OH) D leads to an increase in renin expression, and vice versa - administration of 1,25 (OH) D to rodents suppresses renin expression. The second mechanism is a decrease in the expression of endothelial NO synthetase in the presence of vitamin D deficiency, which leads to an increase in the rigidity of vascular stiffness and the development of endothelial dysfunction. At the same time, the introduction of 1,25 (OH) 2D has a protective effect - it increases the production of NO in the endothelium [11].

The risk of developing hypertension in patients with vitamin D deficiency has been evaluated in many studies. Two prospective cohort studies of 16-18 years, respectively, involving 38388 men and 77,531 women, found that the risk of hypertension in men with 25 (OH) D levels less than 15 ng / ml was significantly higher than those with 25 (OH) levels. D more than 30 ng / ml, when analyzing the risk of developing hypertension in women, significant differences were also obtained [12]. The NHANES III study in 15,000 patients also showed a negative correlation with vitamin D levels and an increase in blood pressure.

As a therapy for hypertension, it is advisable to add vitamin D in combination with antihypertensive drugs, this leads to a decrease in systolic blood pressure and an improvement in left ventricular function [13].

**Heart rhythm disturbances and vitamin D deficiency**

Vitamin D deficiency also affects heart rate, but the pathophysiological mechanisms of this effect are not yet fully understood.

In Scotland, a 6-year study was conducted on the diurnal variability in hospitalization and mortality due to atrial fibrillation (AF). There was a significant
12% increase in the frequency of hospitalizations in winter in women and a significant increase in mortality by 22% from AF in men [14]. In the NHANES study on 27153 patients in two time intervals from 1988 to 1994 and from 2001 to 2006, it was found that the heart rate was significantly higher by 2.1 beats / min in patients with a level of 25 (OH) D (less than 10.0 ng / ml) than in participants with a higher 25 (OH) D level in the reference interval. With regard to blood pressure, an increase in mean blood pressure was also noted in the group of patients with a 25 (OH) D level of less than 10.0 ng / ml, in comparison with patients with a 25 (OH) D level of 15-35 ng / ml.

Left atrial diameter and pulmonary artery pressure are strongly associated with the occurrence of AF. According to the study, it was found that the level of vitamin D correlates with these indicators in patients with nonvalvular persistent AF [15]. A meta-analysis of 8 studies involving 27,307 patients also found that vitamin D deficiency is one of the predictors of AF [16].

Given the studies conducted, vitamin D deficiency plays an important role in the development of cardiac arrhythmias.

**Vitamin D deficiency and chronic heart failure**

Vitamin D has a multifactorial effect on the development of chronic heart failure (CHF). One of the factors is the development of secondary hyperparathyroidism due to vitamin D deficiency. High levels of parathyroid hormone (PTH) provoke calcification of the heart valves, thereby increasing the risk of CHF. The next factor is the suppression of the synthesis of proinflammatory cytokines at normal levels of 1,25 (OH) 2D: IL-1, IL-6, IL-8 and TNF-α, which in turn reduces the incidence of CHF [17]. Also, an important factor in the development of CHF is the regulation of telomerase activity by vitamin D; it is the shortening of telomeres that is one of the causes of aging, which increases the risk of developing CHF and other age-associated diseases [18]. Several large-scale studies have been conducted regarding vitamin D deficiency and the development of CHF. One of them lasted 2.5 years and ended in 2016, a negative correlation was found between the level of vitamin D and the concentration of NT-proBN and the left ventricular ejection fraction, this correlation was also confirmed in another study, but in...
addition, they demonstrated that they are associated myocardial dysfunction and mortality from heart failure were significantly associated with low levels of 25 (OH) D and 1.25 (OH) 2D [19]. The ability of the vitamin to suppress the production of pro-inflammatory cytokines and increase the production of anti-inflammatory was also confirmed in a study on 123 patients. For 9 months they received vitamin D therapy at a dosage of 2000 IU. Control after therapy revealed a decrease in TNF-α and an increase in the level of anti-inflammatory IL-10 [20].

The study of the effectiveness of the use of vitamin D has established its positive effect for the prevention and treatment of cardiovascular diseases. The set of mechanisms of the effect of vitamin D on the cardiovascular system is great, but the pathogenesis of some effects is still unclear, which requires further research.

**Prevention and Treatment of Vitamin D Deficiency**

Widespread population screening for vitamin D deficiency is not recommended by the Russian Association of Endocrinologists (RAE), but is necessary in risk groups for vitamin D deficiency. The risk groups for vitamin D deficiency include: patients with insufficient insolation (people with limited mobility, with photodermatitis, albinism, and for other reasons), patients with chronic kidney disease, malabsorption syndrome, liver failure, obesity, patients taking glucocorticosteroids for a long time.

According to the RAE clinical recommendation: vitamin D deficiency means serum concentration 25 (OH) D <20 ng / ml, deficiency - 25 (OH) D concentration from 20 to 30 ng / ml, Recommended target values 30-60 ng / ml.

In order to prevent vitamin D deficiency, patients aged 18-50 years need to receive at least 600-800 IU of vitamin D per day, patients over 50 years old - at least 800-1000 IU of vitamin D per day. In case of impaired absorption / metabolism of vitamin D, it is necessary to increase the daily dosage by 2-3 times for this age group. Given the toxic effects of large doses of vitamin D (more than 10,000 IU per day) without regular screening of vitamin D levels, such doses are inappropriate.

For the treatment of vitamin D deficiency, saturating and maintenance dose regimens are used: at a serum 25 (OH) D level <20 ng / ml, treatment begins with a total saturating dose of 400,000 IU colecalciferol, at a serum 25 (OH) D level of 20-
29 ng / ml for treatment use a dose of colecalciferol - 200,000 IU. Depending on the frequency of administration, a saturating dose of 400,000 IU colecalciferol can be achieved by taking 200,000 IU every month for 2 months, or 50,000 IU every week, or 7,000 IU.

**Conclusion**

Vitamin D deficiency is widespread and affects the course and development of many cardiovascular diseases. Cardiological patients with CHF, IHD, AH tend to lead a sedentary lifestyle, less often they are in the sun, which is why they are at risk for vitamin D deficiency. It is economically more profitable to prevent vitamin D than to treat the consequences of its deficiency. As a prophylaxis, not only prophylactic dosages and sufficient insolation can be used, but also the fortification of food with vitamin D (in Finland, since 2003, food fortification of vitamin D has been used, which actually eliminated its deficiency in the population). Further randomized controlled trials are needed to introduce into clinical practice the prescription of vitamin D in combination with drugs for the treatment of cardiovascular diseases, and to determine the exact therapeutic dosage for cardiac patients.

**Reference:**


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