

# Cardiovascular Diseases and Vitamin D

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**Abstract** The article provides a review of the literature on the role of vitamin D in the development and course of various diseases of the cardiovascular system. An analysis of the literature showed that the studies performed are often experimental in nature, while clinical trial data are scarce and contradictory. In children, data on the role of vitamin D in the occurrence and progression of cardiovascular diseases are sporadic, which indicates the need for further scientific research in this direction.

**Keywords** Vitamin D, Cardiovascular disease

Vitamin D belongs to the group of secosteroid molecules, enters the body with food, and is contained in a very limited amount of food, and is able to be synthesized in the skin under the influence of ultraviolet rays of sunlight [9].

In recent years, in the process of a thorough study of the broad activity of vitamin D in the body, it has rightly been called the hormone D. Obtained with ultraviolet or oral, vitamin D is metabolized by hepatic hydroxylase to 25-hydroxyvitamin D (25(OH) D), which is converted by the kidney 1 $\alpha$ -hydroxylase to the active form 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D - calcitriol) and directly depends on the level of circulating 25(OH) D. The main indicator in determining the status of vitamin D is 25(OH) D, as it circulates for longer periods (3-4 weeks) in the blood. The optimal level of 25(OH) D is recognized as 75-150 NMOL/L, THE DEFICIENCY IS CONSIDERED TO BE 50-75 NMOL/L, THE DEFICIT IS LESS THAN 50 nmol/L [59].

It exerts diverse biological effects when interacting with specific receptors that are located in more than 40 target tissues (osteoblasts, muscle cells, cardiomyocytes, pancreatic I-cells, endothelium, cells of the nervous system, intestines, immune cells, etc.) [20,43,54,78].

Vitamin D affects the biological reactions of the body through the genomic mechanism (synthesis of Ca-binding protein, osteocalcin, etc.) and rapid reactions of extragenomic origin (synthesis of secondary messengers: cyclic adenosine monophosphate, inositol triphosphate, arachidonic acid). Each tissue controls the activity of processes independently, but depends on an adequate level of circulating 25(OH) D [43,54,77,78].

Vitamin D deficiency is widespread throughout the world and occurs in approximately 30-50% of the population. In most cases, this problem is associated with pathology of the musculoskeletal system: rickets in children and osteomalacia or osteoporosis. According to some researchers, the functions of vitamin D are not limited only to the control of calcium-phosphorus metabolism, it also affects other physiological processes in the body, including modulation of cell growth, neuromuscular conduction, immunity and inflammation [54].

In recent years, convincing data have been obtained on the relationship of vitamin D deficiency with pathology of the cardiovascular system. A low level of vitamin D in humans is associated with unfavorable risk factors for cardiovascular disease, such as arterial hypertension, diabetes mellitus, dyslipidemia, which are predictors of cardiovascular catastrophes, including strokes and heart attacks. Vitamin D has been shown to have a vasoprotective effect by improving endothelial dysfunction, interferes with vascular and myocardial remodeling, improves blood pressure parameters, helps to reduce the risk of left ventricular hypertrophy, slows down fibrosis, reduces the risk of developing atherosclerosis, reduces insulin resistance, and also affects inflammation and immunity. According to studies, the effect of vitamin D deficiency on the development of atherosclerosis, arterial hypertension, cardiac arrhythmias and the progression of chronic heart failure has been demonstrated [10,32,46,55, 73].

Several of studies have shown that vitamin D deficiency increases the risk of developing cardiovascular disease. Thus, in the study, a low level of vitamin D compared with the optimal one increased the risk of coronary heart disease by 40%, the risk of developing myocardial infarction by 64%, the risk of early death by 57%, and at least 81% the increased risk of death from heart disease. Similar data were obtained after a survey of 27,686 people [40], where it was found that

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people with vitamin D deficiency had a 77% higher risk of early death, a 78% higher risk of developing a stroke, and 45% more likely to develop coronary heart disease than those with a normal level of 25(OH) D. It was also found that participants with vitamin D deficiency are twice as likely to suffer from chronic heart failure. Available data show that in most patients with chronic heart failure, levels of 25(OH) D are in the insufficiency range, which can be explained by the insufficient reception of ultraviolet radiation, since diseases of the cardiovascular system accompanied by chronic heart failure significantly reduce the mobility of patients. Patients unable to move have a high risk of developing severe vitamin D deficiency, which is known to lead to osteomalacia [25,37,58].

A number of clinical and epidemiological studies have also proved the relationship between calcitriol deficiency and cardiovascular diseases such as congestive heart failure, coronary heart disease, hypertension, valvular calcification, cerebrovascular accident [1,33,52]. Vitamin D deficiency leads to a change in smooth muscle cells of the vascular wall and its calcification, endothelial dysfunction, an increase in lipid peroxidation and inflammation factors. Vitamin D receptors are found in all cells of the cardiovascular system. Moreover, endothelial cells, cardiomyocytes and vascular smooth muscle cells are capable of producing the enzyme 1 $\alpha$ -hydroxylase, which converts calcium idiol into active calcitriol [17 65,71,72].

The effect of calcitriol on the course of hypertension has been established. When vitamin D is added to antihypertensive therapy in patients with arterial hypertension, a more significant decrease in systolic blood pressure occurs [59]. According to the results of the NHANES population study in the USA (National Health and Nutrition Examination.

Survey), when evaluating the data of 27153 patients, a relationship was found between vitamin D deficiency (the level of the examined was less than 20 ng/ml) and an increase in heart rate and systolic blood pressure compared with patients with normal calcitriol levels [30].

Low levels of vitamin D are a predictor of cardiovascular disease, including strokes and heart attacks. Vitamin D has been shown to have a vasoprotective effect by improving endothelial dysfunction, interferes with vascular and myocardial remodeling, improves blood pressure parameters, helps to reduce the risk of left ventricular hypertrophy, slows down fibrosis, reduces the risk of atherosclerosis, reduces insulin resistance, and also affects inflammation and immunity [5,8,22,27,71,72].

However, patients with heart failure and vitamin D deficiency have an extremely high risk of death by reason of sudden death due to cardiovascular disease. Vitamin D affects genetic expression associated with all types of cardiovascular cells, thereby contributing to the regulation of cell differentiation, apoptosis, hormone production and oxidative stress [10,15,69,73].

Vitamin D supplementation may be effective in hypocalcemic cardiomyopathy, as shown in studies of the

pediatric population with cardiomyopathy and heart failure associated with rickets [54,68].

The first publications on the relationship of vitamin D deficiency with the development of hypertension appeared in the 70s of the last century. So, in 1979 S.G. Rostand reports that people living in higher latitudes around the world have an increased risk of developing atrial hypertension. The author suggested that the cause of this phenomenon is a tendency to develop vitamin D deficiency in people living farther from the equator [58].

The number of studies that confirm the role of vitamin D in the development of arterial hypertension is growing every year. The study proved the inverse relationship between the level of 25(OH) D and an increase in blood pressure [39,71,72]. Other studies have shown an increase in the risk of hypertension by 3.03 times in men and 1.42 times in women with vitamin D deficiency compared with the general population [18,19,28]. It was also found that the initial level of 25(OH) D in blood serum below 30 ng/ml is associated with an increase in the risk of arterial hypertension by 1.47 times [18,28,48,71].

Experimental and clinical data indicate that vitamin D deficiency directly contributes to the development of hypertension [26,29]. Moreover, vitamin D deficiency is an independent predictor of hypertension, which does not depend on age, body mass index, physical activity, race, and the presence of menopause [19].

The renin-angiotensin-aldosterone system occupies a very important place in the control of blood pressure, vascular tone and water-salt metabolism. There are potential mechanisms that may explain the association of vitamin 1.25(OH) 2D deficiency and increased blood pressure. According to recent studies, 1,25(OH) 2D is involved in the regulation of the renin-angiotensin-aldosterone system by suppressing the expression of the renin gene. An experiment was conducted on laboratory mice that inhibited vitamin D receptors by pharmacological preparations, while a sharp increase in the level of renin and angiotensin II was recorded, which in turn stimulated the development of arterial hypertension and left ventricular myocardial hypertrophy [12,42,71].

Carriage of certain polymorphisms of the vitamin D receptor gene may be accompanied by a decrease in the expression of endothelial nitric oxide (NO) synthetase, which will inevitably lead to a decrease in the bioavailability of NO, the manifestation of which will be an increase in vascular stiffness and the development of endothelial dysfunction [2,28]. It has been experimentally shown that 1,25(OH) 2D can increase NO production in endothelial cells [2].

Vitamin D, affecting various pathophysiological processes, such as fibrosis, inflammation and repair, provides structural and functional safety of the kidney and myocardium, is able to slow the progression of cardiorenal syndrome and allograft nephropathy by 38%, which is confirmed in clinical studies of Russian scientists [29]. With an increase in the expression of the nuclear vitamin D

receptor in the glomerulus and proximal nephron, fast non-genomic mechanisms are launched, which are realized in the multilevel defense of the nephron, preventing inflammation, fibrosis and apoptosis, stimulating its natural regeneration and repair. And with the expression of the nuclear vitamin D receptor in the distal nephron, "slow" genomic effects are realized - maintaining the repair and functional activity of the tubules. The renoprotective effect of vitamin D is also realized due to a certain decrease in blood pressure. In the work of A.N. Kharlamova et al. Vitamin D has been shown to be able to reduce systolic blood pressure by at least 8% [29].

In patients with arterial hypertension who were exposed to ultraviolet rays for 3 months more than 3 times a week, the level of calcitriol increased by about 180%, and blood pressure, both systolic and diastolic, decreased by 6 MMHG. ART. A PROVEN CONTRIBUTION TO THE NORMALIZATION OF BLOOD PRESSURE IS THE SUPPRESSION OF VITAMIN D SYNTHESIS OF RENIN IN THE JUXTAGLOMERULAR APPARATUS OF THE KIDNEY BY VITAMIN D [13,58,63,74]. It has been shown that vitamin D reduces the expression of the renin gene through a receptor-dependent mechanism, thus reducing the concentrations of renin and angiotensin II, which ultimately leads to a decrease in aldosterone production and an improvement in the course of arterial hypertension [3,67]. However, according to some authors, there was no association between a decrease in blood pressure and the use of vitamin D in various groups of patients [27,66,68].

The data on the antihypertensive effects of vitamin D need to be clarified in further studies. The correlation between vitamin D deficiency and subsequent serious adverse vascular disorders has been confirmed in the study. Levels of 25(OH) D were measured at the start of the study and after 5.4 years. The frequency of fatal and non-fatal cases (ischemia, stroke, or heart failure) was 53 and 80%, respectively, and it was higher in subjects with low levels of vitamin D. A correlation was found between vitamin D deficiency and arterial hypertension [70].

According to the results of another no less large study, it was found that patients with a low level of 25(OH) D (<37.5 NMOL/L) COMPARED WITH SUBJECTS WITH A SUFFICIENT LEVEL OF 25(OH) D (>75 nmol/L) are at risk of developing myocardial infarction more than doubled [20].

A cohort study in Germany, which included 3258 patients with cardiovascular disease lasting 7.7 years, confirmed that patients with a low level of 25(OH) D double the risk of death of cardiovascular origin, in contrast to patients with a normal level of 25(OH) D [11].

Analyzing the numerous data obtained on the prognostically adverse effects of vitamin D deficiency, the medical community came to the conclusion that it is necessary to correct this hypovitaminosis. This idea was clearly demonstrated by a prospective study conducted in the UK. According to the authors, a two-fold increase in the concentration of 25(OH) D in blood plasma compared with the low initial level was associated with a 20% reduction in mortality from cardiovascular diseases and a 23% decrease

in total mortality [66].

Any damage to the endothelial layer of the vascular wall can lead to endothelial dysfunction, which ultimately plays a key role in the development of atherosclerosis. Moreover, the protective role of vitamin D in reducing the risk of developing atherosclerosis is to increase the production of endothelial NO [44]. Decrease the adhesion and aggregation of platelets, reduce oxidative stress, regulate muscle tone of blood vessels, decrease the release of vasoconstrictive metabolites, and suppress the release of pro-inflammatory cytokines, modulating the immune response and inhibiting the proliferation and migration of smooth muscle cells.

In experimental studies, it was proved that the active metabolite of vitamin D - 1.25 (OH) 2D reduces the deposition of mineral deposits in the inner shell of arteries, and regulates the content of calcium and phosphorus in the blood serum [25,43,50]. An increase in stiffness of the vascular wall is an important factor in the development of atherosclerosis. Studies have shown that vitamin D deficiency affects arterial stiffness. It was shown that in patients with a level of 25(OH) D less than 20 ng/ml, the pulse wave velocity in the aorta was more than 9 m/s (at a rate of 4-6 m/s). An increase in pulse wave velocity is directly correlated with an increased risk of developing atherosclerosis. The authors concluded that the lower the level of vitamin D, the greater the stiffness of the arteries, and regular maintenance of a normal level of vitamin D contributes to a twofold reduction in the risk of developing atherosclerosis [40]. An increase in the concentration of 25(OH) D to 30-60 ng/ml reduces the risk of obliterating atherosclerosis of the vessels of the lower extremities by 80% [24].

Inflammation plays an important role in the development of atherosclerosis. The highly sensitive C-reactive protein (CRP) is one of the most widely studied biomarkers of cardiovascular inflammation, with a proven pro-inflammatory effect. Numerous studies have confirmed that serum vitamin D levels are inversely related to CRP concentrations [35,49,78].

The anti-inflammatory effect of vitamin D is multifactorial; it also lies in the fact that a high blood concentration of 25(OH) D is reliably associated with a high concentration of interleukin (IL) - 10 [76].

The cardioprotective effect of IL-10 is to suppress the production of pro-inflammatory cytokines. It is proved that a low concentration of IL-10 leads to severe atherosclerosis. Vitamin D is able to eliminate this deficiency and, therefore, slow the progression of atherosclerosis [38,59].

The role of vitamin D in inflammation is also undeniable because its ability to suppress the release of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [7,23].

It should be noted that a deficiency of vitamin D leads to an increase in cholesterol synthesis, which undoubtedly provokes the development of atherosclerosis. An important enzyme in the pathogenesis of atherosclerosis is HMG-CoA reductase - 3-hydroxy-3-methylglutaryl-coenzyme A reductase, vitamin D is able to inhibit it, exerting a

synergistic effect with statins. There are publications recommending the combined use of statins with vitamin D to potentiate their effects [37].

Some authors recommend the use of high doses of vitamin D (more than 800 IU PER DAY) TO PREVENT THE DEVELOPMENT OF ATHEROSCLEROSIS [26].

More evidence is being provided showing that vitamin D is associated with many diseases and their complications, including heart failure. Vitamin D deficiency has been found to play a significant role in the pathogenesis of chronic heart failure. However, patients with heart failure and vitamin D deficiency have an extremely high risk of death. Vitamin D3 affects the genetic expression associated with all types of cardiovascular cells, thereby contributing to the regulation of cell differentiation, apoptosis, hormone production and oxidative stress [45,61,68].

Vitamin D supplementation may be effective in hypocalcemic cardiomyopathy, as shown in studies of the pediatric population with cardiomyopathy and heart failure associated with rickets [4,64,68].

Therefore, it is important to evaluate whether taking vitamin D affects the hormonal and inflammatory markers, as well as the health-related quality of life among patients with heart failure, to achieve adequate circulating blood levels [6,20,34, 36,45].

A study conducted in 30 patients on predialysis with chronic kidney disease and with secondary hyperparathyroidism to determine the effect of regular vitamin D intake on left ventricular diastole showed that regular intake of 1.25(OH) 2D increases left ventricular diastole time, which contributes to reduce heart load and the risk of developing chronic heart failure [14,63].

In vitro studies have shown that vitamin D affects cardiomyocyte contractility by altering the distribution of myosin chains and modulating calcium intake in cardiomyocytes. Vitamin D also affects growth, hypertrophy, collagen deposition and cardiomyocyte differentiation, providing a key role for activation of the nuclear vitamin D receptor in heart physiology [3,29].

The need to maintain a normal concentration of vitamin D becomes quite obvious, since its deficiency makes a significant contribution to the onset and progression of chronic heart failure. A clinical study of the effect of vitamin D in 80 children with heart failure revealed its positive effect on the myocardium and pumping function of the heart [22].

In addition, treatment with calcitriol leads to a decrease in plasma renin activity, a decrease in angiotensin II levels, a decrease in blood pressure and a decrease in myocardial hypertrophy [28,37].

Prospective observations show that low concentrations of vitamin D are associated with an increased risk of developing cardiovascular diseases, mortality from them and mortality from all causes [44,51,67,69].

These data are important for health care, as vitamin D deficiency is widespread among children and adults. It is necessary to take into account the fact that patients suffering from hypertension, coronary heart disease, chronic heart

failure, as a rule, people are not always mobile, forced to lead a sedentary lifestyle, are less likely to leave the house, are few in the sun, so they Vitamin D deficiency may well develop.

The medical community is inclined to believe that the correction of vitamin D deficiency is of great prognostic value. Vitamin D treatment has a low cost, ease of use, and prevention additionally contributes to the formation of a healthy lifestyle [5,47,53,56,64,69].

However, further clinical and experimental studies are needed to study in more detail the mechanisms of the negative effects of vitamin D deficiency on the cardiovascular system. Currently, the effect of vitamin D therapy on such indicators of patients with chronic heart failure as the cardiac output fraction, muscle strength, concentration of pro-inflammatory cytokines and cerebral natriuretic peptide, general clinical condition and quality of life has not been studied much. More research is needed to determine the role of vitamin D deficiency in the development and progression of chronic heart failure in children with cardiomyopathies, as well as to determine the role of vitamin D in the treatment of this disease.

Thus, an analysis of the available data suggests that vitamin D plays an important role in the functioning of the cardiovascular system. Conducted studies are often experimental in nature, while clinical trial data are scarce and contradictory. In children, data on the role of vitamin D in the occurrence and progression of cardiovascular diseases are sporadic, which indicates the need for further scientific research in this direction.

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