Chapter

Mechanism of Development of Arterial Hypertension Associated with the Exchange of Level Vitamin D

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Abstract

Arterial hypertension (AH) is one of the most chronic and fatal disorders in the world, the main risk factors for which are age, hereditary predisposition, race, tobacco use, high salt intake, etc., as well as low vitamin D. In the last 10 years, there has been an increasing interest in the extraosseous effects of vitamin D. Being a hormone-like vitamin, it participates in many vital processes of the body. Its level is closely related to various metabolic disorders, diseases of the cardiovascular system (CVS), arterial hypertension (AH), diabetes mellitus, the immune system, cancer, etc. Vitamin D improves vascular endothelial function, due to which it has a vasoprotective effect, improves blood pressure, reduces vascular and myocardial remodeling, reduces the risk of left ventricular hypertrophy, slows down fibrosis, reduces the risk of atherosclerosis, reduces insulin resistance and inflammation, and improves immunity. It has been proven that vitamin D has an inverse relationship with renin, it reduces the expression of the renin gene. At a normal level of vitamin D, the concentration of renin and aldosterone II decreases, which has a positive effect on the course of hypertension.

Keywords: arterial hypertension, blood pressure, vitamin D, receptors, genes

1. Introduction

As we know, diseases of the circulatory system occupy the leading place among diseases leading to disability and mortality of the population. Arterial hypertension (AH) today remains the main risk factor for cardiovascular diseases (CVD).

Hypertension is not just a chronic increase in blood pressure (BP), it is a poly etiological disease, which is based on hemodynamic, neurohumoral, and metabolic disorders, leading to serious consequences (atherosclerosis, myocardial infarction, cerebrovascular diseases—cerebral strokes, heart failure), impairs memory, vision, and negatively affects renal function, leading to renal failure.

Today, an asymptomatic increase in blood pressure is increasingly manifested, which indicates a greater likelihood of the prevalence of hypertension. Therefore, for

early diagnosis of hypertension, frequent measurement of blood pressure is recommended for persons without clinical complaints of high blood pressure.

The term "arterial hypertension" refers to the syndrome of persistent elevation of systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg, which, depending on etio-pathological factors, manifests itself as primary hypertension (essential) or proceeds as a secondary condition. No less important in the pathogenesis of essential hypertension is a change in the arterial wall—a decrease and then a complete loss of the contractile function of the muscle layer and vascular endothelium, as well as atherosclerotic changes [1].

The main pathogenetic factor in the development of hypertension is the activation of the sympatho-adrenal (SAS) and renin-angiotensin-aldosterone system (RAAS)—which, as a rule, is the most powerful neurohormonal system of the body, the activation of which can result in the development of coronary heart disease, heart failure (HF). Heredity, diabetes mellitus (DM), the presence of metabolic syndrome, unhealthy diet, increased consumption of sodium chloride (more than 6 g of table salt per day), obesity (components of the RAAS are produced in the adipocytes of adipose tissue), lack of physical activity (physical inactivity), psycho-emotional exercise, smoking, excessive drinking, and according to recent data, low levels of vitamin D are also risk factors for the development of hypertension. Along with a large number of studies proving the role of vitamin D in reducing SBP and DBP, there are other works confirming the insignificant role of vitamin D deficiency in the pathogenesis of hypertension [2]. The increased blood pressure or the risk of hypertension is hypothesized to be due in part to the patients' baseline vitamin D levels, sample size, and length of follow-up. It should also be borne in mind that diseases such as diabetes mellitus, kidney disease, underlying cardiovascular disease can affect the physiological mechanisms of vitamin D action on blood pressure. This explains the significant differences between individual patients in the values of vitamin D [3–5].

2. Biological role of vitamin D

Vitamin D was discovered in the early 1920s (1922) of the twentieth century by Windaus. The work of recent years indicates that the biological role of vitamin D is not limited to the effect only on calcium metabolism, but also plays an important role in maintaining the immune and endocrine system, metabolic processes, cardiovascular and cerebrovascular health, and also significantly reduces the risk of developing tumors, tuberculosis, rheumatoid arthritis, etc. Biological functions of vitamin D are shown in **Figure 1**.

Since the middle of the twentieth century, vitamin D deficiency (D-deficiency) has acquired not only medical, but also medico-social significance. The causes of D-deficiency are demographic changes—an aging population, an increase in geriatric pathology, unbalanced nutrition, a low level of physical activity, insufficient exposure to the sun, and a decrease in insolation. Receptors to calcitriol are found not only in enterocytes and bones, but also in the kidneys, neurocytes, pancreas, myocytes of striated and smooth muscles, bone marrow cells, immunocompetent cells, and genitals (**Figure 1**). Therefore, the functional role of the hormone vitamin is not limited to participation in the regulation of calcium-phosphorus metabolism. A lot of information has been accumulated on the specific effects of calcitriol that are not related to its calcitropic activity: suppression of hyperproliferation, carcinogenesis, influence on cell growth and development, modulation of apoptosis, regulation of autoimmunity through effects on T- and B-lymphocytes, macrophages [6, 7].

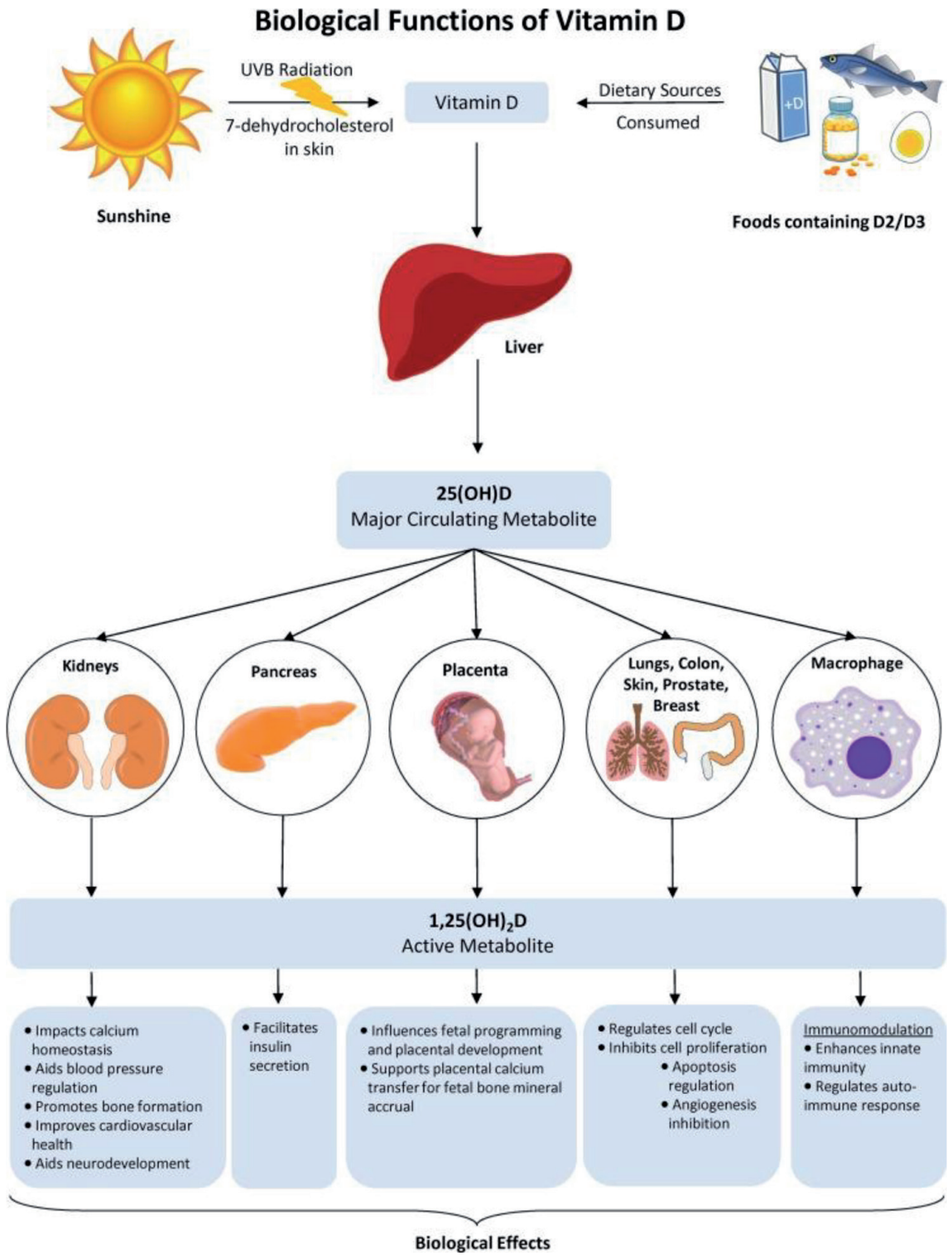

Figure 1.
Biological functions of vitamin D (based on the figure from the article Laura Lockaua Stephanie, A. Atkinson. Vitamin D's role in health and disease: How does the present inform our understanding of the past? International journal of paleopathology, vol. 23, December 2018, pages 6–14).

With sufficient and regular insolation, a person's need for vitamin D is fully met by photochemical synthesis in the skin. This is why vitamin D3 is called the "sunshine vitamin." It is the photochemical stages that are decisive in the activity of the D-hormonal system. Dietary source of vitamin D plays only a compensatory role in cases of endogenous vitamin deficiency.

Vitamin D3 has both endogenous origin (synthesized in the skin under the influence of ultraviolet rays from the precursor of 7-dehydrocholesterol) and exogenous (from animal food: fish oil, liver, egg yolk). All other food products are practically devoid of vitamin D. In this regard, in a number of countries it is specially added to some products, for example, milk, fruit juices, margarine. On the contrary, vitamin D2 (ergocalciferol) enters the body only with plant foods (bread, milk) and in very small quantities [8].

Endogenous vitamin D3 and its metabolites from the skin and/or vitamin D3 supplied with food, with the help of a transport D-binding protein, enter the subsequent stages in the liver, kidneys, where the hormone calcitriol is synthesized. 1,25 (OH) 2 D3- calcitriol or dihydroxycholecalciferol is a hormone similar to other steroid hormones, which controls about 1500–2000 genes through VDR receptors, including genes involved in the production of renin, insulin, growth, and proliferation of smooth muscle cells vessels and cardiomyocytes, and is involved in many processes. Vitamin D receptors, which are involved in the formation of vitamin D, are found in the cardiomyocytes of the ventricles of the heart. It has been proven that a decrease in the activity of vitamin D receptors can lead to remodeling of cardiomyocytes. The introduction of the active form of vitamin D helps to reduce this remodeling due to the effect on the functional, anatomical, molecular, and genetic aspects of hypertrophy and dysfunction of cardiomyocytes. A study conducted on newly diagnosed treatment-naïve hypertensive patients showed that hypovitaminosis D was a strong predictor of increased left ventricular mass index [9].

According to the Institute of Medicine (IOM), vitamin D deficiency is defined as circulating 25-hydroxyvitamin D (25[OH]D) level < 50 nmol/L based on the optimal concentration for skeletal health [10].

3. Role of vitamin D in pathophysiology and development of hypertension

Vitamin D has the potential to affect blood pressure through several mechanisms including those involving the renin-angiotensin-aldosterone system (RAAS), the endothelium, and vascular smooth muscle. Chronic treatment with active vitamin D compounds modulates vascular tone, reduces blood pressure and cyclooxegenase-1, and increases endothelial dysfunction and reactive oxygen species (ROS) in rats [11].

The association of arterial hypertension with low insolation and low levels of vitamin D in the blood serum was noted back in the 1990s of the twentieth century. In 1980, it was found that impaired calcium homeostasis, including hyperparathyroidism, may be involved in the mechanism of the development of hypertension and proved a significant decrease in calcium excretion in patients with hypertension compared with the control group. In 1988, Lind et al. [12] conducted a placebo-controlled study evaluating the effect of 0.5 μg alpha-calcidol, a vitamin D analog, on blood pressure in hypertensive patients with impaired glucose tolerance (mean age 62 years, n = 26) for 12 weeks. They found a significant decrease in SBP/DBP from 171/95 to 150/88 mm Hg after treatment.

The prevalence of vitamin D deficiency is directly related to higher latitudes due to less intense UVB radiation, colder climates due to less skin exposure, and darker skin as it interferes with UVB penetration and decreases vitamin D production [13]. The fact that a higher EH frequency is observed in winter in people living at higher latitudes and in people with deep skin pigmentation living far from the equator suggests that vitamin D deficiency may contribute to an increased prevalence of arterial

hypertension. To test this hypothesis, Krause et al. [14] used ultraviolet radiation to treat patients with untreated mild arterial hypertension (AH) and vitamin D deficiency. These researchers found that UV radiation increased 25 (OH) D levels and lowered blood pressure in patients with vitamin D deficiency with AH. Since 1998, this discovery has generated significant research interest in the relationship between vitamin D deficiency and AH.

The relationship between the concentration of calcitriol in the blood serum and the level of blood pressure has been proven. When analyzing data from the NHANES III (National Health and Nutrition Examination Survey), an inverse significant relationship between the content of vitamin D3 and blood pressure indicators was revealed: in the group with a content of 25 (OH) D3 > 85.7 nmol/L, the levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 3, 0, and 1.6 mm Hg lower than in gr. with a content of 25 (OH) D3 < 40 nmol/L, respectively [15].

Hypertension is an age-dependent complex common feature with interactions between environmental and genetic factors. The incidence rises sharply in men over 45 and in women over 55. Vitamin D deficiency can be considered a risk factor for the development of arterial hypertension, contributing to a shift in the balance between vasodilator and vasoconstrictor factors in favor of vasoconstriction, which leads to the development of hypertension in people, mainly middle-aged people. Therefore, it is believed that an adequately selected dose of vitamin D, contributing to the normalization of the level of 25 (OH) D in the blood, effectively lowers blood pressure in patients with arterial hypertension with vitamin D deficiency. The authors concluded that when people have a stable balance between vasodilatory and vasoconstrictor factors in vitamin D deficiency, vitamin D supplementation has minimal effect on BP in a relatively short period. And when people have an unstable balance between vasodilating and vasoconstrictor factors, vitamin D deficiency becomes a risk factor contributing to the development of hypertension at age > 45 years; In this case, vitamin D supplementation can lower blood pressure [16]. Thus, vitamin D deficiency does not play an important role in the normal regulation of blood pressure, and its excess may have a minimal effect on blood pressure in persons with normotension under the age of 45 years.

Genetic analyses, specifically Mendelian randomization studies, found that individuals with genetically lower serum 25(OH)D levels have an increased incidence of hypertension, implying that vitamin D deficiency may play a role in the development of hypertension. The largest genetic analysis included 142,255 individuals and found that a 10% increase in genetically determined 25(OH)D concentration was associated with a 0.37 mmHg lower systolic pressure (95% CI, 0.003–0.73 mmHg lower) [17].

Most of the main studies showed that BP was inversely and significantly correlated with the level of 25 (OH) D. Burgaz et al. conducted a meta-analysis including four prospective studies and 14 crossover studies to assess the association between circulating 25 (OH) D levels and arterial hypertension. They found an inverse relationship between serum 25 (OH) D concentration and arterial hypertensive incidence [18]. Forman JP et al. [19] conducted a four-beam, double-blind, placebo-controlled, randomized study in 283 black Americans (mean age of 51 years) to evaluate the effect of 1000, 2000, and 4000 IU of vitamin D per day or placebo on blood pressure for a period of 3 months. Baseline 25 (OH) D levels were about 16 ng/ml. The baseline mean blood pressure (122/78 mm Hg) was relatively lower because only 50% of the participants were hypertensive and 40% were taking antihypertensive drugs. The difference between systolic blood pressure at the beginning of the study and after 3 months was +1.7 mm Hg in the placebo group, −0.66 mm Hg in the group

with 1000 IU of vitamin D, −3.44 mm Hg in the group with 2000 IU of vitamin D, and − 4.0 mm Hg In the group with vitamin D 4000 IU (−1.4 mm Hg for every 1000 IU additional intake of vitamin D, p = 0.04). For every 1 ng/ml increase in 25 (OH) D levels, a significant 0.2 mmHg reduction in systolic blood pressure was found.

4. Role of vitamin D in the regulation of RAAS and sympathetic activation

In the regulation of blood pressure, electrolyte homeostasis, the renin-angiotensin-aldosterone system (RAAS) plays an important role. An increase in the activity of the RAAS is considered as the most important link in the pathogenesis of hypertension. It is known that some antihypertensive drugs regulate blood pressure by affecting the renin-angiotensin-aldosterone system (RAAS). This system regulates plasma electrolyte levels, vascular resistance, and fluid volume homeostasis. Renin is an enzyme produced by the cells of the juxtaglomerular apparatus in the nephrons of the kidneys. Its synthesis is activated by renal hypoperfusion and activation of the sympathetic nervous system. Renin converts the angiotensinogen produced in the liver into angiotensin I, which is converted into angiotensin II under the influence of the angiotensin-converting enzyme (ACE) expressed in the lungs. Angiotensin 2, binding to its receptor, has a biological effect on the activity of the brain, heart, kidneys, peripheral vessels, and adrenal glands (**Figure 2**). The relationship between vitamin D levels and RAAS activity has been demonstrated in numerous studies [20, 21].

Numerous epidemiological studies have shown the association of low vitamin D levels with an increased risk of arterial hypertension [20]. Experimental studies in mice with damage to vitamin D receptors showed increased activity of renin and circulating angiotensin II, which led to arterial hypertension, which could be reduced by blocking the RAAS [21–23]. In other studies, mice that were unable to activate vitamin D in the body due to 1-alpha hydroxylase deficiency exhibited a similar phenotype to animals that lacked vitamin D receptors [24]. In this case, the addition of vitamin D led to a complete change in the phenotype, which confirms the role of vitamin D in the activation of the RAAS and in the development of arterial hypertension. Other animal experiments have demonstrated the ability of vitamin D to increase the concentration of intracellular calcium, which led to a decrease in renin secretion by juxtaglomerular cells [25].

Some studies have shown that vitamin D clearly inhibits renin biosynthesis and RAAS activity. Administration of an AT II receptor antagonist or angiotensin-converting enzyme (ACE inhibitor) inhibitor prevented or neutralized the above disorders. Later it was found that the activation of vitamin D receptors helps to reduce left ventricular hypertrophy (LVH) and prevents the activation of some components of the RAAS. An interesting fact is that the suppression of renin secretion by vitamin D through the activation of its receptors occurs independently of calcium homeostasis and disturbances in water-salt metabolism. In obese subjects with vitamin D deficiency, it found that treatment with ergocalciferol reduced kidney-specific RAS activity and blood pressure [26–28]. Thus, RAS activation may be a mechanism linking vitamin D with incident hypertension.

However, in another study, systemic RAS activity measured by plasma renin activity did not change significantly following 8 weeks of treatment with vitamin D (from 0.34 ± 0.37 ng/ml/hour to 0.36 ± 0.44 ng/ml/hour; p-value = 0.72) or placebo (0.42 ± 0.44 ng/ml/hour to 0.44 ± 0.80 ng/ml/hour, p-value = 0.85).

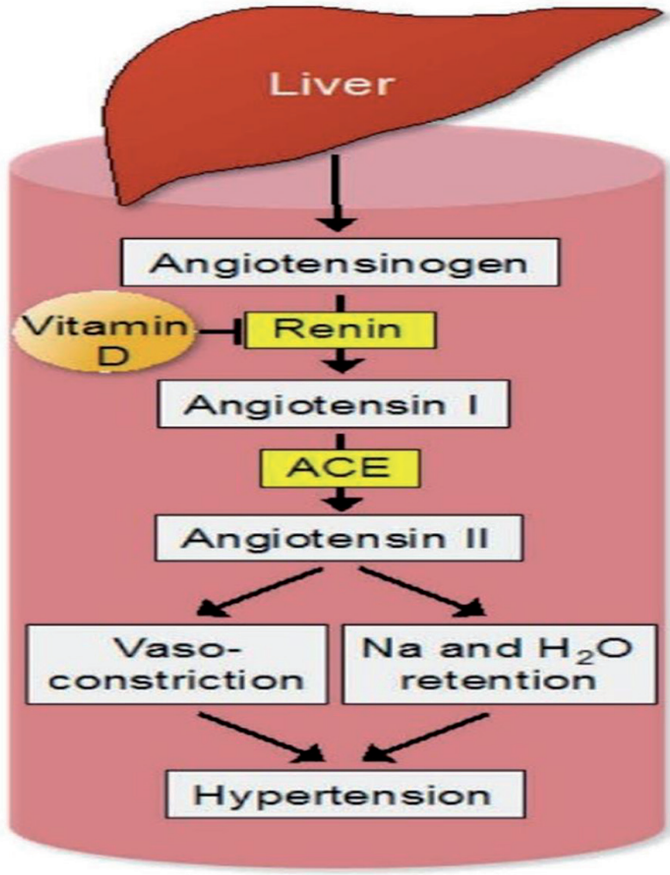

Figure 2.
Role of vitamin D in the regulation of RAAS.

Similarly, serum angiotensin II levels did not change significantly after 8 weeks of treatment with either ergocalciferol or placebo. There was no significant change in mean 24-hour systolic blood pressure or other ambulatory measurements following treatment with either ergocalciferol or placebo [29]. In this placebo-controlled, randomized study, it was found that in obese patients with vitamin D deficiency without arterial hypertension, the correction of vitamin D level does not affect the level of blood pressure and does not correct the renal or systemic activity of the RAAS. These differences in baseline characteristics (blood pressure and renin activity) may indicate that this population was younger, had lower baseline RAS activation, potentially explaining differences between the studies. The 8-week duration of treatment may have been inadequate to affect RAS activity or blood pressure. Although the researchers were able to restore plasma vitamin D levels to normal in the treatment group within 8 weeks, it is assumed that a longer treatment period would be required for the full effect of vitamin D on blood pressure and on RAAS activity.

It is known that increased central or renal sympathetic activation is an important factor in the pathogenesis of human arterial hypertension. There is still no evidence that vitamin D deficiency directly affects sympathetic nervous activity. It is assumed that vitamin D deficiency enhances the signaling effect caused by increased sympathetic activity. For example, angiotensin II promotes hypertension due to increased activation of T cells in the central nervous system, and vitamin D blocks the activity of effector T cells. In this way, vitamin D deficiency enhances the sympathetic effect stimulated by the T cells [30].

The relationship between the development of CVD and low levels of 25-hydroxy-vitamin D in individuals initially without cardiovascular disease was also identified in the prospective study, The Framingham Offspring Study. In this study, with an average duration of 5.4 years, 1739 participants were observed, the average concentration of 25-OH D was 19.7 ng/ml (25-OH D ˂ 15 ng/ml-9%), and the results showed that different kinds of CVDs developed more often in persons with vitamin D deficiency [31].

Studies conducted in Germany for 7.7 years in which 3258 patients with CVD over 20 years old were observed proves that the risk of death from CVD increases two times in those patients whose vitamin D level is below normal, as well as an increase in the level of C-reactive protein and interleukin-6 is also observed in patients with low levels of vitamin D [32, 33]. These and other studies confirm that blood pressure and C-reactive protein levels are inversely related to vitamin D in blood serum. The authors found gender differences in the prevalence of hypertension depending on vitamin D levels. The researchers found hypertension in 50% of women who had very low vitamin D levels (<5 ng/ml) compared with 30% of women who had vitamin D levels not less than 20 ng/ml. No differences in the prevalence of arterial hypertension depending on the level of vitamin D were found among men. Among 4863 participants in the Women's Health Initiative study, over 7 years of follow-up, there was no association between vitamin D levels and changes in blood pressure [34]. But women with plasma vitamin D levels <14 ng/ml had a 50% increased risk of arterial hypertension compared with women with higher vitamin D levels (19–26 ng/ml). In a Michigan study, 413 women with an average vitamin D level of 24 ± 10 ng/ml had higher diastolic blood pressure values (77 ± 9 mm Hg) compared with women with normal vitamin D levels—vitamin D ≥ 32 ng/ml; 75 ± 9 mm Hg [35]. Cross-sectional study with 833 white men who underwent 24-hour blood pressure monitoring (excellent outcome assessment) found that low vitamin D levels (<15 ng/mL) are associated with higher prevalence of hypertension [36].

5. Vitamin D in elderly patients

It was reported that in elderly patients with systolic hypertension, supplementation with vitamin D deficiency did not significantly affect blood pressure. In 2013, Witham et al. [37] reported the VitDISH study results. The study enrolled 159 participants with a mean age of 77 years, mean BP of 163/78 mmHg, and an average level of 25 (OH) D of 18 ng/ml. Participants received 100,000 IU of oral vitamin D3 or a placebo every 3 months for 1 year. Treatment increased 25 (OH) D levels by 8 ng/ml, but did not show significant reductions in blood pressure and arterial stiffness in selected patients with systolic hypertension, which was apparently associated with increased vascular stiffness and calcification. Although these patients were taking one to two antihypertensive drugs, their systolic blood pressure was about 160 mm Hg [37]. In another study on the effect of vitamin D on blood pressure in elderly patients with systolic hypertension, people aged 75 years were treated with (mean BP 144/85 mm Hg, 25 (OH) D 10.1 ng/ml, n = 74) 800 IU vitamin D plus 1200 mg calcium daily for eight weeks. They found a significant increase in 25 (OH) D levels and a decrease in systolic blood pressure with vitamin D and calcium supplementation compared with calcium alone. Clearly, well-designed placebo-controlled trials using 2000–3000 IU of vitamin D daily to treat patients with isolated systolic hypertension and vitamin D deficiency are warranted [38]. The BEST-D study in healthy people examined the

effect of daily vitamin D intake for 1 year on the risk of hypertension and biochemical markers. But the results of this study were not positive. The addition of vitamin D did increase the plasma concentration of 25 (OH), but did not reduce the risk of cardiovascular complications, blood pressure, blood lipid profile, and arterial stiffness [39].

6. Clinical trials with vitamin D in hypertension

More than 40 randomized clinical trials have been conducted to determine the effect of vitamin D supplementation on blood pressure as a primary or secondary endpoint. Since the mechanisms underlying the effect of vitamin D on blood pressure have not yet been elucidated, most clinical trials have shown suboptimal designs, and the results have been mixed. The findings were conflicting. Wu et al. [40] conducted a meta-analysis of four randomized controlled trials of oral vitamin D supplementation in BP. They found that vitamin D supplementation significantly reduced systolic blood pressure by 2.44 mm Hg, but not diastolic blood pressure. Another meta-analysis included 51 randomized trials that enrolled adults who received vitamin D supplementation and that measured several cardiovascular outcomes (stroke, myocardial infarction, cardiovascular death, etc.) [41] found no change in the weighted mean of either systolic or diastolic blood pressure.

Witham et al. [42] investigated eight randomized controlled trials in participants with a mean baseline blood pressure > 140/90 mm Hg, which showed a slight decrease in systolic blood pressure and a small significant decrease in diastolic blood pressure (3.1 mm Hg). In a study involving 701 adolescent girls and boys with average blood vitamin D values of 30 ng/ml, it was shown that there is an inverse correlation between the level of this vitamin and the values of systolic and diastolic blood pressure (respectively, $r = -0.1$, $r = -0.21$; $P < 0.01$) [43]. In a subanalysis of the Hoorn population study in the Netherlands, which included 441 patients, it was shown that blood pressure levels decreased with increasing blood vitamin D values. With the values of vitamin D in plasma on average 32 ng/ml, the systolic and diastolic pressures were respectively 135.0 ± 18.6 mm Hg and 81.6 ± 9.6 mm Hg. At low values of vitamin D in the blood, below 14 ng/ml, the values of systolic and diastolic pressure were 146.6 ± 20.6 mm Hg and 86.3 ± 12.6 mm Hg [44].

Ten studies by other scientists examined the role of vitamin D and ultraviolet radiation in blood pressure regulation, where no significant effect of vitamin D on blood pressure was found. Only those studies using high daily doses of vitamin D (at least 1000 IU/day) were found to have a small statistically significant effect [45]. An ideal test to determine the maximum antihypertensive effect of vitamin D supplementation on blood pressure is the administration of vitamin D to patients with untreated stage 1 hypertension with vitamin D deficiency living in high latitudes in winter. Such a study was conducted ($n = 40$) in Liaoning, northern China, in the winter, administering 3000 IU of vitamin D daily for 3 weeks to patients with an average age of 53 years who did not receive treatment for stage 1 EH and vitamin D deficiency (25 (OH) D levels were < 20 ng/ml). Treatment significantly increased blood 25 (OH) D levels and decreased systolic blood pressure, but not diastolic blood pressure. The negative results for diastolic blood pressure may be associated with a small sample size, a short treatment period, and a recruitment of only stage 1 hypertensive patients. A well-designed, large, randomized study VITAL has demonstrated a significant reduction in the incidence of hypertension after 5 years of vitamin D intake (2000 IU per day) by eliminating vitamin D deficiency in patients aged ≥50 years [46]. It should be noted

that an appropriately high dose (at least>1000 IU per day) of vitamin D supplementation to increase blood 25 (OH) D levels is also needed to see the antihypertensive effect of vitamin D.

Kunutsor et al. [47] conducted a meta-analysis of 16 randomized clinical trials to evaluate the effect of vitamin D supplementation on blood pressure. They did not show significant reductions in systolic and diastolic blood pressure with vitamin D supplementation, suggesting heterogeneity and publication bias. Subgroup analysis showed significant reductions in diastolic blood pressure in participants with preexisting cardiometabolic disease.

The VITAL trial did not find any significant benefits in regard to cardiovascular outcomes. Indeed, only a not significant reduction in cardiovascular events was observed in the group treated with vitamin D when compared with the placebo [48]. In other studies, cholecalciferol supplementation did not reduce the cardiovascular risk. This treatment increased the serum levels of 25(OH)D, the CVD risk did not improve [49]. Another meta-analysis evaluated the cardiovascular benefits of a vitamin D supplementation over 1 year, regardless of calcium supplementation. The results of this meta-analysis showed no significant effect of vitamin D on cardiovascular endpoints (myocardial infarction, cerebral stroke, cerebrovascular accident, mortality from heart disease) and on mortality from all causes [50].

It should be noted that the development of acute toxic effects during treatment with vitamin D is very rare, since the toxicity of this vitamin can be caused by the use of very high doses. Such toxic effects may include hypercalcemia, which stimulates the development of various types of arrhythmias with a shortened QT interval [51]. No less controversial is the issue of vitamin D toxicity. So, according to I. Boer et al. [52], safe level of 25 (OH) D3 in plasma is considered to be 240 nmol/l, the concentration of 25 (OH) D3 in the blood is higher, 375 nmol/L, associated with acute hypercalcemia and hyperphosphatemia. With that said, American Institute of Medicine determines the maximum daily intake of vitamin D for infants from 0 up to 6 months of life 1000 IU; for children from 7 to 12 months life—1500 IU; from 1 to 3 years—2500 IU; from 4 up to 8 years—3000 IU; for teenagers from 9 to 18 years old and adults—4000 IU.

There are small studies in the literature that investigated the effect of vitamin D on blood pressure when taken daily at a dose of 3000 IU versus placebo [53]. As a result of these studies, taking vitamin D did not lead to a significant decrease in blood pressure. However, in a retrospective analysis, patients with vitamin D deficiency (<32 ng/ml) showed a decrease in systolic and diastolic blood pressure during treatment with vitamin D. However, the central systolic blood pressure (blood pressure in the ascending aorta) decreased by 4 mm Hg in the 25(OH)D group compared with placebo (P = 0.007). The results of these studies confirm that the addition of vitamin D to the treatment of hypertensive patients may be beneficial in patients with vitamin D deficiency. It should be noted that high doses of vitamin D were used. In addition, patients with systolic blood pressure levels <150 or diastolic blood pressure < 95 mm Hg, and 84% of participants were taking antihypertensive drugs. All this could mask or reduce the effect of vitamin D on blood pressure in hypertensive patients. These factors, along with the small sample size, may have contributed significantly to negative 24-hour BP outcomes. Besides, most studies did not record the changes of diet, sun exposure or latitudes, genetic factors, and educational status, we are not able to answer the questions of whether these factors would modify the effect of the intervention.

A meta-analysis of cohort studies was conducted that demonstrated a negative association between vitamin D levels and blood pressure. At the same time, with an increase in the level of vitamin D in blood plasma by 25 nmol/l, a decrease in the risk of developing arterial hypertension by 7% was observed. However, there was no direct evidence of a decrease in blood pressure from 25 (OH) D supplementation. Scientists believe that the positive effect of vitamin D on blood pressure levels is mainly due to the fact that the study included young participants with a healthy lifestyle. In addition, low vitamin D levels may be the result of prior medical conditions. Furthermore, differences exist among the various methods used and in the laboratories that measured 25(OH)D levels, which would also influence the accuracy of the study results. Individuals who are taking vitamin D supplements should do so for at least 6 months to reach the maximum attained 25(OH)D level. It is reasonable to assume that the effect of vitamin D is time-dependent [54].

Beveridge et al. [55] conducted a meta-analysis that included clinical trials that used vitamin D supplements and reported BP. Vitamin D did not affect normal blood pressure in 30 studies. They also found no significant reduction in blood pressure with vitamin D in studies with participants whose mean baseline SBP was ≥140 mmHg. The main reason for negative results may be related to suboptimal study design. This may include high rates of background antihypertensive drug treatment that overlap with the antihypertensive role of vitamin D, cohorts with less than 40% of participants with vitamin D deficiency, and low or exceptionally high intake of vitamin D. Chen et al. [56] conducted a placebo-controlled, randomized study to find out if vitamin D supplementation (2000 IU/day) lowered blood pressure for 6 months. The study included 126 patients with arterial hypertension and vitamin D deficiency who received nifedipine at a dose of 30 mg per day. For 6 months of treatment with vitamin D, an increase in its level was observed from 19 ng/ml to 34 ng/ml and a decrease in mean blood pressure over 24 hours by 6.2/4.2 mm Hg. ($p < 0.001$). In patients with vitamin D < 30 ng/ml at baseline (n = 113), the mean blood pressure in 24 hours decreased by 7.1/5.7 mm Hg. In this study, the antihypertensive drug nifedipine could reduce the effects of vitamin D on blood pressure in these Chinese hypertensive patients.

7. Vitamin D, endothelial dysfunction, and atherosclerosis

The endothelium is the main regulator of vascular homeostasis and affects vasoconstriction and vasodilation, smooth muscle proliferation and inflammation, thrombogenesis, and fibrinolysis. As a result, the development of atherosclerosis occurs with endothelial dysfunction, which develops when this layer of the vascular wall is damaged. The role of vitamin D in reducing the risk of atherosclerosis lies in the following mechanisms:

- increase in the formation of endothelial nitric oxide
- decrease in aggregation and adhesion of platelets
- management of musculoskeletal tone
- suppression of oxidative stress
- decrease in the formation of pro-inflammatory cytokines

- decrease in the formation of vasoconstrictor substances
- inhibition of proliferation and migration of smooth muscle cells
- modulation of the immune response.

Vitamin D has beneficial effects on vascular endothelial function and arterial stiffness. Vitamin D plays an important role in vascular and endothelial smooth muscle cells. Therefore, it can be assumed that vitamin D can affect the contraction of blood vessels and the formation of calcifications in the vessels. At the same time, this vitamin can affect the function and structure of blood vessels in different ways. Everyone knows that nitric oxide is a powerful vasoprotective and vasodilator, and several factors are involved in its synthesis, including vitamin D and vitamin D receptors. Scientists believe that vitamin D plays an essential role in the synthesis of nitric oxide. Other mechanisms include endothelial 1-hydroxylase and activated vitamin D, which can modulate the growth of both cell types [3]. In patients with type 2 diabetes, the DIMENSION study examined the effect of 16 weeks of vitamin D supplementation on endothelial function. During the treatment, the values of vitamin D increased. But when conducting a multivariate regression analysis, no effects of vitamin D on endothelial function were found [57].

Arterial stiffness increases in early-stage hypertensive patients, and it is a strong predictor of cardiovascular morbidity and mortality. In a study, Sinem Cakal [23] included 100 patients with arterial hypertension who were diagnosed for the first time, they had not previously received antihypertensive treatment, they did not have any cardiovascular diseases, chronic renal pathology, diabetes mellitus, malignant neoplasms. All patients were divided into two groups: with vitamin D deficiency (<20 ng/ml) and with normal vitamin D content (≥20 ng/ml). The daytime, nighttime, and daily blood pressures were determined. In the result, vitamin D deficiency is associated with increased arterial stiffness in newly diagnosed hypertensive patients.

Everyone knows that inflammation plays an important role in the development of atherosclerosis. The most widely studied biomarker of cardiovascular inflammation with proven anti-inflammatory effects is highly sensitive C-reactive protein. Many studies have shown an inverse relationship between vitamin D and reactive protein C [58, 59]. The level of vitamin D is positively correlated with the concentration of anti-inflammatory cytokines (interleukin 10), which enhances the anti-inflammatory effect of vitamin D. By reducing the production of pro-inflammatory cytokines, interleukin 10 has a cardioprotective effect. A decrease in the level of this interleukin in the blood leads to the development of severe atherosclerosis. Thanks to this mechanism, vitamin D is able to slow down the progress of atherosclerosis. In addition, vitamin D is able to suppress the formation of pro-inflammatory tumor necrosis factor, which once again proves the indisputable role of this vitamin in the development of inflammation. With vitamin D deficiency in the body, the synthesis of atherogenic cholesterol fractions increases, which leads to an increase in atherosclerotic processes in the body. The effect of vitamin D is comparable to the effect of statins, since it inhibits the enzyme HMG-CoA reductase—3-hydroxy-3-methylglutaryl-coenzyme A-reductase, which is an important link in the pathogenesis of atherosclerosis [60].

Several findings currently suggest that there is a link between the vitamin D system and the development of atherosclerotic plaques, possibly mediated by a modulation of immune responses [61]. This study showed that in patients with diabetes

mellitus, vitamin D can affect signaling from vitamin D receptors on the surface of macrophages, which leads to a decrease in the penetration of LDL cholesterol into foam cells, which prevents the development of atherosclerosis. Due to the inhibition of the nuclear factor of gene expression of activated B cells, vitamin D suppresses the synthesis of prothrombogenic and pro-inflammatory cytokines (interleukin 6) and also increases the formation of anti-inflammatory interleukin 10 and thrombomodulin. All this leads to a decrease in vascular calcification and stops the development of atherosclerotic plaques by suppressing the formation of foam cells.

W. John et al. [62] when carrying out an analysis using multivariate models, including the fact the risk of developing diabetes mellitus and ischemic heart disease, found that vitamin D deficiency helps to reduce the content of apolipoprotein A1. Another study carried out with the aim elucidating the relationship between vitamin D content and metabolic risk factors in young men rank without obesity proved that the content in the blood circulator 25 (OH) D3 correlated with the level of LDL [63]. Results of a randomized trial, conducted by G. Major, et al. [64], testimony about the fact that the daily intake of 400 IU of cholecalciferol and 1200 mg calcium led to a decrease total cholesterol levels.

8. The place of vitamin D in the development of chronic heart failure

For the first time in 1995, L. Brunvand et al. [65] presented a clinical case of the association of pronounced vitamin D deficiency, hypocalcemia with myocardial dysfunction, and chronic heart failure. E. Shane et al. [66] proved statistically significant predominance of vitamin D deficiency in patients with chronic heart failure, direct correlation between the level of vitamin D it contains in serum and a fraction of left ventricular throw. A. Zittermann et al. [67] demonstrated low serum 25 (OH) D3 and calcitriol levels in the blood of patients with chronic heart failure sufficiency in comparison with the control group healthy people. The authors have proven that the connection between vitamin D deficiency and chronic heart failure sufficiency is traced in all age groups, with the correlation of the relationship between the low level of 25 (OH) D3 and an increased content of cerebral sodium uretic peptide. Prospective cross-examination and follow-up performed by A. Zittermann et al. demonstrated statistically significant prevalence of vitamin D deficiency in patients with indications for emergency heart transplantation in comparison with patients preparing for a planned transplantation. A lower circulating level vitamin D has been associated with a risk of sudden heart death. Research results of I. Gotsman et al. [68] testified to a statistically significant possessing a deficiency of 25 (OH) D3 in patients with chronic heart failure in comparison with control. The authors proved that less than 9% of such patients had an optimal level of 25 (OH) D3, highlighting significantly adverse consequences of its deficiency. Thus, the carried out studies show that there is a statistically significant prevalence of vitamin D deficiency in patients with chronic heart failure in comparison with nursing patients without it; vitamin D deficiency is associated with the severity of heart failure and higher rates of unfavorable outcomes.

In 2016, a 26.5-month study was completed to establish the incidence of vitamin D deficiency and its relationship with bone mineral density, left ventricular ejection fraction, and brain natriuretic peptide (NT-proBNP) levels. Two groups were formed: the first included 70 patients with chronic heart failure (CHF); the second—40 patients with diseases of the cardiovascular system, but without CHF. Osteoporosis was detected in 61.4% of patients in the first group (they had fractures much more often) and in

32.5% of patients in the second group. In patients with CHF, a statistically significant decrease in the level of vitamin D was recorded, on average, this value was 9.6 ng/ml, in patients without CHF—14.8 ng/ml, and in patients of group 1, a high level of NT-proBNP was observed. A correlation was found between the level of vitamin D in serum and the concentration of NT-proBNP, the left ventricular ejection fraction. As a result, it was concluded that patients with CHF are a group at increased risk of osteoporosis, and such patients are recommended to prescribe additional vitamin D intake at a dosage of more than 1600 IU per day as a preventive measure [69]. The pathophysiological mechanisms of these relationships are not fully understood, there are various hypotheses, according to one—vitamin D deficiency contributes to the development of secondary hyperparathyroidism. A high level of parathyroid hormone provokes calcification of the heart valves (this is especially pronounced in patients with renal failure), as a result of which the risk of developing CHF increases. The reason for the development of CHF is also the "aging" of the myocardium; the key factors that determine the rate of aging are oxidative stress and chronic inflammation. Vitamin D deficiency is associated with a higher incidence of heart failure due to an increase in serum pro-inflammatory markers, including CRP [52, 53, 70].

9. Conclusion

Based on the evidence presented, it can be assumed that the correction of the deficit of vitamin D will help reduce the risk occurrence and progression of cardiovascular diseases, reducing the risk of sudden cardiac death and general mortality of the population.

Based on the conducted studies, it is assumed that the risk of developing arterial hypertension can be explained by the initial content of vitamin D in the blood, sample size, and duration of observation. In addition, the presence of other concomitant cardiovascular diseases, diabetes mellitus, kidney disease, affects the physiological mechanisms of the effect of vitamin D on blood pressure. Therefore, between individual patients there may be significant differences in the physiological effects of vitamin D.

Thus, arterial hypertension is caused by a variety of factors acting through genetic and environmental determinants depending on age. Vitamin D deficiency as a risk factor for the environment contributes to an increase in vascular tone, which, possibly, serves as a trigger that contributes to the development of hypertension in vulnerable middle-aged people. Accumulating data from animal models and observational studies in humans strongly support the hypothesis that vitamin D deficiency contributes to hypertension, and a corresponding high dose of vitamin D with long-term treatment can normalize or nearly normalize blood 25 (OH) D levels and significantly reduce blood pressure in groups of hypertensive patients with vitamin D deficiency.

Correction of vitamin D deficiency is of great prognostic value. Vitamin D treatment is low-cost, easy to administer, and prevention further contributes to a healthy lifestyle. Further clinical and experimental studies are needed to study in more detail the mechanisms of the negative effect of vitamin D deficiency on the cardiovascular system, in particular on arterial hypertension.

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