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The association between vitamin D and myocardial structure and function in congestive heart failure

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Abstract

Objective. Chronic heart failure (CHF) is the most common complication of cardiovascular system diseases associated with unfavorable prognosis. Vitamin D deficiency is an additional factor contributing to the development of cardiovascular pathology. Current evidence on the relationship between vitamin D and the state of the myocardium in patients with CHF is insufficient. The aim of the study was to assess the plasma level of vitamin D in CHF patients and to evaluate its impact on the morphological and functional state of the myocardium. **Design and methods.** The study involved 124 patients with CHF I–II functional class and 16 control subjects without CHF. In all patients, vitamin D level was assessed (25(OH)D total by ELISA) and echocardiography on the apparatus Logiq P5 (USA) was performed. **Results.** The average plasma level of 25(OH)D in CHF patients was 16,6 (10.9; 23.7) ng/mL that was significantly lower ($p = 0.01$) than in the control group 42,1 (27.8; 49.6) ng/mL. All patients with CHF were divided by the plasma level of 25(OH)D according to centile distribution into group I (LQ_0–UQ_{25}) with level of 25(OH)D 10.9 ng/ml, group II (LQ_{25}–UQ_{75}) with level 25(OH)D 10.9–23.7 ng/ml, and group III (LQ_{75}–UQ_{100}) with level of 25(OH)D 23.7 ng/ml and above. Systolic blood pressure (SBP) was significantly higher in group I than in group III ($p = 0.04$), and in the control group this value was significantly lower than in all groups of CHF patients ($p < 0.05$). Dimensions of the aorta and its sections, left atrium, parameters of end-systolic volume, end-diastolic volume (EDV), thickness of the anterior and posterior left ventricle wall during systole were significantly higher in group I as compared to group II, III and the control group. There is a negative correlation between the plasma level of 25(OH)D and EDV ($R = –0.24$; $p = 0.03$), systolic output ($R = –0.28$; $p = 0.01$), dimensions of the aorta at aortal valve (AV) ($R = –0.39$; $p = 0.0002$), ascending aorta ($R = –0.31$; $p = 0.02$) and aortic arch ($R = –0.41$; $p = 0.002$), parameters of anterior ($R = –0.36$; $p = 0.004$) and posterior left ventricular wall thickness during systole ($R = –0.27$; $p = 0.01$) in all patients with CHF. Also, there is a positive correlation between SBP and aorta dimensions at the AV level ($R = 0.44$; $p = 0.00003$) and ascending aorta ($R = 0.36$; $p = 0.006$).

Conclusions. Found association of vitamin D plasma levels with structural and functional state of the myocardium indicates the negative impact of vitamin D deficiency on myocardial contractile function, dimensions of the aorta and anterior and posterior walls of the left ventricle.

Key words: vitamin D, chronic heart failure, echocardiography, myocardium

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Ассоциация уровня витамина D в организме с морфофункциональным состоянием миокарда у лиц с хронической сердечной недостаточностью

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Резюме

Хроническая сердечная недостаточность (ХСН) является наиболее распространенным и прогностически неблагоприятным осложнением всех заболеваний сердечно-сосудистой системы. Дополнительным фактором, вносящим вклад в развитие патологии сосудов и сердца, служит дефицит витамина D; в то же время данных о взаимосвязи уровня витамина D с состоянием миокарда у пациентов с ХСН недостаточно. **Целью исследования** было оценить уровень витамина D в плазме крови у лиц с ХСН, изучить его влияние на морфофункциональное состояние миокарда. **Материалы и методы.** Обследовано 124 пациента с ХСН I–II функционального класса и 16 лиц группы контроля без ХСН. Всем пациентам проводилась оценка уровня общего витамина D (25(OH)D total методом иммуноферментного анализа) и эхокардиография на аппарате Logiq P5 (США). **Результаты.** Средний уровень 25(OH)D в плазме крови пациентов с ХСН составил 16,6 (10,9; 23,7) нг/мл и был ниже (p = 0,01), чем в группе контроля — 42,1 (27,8; 49,6) нг/мл. Все пациенты с ХСН были разделены по уровню 25(OH)D в плазме крови согласно центильному распределению на группу I (LQ_0–UQ_{25}) с уровнем 25(OH)D до 10,9 нг/мл, группу II (LQ_{25}–UQ_{75})

с уровнем 25(OH)D 10,9–23,7 нг/мл и группу III (LQ_{75}–UQ_{100}) с уровнем 25(OH)D 23,7 нг/мл и выше. Уровень систолического артериального давления (САД) в группе I был выше, чем в группе III (p = 0,04), а в группе контроля — ниже, чем во всех группах пациентов с ХСН (p < 0,05). Размеры аорты и ее отделов, левого предсердия, показатели конечного систолического объема, конечного диастолического объема (КДО), толщина передней и задней стенок левого желудочка (ЛЖ) в систолу были больше в группе I, по сравнению с группой II и III и с контрольной группой. Установлены отрицательные корреляции между уровнем 25 (OH)D в плазме крови с показателями КДО (R = –0,24; p = 0,03), ударного объема (R = –0,28; p = 0,01), размером аорты на уровне аортального клапана (АК) (R = –0,39; p = 0,0002), восходящего отдела аорты (R = –0,31; p = 0,02) и дуги аорты (R = –0,41; p = 0,002), а также с толщиной передней стенки ЛЖ (R = –0,36; p = 0,004) и задней стенки ЛЖ в систолу (R = –0,27; p = 0,01) во всей группе пациентов с ХСН. Также нами установлена положительная корреляция между уровнем САД и размером аорты на уровне АК (R = 0,44; p = 0,00003) и восходящего отдела аорты (R = 0,36; p = 0,006). **Выводы.** Установленные нами ассоциации уровня витамина D в плазме крови с морфофункциональным состоянием миокарда указывают на отрицательное влияние сниженного уровня витамина D на сократительную функцию миокарда, размеры аорты и размеры передней и задней стенок ЛЖ.

Ключевые слова: витамин D, хроническая сердечная недостаточность, эхокардиография, миокард

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Introduction

Despite obvious recent achievements in the pathogenesis and therapeutic approaches, chronic heart failure (CHF) remains the most common and prognostically unfavorable cardiovascular complication. Just one year after CHF development, as little as 50–70 % of patients survive, and within the period of 5 years the minority is alive [1]. In the Framingham study, mortality within 5 years after CHF development was 62 % in men and 42 % in women [2].

Today, vitamin D deficiency is considered an additional factor contributing to cardiovascular diseases. Vitamin D receptors (VDR) are present in more than 40 target tissues including cardiomyocytes, vascular smooth muscle and endothelial cells [3, 4]. Interactions between vitamin D and the cardiovascular system (CVS) include the impact of vitamin D on myocardial contractile function, blood pressure regulation, cardiac remodeling, and reduction of left ventricular (LV) hypertrophy [5–7]. Available experimental data show that correction of vitamin D deficiency decreases myocardial hypertrophy and improves the course of arterial hypertension (HTN) [7].

The role of vitamin D in atherosclerosis prevention is of particular importance in the context of the effect on the CVS. Inflammatory process that is usually associated with low vitamin D level is currently considered to be one of mechanisms of atherosclerosis [8]. In addition, low vitamin D levels increase the risk of severe coronary heart disease: in patients with vitamin D deficiency the prevalence of CHF is almost twice as great as in patients with sufficient vitamin D level [9].

Currently, there are very limited data regarding the interaction between vitamin D blood level and myocardial state in patients with CHF.

Objective of our study was to assess vitamin D plasma levels in CHF patients and its association with morphological and functional characteristics of myocardium.

Design and methods

In Grodno and Volkovysk cities, we included 124 patients (43.5 % men, 56.5 % women) with CHF of functional class (FC) I–II secondary to the coronary heart disease and/or HTN. Mean age was 63.5 ± 8.9 years. The control group consisted of 16 subjects without CHF (31.2 % men, 68.8 % women, mean age 59.5 ± 7.4 years). Exclusion criteria were as follows: chronic obstructive

pulmonary disease, bronchial asthma, intake of hormonal drugs, diabetes mellitus, oncological diseases.

All patients underwent a routine physical examination with anthropometry. To confirm the FC of the CHF according to NYHA classification [10] and national recommendations of the Republic of Belarus [11] all patients underwent the 6-minute walk test. During the test, the patient has to walk as far as possible at a comfortable pace in 6 minutes in a corridor with 1-meter markers. The distance > 551 m covered in 6 minutes corresponds to CHF FC 0, 426–550 m — to CHF FC I, 301–425 m — to CHF FC II, 151–300 m — to CHF FC III, < 150 m — to CHF FC IV. At baseline all the patients received complex pathogenetic therapy for CHF in accordance with the national recommendations of the Republic of Belarus [11].

The participants answered to survey concerning consumption of exogenous vitamin D with food rich in vitamin D (cod liver oil, omega-3 polyunsaturated fatty acids, fish oil) as well as with vitamin D-containing medications.

The assessment of the total vitamin D plasma level was carried out by enzyme immunoassay with the determination of total 25-hydroxy-cholecalciferol (25(OH)D total = 25(OH)D_3 + 25(OH)D_2) level. Blood plasma level of 25(OH) D > 30 ng/ml was considered as optimum, 20–29 ng/ml — as insufficient, less than 20 ng/ml — as deficiency, less than 10 ng/ml — as marked deficiency [12, 13]. For the assessment of 25(OH)D blood was collected over the period from October to December.

Echocardiography (echo-CG) (Logiq P5, USA) with a cardiac transducer 3 mHz was carried out in all patients. In the M- and B-mode the following parameters were assessed: aortic size at the levels of the aortic valve (AV), ascending aorta, aortic arch, descending aorta, left atrium anteroposterior diameter, LV end-systolic volume (ESV) and end-diastolic volume (EDV), LV systolic output (SO), LV ejection fraction, interventricular septum thickness in systole and diastole, LV anterior wall thickness, LV posterior wall thickness in systole and diastole, LV mass and LV mass index.

Statistical analysis was carried out with the help of "STATISTICA 10.0" (SN AXAR207F 394425FA-Q).The findings are presented as mean values with standard deviations (M ± SD), in case of non-normal distribution — as median values (Me) and interquartile ranges [LQ–UQ]. The relations among variables were assessed by Spearman correlation analysis (R). Differences were considered to be significant at p-level < 0.05.

Results

Average level of 25(OH)D in blood plasma in patients with CHF made 16.6 (10.9; 23.7) ng/ml vs 42.1 (27.8; 49.6) ng/ml (p = 0.01) in the control group.

All CHF patients were divided into 3 groups according to 25(OH)D blood plasma level with reference to centile distribution. Group I consisted of 31 patients (48.4% men, 51.6% women, mean

Table 1

ANTHROPOMETRIC DATA, FINDINGS OF THE 6-MINUTE WALK TEST, SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN THE GROUPS DIVIDED ACCORDING TO CENTILE DISTRIBUTION OF 25(OH)D IN BLOOD PLASMA

Parameter	Group I	Group II	Group III	Control Group
25(OH)D, ng/ml	≤ 10.9	10.9–23.7	≥ 23.7	42.1 (27.8; 49.6)
Height, cm	168.4 ± 10.6	167.6 ± 9.5	166.0 ± 9.8	166.1 ± 10.0
Weight, kg	81.2 ± 16.3	82.4 ± 10.6	79.5 ± 13.5	77.0 ± 11.1
BMI, kg/m^2	28.5 ± 4.0	28.7 ± 3.9	28.8 ± 4.0	27.7 ± 4.7
SBP, mm Hg	142.0 ± 17.7$^{\#3}$	138.0 ± 16.0$^{\#}$	134.2 ± 14.3$^{\#}$	126.5 ± 15.4
DBP, mm Hg	88.2 ± 11.5	87.6 ± 11.0	85.0 ± 9.1	86.7 ± 11.1
6-minute walk test, m	427.8 ± 48.5	430.4 ± 52.2	416.3 ± 48.7	

Note: BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; # — significant differences with control group (p < 0.05); 3 — significant differences with group III (p < 0.05).

Table 2

ДАННЫЕ ЭХОКАРДИОГРАФИИ В ГРУППАХ, РАЗДЕЛЕННЫХ ПО ЦЕНТИЛЬНОМУ РАСПРЕДЕЛЕНИЮ 25(OH)D В ПЛАЗМЕ КРОВИ

Показатель	Группа I	Группа II	Группа III	Группа контроля
Aortic sizes at the level of the AV, mm	34 (29.5; 37.5)[#.2.3]	32.5 (29; 35)[#]	30 (29; 32)	28 (28; 29)
Ascending aorta, mm	32.5 (31; 39)[#]	31.5 (30; 34)	30.5 (30; 32)	29 (28; 30)
Aortic arch, mm	26 (25; 28)[#.2.3]	25 (24; 26)	24 (24; 25)	24 (24; 25)
Descending aorta, mm	23 (23; 24)	23 (22; 24)	23 (23; 24)	23 (23; 24)
Anteroposterior LA diameter, mm	39.5 (34; 48.5)[#.2.3]	37.5 (34; 42)	37 (32; 41)	34 (31; 37)
LVEDV, mL	136 (104; 191)[#.2.3]	119 (103; 134)[#]	107 (100; 126)	103 (97; 126)
LVESV, mL	43 (37; 76)[#.2]	42 (37; 50)	42 (37; 54)	42 (31; 49)
SV, mL	86.2 (66.5; 100.5)[#.2.3]	73.5 (67; 81)[#]	67 (64; 76)	65 (64; 77)
EF, %	63 (58.5; 66)	63.5 (60; 65)	62 (61; 64)	64 (62; 65)
IVS (diastolic), mm	12 (11; 14)	13 (12; 13)	12 (12; 13)	11 (10; 14)
IVS (systolic), mm	16 (14.5; 18.5)	16 (15; 17)	16 (15; 17)	15 (14; 17)
Anterior wall thicknesses, mm	4 (3; 4)[#.3]	3.35 (3; 4)[#.3]	3 (3;3)	3 (3; 2.75)
Posterior wall end-diastolic thickness, mm	12 (11; 12)	12 (11; 13)	12 (11; 13)	11 (11; 13)
Posterior wall end-systolic thickness, mm	17 (16; 18)	16 (15; 18)	16 (15; 17)	15 (13; 17)
LV mass, g	216 (169; 262)	244 (209; 274)	247 (220; 279)	210 (180; 226)
LVMI, g/m^2	110.5 (92; 137.5)	119 (105; 136)	126 (110; 139)	109 (96; 114)

Note: AV — aortic valve; LA — left atrium; EDV — end-diastolic volume; ESV — end-systolic volume; SV — stroke volume; EF — ejection fraction; IVS — interventricular septum; LV — left ventricular; LVMI — LV mass index; # — significant differences with control group ($p < 0.05$); [2] —significant differences with group II ($p < 0.05$); [3] — significant differences with group III ($p < 0.05$).

age 61.4 ± 8.9 years) with 25(OH)D corresponding to the 25th centile up to 10.9 ng/ml, mean level 8.6 (7.5; 8.9) ng/ml which corresponded to the marked vitamin D deficiency. Group II consisted of 62 patients (40.3 % men, 59.7 % women, mean age 62.8 ± 6.8 years) with 25(OH)D level corresponding to the 25–75th centile: 10.9–23.7 ng/ml, mean level 16.6 (13.6; 19.3) ng/ml. Group III consisted of 31 patients (41.9 % men, 58.1 % women, mean age 65 ± 8.4) with 25(OH)D level corresponding to the 75–100th centile: 23.7 ng/ml and more, mean level 29.1 (26.0; 35.1) ng/ml.

The groups were comparable by anthropometric values (Table 1). However, systolic blood pressure (SBP) that in the group with marked 25(OH)D deficiency was higher than in group III ($p = 0.04$), and in the control group was significantly lower than in all CHF groups ($p < 0.05$). Groups were also comparable by the intake of angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, acetylsalicylic acid, and statins. The survey showed that none of the subjects consumed food rich in vitamin D as well as none of them used vitamin-D containing medications regularly.

The sizes of aorta and its parts, left ventricular dimensions, ESV and EDV, thickness of the anterior and posterior LV walls in systole were significantly higher in the group with marked vitamin D deficiency (group I) as compared to the groups with higher levels of vitamin D (group II and III) and the control group (Table 2). We found a

negative correlation between 25(OH)D blood plasma level and EDV (R = –0.24; p = 0.03), SO (R = –0.28; p = 0.01), aortic sizes at the level of the AV (R = –0.39; p = 0.0002), ascending aorta (R = –0.31; p = 0.02), and aortic arch (R = –0.41; p = 0.002) as well as the thickness of LV anterior wall (R = –0.36; p = 0.004) and posterior wall in systole (R = –0.27; p = 0.01) in the whole group of CHF patients. We also found a positive correlation between SBP level and aortic diameters at the level of the AV (R = 0.44; p = 0.00003) and ascending aorta (R = 0.36; p = 0.006).

Discussion

Vitamin D deficiency was suggested as a factor influencing the progress of such pathologies as HTN, CHF, aortic dilation, and peripheral artery diseases [14–18]. A number of studies demonstrated an inverse relationship between blood pressure and vitamin D level [18, 19]. Vitamin D facilitates blood pressure regulation and prevents cardiac hypertrophy through inhibition of renin activation, prevents vascular calcification and acts as a cardioprotective agent due to secondary hyperparathyroidism prevention [18]. VDR activation in cardiomyocytes has a positive effect on cardiac function and myocardial contractile function in animals [20, 21]. In human studies, vitamin D deficiency was associated with heart failure [22]. However, only few studies examined the effect of vitamin D levels on myocardial morphology and functions.

The findings of our study are indicative of a relationship between low blood plasma levels of 25(OH)D and several echo-CG values in patients with CHF. For example, in the group of patients with marked vitamin D deficiency, EDV, ESV, and SO were increased, and also 25(OH)D blood plasma levels negatively correlated with EDV and SO, which is indicative for a possible unfavorable effect of decreased vitamin D level on myocardial systolic function and predisposition to the cardiac volume overload. Similar results were obtained by R. Mohammed et al. (2015) who showed the association of low vitamin D levels in blood with the deterioration of ESV and LV end-systolic wall diameter [23]. At the same time, the PIVUS study demonstrated that higher concentrations of circulating vitamin D were associated with the improvement of LV systolic function and smaller LV end-systolic diameter [24].

We found a negative correlation between 25(OH)D blood plasma level and the thoracic aorta diameter; as well as an increase of aortic diameters at the level of AV and aortic arch in patients with CHF and marked vitamin D deficiency. These results are consistent with the findings of M. Demir et al. (2012) who also demonstrated an association of vitamin D levels with an increase of aortic diameters in patients with dilated thoracic aorta [17]. In addition, correlation between 25(OH)D blood plasma level and LV diastolic dysfunction in subjects with stable angina was found [25].

Aortic root dilation is considered to be a marker of subclinical left ventricular diastolic dysfunction [26]. The correlation between SBP and the dimensions of thoracic aorta in our groups, as well as an increased SBP level in the group with the marked vitamin D deficiency, may contribute to the development of aortic dilation. The relationship between high blood pressure and low vitamin D level was mentioned in a number of studies [27–30]. At the same time HTN and atherosclerosis are well-known risk factors for aortic dilation [31].

Taking into account VDR found in cardiomyocytes, a direct influence of vitamin D on myocardium was revealed [32]. For example, in experimental studies in animals with vitamin D deficiency, HTN and myocardial hypertrophy developed [33]. Animal studies also showed that 1,25 $(OH)_2D_3$ slows down the aging of cardiomyocytes, regulates their proliferation and inhibits hypertrophy [34, 35]. The negative correlation of 25(OH)D blood plasma level with the thickness of LV anterior and posterior walls in systole in our study confirms possible unfavorable effect of vitamin D deficiency on the development of myocardial hypertrophy. Similar correlation was shown in some studies [36, 37], but the data are still controversial [38].

Conclusions

Therefore, our findings are indicative of an association between reduced vitamin D level and myocardial contractile function, aorta diameters, and dimensions of the LV anterior and posterior walls.

Conflict of interest

The authors declare no conflict of interest.

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