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The Role of Inflammatory Cytokines and the Effect of Complex Treatments on Changes in Vitamin D and Parathyroid Hormone Levels in Chronic Heart Failure

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Abstract The article examines the association of inflammatory cytokines with vitamin D and parathyroid hormone levels in patients with chronic heart failure. Also, on the basis of standard treatment, the combined use of sodium glucose type 2 inhibitor empagliflozin and vitamin D has been found to have a positive effect on inflammatory cytokines, vitamin D, and parathyroid hormone indicators.

Keywords Ischemic heart disease (IHD), Chronic heart failure (CHF), Endocrine, Inflammatory, Hypovitaminosis D, Hypovitaminosis D, Calcium, Phosphorus microelements

1. The Urgency of the Problem

Chronic heart failure (CHF) is a complex of multifactorial and dangerous syndromes, characterized by high morbidity and mortality, a sharp decrease in patients' functional status and quality of life, as well as extremely high costs of treatment. According to data, more than 64 million people in the world have this disease. Therefore, activities aimed at reducing the incidence of CHF are global and one of the priority directions. At the same time, although there is a tendency to its decrease in economically developed countries, the introduction of modern treatment methods for ischemic heart disease (IHD), the improvement of patients' quality of life and its duration, the increase of elderly people among the population, and ultimately the number of patients with IHD causing the number to increase. In population studies, its prevalence among the population is 1-2%, with an increase in age of more than 10% [4,8,14,23].

It is known that CHF is a disease with endocrine, inflammatory and metabolic disorders and polyorgan damage [17]. Disturbances in the metabolism of calcium, phosphorus microelements and related parathormone and vitamin D are also observed in CHF. As a result of this disease, compensatory mechanisms are developed, and the increase in phosphate causes an increase in fibroblast growth factor-23 (FGF-23), a decrease in vitamin D, and an increase in parathyroid hormone [5,6]. Vitamin D deficiency activates the renin-angiotensin-aldosterone system, causing arterial hypertension and inflammation [12,13].

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An epidemiological study conducted in the USA showed that vitamin D plays an important role in the normal functioning of the cardiovascular system. In particular, there is a proportional increase of IHD in hypovitaminosis D, arterial hypertension, diabetes mellitus to the equatorial distance. It has been confirmed that the prevalence of vitamin D deficiency and death from cardiovascular diseases is high in the winter months, i.e. in the days when the activity of the sun's rays is reduced [20].

About 1 billion people in the world have vitamin D deficiency (<20 ng/ml) or deficiency (<21-29 ng/ml). According to the 2018 US National Health and Nutrition Examination Survey (NHANES), the prevalence of this vitamin deficiency was 28.9% [16].

In CHF, hypoxic processes primarily stimulate the production of hypoxia-inducible factor 1 and α-tumor necrosis factor (α-TNF) in cardiomyocytes, leading to the activation of monocytes and macrophages [7]. Their activation increases the synthesis of a number of inflammatory cytokines and causes deeper damage to the myocardial cells that have been exposed to ischemia [3].

Therefore, activation of the immune system and systemic inflammatory processes play an important role in the progression and development of the disease in patients. Regardless of its etiology, serum levels of pro-inflammatory cytokines have been found to be significantly higher than normal in CHF [18,24].

Angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, ß-blockers, mineralocorticoid receptor antagonists have been used for many years in the treatment of CHF. In recent years, drugs such as sacubutril-valsartan and glucose sodium cotransporter type 2 inhibitors (GSTI-2i)

have also been included in the standard treatment of CHF [14].

CHF found that the use of glucose-sodium cotransporter 2 inhibitors in patients with low left ventricular ejection fraction (LVEF) is highly effective. Currently, dapagliflozin, empagliflozin, canagliflozin and other drugs belonging to this group have been created [21,22]. However, despite the positive results achieved in the treatment of CHF in recent years, the death rate from it is still high. In most cases, it is a comorbidity of the disease, and among them, GFR is one of the leading causes of death.

There is insufficient evidence that vitamin D deficiency is associated with CHF and its adverse outcomes. However, it is still controversial whether adding it to treatments can reduce cardiovascular disease and improve the outcome of CHF [11].

According to Witham and co-authors, the addition of vitamin D to the treatment did not have a positive effect on the functional status and quality of life of elderly patients with CHF [19]. In contrast, Shedeed and co-authors found that vitamin D administration in youth with CHF resulted in significant positive changes in heart function and a reduction in inflammatory markers [15].

Inflammatory mediators are known to play a critical role in the pathogenesis of ventricular remodeling, and CHF is evidence-based as a serum biomarker of severity and prognosis [9,10]. Several studies have shown that circulating parathyroid hormone CHF is directly related to weight and may serve as a biomarker of weight [1,2].

The pooled results of a meta-analysis by Jiang WL and co-authors found that adding vitamin D to the treatment of patients with CHF resulted in significant reductions in tumor necrosis factor-alpha, C-reactive protein, and parathyroid hormone. Therefore, they concluded that the recommendation of this vitamin in CHF reduces inflammatory factors and parahormone through a protective function [11].

But until now, the effect of CHF when used together with vitamin D, ß-blockers, mineralocorticoid receptor antagonists, sacubitril/valsatan, angiotensin-converting enzyme inhibitors and sodium glucose cotransporter type 2 inhibitors included in their complex has not been covered in the literature.

2. Materials and Methods

120 CHF Ⅱ and Ⅲ FC patients with advanced renal dysfunction were included in the study. In them, serum creatinine and glomerular filtration rate (GFR), which is a traditional test method for evaluating kidney dysfunction, were taken as criteria. Patients included in the follow-up were divided into two main and control groups according to the treatment received at the beginning. The main group consisted of 80 patients, and their average age was 66.5±5.7, men 43 (53.75%) - women 37 (46.25%). Among them, patients with CHF Ⅱ and Ⅲ FC were 14 (17.5%) and 66 (82.5%), respectively. GER in the main group was equal to 80.6 ± 5.5 ml per 1 minute per 1.73 m2 of body surface.

The control group consisted of 40 patients with a mean age of 67.6 ± 5.5 ha, 20 (50%) men and 20 (50%) women, including 8 (20%) patients with CHF Ⅱ and Ⅲ FC, respectively. and made up 32 (80%). CHF in the main group was equal to 78.4 ± 5.2 ml per 1 minute per 1.73 m2 body surface.

The main and control group of patients involved in the study were divided into two subgroups based on the serum vitamin D levels during the examinations. The first subgroup was made up of patients whose blood serum vitamin D level decreased from normal values (Vit D≤30, ng/ml) and the second subgroup was made up of patients whose level was maintained (Vit D≥30, ng/ml). 40% (32) of patients in the main group and 42.5% (17) of the control group were found to have reduced vitamin D levels.

Patients with vitamin D deficiency in the main group were prescribed CHF complex standard treatment (sacabutril-valsartan, ß-blocker, mineralocorticoid receptor antagonist-eplerenone, sodium glucose cotransporter type 2 inhibitor-empagliflozin) and vitamin D 4000 units per day for 8 weeks. A maintenance dose of 2,000 units was then recommended for 4 weeks. Only complex standard (sacabutril-valsartan, ß-blocker, mineralocorticoid receptor antagonist-eplerenone, sodium glucose cotransporter type 2 inhibitors-empagliflozin) treatment was applied to patients with normal vitamin D levels. At this point, we would like to point out that there is no information published in the available literature about the effectiveness of sodium glucose cotransporter type 2 inhibitors and vitamin D when used in combination with GFR patients on the basis of CHF.

Patients with reduced vitamin D serum levels in the control group were prescribed CHF complex standard treatment (sacabutril-valsartan, ß-blocker, mineralocorticoid receptor antagonist-eplerenone) and vitamin D 4000 units per day for 8 weeks. A maintenance dose of 2,000 units was then recommended for 4 weeks. Patients with normal vitamin D levels were prescribed only complex standard treatment (sacabutril-valsartan, ß-blocker, mineralocorticoid receptor antagonist-eplerenone).

Vitamin D, parathyroid hormone, S-reactive protein, interleukin-6, and tumor necrosis factor-alpha indicators were determined in the blood serum of all subjects involved in the study, along with routine laboratory tests, before and 6 months after treatment. Intracardiac hemodynamics were assessed using echocardiography and electrocardiography, and renal functional status was assessed by calculating GFR using creatinine.

3. Research Results and Discussion

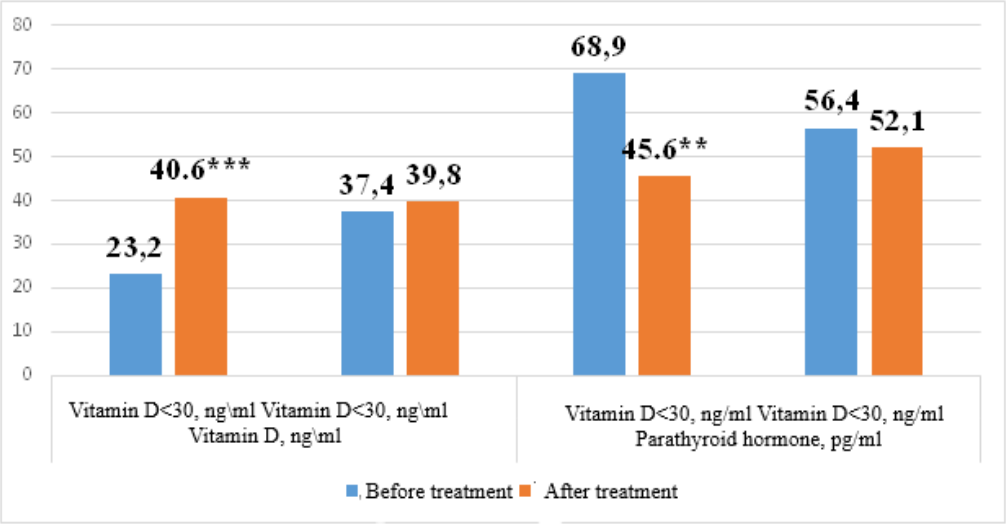
Based on CHF, it has been proven in a number of scientific studies that in patients with developed kidney dysfunction, changes in other indicators are observed, depending on the decrease of vitamin D, calcium, on the contrary, the increase of phosphorus and parathormone. We also compared vitamin D and parathormone levels in the blood serum after the

treatment in the follow-up patients. Figure 1 below shows the dynamics of vitamin D and parathyroid hormone levels in the main group of patients.

In the main group of patients, there was a reliable difference in the change of vitamin D indicators between the groups after treatment. This is primarily due to the small group of patients with low serum vitamin D taking vitamin D. But even in the group that didn't take it, there was a significant increase due to the positive anti-inflammatory and organ-protective effects of the sodium-glucose cotransporter type 2 inhibitor. Vitamin D increased 1.75 times from 23.2±3.6 ng/ml to 40.6±2.8 ng/ml in the first group and a highly reliable difference (r<0.001) was found when comparing them. In the second group, it increased 1.06 times from 37.4±6.2 ng/ml to 39.8±5.3 ng/ml, but the difference was not reliable (r>0.05). In the second group, it increased 1.06 times from 37.4±6.2 ng/ml to 39.8±5.3 ng/ml, but the difference was not reliable (r>0.05).

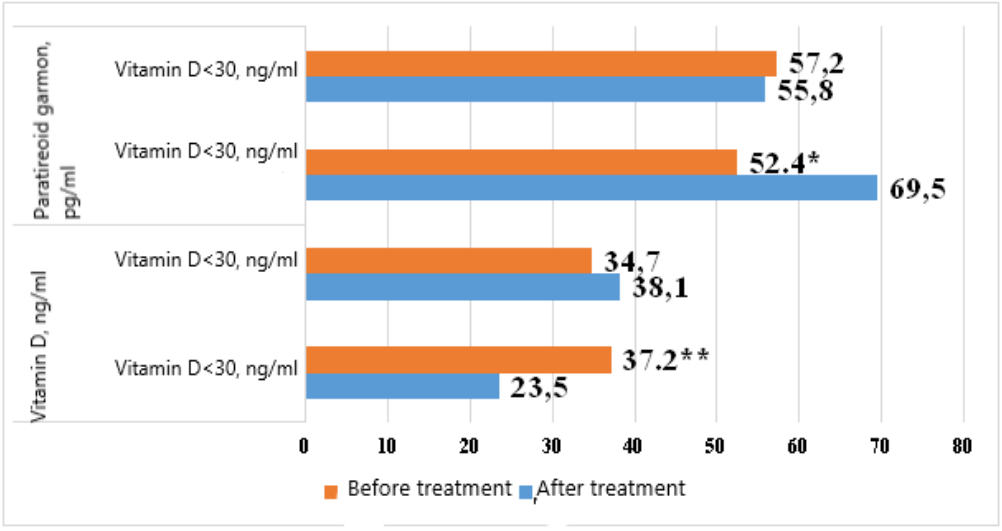
Parathormone readings were also noted to improve in accordance with changes in vitamin D. Before treatment, its amount was 68.9±6.2 pg/ml in the subgroup with low vitamin D, and after it was 45.6±5.4 pg/ml, it decreased by 1.5 times. When they were compared, a reliable difference (r<0.01) was noted. Vitamin D decreased from 56.4±5.2 to 52.1±4.2 pg/ml in the subgroup with normal values, but no significant difference (r>0.05) was observed.

In the control group as well as in the subgroup that added vitamin D to the complex treatments, significant positive changes were found after the treatment. On the contrary, only in the subgroup that received standard treatment, it was noted that its amount decreased slightly in dynamics. Figure 2 below shows the results obtained.



Note: * - the reliability of the difference between indicators before and after treatment: ** - r<0.01, ***r<0.001.

Figure 1. Post-treatment changes in vitamin D and parathormone levels in the main observation group of patients



Note: * - the reliability of the difference between indicators before and after treatment: * - r<0.05., ** - r<0.01

Figure 2. Post-treatment changes in vitamin D and parathyroid hormone levels in control group patients

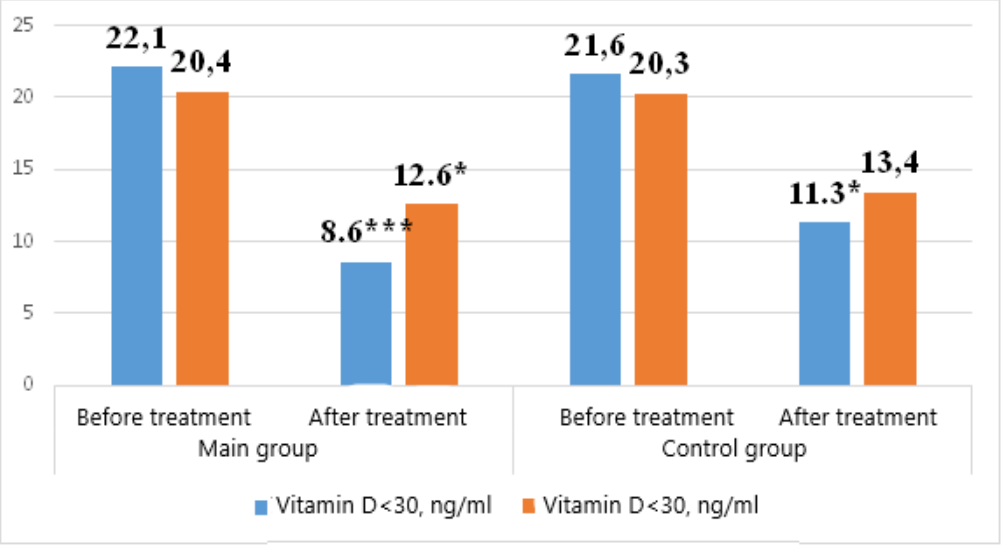
As shown in the Figure, vitamin D indicators improved by 36.8% from 23.5±5.4 ng/ml to 37.2±3.6 ng/ml in the first subgroup, and a positive change (r<0.01) was detected. In the second subgroup, on the contrary, its amount decreased from 38.1±6.3 ng/ml to 34.7±4.8 ng/ml (r>0.05) and the differences were not reliable.

Parathyroid hormone level was 69.5±8.0 before treatment and 52.4±6.7 pg/ml in vitamin D subgroup, and a reliable difference (r<0.05) was noted. In the second subgroup, which received only standard treatment, its amount increased from 55.8 ± 5.5 to 57.2 ± 6.2 pg/ml after treatment (r>0.05) and no reliable change was observed.

The results obtained in the control group showed that when prescribing treatments to patients with advanced kidney dysfunction, it is necessary to take into account not only cardio, but also nephroprotective effects of CHF. Their nephroprotective effect stabilizes the development of GFR by reducing oxidative stress inflammation and fibrosis processes in the kidneys.

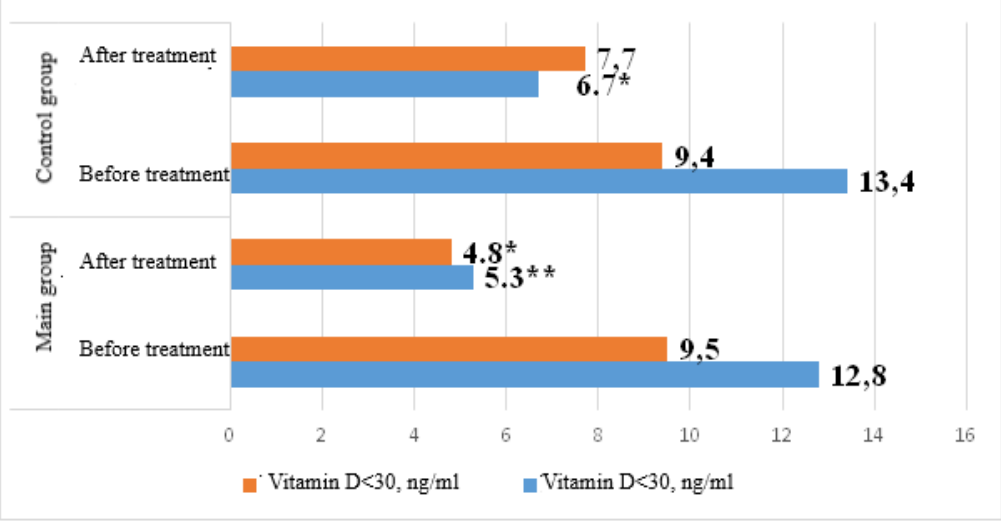
The role of serum inflammatory cytokines in the development of renal dysfunction in patients with CHF is considered important. Their higher than normal level causes inflammatory processes in the kidney tubules and has a negative effect on the functioning of the nephrons.

Also, during our research, we studied the effect of medical treatments on inflammation and fibrosis processes in the body. In this case, we evaluated the dynamics of interleukin-6 and α-tumor necrosis indicators. Figure 3 below shows the post-treatment change in serum interleukin-6 in baseline and control patients.



Note: * - the reliability of the difference between indicators before and after treatment: * - r<0.05., *** - r<0.001

Figure 3. Interleukin-6 levels after treatment in patients enrolled in the study



Note: * - the reliability of the difference between indicators before and after treatment: * - r<0.05., ** - r<0.01

Figure 4. Comparative analysis of post-treatment tumor necrosis factor-α indicators in study patients

In the first period of our observation, even though high levels of interleukin-6 were found in all groups of patients, changes were more evident in subgroups with low vitamin D. In the subgroup that received vitamin D based on the first of the main group, that is, CHF complex treatment containing empagliflozin, interleukin-6 before and after treatment decreased from 22.1±3.4 pg/ml to 8.6±2.8 pg/ml, respectively. It decreased by 5 times and the differences were highly reliable (r<0.001). In the second subgroup, the values before treatment decreased by 2.1 times from 20.4±3.5 pg/ml to 9.4±2.4 pg/ml, respectively, and a significant difference (r<0.05) was noted.

In the control group, interleukin-6 indicators before treatments were 21.6±3.2 and 20.3±2.6 pg/ml, respectively. After treatment, it decreased by 2.1 times to 10.2±3.4 pg/ml in the first subgroup and a reliable (r<0.05) difference was found. In the second subgroup, it improved 1.5 times from 20.3±2.6 to 13.4±2.8 pg/ml, but no reliable (r>0.05) difference was observed.

A highly reliable decrease in interleukin-6 levels in the group receiving vitamin D and empagliflozin is associated with a reduction in the synthesis of inflammatory cytokines.

Thus, although positive results were observed after complex treatments in the groups of patients under observation, in most cases, positive changes were evident in the group with added vitamin D. In addition, it was observed that the main group of patients who received empagliflozin had a reliable decrease in systemic inflammatory processes in the body, and this was shown by a decrease in the level of interleukin-6 in the blood of these patients.

Changes in the parameters of α-tumor necrosis factor in patients involved in the study after treatment are presented in Figure 4.

Indicators of α-tumor necrosis factor CHF were reliably higher than reference values before treatment in all patients with existing renal dysfunction. A decrease in vitamin D in patients also plays an important role in its increase. In patients with low levels of vitamin D in the main group, its amount was 12.8±2.5 pg/ml before treatment and 5.3±2.1 pg/ml after it, and decreased by 2.4 times. When they were compared, a reliable difference (r<0.01) was noted. In the second subgroup, the amount of α-tumor necrosis factor decreased by 2.05 times from 9.5±2.1 pg/ml to 4.8±1.6 pg/ml, respectively, and a reliable difference (r<0.05) was detected.

In the control group, the index of α-tumor necrosis factor decreased by 2 times from 13.4±2.2 to 6.7±1.8 pg ml in the first subgroup after treatments, and when they were compared, a reliable difference (r<0.05) was noted. In the second subgroup, indicators decreased from 9.4±2.3 pg/ml to 7.7±1.5 pg/ml (r>0.05), respectively.

Also, C-reactive protein indicators, one of the main inflammatory markers in patients, were compared between groups after treatments. Vitamin D content of the main group decreased 1.82 times from 9.5±3.2 mg/l to 5.2±2.6 mg/l after treatment and a reliable difference (R<0.05) was noted. In patients with normal vitamin D content, it improved 1.4 times from 7.4±2.8 mg/l to 5.5±1.8 mg/l (R<0.05). In the control group, these indicators were 1.5 times (R<0.05) from 9.8±2.7 mg/l to 6.6±2.4 mg/l and 7.2±2.4 mg/l, respectively. decreased by 1.05 times (R>0.05) from 6.8±1.8 mg/l.

4. Conclusions

In patients with chronic heart failure and advanced renal dysfunction, determination of vitamin D indicators in blood serum and coordination of medical treatment using it slows down the development of pathological processes in the kidneys and leads to improvement of its function. This is confirmed by the results obtained by co-prescribing empagliflozin with vitamin D in patients in the main and control groups in our study.

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