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THE EFFECT OF VITAMIN D DEFICIENCY ON DISEASE SEVERITY IN CHRONIC HEART FAILURE

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Abstract

Objective. The aim of this study was to investigate the role of certain biochemical parameters in the relationship between vitamin D levels and the severity of chronic heart failure (CHF).

Materials and Methods. The study included 219 patients with CHF aged 30–89 years: 123 patients (mean age 60.4 ± 1.0 years) with NYHA class I–II and 96 patients (mean age 62.9 ± 1.0 years) with NYHA class III–IV. Blood samples were analyzed for creatinine, vitamin D, calcium, phosphorus, parathyroid hormone (PTH), endothelin-1, and fibroblast growth factor-23 (FGF-23). Left ventricular ejection fraction (EF) was measured using echocardiography.

Results. In patients with NYHA class I–II CHF, the serum concentration of vitamin D decreased by approximately 50% compared to the control group ($p<0.001$), while in NYHA class III–IV the decrease reached 2.5-fold ($p<0.001$). Calcium levels were reduced mainly in NYHA class III–IV patients by 9.3% ($p<0.001$). Phosphorus concentrations increased significantly both in the early and advanced stages of CHF, by 58.6% ($p<0.001$) and 62.0% ($p<0.001$), respectively. Compared with controls, PTH, endothelin-1, and FGF-23 levels were elevated in NYHA class I–II by 54.2% ($p<0.001$), 10.8% ($p=0.003$), and 53.1% ($p<0.001$), respectively; in NYHA class III–IV, the increases were 95% ($p<0.001$), 20.0% ($p<0.001$), and 62.3% ($p<0.001$), respectively. Correlation analysis revealed a statistically significant positive correlation between vitamin D levels and EF, whereas negative correlations were observed between vitamin D and PTH, FGF-23, and endothelin-1. These findings indicate that heart failure progresses through both metabolic and immunological mechanisms.

Conclusion. The present study demonstrated that vitamin D deficiency in patients with CHF worsens progressively with higher NYHA functional classes, and this deficiency is closely associated with alterations in several biochemical markers. A strong positive correlation was established between vitamin D levels and EF. These results confirm the essential regulatory role of vitamin D in the cardiovascular system.

Keywords: *chronic heart failure, vitamin D, parathyroid hormone, FGF-23, endothelin*

Introduction

The global prevalence of arterial hypertension, ischemic heart disease, and type 2 diabetes mellitus has led to an increasing number of patients with chronic heart failure (CHF). Despite advancements in treatment and preventive strategies, CHF remains associated with high mortality, frequent hospitalizations, and the progression of comorbid conditions (Kampka, Z., Czapla, D., Wojakowski, W., Stanek, A. 2025; Iyngkaran P., Thomas M., Horowitz J. D., Komesaroff P., Jelinek M., Hare D. L., 2021). Therefore, additional therapeutic approaches are needed to improve prognosis and quality of life in patients with CHF. Recent studies have demonstrated that vitamin D plays an important role in cardiovascular health, particularly in individuals with heart failure. Vitamin D deficiency has been associated with an increased risk of CHF and a more severe clinical course of the disease (Kampka, Z., Czapla, D., Wojakowski, W., Stanek, A. 2025; Mohanty V., Pathania M., Bhasi A., 2022). The relationship between vitamin D deficiency and heart failure can be explained by multiple pathophysiological mechanisms. Vitamin D deficiency may directly and indirectly contribute to the development of CHF. Low vitamin D levels activate the renin–angiotensin–aldosterone system (RAAS), resulting in sodium and water retention (Deng C., Wu Y., 2025). Decreased serum calcium levels, often observed in vitamin D deficiency, impair myocardial contractility, leading to systolic dysfunction. The active form of vitamin D, 1,25(OH)$_2$D, stimulates calcium influx into cardiomyocytes through calcium channels, exerting a positive chronotropic effect (Hagău A. C., Puşcaş A., Togănel R., Muntean I., 2023). Calcium deficiency also contributes to secondary hyperparathyroidism and increased parathyroid hormone (PTH) secretion, which in turn promotes myocardial fibrosis, hypertrophy, and impaired left ventricular systolic function (Busa V., Dardeir A., Marudhai S., Patel M., Subas S. V., Ghani M. R., Cancarevic I., 2020). Preclinical studies have shown that calcitriol, the active metabolite of vitamin D, can inhibit cardiomyocyte hypertrophy and proliferation, leading to a reduction in natriuretic peptide secretion (Mohanty V., Pathania M., Bhasi A., 2022).

In CHF, there is a complex interplay between PTH, endothelin-1 (ET-1), and fibroblast growth factor 23 (FGF-23), with their circulating levels varying according to disease severity. PTH regulates calcium and phosphate metabolism by increasing phosphate reabsorption in the kidneys and stimulating active vitamin D synthesis. In contrast, FGF-23 enhances phosphate excretion and inhibits active vitamin D synthesis by activating the Klotho-FGFR1 complex in parathyroid cells, thereby initiating the MAPK signaling pathway and suppressing PTH secretion. ET-1, a potent vasoconstrictor peptide produced by endothelial cells, exerts regulatory effects on both the heart and kidneys. Elevated ET-1 levels in CHF contribute to vascular dysfunction and cardiac hypertrophy. Some studies have also suggested interactions between ET-1 and FGF-23 in the progression of cardiovascular disease (Vergaro, G., Del Franco, A., Aimo, A. *et al.,* 2023; Faul C., 2018).

Although vitamin D deficiency has been implicated in the pathogenesis of CHF, particularly in myocardial fibrosis, its role is not yet fully elucidated. Moreover, the relationship between vitamin D levels, CHF severity, and fibrotic markers remains insufficiently studied. The most active form of vitamin D, 1,25(OH)$_2$D (calcitriol), is widely used in the diagnosis of vitamin D deficiency (Kampka, Z., Czapla, D., Wojakowski, W., Stanek, A., 2025).

The functional status of CHF patients is classified according to the New York Heart Association (NYHA) functional classes, which reflect disease progression and quality of life. Comparing clinical and laboratory indicators across NYHA I–II and NYHA III–IV functional classes provides valuable insights into patients' pathophysiological state and therapeutic needs.

Objective. The aim of this study was to investigate the role of selected biochemical markers in the relationship between vitamin D levels and disease severity in patients with CHF.

Materials and Methods

This study included 219 patients with CHF aged 30–89 years (mean 61.5 ± 0.7 years). Among them, 123 patients (mean age 60.4 ± 1.0 years) were classified as NYHA I–II, and 96 patients (mean age 62.9 ± 1.0

years) as NYHA III–IV. A control group consisted of 51 clinically healthy individuals (mean age 54.3 ± 0.5 years). Patients with impaired renal function were excluded from the study. Only patients with reduced ejection fraction (HFrEF) were included, i.e., those with impaired myocardial contractility and ejection fraction (EF) <40%.

Serum concentrations of vitamin D, PTH, ET-1, and FGF-23 were measured using ELISA kits (Bioaktiva Diagnostic). Serum creatinine, calcium, and phosphorus concentrations were analyzed by biochemical methods using kits manufactured by "Human."

For statistical analysis, the nonparametric Mann–Whitney U test was applied. Data were expressed as Me (median), Q1 (first quartile, 25%), and Q3 (third quartile, 75%). Statistical analysis was performed using SPSS version 26. Correlations were assessed using Spearman's rank method. Differences between groups were considered statistically significant at $p<0.05$.

Results and Discussion

According to echocardiographic data, the mean EF in NYHA class I–II patients was 39.5 ± 0.7%, and in NYHA class III–IV patients it was 35.8 ± 0.8%, compared with 66.9 ± 0.8% in the control group. EF was reduced by 69.4% ($p<0.001$) in NYHA class I–II and by 86.9% ($p<0.001$) in NYHA class III–IV patients compared with healthy controls. Moreover, EF in NYHA class III–IV patients was 10.3% lower than in those with NYHA class I–II CHF ($p=0.003$) (Table 1).

Table 1. *Functional and some biochemical parameters of patients with CHD*

parameters	Groups											
	Control				I–II NYHA				III–IV NYHA			
	M	Me	Q1	Q3	M	Me	Q1	Q3	M	Me	Q1	Q3
Ejection fraction, %	66,9	68,0	62,0	71,0	39,5	40,0	33,0	46,0	36,8	37,5	31,5	41,5
p; p_1		<0,001				<0,001				0,003		
Creatinin, mq/dl	0,86	0,88	0,76	0,96	0,90	0,92	0,79	1,00	0,89	0,89	0,76	1,01
p; p_1		0,112				0,488				0,376		
Vit.D, nq/ml	43,5	42,0	38,0	48,0	28,6	29,0	21,0	37,0	20,5	17,5	12,5	28,0
p; p_1		<0,001				<0,001				<0,001		
PTH, pq/ml	38,4	37,7	25,9	50,9	58,6	57,1	48,3	67,2	61,9	61,2	50,6	69,4
p; p_1		<0,001				<0,001				0,099		
P, mmol/l	1,14	1,16	1,05	1,23	1,89	1,84	1,50	2,31	1,91	1,88	1,62	2,22
p; p_1		<0,001				<0,001				0,804		
Ca, mq/dl	9,3	9,4	8,9	9,6	9,2	9,1	8,4	9,8	8,6	8,6	8,0	9,1
p; p_1		0,083				<0,001				<0,001		
FGF-23, pq/ml	48,3	48,2	39,1	61,2	55,0	53,4	48,9	62,9	58,2	56,4	47,1	65,9
p; p_1		0,003				<0,001				0.194		
Endotelin-1, pq/ml	5,6	5,9	4,0	6,7	9,2	9,1	7,9	10,5	11,8	11,5	9,9	13,6
p; p_1		<0,001				<0,001				<0,001		

Note: M represents the mean value; Me – the median; Q1 – the first quartile (25th percentile); Q3 – the third quartile (75th percentile). p indicates statistical significance compared with the control group, and p1 – compared with patients in NYHA class I–II

The present study demonstrated that vitamin D deficiency in patients with chronic heart failure (CHF) progressively worsens in parallel with the severity of the disease. Specifically, serum vitamin D levels were approximately 50% lower in patients with NYHA class I–II compared to the control group ($p<0.001$), while in NYHA class III–IV, the reduction reached 2.5-fold ($p<0.001$). Moreover, vitamin D concentrations in the NYHA III–IV group were 65.7% lower than in the NYHA I–II group ($p<0.001$), indicating a more pronounced deficiency in advanced stages. These findings suggest that the effects of vitamin D extend beyond bone metabolism, influencing myocardial structure, cellular signaling pathways, and immune regulation (Bae S., Singh S. S., Yu H., Lee J. Y., Cho B. R., Kang P. M. 2013).

The active form of vitamin D, $1,25(OH)_2D_3$, regulates calcium and phosphate homeostasis through the vitamin D receptor (VDR) and also modulates the renin-angiotensin-aldosterone system (RAAS), oxidative stress, and inflammatory cytokine production (Dentino P., Mora J., Zuo L., 2025). In our study, patients in NYHA III–IV exhibited a 9.3% decrease in serum calcium ($p<0.001$), whereas phosphate levels increased by 58.6% ($p<0.001$) and 62.0% ($p<0.001$) in the early and advanced stages, respectively. Comparatively, in NYHA III–IV, phosphate levels did not significantly differ from those in NYHA I–II ($p=0.804$), while calcium decreased by 5.8% ($p<0.001$). One of the main regulators of calcium-phosphate metabolism is PTH, which increased by 53.1% in NYHA I–II ($p<0.001$) and 62.3% in NYHA III–IV ($p<0.001$). PTH, FGF-23, and calcitriol (1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$]) are key endocrine hormones controlling calcium and phosphate balance through their actions on the kidney, bone, and intestine (Murray S. L., Wolf M., 2024).

Vitamin D and PTH levels closely correlate with CHF severity. As clinical heart failure progresses, serum vitamin D significantly decreases, whereas PTH markedly increases (Belen E., Tipi F. F., Aykan A. C., Findikçioğlu U., Karakuş G., Yeşil A., Helvaci A., Kalaycioğlu E., Cetin M. 2014). These alterations reflect the hypocalcemia and hyperphosphatemia associated with vitamin D deficiency, which naturally coincides with elevated FGF-23 levels (Scialla J. J., Wolf M. 2014). FGF-23 is predominantly synthesized by osteocytes and osteoblasts and plays a critical role in phosphate homeostasis and vitamin D metabolism. It reduces renal phosphate reabsorption and inhibits the synthesis of $1,25(OH)_2D_3$. In CHF, elevated FGF-23 is associated with left ventricular hypertrophy, myocardial fibrosis, and electrophysiological changes. Notably, FGF-23 can act in the heart independently of its cofactor Klotho, contributing directly to myocardial injury and remodeling. Literature evidence indicates that FGF-23 stimulates left ventricular hypertrophy and fibrosis and can activate pro-inflammatory signaling pathways (Stöhr R., Schuh A., Heine G. H., Brandenburg V., 2018).

In our study, FGF-23 levels increased by 10.8% in NYHA I–II ($p=0.003$) and by 20.0% in NYHA III–IV ($p<0.001$), reflecting myocardial remodeling mechanisms associated with vitamin D deficiency and phosphate load. FGF-23, a ~32 kDa hormone secreted by osteocytes and osteoblasts, is a principal regulator of vitamin D and phosphate homeostasis and has been linked to multiple cardiovascular manifestations. Experimental studies demonstrated that FGF-23 infusion induces cardiomyocyte hypertrophy and left ventricular hypertrophy (LVH). Higher circulating FGF-23 levels are associated with an increased risk of cardiovascular events, independent of renal function or other mineral metabolites (Batra J., Buttar R. S., Kaur P., Kreimerman J., Melamed M. L., 2016).

FGF-23 receptors are expressed in the myocardium, and experimental and clinical studies support its role in LVH, fibrosis, and dysfunction. The combination of elevated FGF-23 and low Klotho levels is associated with increased risk of cardiovascular death or hospitalization for heart failure in patients with stable ischemic heart disease. Similarly, higher FGF-23 levels correlate with a significant risk of heart failure development in hypertensive patients. FGF-23 enhances renal phosphate excretion and suppresses PTH synthesis. It is independently associated with mineral biomarkers including 25-hydroxyvitamin D, plasma phosphate, calcium, PTH, and endothelin. FGF-23 correlates with left ventricular hypertrophy and remodeling

post-myocardial infarction. Recent evidence indicates myocardial production and release of FGF-23, with increased protein and mRNA expression, suggesting at least partial myocardial origin of circulating FGF-23 after infarction (Binnenmars, S. H., Hoogslag, G. E., Yeung, S. M. H., Brouwers, F. P., Bakker, S. J. L., van Gilst, W. H., Gansevoort, R. T., Navis, G., Voors, A. A., & de Borst, M. H., 2022).

Current data also suggest that RAAS activation induces FGF-23 expression in the myocardium, which may promote fibrotic pathways in fibroblasts, contributing to cardiac remodeling and dysfunction (Vergaro, G., Del Franco, A., Aimo, A. *et al.*, 2023). FGF-23, in turn, activates RAAS and induces left ventricular hypertrophy, partly through vitamin D suppression. Cross-talk between FGF-23 and RAAS contributes to myocardial hypertrophy and fibrosis. Previous studies have shown a significant association between high circulating FGF-23 and reduced ejection fraction (Nakano T., Kishimoto H., Tokumoto M., 2023). Elevated FGF-23 is also clinically linked to endothelial dysfunction, potentially by impairing nitric oxide bioavailability, a central mechanism of endothelial dysfunction (Silswal N., Touchberry C. D., Daniel D. R., McCarthy D. L., Zhang S., Andresen J., Stubbs J. R., Wacker M. J., 2014).

In our cohort, endothelin-1 levels increased by 54.2% in NYHA I–II ($p<0.001$) and by 95% in NYHA III–IV ($p<0.001$). Levels in NYHA III–IV were 26% higher than in NYHA I–II ($p<0.001$). Endothelin-1 is a potent vasoconstrictor promoting endothelial dysfunction and increasing cardiac load. Its elevation in CHF is associated with left ventricular hypertrophy, fibrosis, and myocardial dysfunction. Vitamin D deficiency–related pro-inflammatory cytokines can directly and indirectly modulate endothelin-1 synthesis. Reduced endothelial NO production in vitamin D deficiency contributes to increased ET-1 levels (Dmour B. A., Badescu M. C., Tuchiluş C., Cianga C. M., Constantinescu D., Dima N., Duca Ş. T., Dmour A., Costache A. D., Cepoi M. R., Crişan A., Leancă S. A., Loghin C., Şerban I. L., Costache-Enache II. 2025; Shantsila E., Wrigley B. J., Blann A. D., Gill P. S., Lip G. Y. 2012; Woo J. S., Woo Y., Jang J. Y., Ha S. J., 2022). Endothelin-1 belongs to a family of peptide hormones of endothelial origin, which also regulate bone cell proliferation and differentiation, influencing FGF-23 synthesis (Feger M., Ewendt F., Menzel M., Hocher B., Föller M., 2020).

Our correlation analysis confirmed a significant inverse relationship between vitamin D and FGF-23 levels ($\rho = -0.627$; $p < 0.01$), highlighting the compensatory increase in FGF-23 in response to vitamin D deficiency. Furthermore, a negative correlation between FGF-23 and ejection fraction (AF) was observed ($\rho = -0.60$; $p < 0.01$), indicating that elevated FGF-23 contributes to myocardial hypertrophy and diastolic dysfunction.

Endothelin-1 (ET-1), a potent vasoconstrictor promoting endothelial dysfunction and increasing cardiac load, was significantly elevated: 54.2% in NYHA I–II ($p<0.001$) and 95% in NYHA III–IV ($p<0.001$). Levels in NYHA III–IV were 26% higher than in NYHA I–II ($p<0.001$). ET-1 elevation in CHF is associated with left ventricular hypertrophy, fibrosis, and impaired myocardial function. Correlation analysis demonstrated a significant inverse relationship between vitamin D and ET-1 ($\rho = -0.528$; $p < 0.01$), supporting the role of vitamin D deficiency in endothelial dysfunction and inflammatory activation.

Vitamin D levels also positively correlated with AF ($\rho = 0.724$; $p < 0.001$), indicating that higher vitamin D concentrations are associated with improved myocardial contractility. These findings highlight the multifaceted role of $1,25(OH)_2D_3$ in cardiovascular function, including the regulation of calcium-phosphate balance, suppression of RAAS activity, and modulation of inflammatory processes.

Conclusion

Overall, the observed hormonal and biochemical changes – reduced vitamin D and calcium, increased phosphate, PTH, FGF-23, and ET-1-contribute to myocardial remodeling, fibrosis, and worsening cardiac function in CHF patients. This study emphasizes that correcting vitamin D deficiency may have a beneficial impact on disease progression and prognosis in patients with chronic heart failure.

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