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Association of Vitamin D Serum Levels with Clinical Outcomes in Patients with Acute Decompensated Heart Failure

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Abstract

Background: Heart failure (HF) stands out as a major reason for hospital admissions. Vitamin D deficiency is also associated with a higher risk of cardiovascular diseases. Due to recent conflicting findings, this study aimed to investigate clinical outcomes based on serum vitamin D levels in hospitalized patients with HF.

Methods: In this cross-sectional study, 258 hospitalized patients with acute decompensated heart failure (ADHF) were investigated during 2022–2023. Demographic, clinical and laboratory parameters of patients were recorded. They were divided into two groups based on 25-hydroxyvitamin D ([25-OH] D) levels: sufficient ≥30 ng/ml and insufficient <30 ng/ml. Finally, the studied variables were compared between the groups. All data analysis was performed by SPSS version 16.0.

Results: In this study, the mean age of the patients in sufficient and insufficient vitamin D groups was 66.91±14.38 and 63.88±13.74 years, respectively. There was no significant difference in terms of age, underlying diseases, smoking status among the groups (P>0.05). The ejection fraction (EF) was lower in patients with insufficient vitamin D (20.66±10.91% vs. 23.98±11.82%). Moreover, vitamin D deficiency was associated with history of hospitalization (P<0.05). The incidence of edema and arrhythmia was higher in patients with insufficient vitamin D (P<0.05) and it was not related to mortality rate during hospitalization in the studied population (P>0.05).

Conclusions: Our findings indicate that vitamin D deficiency in patients with ADHF is associated with lower EF, recurrent hospitalizations, edema, and arrhythmia. Consequently, regular monitoring and appropriate treatment of vitamin D levels in these individuals may help mitigate its associated complications to some extent, as much as possible.

Keywords: Cardiovascular diseases, Heart failure, 25-Hydroxyvitamin D, Outcome

Introduction

Heart failure (HF) is a clinical syndrome characterized by impaired cardiac supply of sufficient blood flow to meet metabolic needs or impaired venous return and filling of heart cavities [1]. It is estimated that approximately 64 million people worldwide suffer from HF [2]. According to the European Society of Cardiology, HF stands out as a leading reason for hospital admissions among individuals aged 65 and older. The incidence is approximately 1–2% in the general population, but it escalates to more than 10% in patients aged 70 years and above [3]. Acute decompensated heart failure (ADHF) encompasses a diverse range of conditions, commonly manifesting as shortness of breath, swelling, and fatigue. Although this condition is widespread and linked to significant health risks and mortality, moreover, diagnosing it can be challenging [4]. HF can be divided into 3 main categories: 1) HF with reduced ejection fraction (EF) (HFrEF) characterized by left ventricular EF (LVEF) < 40%, 2) HF with mildly reduced EF (HFmrREF) which is defined by LVEF = 41–

49%, 3) HF with preserved EF (HFpEF) which is defined as LVEF >50% [5].

Emerging risk factors, particularly hypovitaminosis D, are gaining attention for their potential impact on prognosis and treatment [6,7]. Vitamin D, an essential micronutrient, is crucial for calcium homeostasis and bone health. Beyond its skeletal benefits, low vitamin D levels are linked to an increased risk of cardiovascular diseases (CVDs), mortality, diabetes mellitus (DM), arterial hypertension (HTN), and chronic kidney disease (CKD) [8–11]. Recent studies indicate that vitamin D deficiency is prevalent among individuals with coronary artery disease or HF [12,13]. A meta-analysis has shown that vitamin D supplementation can improve EF in HF patients [14].

Based on current evidence, vitamin D supplementation has been recommended for the prevention and treatment of various CVDs. However, due to conflicting findings, further research is needed [15,16]. This study aimed to examine clinical outcomes in hospitalized heart failure (HF) patients based on their serum vitamin D levels.

Material and Methods

Study design

In this cross-sectional study all patients with ADHF who were hospitalized in Dr. Heshmat Hospital, Rasht, Iran from September 2022 to March 2023, were investigated. Inclusion criterion was hospitalized patients with HFrEF and HFmrREF (LVEF ≤49%). Exclusion criteria were taking calcium and vitamin D supplements, corticosteroids and anticonvulsants drugs before the study, having chronic granulomatous diseases that secrete calcium, such as sarcoidosis or blood dyscrasias, any types of malignancy, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) or pacemaker placement indication during the study period. Written informed consent obtained from all participants.

Data collection

Demographic characteristics (including age, gender, and smoking status), medical history (including HTN, HLP, DM, and CKD), echocardiographic findings (including LVEF, left ventricular hypertrophy (LVH), right ventricular (RV)-dilation, and valvular disorders (both valvular stenosis and regurgitation more than mild were considered as valvular disorders), previous hospitalization history, current length of hospitalization, in-hospital mortality, presence of chest pain, edema, arrhythmia and dyspnea severity according to New York Heart Association (NYHA) classification were recorded for all patients.

Moreover, serum level of 25-hydroxyvitamin D ([25-OH] D) measured by spectrophotometry using ELISA method via 5 cc of blood sample. Then, patients were divided into two groups based on 25(OH)D level: sufficient ≥30 ng/ml and insufficient <30 ng/ml [17]. Finally, the studied variables were compared between two groups of patients.

It should be noted that the studied population were initially treated with intravenous furosemide until their condition stabilized. Then standard treatment of HF based on guideline including beta-blockers such as metoprolol, bisoprolol and carvedilol, angiotensin-converting-enzyme inhibitors (ACE) inhibitors including captopril, enalapril, valsartan and empagliflozin, spironolactone and eplerenone were set and prescribed for all patients until discharge.

Sample size calculation

Based on the study by Aparicio-Ugarriza [1], the initial sample size was 232 people. Considering a 10% attrition rate, 258 participants were included. Assumptions: 95% confidence level, 90% study power, prevalence calculated in other studies: 68%.

Statistical analysis

In this study, the quantitative variables were presented as mean (standard deviation) and qualitative variables presented as frequency (percent). Quantitative variables were compared using independent t-tests if normally distributed (assessed via Shapiro-Wilk test) or Mann-Whitney U test if non-normal. Qualitative variables were analyzed using chi-square or Fisher's exact test. To assess the association between vitamin D status (independent variable) and clinical outcomes (dependent variables), binary logistic regression was employed for dichotomous outcomes (e.g., mortality, arrhythmia), adjusting for covariates. Multivariate linear regression was used to evaluate the relationship between vitamin D levels (continuous) and ejection fraction (continuous), adjusting for confounders. Results are reported as odds ratios (OR) with 95% confidence intervals (CI) for logistic regression and regression coefficients (β) for linear regression. Significance level considered as P-value <0.05. All data analysis was performed by SPSS version 16.0.

Results

In this study, a total of 258 participants were investigated and divided into 2 groups of sufficient (n=91) and insufficient (n=167) vitamin D level. The mean age of the patients in sufficient and insufficient vitamin D groups was 66.91±14.38 and 63.88±13.74 years, respectively. Most of the patients were male and 70.4% of them had insufficient vitamin D level. There was no significant difference in terms of age (P=0.142), medical history (HTN P=0.614) and smoking status (P=0.668) between the groups.

In our study, most of the patients were in III and IV NYHA Classification and demonstrated higher dyspnea and fatigue, which were not significantly different between the two groups (P=0.819) (**Table 1**).

Among echocardiography findings, only LVEF had a significant statistical difference between the two group (P=0.024), which was lower in patients with insufficient vitamin D (20.66±10.91 vs. 23.98±11.82%). Moreover, vitamin D deficiency was related to previous hospitalization of patients (P=0.038) and it had no association with length of hospitalization. The incidence of edema (P=0.008) and arrhythmia (P=0.005) was higher in patients with insufficient vitamin D. Based on our findings, higher rate of mortality was seen in patients with insufficient levels of vitamin D during hospitalization, but it was not significant (P=0.236). From 11 patients who died, only 3 of them had sufficient level of vitamin D (**Table 2**).

Based on logistic regression analysis, only history of hospitalization showed a significant relationship with vitamin D (OR: 1.725, CI 1.029-2.894, P=0.039) (**Table 3**).

According to multivariate linear regression, only gender and HF with p-value of 0.006 and standard deviation of 1.545 revealed significant difference (**Table 4**).

Table 1. Distribution of demographic characteristics of patients between the groups.

Variables		**Vitamin D**		***P*-value**
		Sufficient	**Insufficient**	
Age (years)		66.91±14.38	63.88±13.74	0.142
Gender	Male	47 (29.6)	112 (70.4)	0.015
	Female	44 (44.4)	55 (55.6)	
Medical history	HTN	51 (56)	99 (59.3)	0.614
	HLP	69 (41.3)	33 (36.3)	0.428
	DM	34 (37.4)	68 (40.7)	0.598
	CKD	15 (16.5)	18 (10.8)	0.19
Smoking		26 (28.6)	52 (31.1)	0.668
History of hospitalization		39 (29.1)	95 (70.9)	0.038

HTN: Hypertension; HLP: Hyperlipidemia; DM: Diabetes Mellitus; CKD: Chronic Kidney Diseases

Table 2. Distribution of clinical outcomes of patients between the groups.

Variables		**Vitamin D**		***P*-value**
		Sufficient	**Insufficient**	
Echocardiographic findings	EF (%)	23.98±11.82	20.66±10.91	0.024
	LVH	46 (35.4%)	84 (64.6%)	0.987
	RV-dilation	9 (22.5%)	31 (77.6%)	0.06
	Valvular disorders	85 (36.2%)	150 (63.8%)	0.388
NYHA_FC	2	11 (12.1%)	16 (9.6%)	0.819
	3	24 (26.4%)	46 (27.5%)	
	4	56 (61.5%)	105 (62.9%)	
Chest pain		40 (39.2%)	62 (60.8%)	0.284
Edema		24 (25%)	72 (75%)	0.008
Arrhythmia		43 (28.3%)	109 (71.7%)	0.005
Length of hospitalization (days)		5.40 ± 26.1	5.86 ± 4.90	0.321
Mortality		3 (27.2%)	8 (72.7%)	0.236

EF: Ejection Fraction; LVH: Left Ventricular Hypertrophy; RV: Right Ventricular; NYHA_FC: New York Heart Association Functional Classification

Table 3. Logistic regression analysis of relation between vitamin D and clinical variables.			
Variables	**OR**	**95% CI**	**P-value**
LVH	1.004	0.600–1.680	0.987
RV-dilation	2.114	0.957–4.667	0.064
Valvular disorders	1.587	0.552–4.558	0.391
History of hospitalization	1.725	1.029–2.894	0.039
OR: Odds Ratio; CI: Confidence Interval; LVH: Left Ventricular Hypertrophy; RV: Right Ventricular			

Table 4. Multivariate linear regression for heart failure and covariates.			
Variable	**β**	**Standard Error**	**P-value**
Vitamin D Level	0.062	0.047	0.183
Age	0.016	0.052	0.766
Gender	4.259	1.545	0.006
Smoker	1.4	1.616	0.387
Diabetes Mellitus	-1.607	1.497	0.284
Hypertension	-0.768	1.535	0.617
Hyperlipidemia	-0.148	1.493	0.921
Reference categories: Male (gender), non-smoker (smoking status), absence of condition (medical history).			

Discussion

Recent studies have shown that vitamin D deficiency is very common in people with HF [12,13]. Vitamin D as an essential micronutrient is associated with a higher risk of CVDs and mortality [8–10]. In this study, we evaluate the relationship between serum vitamin D levels during hospitalization and clinical outcomes in hospitalized patients with HF. Based on our findings, patients who had lower vitamin D levels, had lower LVEF on echocardiography. In line with our findings, Naghedi *et al*. revelad that vitamin D supplements can be significantly effective in increasing the EF as the most important and common index of myocardial function [14]. In addition, Zhao *et al*.'s study found a significant positive effect of vitamin D supplementation on EF [18]. Contrary to our findings, Wang *et al*. and Jiang *et al*. reported no effect of vitamin D levels on LVEF [19,20]. Moreover, it has been shown that, vitamin D positively affect left ventricular (LV) structure and function [21].

In our study, insufficient vitamin D was in relation with history of hospitalization in patients with HF. There is not a unanimous agreement on the ideal vitamin D levels [7]. Based on a prevouse study, measuring serum 25(OH)D levels within the first 24 hours of admission to the intensive care unit (ICU), can help identify patients who are at an elevated risk for extended hospital stays, readmission, and mortality [22].

Patients who had insufficient vitamin D levels, had a higher prevalence of arrhythmia and edema and this indicates the chronicity and advanced phase of the disease in this group. Systemic edema is commonly observed in patients with a history of chronic HF, particularly in more advanced stages of the disease [23]. Additionally, a deficiency in vitamin D can lead to uninhibited activation of the renin-angiotensin-aldosterone system (RAAS), which exacerbates HF by causing the retention of salt and water [24]. Similary in another study by Porto *et al*., low vitamin D level were shown to be associated with an increased risk of developing HF and cardiac arrhythmias [25]. The other study indicates that the levels of vitamin D and calcium in the blood, as well as their relationship in patients with cardiac arrhythmia, play a crucial role in the pathophysiology of this condition [26]. Forman *et al*. found that insufficient vitamin D levels lead to an overactive RAAS. This results in elevated aldosterone levels and subsequent hypokalemia, increasing the risk of ventricular arrhythmias [27]. Additionally, an elevated concentration of parathyroid hormone may contribute to arrhythmias in individuals with ischemic heart disease. Factors such as low vitamin D levels, inadequate calcium intake, and renal calcium leakage due to salt sensitivity and aging contribute to chronic, moderate increases in parathyroid hormone. These hormonal changes can lead to weight gain, insulin resistance, high blood pressure, and LVH [28]. One of the limitations of our study was the exclusion of right ventricular (RV) function assessment, as it was not assessed uniformly across all patients.

Conclusion

The present study was designed to determine the association between vitamin D levels and ADHF presentations. It found that insufficient vitamin D levels (<30 ng/ml) were associated with lower LVEF, a higher frequency of hospitalizations, increased edema, and more frequent arrhythmias. These findings highlight the importance of monitoring serum vitamin D levels to improve clinical outcomes in patients with ADHF.

Conflict of Interest

The authors declared no conflict of interest.

Funding

This study received no fund.

Ethical Statement

This study complies with the Declaration of Helsinki. Ethical approval code was obtained from Guilan University of Medical Sciences (code: IR.GUMS.REC.1401.009).

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