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Serum galectin-3 levels and vitamin D relationship in heart failure

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Ethics Committee Approval
The study was approved by the Okmeydanı Education and Research Hospital Ethics Committee dated 03/04/2018 and numbered 864.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Heart failure is an important health problem with an increasing incidence in the world and poor prognosis. Galectin-3 is associated with progressive fibrosis, an underlying pathology of heart failure, just as vitamin D deficiency. We examined the relationship between the stage of heart failure and galectin-3 and 25-OH vitamin D levels.
Methods: Sixty patients with heart failure and 30 healthy volunteers were included in this prospective case-control study. Demographic data, comorbid diseases and laboratory data were examined, and 25-OH vitamin D and galectin-3 levels were compared between the patients with CHF and the control group.
Results: Galectin-3 levels were high in patients with heart failure (P<0.001) and increased as the ejection fraction (EF) decreased (P=0.001). 25-OH vitamin D levels were lower in the patient group compared to the control group (P<0.001). There was no significant correlation between serum galectin-3 and vitamin D levels (r=-0.22; P=0.094); however, serum galectin-3 levels and the stage of CHF were correlated (r=0.66; P=0.001).
Conclusions: We found high serum galectin-3 levels in patients with heart failure and low 25 OH vitamin D levels. We think that both molecules are important prognostic biomarkers in cardiac inflammation and fibrosis.

Keywords: Galectin 3, Congestive heart failure, Vitamin D3 level

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Introduction

Heart failure is a complex clinical syndrome characterized by inadequate blood perfusion to the tissues and organs with hemodynamic, renal and neurohormonal effects caused by structural or functional abnormalities in the heart [1]. It is a serious health problem with increasing morbidity and mortality with age [2]. Pump failure due to myocardial contractile disorder is the key factor in heart failure. However, systolic and diastolic dysfunctions of the heart, valvular disorders, vascular and endocrine diseases may also be the cause.

Galectin-3, a member of the lectin family, binds to beta galactoside and weighs 29 to 35 kDa. It is found in the cytoplasm, nucleus and extracellularly in many tissues, especially the myocardium, fibroblasts, endothelial cells, and inflammatory cells such as macrophages, and binds to the cell surface [3, 4]. Studies show that galectin-3 is associated with cardiac fibroblast proliferation, collagen storage and ventricular dysfunction [5, 6]. These changes in the heart lead to a decrease in left ventricular ejection fraction and cardiac output [6].

Vitamin D deficiency has many metabolic effects. Previous studies reported an association between vitamin D deficiency and atherosclerosis, hypertension, heart failure and fibrosis, cardiomyopathy, coronary artery disease and peripheral arterial diseases [7, 8]. It has also been shown that vitamin D deficiency increases the severity of chronic inflammation and is closely related to inflammatory cytokines such as TNF-alpha and interleukin-6 (IL-6), which mediate the development of chronic heart failure [9]. Vitamin D replacement decreases TNF-alpha and IL-6 levels in chronic heart failure [10].

Galectin-3 was shown to have a role in myocardial fibrosis and cardiac failure via cardiac remodeling in a few previous studies. In our study, we investigated the relationship between systolic function, cardiac functional capacity and vitamin D and galectin-3 levels in patients with heart failure at different stages.

Materials and methods

Design and patients

Ninety patients aged between 39-88 years who were admitted to our Internal Medicine Department between 2018 and 2019 were included in our study. Sixty cases with decompensated heart failure formed the patient group and 30 healthy subjects were included as controls. Heart failure was diagnosed according to the European Society of Cardiology guidelines and the group consisted of patients with low and mid-range ejection fractions. Laboratory data and vitamin D and galectin-3 levels were compared between the groups. Heart failure and its duration were classified according to the New York Heart Association (NYHA) criteria [11]. The age, height, weight, BMI values of the patients, concomitant diseases (HT, DM, CHF, hyperlipidemia, COPD, CRF and other), smoking and alcohol use, all of which were recorded in our outpatient clinic, were evaluated for the study.

Two more tube tubes of blood were obtained from the volunteers in addition to the routine laboratory tests during follow-up. After keeping the blood tubes at room temperature for 15 minutes, they were centrifuged for 15 minutes on 4000 rpm and the obtained sera were preserved at -80°C.

Measurements of Galectin-3 and Performance Characteristics of the Galectin-3 and 25-OH-D vitamin Assay

On the day of analysis, the sera were thawed at room temperature. Enzyme-Linked ImmunoSorbent Assay (ELISA) kits were used for serum measurements of Galectin-3. The analytical (linear) measurement range and the minimal detection limit were 42.3 (19.1) ng/mL and 10.2 ng/mL, respectively, for Galectin-3 and 15.1(7.8) mcg/L and 2.8 mcg/L, respectively, for 25-OH vitamin D.

Ethics committee approval

The study was approved by the Ethics Committee of Okmeydanı Training and Research Hospital on 03/04/2018 with the decision number 864.

Statistical analysis

Mean, standard deviation, median, minimum, maximum, frequency and ratio values were used to present the descriptive statistics. The distribution of the variables was assessed with the Kolmogorov-Smirnov test. The independent samples t-test, Kruskal-Wallis, and Mann-Whitney U tests were used to analyze quantitative independent data. In the analysis of qualitative independent data, the Fischer test was used when the Chi-square test conditions were not met. Effect level and cut off were investigated with the ROC curve. The effect level was investigated by univariate logistic regression. SPSS 22.0 program was used for all analyses. The relationship between the two groups was investigated by the Pearson correlation test. All calculated *P*-values were bidirectional and *P*-values of<0.05 were considered significant.

Power analysis

Power analysis was performed with the G-power program. Based on previous data in the literature, for an effect size of 1.39, an alpha error of 5% and a power of 80%, the smallest sample size for each group to represent the population was 24.

Results

Age and gender distribution were similar between the two groups (P=0.408 and P=0.456, respectively). EF and vitamin D levels were lower among the patients compared to the controls while Galectin-3 levels were higher P=0.001 for all). EF values, serum MPV, total cholesterol, HDL-cholesterol, and CRP levels significantly differed between the two groups. Other laboratory parameters (urea, creatinine, AST, ALT, glucose, LDL-cholesterol, triglyceride, sedimentation rate, sodium, potassium, calcium, chloride, phosphorus and other hemogram parameters except MPV) were similar. All demographic data and the results are shown in Tables 1 and 2 and Figure 1.

Although this was a pilot study, a cut-off value of 40 ng/mL for Galectin-3 was significant in the differentiation of CHF patients from the controls [an area under the curve of 0.800 (0.712-0.888)] (Table 3, Figures 2a and 2b).

Table 1: Data of patient group

	Minimum	Maximum	Median	Mean(SD)
Male, n(%)				44(48.9%)
Female, n(%)				46(51.1%)
Age(year)	39.0	88.0	66.5	66.4(8.9)
Ejection Fraction(%)	15.0	65.0	40.0	41.0(14.7)
CHF duration(year)	2.0	20.0	5.0	5.6(3.1)
WBC(µL)	2.4	21.8	8.7	9.3(3.7)
HGB(g/dl)	6.9	17.5	11.6	11.6(2.3)
HTC(%)	20.4	52.3	36.0	35.9(6.5)
PLT(103µL)	79.0	519.0	246.0	252.7(80.7)
MCV(fl)	61.8	106.0	85.1	84.3(8.6)
MPV(fl)	7.6	13.7	10.1	10.2(1.2)
Glucose(mg/dl)	66.0	547.0	135.0	150.2(74.7)
Creatinine(mg/dl)	0.0	1.0	0.5	0.5(0.3)
AST(IU/L)	8.0	958.0	22.0	36.3(99.9)
ALT(IU/L)	3.0	647.0	17.0	30.4(70.5)
CK(IU/L)	12.0	1311.0	74.5	105.1(158)
Total Cholesterol(mg/dl)	41.0	321.0	159.0	162.4(48)
Triglyceride(mg/dl)	41.0	338.0	113.5	134.1(68.7)
HDL(mg/dl)	3.0	74.0	38.0	37.7(14.5)
LDL(mg/dl)	19.0	217.0	92.0	99.0(37)
CRP(mg/dl)	1.0	239.0	13.0	26.4(36.4)
Sedimentation(mm/h)	3.0	87.0	17.0	28.6(23.5)
TSH(mU/L)	0.0	4.1	1.7	1.8(1.1)
Sodium(mmol/L)	130.0	156.0	139.0	138.9(3.6)
Potassium(mmol/L)	3.3	5.7	4.3	4.3(0.6)
Calcium(mg/dl)	6.2	99.0	9.0	10.0(9.5)
Chlorine(mmol/L)	86.0	110.0	99.1	98.9(5.5)
Phosphorus(mg/dl)	1.4	6.0	3.8	3.6(0.6)
Parathormone(pg/ml)	8.9	297.0	64.9	72.7(52.8)
Vitamin D(mcg/L)	2.8	33.6	12.7	15.1(7.8)
Galectin3(ng/mL)	10.2	88.3	36.2	42.3(19.1)

CHF: Congestive Heart Failure

Table 2: Comparisons between groups

	Patient group		Control group		*P*-value
	Mean(SD)	Median	Mean(SD)	Median	
Male, n(%)	31(51.7%)		13(43.3%)		0.456
Female, n(%)	29(48.3%)		17(56.7%)		
Age(year)	66.8(10.8)	67	65.8(2.7)	66	0.408
Ejection Fraction(%)	32.2(9.1)	33.5	58.6(3.8)	60.0	<0.001
WBC(µL)	8.9(3.5)	8.4	10.2(4.0)	8.9	0.174
HGB(g/dl)	11.7(2.4)	11.6	11.4(2.1)	11.3	0.600
HTC(%)	36.4(6.9)	36.2	35.0(5.7)	34.7	0.354
PLT(10^3µL)	251.2(78.8)	247.0	255.7(85.8)	244.0	0.804
MCV(fl)	83.7(8.3)	83.4	85.5(9.2)	86.6	0.356
MPV(fl)	10.4(1.2)	10.3	9.8(1.3)	9.7	0.024
Glucose(mg/dl)	153.9(68.6)	140.5	142.9(86.6)	116.5	0.317
Creatinine(mg/dl)	0.5(0.3)	0.5	0.6(0.2)	0.6	0.590
AST(IU/L)	41.5(121.9)	21.0	25.9(14.5)	22.5	0.461
ALT(IU/L)	31.9(83.5)	17.0	27.4(32.3)	19.0	0.423
CK(IU/L)	113.8(187.9)	72.0	87.6(65.7)	90.0	0.794
Total Cholesterol(mg/dl)	154.6(48.4)	146.5	178.1(44.1)	180.0	0.009
Triglyceride(mg/dl)	128.0(67.2)	107.5	146.1(71.0)	116.0	0.208
HDL(mg/dl)	35.4(14.6)	35.5	42.2(13.4)	40.5	0.038
LDL(mg/dl)	95.9(38.5)	84.0	105.2(33.5)	101.0	0.073
CRP(mg/dl)	30.7(39.8)	14.0	17.9(27.0)	6.2	0.013
Sedimentation(mm/h)	27.8(23.9)	16.0	30.3(25.0)	20.5	0.908
TSH(mU/L)	1.6(1.1)	1.4	2.3(1.1)	2.4	0.009
Sodium(mmol/L)	138.8(3.9)	139.0	139.2(3.0)	140.0	0.304
Potassium(mmol/L)	4.3(0.6)	4.2	4.3(0.5)	4.3	0.904
Calcium(mg/dl)	9.0(0.7)	9.0	11.9(16.5)	9.2	0.483
Chlorine(mmol/L)	98.5(5.7)	98.9	99.7(5.0)	101.9	0.240
Phosphorus(mg/dl)	3.8(0.9)	3.8	3.4(0.9)	3.8	0.236
Parathormone(pg/ml)	82.7(54.3)	72.3	52.5(43.8)	33.4	0.003
Vitamin D(mcg/L)	10.7(4.8)	10.1	23.8(4.8)	24.0	<0.001
Galectin3(ng/ml)	49.2(19.3)	48.1	28.5(8.3)	30.6	<0.001

[m] Mann-Whitney u test/t-t test, [X²] Chi-square test

Table 3: Galectin-3 values in patient and control groups

	Area under the curve	% 95 Confidence interval	*P*-value
Galectin 3	0.823	0.740-0.906	<0.001
Cut-Off Value 40	0.800	0.712-0.888	<0.001
		Sensitivity	60.0%
		Positive Predictive Value	100.0%
		Specificity	100.0%
		Negative Predictive Value	55.6%

Figure 1: Levels of vitamin D and galectin-3 in the patient and control groups

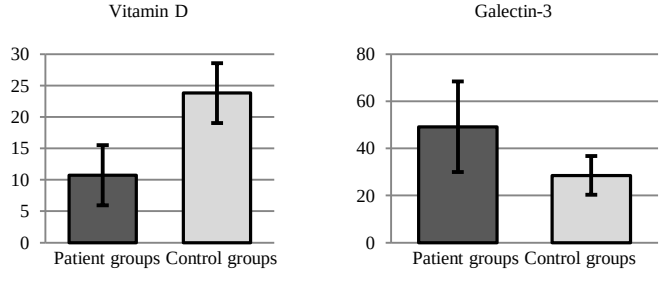
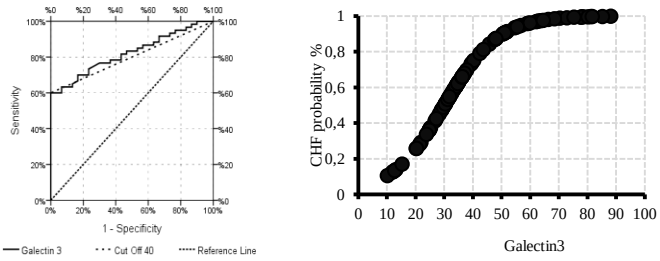


Figure 2a (left) and 2b (right): Galectin-3 values in case and control groups



The relationship between 25-OH vitamin D, Galectin-3 and CHF stage is shown in Table 4. A significant relationship was found between the CHF stage and vitamin D levels in the Kruskal-Wallis test (P=0.011). Galectin-3 levels was significantly correlated with the CHF stage (P=0.001), but not with the age of the CHF patient. The correlation coefficients were -0.01 and 0.66, respectively. Galectin-3 and vitamin D showed no significant correlation (r = -0.22) (Table 5).

Table 4: Levels of 25-OH vitamin D and galectin -3 according to the stages of heart failure

	Min	Max	Median	Mean(SD)	*P*-value
Vitamin D					0.011
Stage I	3.8	20.8	12.2	13.1(4.3)	
Stage II	6.0	30.5	10.4	12.2(6.3)	
Stage III	4.1	16.1	8.7	9.2(3.3)	
Stage IV	2.8	15.5	8.3	8.5(3.7)	
Galectin3					<0.001
Stage I	12.8	56.9	31.9	33.9(12.4)	
Stage II	15.4	81.8	38.2	44.2(17.4)	
Stage III	26.8	72.9	46.8	48.0(13.9)	
Stage IV	51.1	88.3	75.4	70.4(12.8)	

Kruskal-wallis

Table 5: Correlation of Galectin-3 with vitamin D, CHF stage and age of CHF

	r	*P*-value
Vitamin D	-0.22	0.094
CHF stage	0.66	0.001
CHF duration	-0.66	0.511

r: correlation coefficient

Discussion

Galectin 3, a member of the beta-galactoside-binding lectin family, was proven to be a biomarker for mortality in heart failure in many clinical trials [12, 13]. Fibrosis is one of the main mechanisms for heart failure, and Galectin 3 is associated with fibrosis in many organs, particularly the heart [14].

Plasma renin activity is increased in vitamin D deficiency because of renin transcription, which accelerates the course of heart failure. In addition to ACE inhibitors and ARB, vitamin D replacement impedes the progression of heart failure [15].

In our study, we found that galectin-3 levels were higher in patients with heart failure compared to the controls and were correlated with CHF stage.

There was no direct correlation between vitamin D and Galectin-3. However, galectin-3 levels were associated with increased degree of inflammation and fibrosis when the patients were evaluated in terms of NYHA stages, which reveals that galectin-3 could be responsible for the pathogenesis in patients with clinical progression.

In a study of Rossel et al. [16] among hospitalized patients with decompensated heart failure, galectin-3 was increased. Our study was consistent with the meta-analysis data on acute and chronic heart failure [17, 18]. Cho-Kai Wu et al. [19] found that galectin 3 levels were associated with heart failure and myocardial fibrosis in 77 heart failure patients with preserved ejection fraction. A prospective cohort study revealed

that galectin-3 level was an independent predictor of mortality in patients who had chronic heart failure for 26 months when galectin-3 >21 ng/ml [20]. We believe that elevated galectin-3 is not a result but rather, the molecule contributes the process. It is directly proportional to the severity and stage of the disease. In our study, Galectin-3 levels and duration of heart failure were unrelated, and on the contrary, the relationship between the stage of heart failure and the diagnosis of heart failure suggest that this molecule has a direct role in the pathogenesis of the disease.

In addition to its association with plasma renin activity, supplementation of 25-OH vitamin D has been shown to reduce proinflammatory cytokines (TNF-alpha, interleukin -6, IL-1 beta), atherosclerosis and plaque formation and thus plays an important role in the treatment of cardiovascular diseases [21]. Regarding the results of this study, 25-OH vitamin D is thought to play a role in myocardial fibrosis and left ventricular remodeling [22]. Vitamin D deficiency causes secondary hyperparathyroidism, and both primary and secondary hyperparathyroidism are associated with cardiovascular pathologies [23]. In the Tromso study, a relationship was shown between parathormone, calcium and vitamin-D levels and cardiovascular disease [24]. In the Ludwingshafen Risk and Cardiovascular Health Study recently conducted on 3232 patients who underwent angiography, elevated PTH levels were related to cardiovascular death [25]. In our study, 25-OH vitamin D levels were significantly lower in the patient group compared to the control group. As a result, parathormone levels were significantly increased. Increased parathormone level due to vitamin D deficiency worsens the prognosis. The 25-OH vitamin D values were significantly lower among stage III and stage IV patients compared to those with stage I.

In an experimental study, Assalin et al. [26] showed that vitamin D deficiency increased cardiac inflammation, and various cytokines such as tumor necrosis factor (TNF-alpha) and interferon gamma (INF-gamma) caused oxidative stress, increasing left ventricular and atrial fibrosis and apoptosis. The exceptionally low levels of vitamin D in our study group with highly decreased ejection fraction may aggravate heart failure through these cytokines.

Decreased intake, dysfunctional absorption of vitamin D taken orally, less exposure to the sun and outdoor air can explain the lack of vitamin D in these patients. However, considering that heart failure is a process, it would not be wrong to think that the deficiency of vitamin D negatively affects it. This suggests that vitamin D supplementation may be important in patients with heart failure in suppressing cardiac inflammation and decreasing cytokines.

Limitation

The small number of patients was the most important limitation of our study. Further studies are needed with more patient groups.

Conclusion

We found that serum galectin-3 levels increased in patients with heart failure and this elevation was associated with the stage of the disease. Galectin-3 biomarker increases inflammation and fibrosis in heart failure. The association with the clinical stage rather than the duration of heart failure suggests that it may play a role in the pathogenesis of the disease. Similarly, we think that vitamin D deficiency and increased parathormone may be a contributing factor to the process of heart failure and this process can be slowed down by proper replacement. Based on our clinical study, Galectin-3 and 25-OH vitamin D may be involved in the pathophysiology of heart failure and will contribute significantly to the development of new therapies.

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