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Evaluation of galectin-3 in patients with heart failure and its relationship with NT-proBNP levels: A case-control study

Kalp yetersizliği olan hastalarda galektin-3'ün değerlendirilmesi ve NT-proBNP düzeyleri ile ilişkisi: Vaka-kontrol çalışması

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Abstract

Aim: Cardiac fibrosis, a pathological phenomenon in cardiac remodeling, is associated with heart diseases. The aim of this study was to investigate the relationship of Galectin-3 with N-terminal pro B-type natriuretic peptide (NT-pro-BNP) levels in patients with heart failure (HF).

Methods: A total of 50 patients with HF (patient group) and 30 subjects with normal ejection fractions (control group) were enrolled in this study. Serum galectin-3 levels and plasma NT-pro-BNP were measured in all subjects. Demographic and clinical characteristics of the patients were recorded. The Galectin-3 and NT-pro-BNP levels were compared between the groups.

Results: Patients with HF had significantly higher Galectin-3 and NT-pro-BNP levels than control subjects (37.5 (18.0-80.0) versus 12.00 (8.00-14.00), $P<0.001$; 467.0 (1157.5-5107.2) versus 50.0 (35.0-102.0), $P<0.001$, respectively). Galectin-3 was correlated with serum glucose, creatine, left atrial diameter, ejection fraction and NT-pro-BNP in the HF patients. There was a positive and significant correlation between the NT-pro-BNP and Galectin-3 levels (r=0.742, $P=0.001$). In addition, there was an inverse and significant correlation between the ejection fraction and Galectin-3 levels (r=-0.556, $P=0.001$).

Conclusion: The present study demonstrates that galectin-3 and NT-pro-BNP levels are significantly higher in patients with systolic HF. Galectin-3 was positively and significantly correlated with the NT-pro-BNP and inversely correlated with ejection fraction.

Keywords: Galectin-3, NT-pro-BNP, Heart failure, Ejection fraction

Öz

Amaç: Kardiyak fibroz kardiyak remodelingde patolojik bir durumdur ve kalp hastalıkları ile ilişkilidir. Bu çalışmanın amacı galaktin-3'ün kalp yetmezliği (KY) olan hastalarda N-terminal pro B tipi natriüretik peptid (NT-pro-BNP) düzeyleri ile ilişkisini araştırmaktır.

Yöntemler: Çalışmaya KY tanısı olan toplam 50 hasta (hasta grubu) ve ejeksiyon fraksiyonu normal olan 30 birey (kontrol grubu) dahil edildi. Tüm bireylerde serum galektin-3 ve plazma NT-pro-BNP düzeyleri ölçüldü. Bireylerin demografik ve klinik özellikleri kaydedildi. Galaktin-3 ve NT-pro-BNP düzeyleri gruplar arasında karşılaştırıldı.

Bulgular: KY olan hastalarda galaktin-3 ve NT-pro-BNP düzeyleri kontrol grubundan (37.5 (18.0-80.0), 12.0 (8.0-14.0), $P<0.001$; 467.0 (1157.5-5107.2), 50.0 (35.0-102.0) $P<0.001$, sırasıyla) anlamlı derecede yüksek bulundu.. Galaktin-3, KY hastalarında serum glukoz, kreatin, sol atriyal çap, ejeksiyon fraksiyonu ve NT-pro-BNP düzeyleri ile korele olarak bulundu. NT-pro-BNP ve Galaktin-3 düzeyleri arasında pozitif ve anlamlı bir ilişki vardı (r=0.742 $P=0.001$). Ayrıca, ejeksiyon fraksiyonu ile Galaktin-3 seviyeleri arasında negatif ve anlamlı bir korelasyon vardı (r=-0.556, $P=0.001$).

Sonuç: Sonuç olarak, bu çalışma, sistolik HF hastalarında galektin-3 ve NT-pro-BNP düzeylerinin anlamlı şekilde daha yüksek olduğunu göstermektedir. Galektin-3, NT-pro-BNP ile pozitif ve anlamlı, ejeksiyon fraksiyonu ile negatif korelasyon gösterdi.

Anahtar kelimeler: Galaktin-3, NT-pro-BNP, Kalp yetmezliği, Ejeksiyon fraksiyonu

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Introduction

Heart failure (HF), the leading cause of hospitalization in patients older than 65 years, is responsible for high mortality rates each year. Cardiac fibrosis is a pathological phenomenon in cardiac remodeling and is associated with heart diseases, including HF and cardiomyopathy [1].

Galectin-3, a member of the galactic family, is a 30 kDa protein. It is expressed intracellularly by inflammatory cells such as macrophages, neutrophils, mast cells, and fibroblasts [2,3]. Fibrosis and inflammation are principal mechanisms in heart failure development and cardiac remodeling [4]. Galectin-3 plays a principal role in fibroblast activation, is reportedly related to the development of cardiac hypertrophy and fibrosis [5,6]. Galectin-3 expression is increased in the remodeling myocardium, and it has been used as a prognostic biomarker in patients with heart failure [7]. Previous studies have shown that high circulating Gal-3 levels are indicative of the severity of heart diseases or related to increased risk of major adverse cardiovascular events including HF, arrhythmias or mortality [8–10].

B-type natriuretic peptides (BNP) are secreted by ventricular cardiomyocytes, and they reflect the severity of hemodynamic overload [11]. BNP levels are closely related to HF severity, and commonly used as a diagnostic and prognostic biomarker for HF [12]. BNP is linked to increased adverse cardiovascular outcomes in heart diseases [13,14]. In addition, NT-proBNP levels are strongly related to survival in HF regardless of ejection fraction [15]. Both BNP and NT-proBNP are established as HF biomarkers and suggested for use by international guidelines [16,17]. We hypothesized that Galectin-3 might be related to NT-proBNP levels in patients with chronic systolic HF. Hence, we aimed to evaluate the galectin-3 and NT-proBNP in systolic HF patients in this study.

Materials and methods

This cross-sectional, prospective observational study included 80 individuals, 50 patients with systolic HF and 30 subjects with normal EFs, who were referred to our Cardiology and Internal Medicine Outpatient Clinics between November 2014 and March 2015. All subjects' histories were taken in detail, and they underwent clinical, biochemical, electrocardiographic, and transthoracic echocardiographic examinations. Inclusion criteria were as follows: Patients >35 years of age with a left ventricular ejection fraction ≤0.5. Exclusion criteria included refusal to participate in the study, acute or chronic pancreatitis, acute coronary syndromes, abnormal thyroid function, uncontrolled hypertension, anemia, chronic lung disease, renal or hepatic dysfunction, severe valvular stenosis or regurgitation, pericardial effusion on transthoracic echocardiography, atrial fibrillation, known malignancy, systemic infection and inflammatory diseases.

Blood samples were collected from the antecubital vein by atraumatic needles and sent to the laboratory for analysis. The blood was collected in tripotassium EDTA (7.2 mg) tubes and analyzed using an automatic blood counter immediately. Hematological parameters were analyzed by LH 780 analyzer (Beckman Coulter Inc, Miami, Florida). Fasting blood glucose, serum creatinine, alanine transaminase (ALT), aspartate transaminase (AST) levels were recorded.

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or requirement for the antihypertensive medication [18]. Hyperlipidemia was defined as total cholesterol higher than 220 mg/dl or triglycerides ≥150 mg/dl [19]. Type 2 diabetes mellitus was diagnosed according to the American Diabetes Association criteria [20]. Smoking included active or previous (>10 pack-years) tobacco use. 12-lead electrocardiography (ECG) was recorded. Informed consent was obtained from all patients before the study. This study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by the local Ethics Committee of the Hospital (Bülent Ecevit University, Number: 171/2014).

Each patient underwent a complete transthoracic echocardiographic examination using the American Society of Echocardiography guidelines of measurement [21]. The transthoracic echocardiography was performed at rest, in the left lateral decubitus position, using an echocardiographic device (Vivid S6, General Electric, Horton, Norway) with a 3.0 MHz transducer, by one experienced cardiologist who was blinded to the patients' clinical data. Echocardiographic images were recorded into a computerized database, and the off-line measurements were performed. Left ventricular end-systolic and end-diastolic diameters (LVESD, LVEDD) were determined by M-mode and left atrium diameter was measured using the biplane from the parasternal long-axis view. Left ventricular ejection fraction (EF) was determined using the biplane modified Simpson's method [22].

Venous blood samples were collected from each patient and centrifuged at 3000 rpm for 15 min after clotting occurred in the serum tubes. After centrifuging, samples were stored at −80^{o}C until analysis. Serum galectin-3 levels were measured by a commercially available Enzyme-linked Immunosorbent Assay Kit (Bioassay Technology Laboratory) according to the manufacturer's protocol, with a detection range of 5 pg/ml-2.000 pg/ml. Biochemical analyses were made by clinicians who were blinded to clinical information and to ensure accurate measurements, all samples were analyzed in duplicates. Plasma NT-pro B-type natriuretic peptide (NT-proBNP) was also measured by an Enzyme-linked Immunosorbent Assay Kit (Bioassay Technology Laboratory).

Statistical analysis

Data were analyzed with SPSS software version 20.0 for Windows (SPSS Inc, Chicago, Illinois). The Kolmogorov-Smirnov test was used to verify that continuous variables were normally distributed, which were expressed as mean ± standard deviation (SD), while non-normally distributed variables were presented as median with interquartile range (IQR). The categorical variables were presented as percentages. Differences between two groups were evaluated with Student's unpaired t-test or the Mann–Whitney U test for parameters with a normal or non-normal distribution. The frequencies of nominal variables were compared using Fisher's exact test or chi-square test. The Spearman test was used for correlation analysis. With 90% power and a two-sided type 1 error of 5%, we calculated that 50

patients were needed in the HF group. Statistical significance was defined as *P*-value <0.05.

Results

The demographic and clinical data of the study population are presented in Table 1. No difference was found in the demographic characteristics between the groups regarding gender, hypertension, diabetes mellitus, and smoking. The age, hyperlipidemia, and CAD were higher in the HF group. In blood analysis, serum glucose, creatinine, and AST were higher in the HF group, whereas the hemoglobin levels were significantly lower. In the echocardiographic analysis, the ejection fraction and left atrium diameter were higher in the HF group. Figure 1 presents a significant difference in NT-pro-BNP and Galectin-3 values between groups. Tables 2 and 3 show the correlation analyses between NT-pro-BNP, Galectin-3, and clinical parameters. NT-pro-BNP was positively and significantly correlated with glucose, creatine, left atrium diameter, LVEDD, LVESD, and Galectin-3 levels, and inversely and significantly correlated with hemoglobin levels and ejection fraction. Figure 2 shows the positive and significant correlation between the NT-pro-BNP and Galectin-3 levels (r=0.742, *P*=0.001). Correlation analysis between Galectin-3 levels and clinical parameters revealed a positive and significant correlation between Galectin-3 and serum glucose, creatine, left atrium, and NT-pro-BNP levels, and a negative correlation between Galectin-3 and ejection fraction (r=-0.556, *P*=0.001).

Table 1: Demographic and clinical characteristics of the study population

	Control (n=30)	Heart Failure (n=50)	*P*-value
Age (years)	51.3(6.1)	66.0(12.2)	<0.01
Male n(%)	19(63%)	23(46%)	0.13
Hypertension n(%)	9(20%)	18(36%)	0.13
Diabetes mellitus n(%)	4(13%)	15(30%)	0.09
Hyperlipidemia n(%)	6(20%)	22(44%)	0.02
Smoking n(%)	14(46%)	25(50%)	0.77
CAD n(%)	6(20%)	50(100%)	<0.01
ASA n(%)	6(20%)	50(100%)	<0.01
Beta-blocker n(%)	18(26%)	50(100%)	<0.01
ACE inhibitor n(%)	5(16%)	38(76%)	<0.01
Aldosterone antagonist n(%)	3(10%)	21(42%)	<0.01
Sodium (mEq/L)	139.0(2.3)	139.0(2.3)	0.98
Serum glucose (mg/dl)	109.2(19.0)	136.7(51.9)	<0.01
Creatinine (mg/dl)	0.7(0.6-0.8)	0.9(0.8-1.0)	<0.01
Alanine transaminase (U/l)	16.0(13.0-19.0)	17.5(12.0-21.2)	0.79
Aspartate transaminase (U/l)	18.6(3.1)	22.9(8.9)	0.01
Hemoglobin (g/dL)	13.6(1.9)	12.6(2.1)	0.03
LVEDD (cm)	4.8(4.5-4.8)	5.0(0.5)	0.04
LVESD (cm)	3.2(3.1-3.4)	3.7(0.6)	<0.01
LA (mm)	36.3(2.5)	42.3(4.3)	<0.01
Ejection Fraction (%)	58.1(3.7)	37.7(5.5)	<0.01
NT-pro-BNP (pg/ml)	50.0(35.0-102.0)	467.0(1157.5-5107.2)	<0.01
Galectin3 (pg/ml)	12.0(8.0-14.0)	37.5(18.0-80.0)	<0.01

CAD: Coronary artery disease, ASA: Acetyl salicylic acid, ACE: Angiotensin-converting enzyme, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LA: Left atrium

Table 2: The univariate correlations of the Nt-pro-BNP levels

	r	*P*-value
Glucose	0.274	0.014
Creatine	0.363	0.001
Hemoglobin	-0.248	0.026
Left atrium	0.460	0.001
LVEDD	0.222	0.048
LVESD	0.230	0.040
Ejection fraction	-0.65	0.001
Galectin-3	0.742	0.001

LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter

Table 3: The univariate correlations of the Galectin-3 levels

	r	*P*-value
Glucose	0.221	0.049
Creatine	0.283	0.011
Hemoglobin	-0.205	0.069
Left atrium	0.418	0.001
Ejection fraction	-0.556	0.001
NT-pro-BNP	0.742	0.001

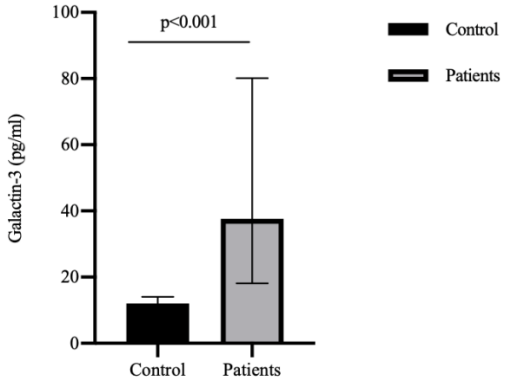

Figure 1: Galectin-3 levels between groups

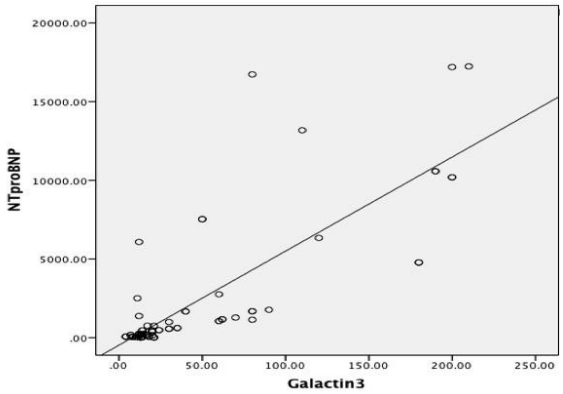

Figure 2: Correlation between NT-pro-BNP and Galectin-3 levels (r=-0.742, *P*=0.001)

Discussion

This study demonstrated two significant findings in patients with HF. First, the galectin-3 and NT-pro-BNP levels were significantly higher in the HF group. Second, there was a positive, significant association between galectin-3 and NT-pro-BNP levels. These results suggest increased galectin-3 and NT-pro-BNP levels might be related to remodeling in HF patients.

Systolic heart failure is a clinical syndrome characterized by a loss of pumping capacity. Galectin-3 over-expression by macrophages was observed in heart failure and it is reportedly useful in the diagnosis and prediction of prognosis in HF patients [4,10]. The essential role of galectin-3 in HF was first described by Sharma et al. and they found that even without occult heart failure, galectin-3 over-expression is detectable in macrophages during the early stages of myocardial dysfunction [4]. Galectin-3 induces fibroblast proliferation, leading to loss of systolic cardiac function [4,23]. A previous study showed that galectin-3 was a predictor of ejection fraction and infarct size after myocardial infarction (MI) [24]. Also, elevated galectin-3 levels were associated with post-MI left ventricular remodeling [4,25]. Lisowska et al. [26] evaluated the predictive value of galectin-3 for the occurrence of coronary artery disease (CAD) and prognosis after myocardial infarction to find that galectin-3 was related to severe coronary disease in patients with CAD, and an independent predictor of post-MI mortality. In our study, we found that galectin-3 levels were higher in the HF group compared to the control group. Our findings support the previous studies with higher galectin-3 levels in the HF group and its relation to cardiac fibrosis and remodeling in patients with systolic HF.

BNP and NT-pro-BNP are currently suggested biomarkers for use in patients with HF in several clinical settings [27,28]. They can both be used as an initial diagnostic test in

patients with dyspnea to rule out the possibility of HF [28]. Measurements of BNP and NT-pro-BNP provide independent prognostic information in patients with HF. It was reported that BNP levels were lower in patients with HF with preserved ejection fraction than in those with reduced ejection fraction [29]. NT-pro-BNP was better than BNP in predicting morbidity, mortality, and hospitalization in patients with HF [30]. Linssen et al. [31] evaluated the prognostic performance of BNP versus NT-pro-BNP measurements in a large population of HF patients, and found that BNP and NT-proBNP were strong and independent predictors of all-cause death and HF-related re-hospitalization. In a study that evaluated the galectin-3 levels concentration and its association with the severity of HF, the authors demonstrated that galectin-3 levels showed a progressive increase with increasing severity of HF, and it was positively correlated with the level of plasma NT-pro-BNP. Moreover, a study by Barman et al. showed that galectin-3 levels were positively and significantly correlated with NT-pro-BNP levels [32]. Similar to the literature, we also found that NT-pro-BNP levels were higher in the HF group than the control group. In addition, in our study, left ventricular diameters and left atrial diameter were significantly correlated with NT-pro-BNP levels in patients with HF.

Limitations

This present study has some limitations: This was a single-center study and based on a relatively small group of patients. Single baseline measurements of NT-pro-BNP and galectin-3 were used, and these levels might change in time course, especially with medications. Moreover, patients with preserved ejection fraction and non-ischemic cardiomyopathy were not included in the study.

Conclusion

This study demonstrates that galectin-3 and NT-pro-BNP levels are significantly higher in patients with systolic HF. Galectin-3 was positively and significantly correlated with the NT-pro-BNP and inversely correlated with ejection fraction. From our study, we may suggest that the galectin-3 is a reliable marker of remodeling in patients with systolic HF. Further and large-scale studies are needed to confirm these findings.

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