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Galectin-3 as a novel biomarker for the diagnosis of essential hypertension with left ventricular hypertrophy

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ABSTRACT

Galectin-3 (Gal-3) is a carbohydrate-binding protein that has important regulatory roles in inflammation, immunity and cancer. The aim of this study was to investigate the relationship of Gal-3 level with left ventricular hypertrophy (LVH) related to hypertension (HT). Thirty seven patients (Group I) with newly diagnosed hypertension (HT) and left ventricular hypertrophy (LVH)were included in the study. Thirty eight patients with newly diagnosed hypertension without LVH (Group II) and 38 normotensive healthy volunteers (Group III) were included in the study as control group. Transthoracic echocardiography was performed and Gal-3 was measured in all patients.Although demographic characteristics of the groups were similar, systolic and diastolic blood pressure levels of Group I and Group II were significantly higher than Group III ($p<0.001$). Interventricular septum (IVS) thickness, posterior wall (PW) thickness and left ventricular mass index (LVMI) were also significantly increased in Group I compared to Group II and Group III. Serum Gal-3 levels in all three groups were seen to be different from each other ($p<0.001$). Increase of Gal-3 levels has a significant correlation with LVMI, IVS and PW thickness ($p<0.001$).We determined that Gal-3 levels, even at the newly diagnosed stage of HT,were increased. Moreover, we found strong correlation between Gal-3 levels and left ventricular muscle mass. These results may indicate that increased Gal-3 level is an important marker for target organ damage and high cardiovascular risk in patients with HT.

Introduction

Precise risk assessment should be done in order to manage the treatment of hypertension (HT) with proper density. For this determination, the risk factors such as diabetes, dyslipidemia and smoking as well as findings of subclinical organ damage should be examined. Left ventricular hypertrophy (LVH) is a HT-induced subclinical organ damage. It was shown that LVH was related with increased cardiovascular events and death in many previous studies (Lewington et al., 2002;

Kannel et al., 2000). Similarly, cerebrovascular events due to HT such as stroke are increased in patients with LVH (Devereux et al., 2004; Levy et al., 1990). Besides, antihypertensive treatment decreases left ventricular hypertrophy, and cardiovascular morbidity (Verdecchia et al., 1998; Bahlf and Pennert, 1992).

Galectin-3 (Gal-3) is a carbohydrate-binding protein that has significant regulatory roles in inflammation, immunity and cancer (Rabinovich et al., 2002). The relationship of Gal-3 with the severity and mortality of the disease in patients with heart failure both with preserved ejection fraction (EF) and with low EF was investigated in studies in recent years (Lok et al., 2010; Lopez-Andrès et al., 2012). Increased Gal-3 expression induces cardiac fibroblasts to proliferate and deposit type I collagen, contributing to myocardial fibrosis and adverse remodeling (De Boer et al., 2010). Therefore, increased collagen synthesis and myocardial fibrosis occurring during LVH may be related to Gal-3. Moreover, this condition may also be detected in patients in whom there is no detectable hypertrophy. We tried to clarify this issue by measuring galectin-3 levels in hypertensive patients with LVH in our study.

2. Material and method

Study Population

This study was designed as cross-sectional trial. Patients diagnosed with new hypertension and healthy individuals who were admitted to the Kırşehir outpatient clinics of cardiology of Ahi Evran University Training and Research Hospital between January 2013 and March 2014 were enrolled in this study. Their ages were between 18 and 70 years. They were investigated in three different groups. Group I was consisted of new hypertension patients with LVH. Group II was consisted of hypertension patients without LVH. Group III was consisted of healthy individuals matched for age and gender.

Permanent cardiovascular disease, diabetes mellitus, renal failure (serum creatinine>2.0 mg/dL), liver disease, autoimmune diseases, hematologic disorders, obesity (BMI>30 kg/m^2), cancer, presence of systemic inflammatory disease, and history of drug use were considered as a criteria for exclusion from the study. The study was conducted in accordance with the ethical principles described by the Declaration of Helsinki (Williams, 2008).

Description of hypertension

Diagnosis of hypertension in an office location was made in accordance with ESC/ESH 2007 arterial hypertension guidelines (Mancia et al., 2007). Hypertension was defined as an average systolic blood pressure (SBP)≥140 mmHg or an average diastolic blood pressure (DBP)≥90 mmHg.

Echocardiography

All patients experiencedtransthoracic echocardiographic examination in the left lateral decubitus position by using GE Vingmed Vivid 7 (GE Vingmed Ultrasound, Horten, Norway) echocardiography. All measurements were achieved by two cardiologists experienced in echocardiography who were uninformed of the clinical status of patients. The calculation was done rendering to the criteria of the American Society of Echocardiography (Quinones et al., 2002).

Description of left ventricular hypertrophy:

Left ventricular mass index (LVMI) was measured by using the calculation previously defined Devereux et al. (1991). Therefore, left ventricular mass index were associated to body surface area. LVM's higher than 125 gr/m^2 in men, 110 gr/m^2 in women were observed as the occurrence of LVH.

Biochemical measurements

The biochemical parameters were measured using commercial kits in ARCHITECT C8000 Abbott (Abbott Laboratories, IL, USA) autoanalyzer.

Serum Galectin-3 measurements

Blood samples were taken in the morning from 7:00 to 9:00, after 8-12 hours of fasting with the purpose of escape to be affected by diurnal rhythm. Blood samples serums were separated by centrifuging samples for 10 minutes at 4000'g. Biochemical and hematological parameters were calculated on the same day. The serums were protected at -80^{0}C until Galectin ELISA study was done. Serum Galectin-3 levels were resolute by studying consistent with producer's instructions by using Multiwash (Tricontinent Scientific, USA) etc. Synergy 4 Microplate Reader (Biotek, USA) procedures and Platinum Human Galectin-3 ELISA kit (eBioscience, Inc. San Diego, USA) with enzyme-linked immunosorbent assay (ELISA) method.

Statistical analysis

Statistical analyses were based on SPSS 15.0 (Statistical Pack age for Social Sciences) program. Kolmogorov-Smirnov test was used to check normal distribution of all parameters. Categorical variables were expressed in percentage, whereas numerical variables were presented as mean ± standard deviation (SD). Categorical variables of the patients were compare dusing the Chi-Square test. Comparison of groups was based on One-way ANOVA or Kruskal-Wallis Test and multiple comparisons were made using either the Student's t-test or the Mann-Whitney U-test. $P<0.05$ was accepted as statistically significant. Bonferroni's correction was performed when statistical comparisons of the three groups were made as <0.016. The correlation between data was tested with Pearson or Spearmen correlation analysis.

Table 1. Baseline clinical and laboratory characteristics of study population and comparison between groups

	Group I (n=37)	Group II (n=38)	Group III (n=38)	p
Ages, years	55.32 ± 7.34	56.73 ± 8.62	53.05 ± 8.48	0.166
Male sex % (n)	45 (17)	47(18)	50 (19)	0.622
Body mass index (kg/m²)	26.71 ± 2.81	25.73 ± 2.53	26.39 ± 3.01	0.356
Smoking % (n)	55 (20)	53 (20)	53(20)	0.556
Heart rate (beats/minute)	74.25 ± 10.91	72.36 ± 11.61	73.78 ± 9.76	0.684
Mean systolic blood pressure (mmHg)	157.16 ± 12.55*	155.78 ± 14.63*	116.57 ± 14.75	<0.001
Mean diastolic blood pressure (mmHg)	99.45 ± 8.23*	98.81 ± 9.68*	70.78 ± 11.99	<0.001
Serum glucose (mg/dL)	89.54 ± 11.09	90.36 ± 20.40	89.18 ± 8.85	0.791
Creatinine (mg/dL)	0.86 ± 0.26	0.89 ± 0.28	0.95 ± 0.16	0.371
Triglyceride (mg/dL)	148.00 ± 57.47	127.39 ± 61.47	140.26 ± 68.92	0.182
Low-density lipoprotein cholesterol (mg/dL)	93.37 ± 25.74	103.10 ± 32.39	94.36 ± 27.42	0.359
High-density lipoprotein cholesterol (mg/dL)	34.01 ± 10.07	36.21 ± 8.17	38.13 ± 9.97	0.073
Total cholesterol (mg/dL)	178.29 ± 35.19	186.78 ± 36.30	184.01 ± 24.27	0.667
Hemoglobin (g/L)	13.72 ± 1.96	14.21 ± 1.48	13.84 ± 1.43	0.308
Sodium (mmol/L)	136.94 ± 3.64	137.39 ± 3.11	138.15 ± 3.56	0.277
Potassium (mmol/L)	4.28 ± 0.35	4.15 ± 0.47	4.24 ± 0.50	0.407
AST (U/L)	31.59 ± 14.88	35.92 ± 13.79	33.21 ± 17.04	0.330
ALT (U/L)	25.83 ± 10.43	32.13 ± 17.51	30.15 ± 14.52	0.214

* p<0.001between Group III
ALT: Alanine aminotransferase; **AST:** Aspartate aminotransferase

3. Results

Totally 113 subjects, consisting of 75 patients newly diagnosed HT and 38 healthy individuals, were enrolled in this study. There were 37 newly diagnosed hypertensive patients with LVH (Group I), 38 newly diagnosed hypertensive patients without LVH (Group II), and 38 healthy normotensive controls (Group III). The demographic, clinical and laboratory characteristics of the patients are as long as in Table 1. There is no significant difference between the groups at the values of heart rate, lipid parameters, creatinine, glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), hemoglobin, age, gender, body mass index (BMI), smoking (p>0.05). But systolic and diastolic blood pressure levels were significantly higher in Group I and II (p<0.001).

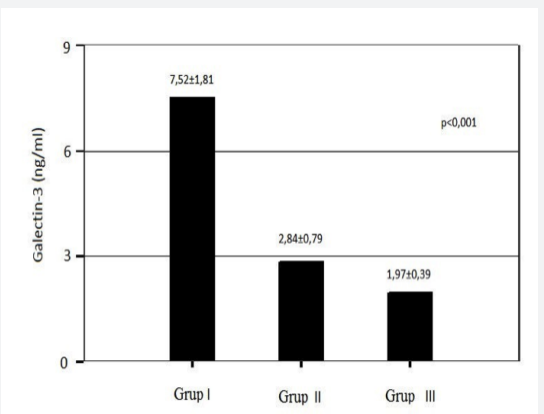

Fig. 1. Galectin-3 levels of the groups.

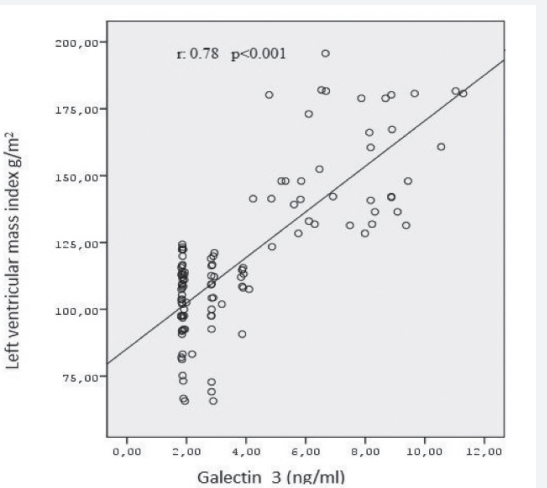

Fig. 2. Correlation graphs of left ventricular mass index with Galectin-3 levels

When the groups were evaluated in terms of echocardiographic measurements, left ventricular diameters and systolic functions were parallel. But, IVS thickness, PW thickness, left ventricular mass index, left atrium dimension, deceleration time, isovolumetric relaxation time, early diastolic flow, atrial contraction signal were significantly higher in Group I and II (P<0.016). Also, IVS thickness, PW thickness, left ventricular mass index values were also different between Group I and Group II (P<0.016) (Table 2).

A significant difference was observed between three groups in terms of serum Gal-3 levels (p<0.001). While the serum Gal-3 level was 7.52±1.81 ng/ml in Group I, it was significantly higher than both Group

Table 2. Comparison of echocardiographic parameters and Galectin-3 levels between groups

	Group I (n=37)	Group II (n=38)	Group III (n=38)	p
IVS thickness (mm)	13.72 ± 1.23*ɣ	10.81 ± 0.86 ˜	10.13 ± 1.01	<0.001
PW thickness (mm)	12.97 ± 1.06* ɣ	10.60 ± 0.91°	9.65 ± 1.34	<0.001
LVEDD (mm)	48.21 ± 4.58	46.39 ± 3.69	46.94 ± 4.29	0.162
LVESD (mm)	33.75 ± 4.85	32.10 ± 3.61	32.28 ± 4.56	0.324
LA dimension (mm)	37.43 ± 4.74	33.84 ± 3.75⁺	34.18 ± 3.43⁺	0.002
LVEF (%)	58.72 ± 5.66	60.32 ± 4.92	61.57 ± 3.92	0.107
DT (msn)	236.40 ± 27.29 ɣ	233.07 ± 38.55 ɣ	176.18 ± 28.74	<0.001
IVRT (msn)	124.56 ± 25.20 ɣ	117.75 ± 20.35 ɣ	82.44 ± 15.43	<0.001
E (m/sn)	66.13 ± 10.83 ɣ	66.71 ± 12.59 ɣ	78.21 ± 11.54	<0.001
A (m/sn)	81.08 ± 12.42 ɣ	81.65 ± 16.73 ɣ	67.15 ± 8.73	<0.001
E/A	0.82 ± 0.13 ɣ	0.82 ± 0.12 ɣ	1.18 ± 0.23	<0.001
Galectin-3	7.52 ± 1.81* ɣ	2.84 ± 0.79 ɣ	1.97 ± 0.39	<0.001
LVMI (g/m²)	154.38 ± 20.19* ɣ	104.66 ± 13.36ɣ	101.84 ± 16.24	<0.001

* p<0.0001 for the two-way comparison with Group II
ɣ p<0.0001 for the two-way comparison with Group III
° p=0.0011 for the two-way comparison with Group III
˜ p=0.0071 for the two-way comparison with Group III
⁺ P=0.0021 for the two-way comparison with Group I
A: Atrial contraction signal; **DT:** Deceleration time; **E:** Early diastolic flow; **IVRT:** Isovolumetric relaxation time; **IVS:** Ventricular septal thickness; **LA:** Left atrium; **LVEDD:** Left ventricular end-diastolic dimension; **LVEF:** Left ventricular ejection fraction; **LVMI:** Left ventricular mass index; **LVESD:** Left ventricular end-systolic dimensions; **PW:** Posterior wall thickness

II and III (P<0.001). Furthermore Galectin-3 level of Group II was higher than Group III (2.84±0.79 ng/ml versus 1.97±0.39 ng/ml, P<0.001) (Table 2, Fig 1).

In the hypertension group, A strong correlation was observed between Gal-3 levels and LVMI (r=0.78, p<0.001), IVS thickness (r=0.77, p<0.001), PW thickness (r=0.72, p<0.001) and a moderate level of correlation between mean systolic blood pressure (r=0.47, p<0.001), mean diastolic blood pressure (r=0.45, p<0.001), IVRT (r=0.45, p<0.001), DT (r=0.44, p<0.001) in the correlation analysis (Table 3, Fig 2).

Table 3. The univariate correlations of the Galectin-3 level in the hypertension group

Variables	R value	P value
LVMI (g/m²)	0.78	<0.001
IVS thickness (mm)	0.77	<0.001
PW thickness (mm)	0.72	<0.001
Mean systolic blood pressure (mmHg)	0.47	<0.001
Mean diastolic blood pressure (mmHg)	0.45	<0.001
IVRT (msn)	0.45	<0.001
DT (msn)	0.44	<0.001

DT: Deceleration time; **IVRT:** Isovolumetric relaxation time; **IVS**: Ventricular septal thickness; **PW:** Posterior wall thickness

In the hypertension group, a strong correlation was observed between Gal-3 levels and LVMI (r=0.78, p<0.001), IVS thickness (r=0.77, p<0.001), PW thickness (r=0.72, p<0.001) and a moderate level of correlation between mean systolic blood pressure (r=0.47, p<0.001), mean diastolic blood pressure (r=0.45, p<0.001), IVRT (r=0.45, p<0.001), DT (r=0.44, p<0.001) in the correlation analysis (Table 3, Fig 2).

4. Discussion

We have achieved two important results in this study. First, Gal-3 levels were found higher in HT patients with LVH. Second, there was a strong correlation between Gal-3 and LV mass, septal and posterior wall thickness. Galectin-3 is a soluble β-galactoside-binding lectin obtainable by activated macrophages in the heart. It functions as a probable mediator in the inflammation. It is expressed by activated macrophages and encourages cardiac fibroblasts to proliferate and deposit type I collagen in the myocardium (Sharma et al., 2004). Thus, the researches on the cardiovascular effects of Gal-3 have focused on heart failure patients. The correlation between the increased serum Gal-3 and the increased mortality and prolonged hospitalization in heart failure patients with preserved EF, other than heart failure patients with low EF, has been shown in the studies (van der Velde et al., 2013;de Boer et al., 2011). Even, stronger correlation was observed between Gal-3 and the heart failure patients with preserved EF than heart failure patients with low EF (de Boer et al., 2011; Shah et al., 2010). Playing of fibrosis and matrix markers such as Gal-3 a more significant role in HF patients with preserved ejection fraction was supposed as a reason for this. Higher Gal-3 levels in patients with LVH may also be related to increased fibrosis and remodeling in our study.

The relationship of Gal-3 with LVH in patients with newly diagnosed hypertension has not been investigated in previous studies. But De Boer et al., (2012) have showed a relation between Gal-3 and age, blood pressure, serum lipids, body mass index, renal function and cardiovascular risk factors such as N-terminal pro-

B-type natriuretic peptide in their large observational study. The Gal-3 levels of 3353 people, composed of the children of the original volunteers of Framingham heart study, were evaluated in study Ho et al. (2012). Gal-3 levels were seen to be associated with heart failure and increased mortality in the analysis. In addition, increased Gal-3 levels have been found associated with increased cardiac fibrosis in asymptomatic patients. Another interesting point in the study was to find a relationship between increased levels of Gal-3 and increased LV mass. The relationship of Gal-3 with LVH was investigated in rats with cardiac hypertrophy with endocardial biopsy in an animal study and Gal-3 levels were found increased (Sharma et al., 2004). Similarly, Gal-3 levels were higher in HT patients with LVH in our study. Additionally, a strong relation between Gal-3 and LVMI, septum and posterior thickness was determined.

As is known, the main purpose of the HT treatment is to prevent the target organ damage. Thus, the risk rating is the first step of treatment. In particular, hypertensive patients with target organ damage such as left ventricular hypertrophy, irrespective of their blood pressure levels, bring high cardiovascular risk. Therefore, accurate and early detection of patients at high cardiovascular risk is very important. The association between Gal-3 and LVMI in our study has shown that Gal-3 may be helpful as an early marker of target organ damage in recognition of patients with high cardiovascular risk. Another remarkable point in our study is the high level of Gal-3 even in hypertensive patients without organ damage related to HT. The reason of this condition may be diastolic weakening in hypertensive patients and the detection of the relationship between Gal-3levels and diastolic parameters IVRT, DT supports this. The increased Gal-3 level has been associated with the deterioration of diastolic parameters particularly in heart failure patients with preserved EF in previous studies. Sharma et al., (2004) have showed that Gal-3 was related to the diastolic functions in patients with acutely decompensated heart failure in their study. Moreover, the myocardial changes in patients with no detectable hypertrophy may be also responsible for this increase.

Increased angiotensin-aldosterone system takes an important place in the pathophysiology of HT. Clinical and preclinical studies particularly have revealed that increased aldosterone causes cardiac hypertrophy and fibrosis, plays an vital role in cardiovascular diseases and cardiovascular remodeling by increasing arterial stiffness (Struthers and Mac Donald, 2004; Young, 2008). Recent studies have revealed the importance of Gal-3 on fibrotic effects of aldosterone. Laurent al., (2013) in their study, have determined that Gal-3 was necessary in the inflammatory and fibrotic response of vascular smooth muscle cells to aldosterone and Gal-3 had a key role in vascular fibrosis. Similarly, Gal-3 has been shown to play a critical role in renin angiotensin aldosterone (RAAS) system by increasing salt and water retention in another study (Sherwi et al., 2012). This interaction of Gal-3 with RAAS may help us understand the mechanism of increased Gal-3 level in our study.

Another reason of the increased Gal-3 level in HT patients may be the inflammation. As is known, inflammation takes an important place in many diseases of cardiovascular system. The relationship between HT and many inflammatory cytokines were determined in studies conducted in recent years. Gal-3 is also an inflammatory marker and Gal-3, released from blood vessels other than the heart, plays a systemic role in proliferation and inflammation (Yang et al., 2008). Gal-3 improves neutrophil-endothelial interaction by temporary as a proinflammatory agent (Sato et al., 2002) and activates multiple cell types involved in immune response and inflammation that causes fibrosis (Suzuki et al., 2008). Increasing evidence shows that inflammatory changes in the vascular system take an important place in the pathophysiology of HT. Being of Gal-3 a direct mediator of profibrotic pathways and the effects of Gal-3 on inflammation may help us to understand the increased Gal-3 level in HT patients in our study.

Study limitations

Our study population is comparatively small and cross-sectional study. Larger study population with long-term follow-up of patients may be suggested for more influential statistical data. In addition, lack of assessing the relationship between Gal-3 and the parameters (microalbuminuria, carotid intima-media thickness of the carotid-femoral pulse wave velocity, etc.) that show non-cardiac subclinical organ damage is another limiting factor.

5. Conclusion

We have found that Gal-3 has increased in patients with newly diagnosed hypertension in our study. Moreover, we have determined a strong correlation between Gal-3 level and LVH. These results indicate that increased Gal-3 levels may be a marker in noticing subclinical cardiac damage in patients with newly diagnosed HT. Mainly, results to be achieved by prospective follow-up studies would more explain this topic.

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