

Galectin-3 levels in patients with hypertrophic cardiomyopathy and its relationship with left ventricular mass index and function

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ABSTRACT

Objective: Cardiac fibrosis is an important contributor to adverse left ventricular (LV) remodeling and arrhythmias in patients with hypertrophic cardiomyopathy (HCM). Galectin-3 (Gal-3) is a novel marker of cardiac fibrosis and inflammation. In this study, we investigated Gal-3 levels in patients with HCM and controls and assessed the relationship between Gal-3 level and echocardiographic indices using strain echocardiography in patients with HCM.

Methods: Forty patients with HCM in sinus rhythm and 35 healthy controls were prospectively enrolled in this case-control study. The HCM diagnosis was based on two-dimensional echocardiographic demonstration of a hypertrophied and non-dilated left ventricle (LV) with a wall thickness ≥ 15 mm in one or more LV myocardial segments in the absence of any cardiac or systemic disease capable of inducing LV hypertrophy. Patients with one of the followings were excluded: coronary artery disease, atrial fibrillation episodes on 24-h Holter electrocardiogram (ECG) monitoring, history of an invasive intervention to alleviate an LV outflow (LVOT) obstruction, inadequate image quality, renal disease, diabetes mellitus, hyperlipidemia, liver cirrhosis, and pulmonary fibrosis. Global LV longitudinal, circumferential strain and strain rates, peak torsion, and LV mass index (LVMI) of all subjects were assessed by echocardiography. Gal-3 levels were measured in all subjects.

Results: Left ventricular global longitudinal strain ($-13.37 \pm 4.6\%$ vs. $-18.93 \pm 2.5\%$, $p < 0.001$) and strain rate (0.66 ± 0.22 s⁻¹ vs. 1.08 ± 0.14 s⁻¹, respectively; $p < 0.001$) values were lower in patients with HCM than in controls. Gal-3 levels were significantly higher in patients with HCM than in controls (16.9 ± 6.64 ng/mL vs. 13.21 ± 3.42 ng/mL, $p = 0.005$). Gal-3 levels were associated with the thickness of the interventricular septum ($r = 0.444$, $p = 0.004$) and LVMI ($r = 0.365$, $p = 0.021$); however, they were not associated with LV global longitudinal strain ($p = 0.42$) or strain rate ($p = 0.28$).

Conclusion: Gal-3 levels increased and were correlated with the degree of LV hypertrophy in patients with HCM. Gal-3 is not a good marker of decreased myocardial LV diastolic and systolic functions in these patients. (*Anatol J Cardiol* 2016; 16: 344-8)

Keywords: Galectin-3, hypertrophic cardiomyopathy, left ventricular mass index, strain imaging

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic cardiovascular disease characterized by a marked increase in both interstitial and replacement fibrosis that may be patchy or diffuse (1). Cardiac fibrosis is an important contributor to the pathophysiology of HCM and is responsible for arrhythmias, sudden cardiac death, or adverse left ventricular (LV) remodeling (2).

Novel ultrasound technologies, including strain and speckle-tracking echocardiography, are widely used to detect reduced longitudinal LV systolic function in patients with HCM (3). Myocardial fibrosis is associated with depressed LV longitudinal strain in patients with HCM (4).

Galectin-3 (Gal-3) is a beta-galactoside-binding lectin that appears to mediate cardiac fibrosis or inflammation in patients with heart failure (HF) (5), atherothrombosis (6), chronic kidney disease (7), and atrial fibrillation (AF) (8). Gal-3 levels in patients

with HCM and their associations with LV systolic and diastolic functions and other echocardiographic parameters have not been investigated. Therefore, in this study, we investigated Gal-3 levels in patients with HCM and the association between Gal-3 level and echocardiographic indices and strain parameters.

Methods

Study population

Seventy-one patients with HCM were prospectively included in this case-control study. All patients were in sinus rhythm (SR). The HCM diagnosis was based on two-dimensional echocardiographic demonstration of a hypertrophied and non-dilated LV with a wall thickness ≥ 15 mm in one or more LV myocardial segments in the absence of any cardiac or systemic disease capable of inducing LV hypertrophy (9). The clinical and echocardiographic data of the

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referred patients were acquired in one center. Thirty-one patients were excluded for the following cardiac and/or systemic diseases: coronary artery disease ($\geq 70\%$ stenosis of any major epicardial vessel; $n=4$), history of myocardial infarction ($n=3$), AF episodes on 24-h Holter ECG monitoring ($n=4$), history of an invasive intervention to alleviate an LV outflow (LVOT) obstruction ($n=5$), inadequate image quality which was rejected by the software ($n=1$), renal disease ($n=2$), diabetes mellitus ($n=6$), hyperlipidemia (low-density lipoprotein >130 mg/dL) ($n=4$), liver cirrhosis ($n=1$), and pulmonary fibrosis due to amiodarone therapy ($n=1$). Consequently, the patient population was composed of 40 patients with HCM who were in SR at the time of recruitment. If a patient took any medication, this was stopped ≥ 48 h before enrolment, if possible. The findings of the patients with HCM were compared with those of 35 healthy controls who had normal physical examination and echocardiographic findings. The presence of a normal invasive or computed tomography coronary angiogram within 1 year before enrolment was necessary for inclusion of all subjects ≥ 40 years. This study protocol was approved by the local Ethics Committee. All participants provided written informed consent.

Echocardiographic evaluation

All subjects underwent a transthoracic echocardiography evaluation, tissue Doppler, and strain imaging. A commercially available ultrasound machine (Vivid S5; GE-Vingmed Ultrasound AS, Horten, Norway) equipped with a 2.5–3.5 MHz transducer was used for all echocardiographic examinations. Standard two-dimensional and Doppler echocardiographies were performed according to the American Society of Echocardiography/European Association of Echocardiography recommendations (10). All echocardiographic examinations were recorded and analyzed at the end of the study by two independent experienced echocardiographers who were blinded to the subjects' clinical characteristics and plasma Gal-3 levels. Left ventricular end-systolic and end-diastolic diameters, posterior wall and interventricular septal thicknesses, and left atrial (LA) diameter were measured. LV mass was calculated as per the method used by Devereux et al. (11) and was indexed to the body surface area. The left ventricular ejection fraction (LVEF) was measured using the biplane Simpson method (10). Mitral inflow velocities were studied using pulsed-wave Doppler after placing the sample volume at the leaflets' tips (12). Peak early filling (E-wave) velocity was measured. The pulsed Doppler sample volume was placed on the lateral and septal sides of the mitral annulus to obtain tissue Doppler velocities. The average E' velocity (E'av) was obtained from the septal and lateral annular E' velocities, and the ratio of the mitral inflow E velocity to average tissue Doppler velocity (E/E'av) was calculated to predict LV filling pressure (13). Dynamic obstruction of the LVOT was measured using continuous wave Doppler and estimated using the simplified Bernoulli equation (14).

Left ventricular strain and strain rate were measured using a dedicated software package (Echo PAC PC; GE Healthcare, Waukesha, WI, USA). Digital cine loops at a frame rate of 50–90

frames/sec were acquired at end-expiration from the R-wave peak and stored on optical disks for offline analysis. The averages of three cardiac cycles were used for analysis. This software tracks the endocardial contour on an end-diastolic frame and automatically generates a region of interest divided into segments. The quality of myocardial tracking was checked visually. The process was repeated by adjusting the region of interest or by manually correcting the contour to ensure optimal tracking if unsatisfactory tracking was obtained. Deformation parameter graphics of each segment were then automatically formed, and the average peak strain and systolic strain rate were obtained. Global strain and strain rates were assessed as the average of the segmental values (Fig. 1a, b).

Measuring plasma Gal-3 levels

All blood samples were collected after an overnight fast, centrifuged immediately, and stored at -80°C until analysis. The blood samples were taken on the same day that the echocardiographic study was conducted. Gal-3 levels were measured in ethylenediaminetetraacetic acid (EDTA)-treated plasma using the ARCHITECT i2000_{SR} (Abbott Diagnostics, Abbott Park, IL, USA). The manufacturer-provided measurement range was 4–114 ng/mL.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Results are presented as means \pm standard deviations for continuous data or as frequencies and percentages for categorical data. Categorical variables were analyzed using chi-square test. Shapiro–Wilk W test was performed for testing normality. According to the results of a normality test, statistically significant differences between two groups of continuous variables were determined using the independent t-test and Mann–Whitney U test, as appropriate. Associations between variables were examined by calculating Pearson correlations. Comparison of Gal-3 levels between patients with two different types of HCM was assessed using Mann–Whitney U test. A p value of <0.05 was considered statistically significant.

Results

The demographic characteristics of the patients and controls are listed in Table 1. No differences were detected between the groups in terms of age, sex, body surface area, or blood pressure. Twenty-nine (72.5%) had asymmetric septal hypertrophy and 11 (27.5%) had concentric type HCM. Nineteen (47%) patients had a significant LVOT gradient (>30 mm Hg) at rest. A comparison of the echocardiographic characteristics of the patients and controls is displayed in Table 2. LVEF was similar between the groups, but the thicknesses of the posterior and interventricular septal walls and LV mass index (LVMI) were significantly higher in patients with HCM than in controls. The comparison of the strain echocardiographic evaluation results of LV function showed that global LV

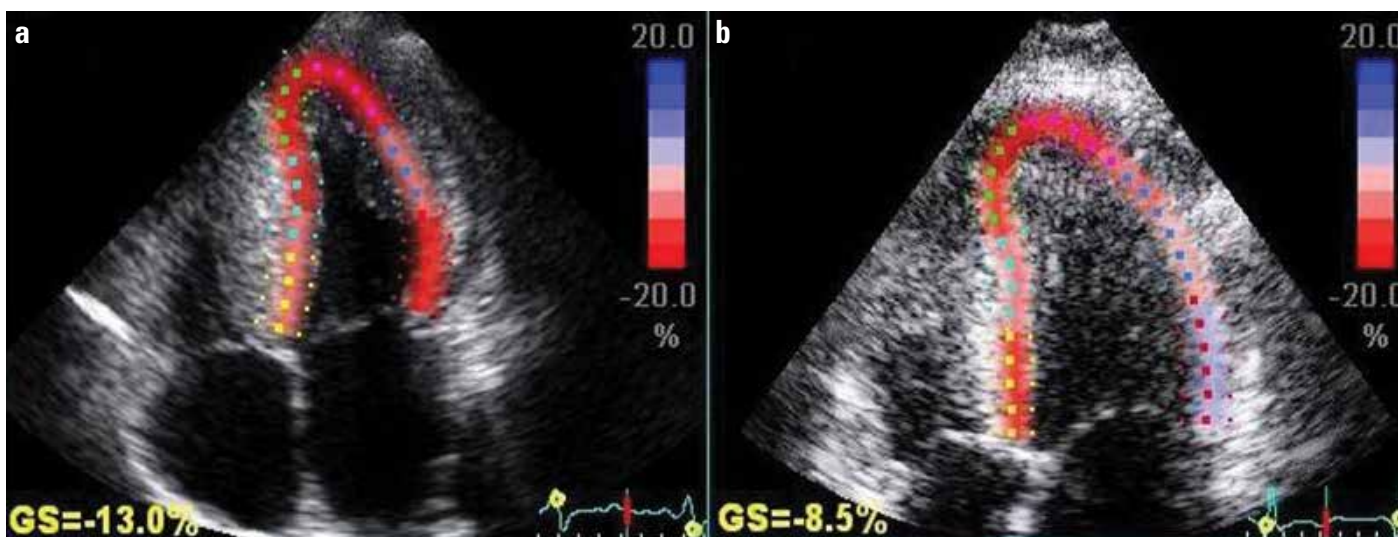


Figure 1. a, b. Galectin-3 (Gal-3) level, left ventricular global longitudinal strain (LVGLS), and left ventricular mass index (LVMI) values in two patients with hypertrophic cardiomyopathy (a) A patient with Gal-3 level, 38.3 ng/mL; LVMI, 332.7 g/m²; and LVGLS, 13% (b) A patient with Gal-3 level, 13.9 ng/mL; LVMI, 163.1 g/m²; and LVGLS, 8.5%

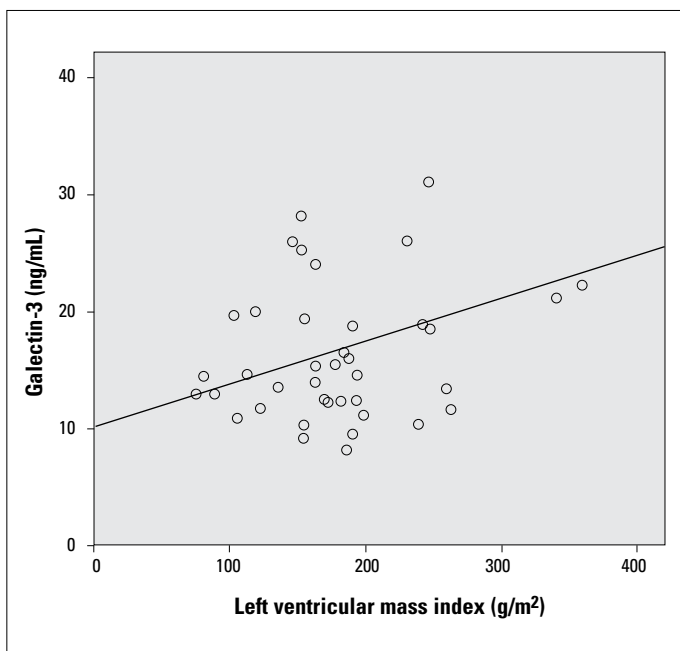


Figure 2. Correlation between Galectin-3 level and left ventricular mass index ($r=0.365$, $p<0.021$)

longitudinal strain ($-13.37\pm 4.6\%$ vs. $-18.93\pm 2.5\%$, $p<0.001$) and strain rate (0.66 ± 0.22 s⁻¹ vs. 1.08 ± 0.14 s⁻¹; $p<0.001$) values were lower in patients with HCM than in controls; however, global circumferential strain and peak torsion were similar between the two groups. Gal-3 levels were significantly higher in patients with HCM than in controls (16.9 ± 6.64 ng/mL vs. 13.21 ± 3.42 ng/mL, $p=0.005$). Gal-3 levels were similar in females and males in both patients with HCM (16.44 ± 4.82 ng/mL vs. 17.16 ± 7.19 ng/mL, $p=0.7$) and controls (13.68 ± 4.3 ng/mL vs. 12.78 ± 2.7 , $p=0.5$). The associations between Gal-3 levels and other variables in patients with HCM are presented in Table 3. Gal-3 levels were correlated with the thickness of the interventricular septum (IVS) ($r=0.444$, $p=0.004$) and LVMI

Table 1. Demographic characteristics of the study population

	HCM group (n=40)	Control group (n=35)	P
Age, years	51.15±13.4	46.6±10.9	0.118
Men, %	77.5	77.1	0.971
BSA, m ²	1.93±0.21	1.83±0.2	0.285
Systolic BP, mm Hg	110.2±9	111.2±10.3	0.413

BP - blood pressure; BSA - body surface area; HCM - hypertrophic cardiomyopathy

($r=0.365$, $p=0.021$) (Fig. 2); however, they were not associated with global LV longitudinal strain ($p=0.42$) or strain rate ($p=0.28$) (Table 3). Gal-3 levels were not associated with the magnitude of LVOT obstruction ($p=0.818$) either. When patients were divided into two groups according to the type of LV hypertrophy, median Gal-3 levels of patients with concentric type HCM ($n=11$) were similar to the ones with asymmetric septal hypertrophy ($n=29$) ($p=0.9$). In the controls, Gal-3 levels were not associated with any of the following parameters: age ($p=0.6$), body surface area ($p=0.5$), LVMI ($p=0.07$), LVEF ($p=0.2$), global LV longitudinal strain ($p=0.9$), circumferential strain ($p=0.4$), peak torsion ($p=0.6$), and E/E' av ($p=0.6$).

Discussion

We detected significantly elevated plasma Gal-3 levels in patients with HCM compared with those in controls. We investigated the relationship between plasma Gal-3 level and echocardiographic indices and found no correlations between Gal-3 level and LV global longitudinal strain or strain rates. Increased Gal-3 level was positively correlated with LVMI and thickness of IVS. Our results indicate that the extent of LV hypertrophy in patients with HCM is related with an increase in Gal-3 level; however, Gal-3 level is not associated with LV diastolic and systolic function in patients with HCM.

Table 2. Comparison of echocardiographic findings and galectin levels between two groups

	HCM group (n=40)	Control group (n=35)	P
LVEDD, mm	43.14±6.04	44.66±4.58	0.229
LVESD, mm	25.75±5.15	25.4±3.71	0.740
LVEF, %	64.5±4.88	63.4±2.64	0.222
IVS, mm	23.28±6.25	9.57±0.94	<0.001
PW, mm	12.44±3.2	9±0.9	<0.001
LVMI, g/m ²	183.24±66.5	73.38±13.05	<0.001
E/E' septal	18.5±7.7	7.3±1.5	<0.001
E/E' lateral	13.05±7.3	6±1.6	<0.001
E/E' average	14.5±6.3	6.5±1.5	<0.001
LVGLS, %	-13.37±4.6	-18.93±2.5	<0.001
LVGCS, %	-17.02±4.16	-18.67±3.5	0.071
Peak Torsion, degrees	12.28±5.59	13.15±5.39	0.052
Galectin, ng/mL	16.9±6.64	13.21±3.42	0.005

HCM - hypertrophic cardiomyopathy; IVS - interventricular septum; LVEDD - left ventricular end-diastolic diameter; LVEF - left ventricular ejection fraction; LVESD - left ventricular end-systolic diameter; LVGCS - left ventricular circumferential strain; LVGLS - left ventricular global longitudinal strain; LVMI - left ventricular mass index; PW - posterior wall
Normally disturbed variables were analyzed using independent t-test; otherwise with Mann-Whitney U test

In a study evaluating the serum levels of the C-terminal propeptide of type I procollagen (PICP) in patients with pathogenic sarcomere mutations and overt HCM, mutation carriers without LV hypertrophy, and healthy controls, increased PICP levels in both patients with HCM and mutation carriers compared with those in the controls were observed. Despite normal LV function in mutation carriers, the early elevation of serum fibrosis markers before apparent phenotypic HCM expression indicates that myocardial fibrosis is an early manifestation of the sarcomere gene mutation (15). No significant correlations were found when collagen turnover markers were compared with the extent of late gadolinium enhancement (LGE) determined on cardiac magnetic resonance imaging (MRI) in patients with overt HCM (15). Similarly, we detected high plasma Gal-3 levels in patients with HCM compared with those in controls; however, no correlation was detected between Gal-3 level and LV longitudinal strain.

A study evaluating the relationship between LVEF and extent of LGE on cardiac MRI in patients with HCM showed that LGE was detectable in 67% of HCM cases with low-normal LVEF values of 50%–65%, which constituted a median of 5% of the LV mass with an interquartile range of 2%–20%. These values exceeded those seen in patients with HCM and hyperdynamic LV (LVEF > 65%) (2). Our HCM cohort was composed of patients with HCM and an LVEF of >65% and 55%–65% which could explain the lack of the correlation between Gal-3 level and LV strain, indicating a heterogeneous HCM group. A study assessing the value of Gal-3 level in patients with HCM and LVEF of 50%–65% for predicting those who will develop end-stage disease may be clinically important.

Table 3. Relationship between galectin-3 levels and other variables in patients with hypertrophic cardiomyopathy

Variables	R	P
Age	-0.172	0.288
LVEF	0.077	0.664
PW	0.235	0.145
IVS	0.444	0.004
LVMI	0.365	0.021
E/E' av	0.142	0.455
LVGLS	0.131	0.422
LVGCS	-0.109	0.504
Peak Tor	-0.142	0.439
LVOT gradient	-0.051	0.818

av - average; IVS - interventricular septum; LVEF - left ventricular ejection fraction, LVGCS - left ventricular circumferential strain; LVGLS - left ventricular global longitudinal strain; LVMI - left ventricular mass index; PW - posterior wall; Tor - torsion. Pearson's correlation analysis was performed.

The diagnostic value of Gal-3 remains unclear in patients with cardiac dysfunction. Gal-3 has been compared with N-terminal pro-brain natriuretic peptide (BNP) as a diagnostic marker in patients with HF, but it added no additional effectiveness to diagnose HF (16). The relationships between Gal-3 level and echocardiographic indices have been investigated in a few studies (5, 17-19). No association was detected between Gal-3 level and echocardiographic indices in patients with HF, including LVEF (18). We did not find a relationship between Gal-3 level and the echocardiographic indices, including LV longitudinal strain, which is a good marker of LV function in patients with HCM. Similar to a study which investigated the utility of Gal-3 in preceding HF development in the Framingham Offspring Cohort (5), we found a positive correlation between LVMI and Gal-3 level in our HCM cohort, suggesting that Gal-3 is an LV hypertrophy marker.

The associations between Gal-3 level and hemodynamic parameters have been investigated previously in patients with preserved or impaired LVEF (20, 21). Plasma levels of natriuretic peptides were associated with LV filling pressure at rest and during exercise in a study of patients recovering from acute myocardial infarction with preserved LVEF, but no correlation was found with Gal-3 level (20). Another study investigated the kinetics of Gal-3 and BNP in patients with end-stage HF with the need for mechanical circulatory support. Initial Gal-3 levels of patients were higher than those of controls; however, no decrease in Gal-3 level was observed due to mechanical circulatory support, but the loading-related biomarker BNP decreased, and patients who did not survive on mechanical circulatory support had a higher baseline Gal-3 level (21). In the present study, we hypothesized that Gal-3 could be used to identify patients with elevated filling pressure; however, we detected no correlation between Gal-3 level and filling pressure, which was estimated using E/E' ratio in patients with HCM. These results suggest that Gal-3 level is independent of loading parameters in patients with HCM.

Study limitations

Our study had a few limitations. First, the sample size of the HCM group was relatively small. However, we carefully selected the patients and controls to avoid comorbidities that could also induce Gal-3 expression. Second, we did not use cardiac MRI to detect the extent of fibrosis in patients with HCM. Third, we only assessed circulating Gal-3 level which may not sufficiently reflect cardiac tissue deposits.

Conclusion

Gal-3 level increased and was related with the degree of LV hypertrophy in patients with HCM. Gal-3 was not a good marker of LV diastolic and systolic dysfunction or filling pressure in these patients. Our results may prompt further studies investigating the utility of Gal-3 level for predicting adverse cardiac events in the HCM population.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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