Galectin-3: A Novel Biomarker of Left Ventricular Remodelling in Chronic Heart Failure

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ABSTRACT

BACKGROUND

Heart failure (HF) is a serious condition in which the heart is unable to pump enough blood to meet the demands of the body. The development of HF is often a clinically silent process, with progressive cardiac remodelling eventually leading to symptomatic presentation later in the course of disease progression with high mortality rate. Natriuretic peptides (NPs) help in selecting patients at high risk for future events such as re-hospitalization which only indicate ventricular loading conditions and do not reveal other important mechanisms in HF. The use of novel markers like Galectin-3, could add information about relevant structural changes in the heart, including inflammation, fibrosis, remodelling and a possible guide for treatment. Galectin- 3 has been found to be up-regulated in the plasma of patients with acute and chronic heart failure.

METHODS

80 subjects of both sexes between 20-80 years diagnosed with chronic heart failure based on Framingham criteria and left ventricular ejection fraction (LVEF) of ≤45% or diastolic dysfunction were selected for the study. Subjects with abnormal renal function were excluded. 80 CHF patients were divided into two groups: (i) CHF with moderate LVD (LVEF >36% and ≤45%) and (ii) CHF with severe LVD (LVEF ≤35%). Serum Galectin-3 levels were compared with BNP, clinical and echocardiographic indices of LV structural remodelling between the two groups.

RESULTS

Serum Galectin-3 levels were higher in the CHF patients with severe LVD (p <0.001*) compared to moderate LVD patients. Pearson's correlation analysis showed a significant positive correlation between Galectin-3 levels and NYHA class III, IV and echocardiographic indices (LVIDD, LVIDS, LVESV, LVEDV) and significant negative correlation between LVEF and Galectin-3 levels.

CONCLUSIONS

Serum Galectin-3 levels being higher in CHF patients with severe LVD compared to moderate LVD and significant positive correlation between Galectin-3 levels between NYHA class III, IV and LVEDD, LVESD, LVEDV, LVESV while there is a significant negative correlation between Galectin-3 levels and LVEF, thus proving that Galectin-3 levels are closely correlated with the degree of left ventricular structural and functional remodelling in CHF patients.

KEYWORDS

Chronic Heart failure (CHF), NYHA (New York Heart Association), Left Ventricular Dysfunction (LVD), Left Ventricular End Diastolic Diameter & Volume (LVEDD & LVEDV), Left Ventricular End Systolic Diameter & Volume (LVESD & LVESV), LVEF (Left Ventricular Ejection Fraction), Brain Natriuretic Peptide (BNP), Galectin-3

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BACKGROUND

Heart failure (HF) is a serious condition in which the heart is unable to pump enough blood to meet the demands of the body.[1] Heart failure is a global public health pandemic characterized by high mortality with increased rate of hospitalization and rehospitalizations.[2] About 26 million adults worldwide are living with heart failure[3] and across the globe, 17 – 45% of CHF patients die within one year of admission and majority die within 5 years of admission.[4] In the recent years, survival rates of such patients have improved with the introduction of modern evidence based therapies and patient management systems.[5] However latest therapies targets only symptoms, without slowing the progression of their disease[6] as heart failure results from varied underlying problems affecting either the structure or functions of the heart.

Normal cardiac aging is characterized by morphological and structural changes with increase cardiomyocyte size, increased apoptosis and decreased myocytes, increased collagen deposition, functional changes at cellular level, contributing to fibrotic remodelling which causes LV diastolic stiffness and impaired diastolic function.[7] The development of heart failure is a clinically silent process, with progressive cardiac remodelling leading to symptoms in the later stages.[8] Considering heart failure to be one of the most frequent and challenging medical disorders characterized by ventricular remodelling, which is a determinant of disease progression and poor prognosis, it has become imperative to identify those patients with the highest risk of adverse outcome.[9] Early changes in the heart's structure and function can be detected using medical imaging technology; however it is not practically feasible to perform these complex procedures in the enormous number of individuals with heart failure.[10] Hence a biomarker strategy to screen and identify patients to refer for diagnostic non-invasive cardiac imaging may be useful. This may facilitate the early recognition of asymptomatic left ventricular (LV) dysfunction and initiation of therapy to favourably alter the course of progression of HF.[11]

Natriuretic peptides (NPs) only indicate ventricular loading conditions and do not reveal other important mechanisms in HF. The use of novel markers, such as Galectin-3, could add information about relevant structural changes in the heart including inflammation, fibrosis, remodelling and a possible guide for treatment.[12] Galectin - 3 (Gal-3) is a member of Galectin family that binds β-galactosides. In the failing heart, Gal-3 is produced by activated macrophages and cardiac fibroblasts.[13,14,15] After acute or chronic damage, Gal-3 is released in the myocardium, via a paracrine effect, stimulating the release of inflammatory mediators like TGF-β1, promoting cardiac myofibroblast proliferation, procollagen- I deposition.[13,16] Cardiac fibrosis results due to the activation of fibroblasts, myofibroblasts leading to procollagen deposition into the extracellular matrix and eventually causing ventricular dysfunction.[17,18] Galectin- 3 has been found to be up-regulated in the plasma of acute and chronic heart failure patients.[19] Increased plasma Gal-3 were detected in failure - prone hypertrophied rat and human hearts[13] as well as in acute[20,21] and chronic HF patients.[22,23] Studies have demonstrated that Gal-3 infusion into the pericardium of normal rats led to the development of cardiac remodelling and highest levels of Gal- 3 were associated with the highest degree of cardiac fibrosis and developed HF.[14,20] These observations strongly suggest that circulating Gal-3 are useful in identifying patients at risk for developing cardiac remodelling . Gal-3 levels are also elevated in CHF patients with left ventricular remodelling, determined by serial echocardiography, compared to Gal-3 levels of CHF patients without remodelling.[24]

We wanted to determine the relationship of serum Galectin -3 with moderate and severe LV dysfunction and also to correlate the Galectin-3 levels with both clinical and echocardiographic indices of LV structural remodelling in chronic heart failure patients.

METHODS

After obtaining ethical clearance for this study from Institutional Ethics Committee (IEC) a cross- sectional study was conducted among 80 subjects diagnosed with chronic heart failure (CHF) based on Framingham criteria and Left ventricular ejection fraction (LVEF) of ≤45% or diastolic dysfunction, from both sexes, between the age group of 20-80 years, admitted as inpatients in the Cardiology department at Sri Ramachandra Medical college and Research Institute hospital were selected for this study.
Overall, 80 chronic heart failure patients with NYHA Class III & IV of heart failure with ECHO findings of reduced LVEF of ≤45% or diastolic dysfunction and normal renal function with serum creatinine levels of 0.8-1.3 mg/dL and 0.6 – 1.2 mg/dL for males and females respectively were included in the study.

The study group were divided into two groups: (i) CHF with moderate LV dysfunction (LVEF >36% and ≤45%) and (ii) CHF with severe LV dysfunction (LVEF ≤35%). Chronic heart failure patients of less than 20 years and above 80 years, LVEF >45% or normal diastolic function and subjects with increased serum creatinine levels (greater than the above-mentioned cut- off) were excluded from the study.
Data regarding full medical history that included age, sex, occupation, duration of illness, history of diabetes mellitus, hypertension and ischemic heart disease, previous history of any other illnesses were collected from the study subjects.
A written informed consent was obtained from each participant before commencement of the study.

Laboratory Measurements

- Serum Galectin -3 were measured using Human Galectin-3 ELISA kit.
- Serum Brain Natriuretic peptide (BNP) were measured by Micro- particle enzyme immunoassay (MEIA) using Abbott AxSYM system.
- Blood Urea Nitrogen (BUN) measured by Urease / GLDH kinetic method using Siemens Advia 1800.

- Serum creatinine by Jaffe's kinetic method using Siemens Advia 1800.
- Transthoracic Echocardiography (TTE) done using VIVID 9 GE system and the following parameters were noted.
  - LVEDV- Left ventricular end diastolic volume in ml.
  - LVESV- Left ventricular end systolic volume in ml.
  - LVIDD- Left ventricular internal diameter diastole in mm.
  - LVIDS- Left ventricular internal diameter systole in mm.
  - LVEF- Left ventricular ejection fraction in%.
- Echo was done in all study subjects by the same investigator using the same instrument to limit variability.

Statistical Analysis

Statistical analysis was performed using SPSS software version 16.0 Parametric continuous variables were given as mean± standard deviation and non-parametric values were given as percentage. Independent sample t- test was used to compare parametric continuous variables to check the statistical significance between the groups. Two - tailed p-values of less than 0.05 were considered to indicate statistical significance. Association of two sets of data was evaluated using Pearson's test for correlation analysis.

RESULTS

		CHF (n= 80)
Sex	(i) Male	56 (70%)
	(ii) Female	24 (30%)
NYHA Class	Class III	32 (40%)
	Class IV	48 (60%)
Hypertension	(+)	11 (13.8%)
	(-)	69 (86.3%)
Diabetes mellitus	(+)	41 (51.2%)
	(-)	39 (48.8%)
	Ischemic cardiomyopathy	45 (56.3%)
	Dilated cardiomyopathy	35 (43.8%)
Echo (LVEF)	(i) Moderate LVD	33 (41.3%)
	(ii) Severe LVD	47 (58.8%)
Galectin -3 (ng/ml)	(i) Low risk (<17.8)	27 (33.8%)
	(ii) Intermediate (17.9-25.9)	27 (33.8%)
	(iii) High risk (>25.9)	26 (32.5%)

Table 1. Baseline Characteristics of 80 CHF Patients

NYHA: New York Heart Association, LVEF: Left Ventricular Ejection Fraction, LVD: Left Ventricular Dysfunction

		Moderate LVD (n = 33)	Severe LVD (n = 47)
Sex	(i) Male	26 (78.8%)	30 (63.8%)
	(ii) Female	7 (21.2%)	17 (36.2%)
NYHA Class	Class III	32 (97%)	0 (0%)
	Class IV	1 (3%)	47 (100%)
Diabetes mellitus	(+)	18 (54.5%)	23 (48.9%)
	(-)	15 (45.5%)	24 (51.1%)
Hypertension	(+)	6 (18.2%)	5 (10.6%)
	(-)	27 (81.8%)	42 (89.4%)
	Ischemic cardiomyopathy	24 (72.7%)	21 (44.7%)
	Dilated cardiomyopathy	9 (27.3%)	26 (55.3%)

Table 2. Demographic Data Across the Study Groups

Parameters	Moderate LVD (n = 33)	Severe LVD (n= 47)	p
	Mean ± S.D.	Mean ± S.D.	
BNP (pg/ml)	743.00 ± 685.17	1583.61 ± 1367.02	0.002*
Galectin-3 (ng/ml)	17.28 ± 1.65	26.21 ± 3.24	<0.001*

Table 3. Comparison of BNP and Galectin-3 Levels between the Two Groups

BNP- Brain Natriuretic peptide, p value* <0.05- statistically significant

Echocardiographic Indices	r value	p value
LVIDD (mm)	0.457	<0.001*
LVIDS (mm)	0.513	<0.001*
LESV (ml)	0.388	<0.001*
LVEDV (ML)	0.270	0.015*
LVEF (%)	-0.937	<0.001*

Table 4. Pearson Correlation between Galectin-3 Levels and Various Echocardiographic Indices

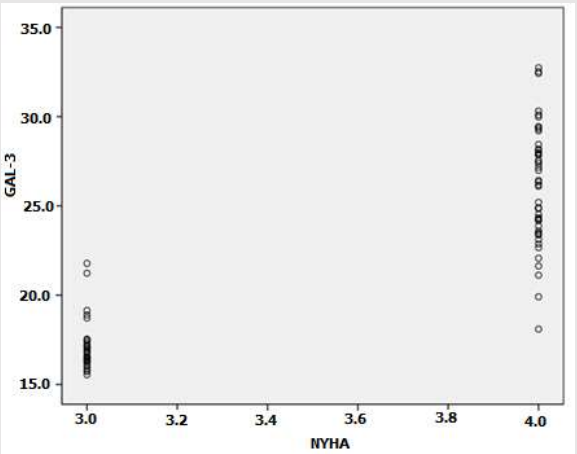

Figure 1. Correlation between Galectin-3 Levels (GAL - 3) and NYHA Functional Class III and IV

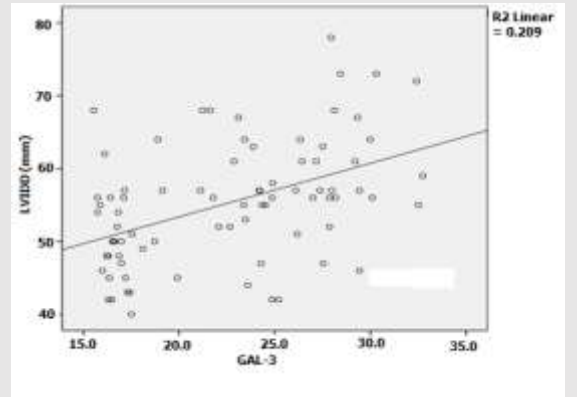

Figure 2A

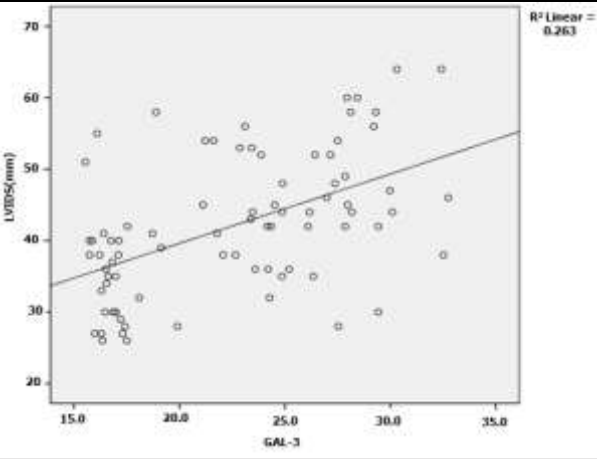

Figure 2B

The study group comprising of 80 chronic heart failure (CHF) patients were divided into two groups: (i) CHF with moderate LV dysfunction (LVEF >36% and ≤45%) and (ii) CHF with severe LV dysfunction (LVEF ≤ 35%) Baseline

characteristics of 80 CHF patients are presented in Table 1. Demographic data across the study groups are shown in Table 2. Comparison of BNP and Galectin -3 levels between the two groups are seen in Table 3. BNP levels showed a statistically significant difference in their mean values between the two study groups with p= 0.002*. Galectin-3 also showed a statistically significant difference in their mean values between the two study groups with p <0.001* as shown in Table 3.

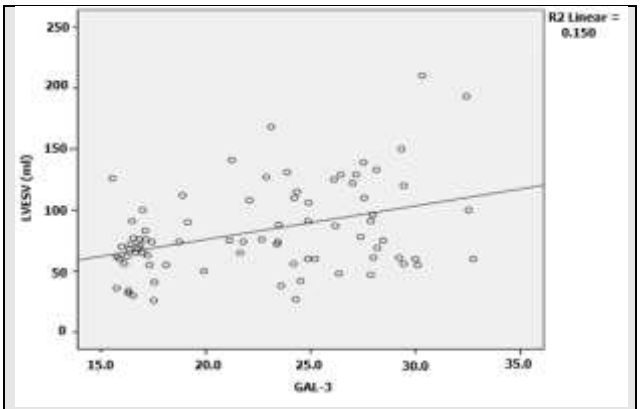

Figure 2C

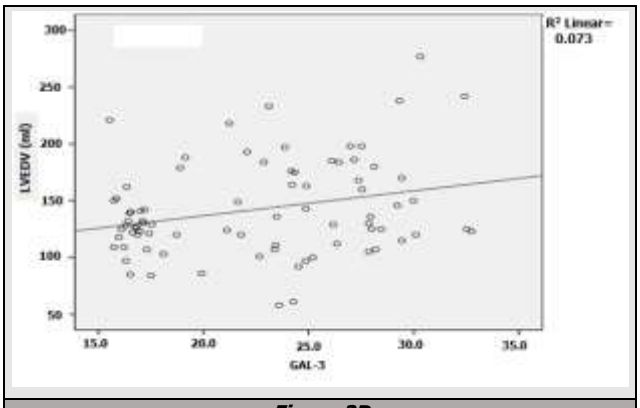

Figure 2D

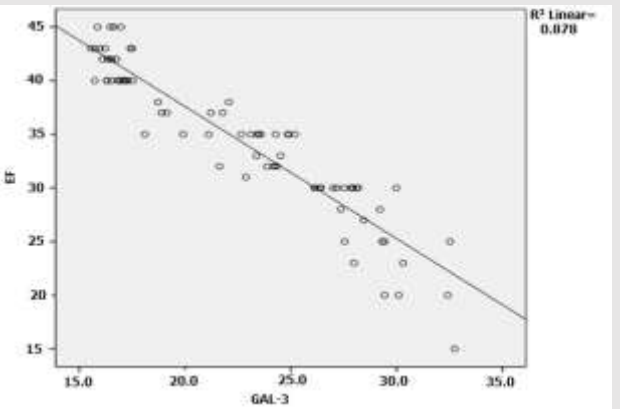

Figure 2E

NYHA Class and Galectin-3 Levels- Correlation

A statistically significant positive correlation was found between Galectin-3 levels and NYHA functional class III and IV using Pearson correlation with 'r' value of 0.857 and p<0.001*. (Figure 1).

Figure 2. Correlation between Galectin-3 Levels and Various Echocardiographic Indices of Structural Remodelling. Pearson correlation showed a significant positive correlation between the levels of Galectin-3 and echocardiographic indices LVIDD (Figure 2A), LVIDS (Figure 2B), LVESV (Figure 2C) and LVEDV (Figure 2D) while there was a significant negative correlation between LVEF and Galectin -3 levels (Figure 2E).

DISCUSSION

In this study, the levels of Galectin - 3 were significantly higher in CHF patients with severe LV dysfunction compared to CHF patients with moderate LV dysfunction with p value<0.001 as shown in Table 3. In the study by Milting et al,[25] chronic heart failure patients were compared to healthy controls and Galectin -3 were higher in CHF patients than in controls. Mean values of BNP (Table 3) were also significantly higher in CHF patients with severe LV dysfunction compared to moderate LV dysfunction with p =0.002. Wide variation in BNP levels of both the study groups were mainly due to low BNP levels in dilated cardiomyopathy whereas higher BNP levels were seen in ischemic cardiomyopathy. Based on Galectin-3 levels (Table 1), these 80 CHF patients were categorized into 3 risk groups. Of which 33.8% belonged to low risk group, 33.8% intermediate risk and 32.5% high risk.

In this study, the levels of Galectin-3 had a significant positive correlation with NYHA functional class as shown in Figure 2. Milting et al[25] also demonstrated elevated serum Galectin-3 levels in patients with chronic heart failure (CHF) were associated with higher NYHA class and predicted poorer outcome. Chen et al,[26] concluded that increased plasma Galectin-3 levels positively correlated with the severity of HF since Galectin-3 levels had statistical differences between CHF patients with the different NYHA functional classes, especially higher in class III and IV. Tang et al[27] also showed that higher Galectin-3 levels were associated with higher NYHA functional class, advanced age and poor renal function.

Up-regulation of Galectin-3 expression have been demonstrated in murine models of hypertensive heart disease, myocarditis and cardiomyopathy and in the hypertrophied ventricular myocardium of humans with aortic stenosis and depressed LV systolic function. Several studies in animal models have been performed implicating Galectin-3 in cardiac remodelling and LV dysfunction, it is critically important to identify associations between Galectin-3 levels and cardiac structure and function.[28,29] Systolic HF, known as HF with reduced ejection fraction (HFrEF) has been classically related with LV dysfunction leading to congestion and reduced systemic perfusion, manifest clinically as dyspnoea and fatigue. The advanced stages of myocardial disorders lead to progressive LV dilatation with or without hypertrophy followed by LV spherical remodelling causing increased wall tension and stress on the myocardium.[30] Given the link between cardiac fibrosis, hypertrophy and HF

in animal models, several associations between LV structure and function and Galectin-3 concentrations were investigated in this study.

In this study, Pearson correlation analysis (Table 4) was done to correlate the levels of Galectin-3 with echocardiographic indices of CHF patients. The levels of Galectin-3 had highly significant positive correlation with LV end diastolic (LVIDD) and systolic dimensions (LVIDS) with $p < 0.001$ and $p < 0.001$ respectively as shown in Figure 2A & 2B. Similarly, Galectin-3 levels had statistically significant positive correlation with LV end diastolic (LVEDV) and systolic volumes (LVESV) with $p = 0.015$ and $p<0.001$ respectively explained in Figure 2C & 2D. But Galectin-3 levels had highly statistically significant negative correlation with LV ejection fraction (LVEF) with $p < 0.001$ (Figure 2E), thus suggesting significant association of Galectin-3 levels with echocardiographic indices of systolic dysfunction. Similar to our study, Hamdy et al[31] also demonstrated a statistically significant positive correlation with LV end diastolic and systolic volumes and dimensions and significant negative correlation with LV ejection fraction.

It is well recognized that LV ejection fraction is an important determinant of prognosis in various cardiac disorders, especially CAD. Survival rates decline in relation to LV dysfunction.[30] In a study by Aronow et al[32] in patients with CAD and heart failure, a survival rate in those CAD patients with normal EF was 78% at 1 year, 62% at 2 years and 44% at 4 years. LVEF has a short-term prognostic value also. Sharma et al,[13] in his study showed that Galectin-3 can induce cardiac fibroblast proliferation via the activation of cyclin D1, thus allowing cardiac fibroblast proliferation and increases collagen I production which is an essential component of the myocardium, maintaining its structural and functional integrity. At the same time cross-linking of collagen including the formation of advanced glycation end products and increased tissue inhibitor of matrix metalloproteinase -1 expression enhance and promote fibrosis and stiffening.[33] Increased collagen deposition may therefore have a major impact on the diastolic and systolic function of the heart, thus proving that Galectin-3 is over expressed well before the transition to overt HF. Also early recruitment and activation of Galectin-3 producing macrophages can drive the progression from compensated hypertrophy towards overt heart failure besides its anti-apoptotic and growth promoting actions.[13]

Failure- prone and dysfunctional rat and human heart specimens all share an increased lectin presence. Therefore, an early recognition of failure- prone hearts and intervention with new anti-inflammatory and anti-fibrotic agents might provide additional benefit over existing treatment strategies. These results shape the concept of considering Galectin-3 as a new target for therapeutic intervention at an early stage of compensated hypertrophy in failure-prone hearts.[13] Also studies by Calvier et al[34] and Toprak et al,[35] on the patho-physiological role for Galecin-3 in the development and progression of HF suggest that the blockade of Galectin-3 may slow the progression of heart failure and reduce HF associated morbidity and mortality.[36] Therefore targeting Galectin-3 may be an upstream therapeutic option for the treatment of all types of heart failure. There is still much uncertainty regarding the development of a therapy which can target Galectin-3 directly, since knowledge is lacking regarding the regulation of Galectin-3 at the transcriptional and translational levels in the heart. Although inflammatory signals also contribute to the regulation of Galectin-3, the cytokines and other factors which govern the production and secretion of Galectin-3 remain enigmatic, warranting future explorative pharmacological studies.[14]

Limitations

Major limitations are relatively small sample size and follow up of patients were not done. The effect of medications used for treatment of heart failure in relation to Galectin -3 and ventricular remodelling needs to be evaluated in a prospective cohort study involving larger group of CHF subjects.

CONCLUSIONS

Galectin-3 levels were significantly higher in chronic heart failure (CHF) patients with severe LV dysfunction compared to those with moderate LV dysfunction similar to higher BNP levels. Galectin-3 levels revealed a significant positive correlation with NYHA functional class and echocardiographic indices such as LVEDD, LVESD, LVEDV and LVESV while there was a significant negative correlation between Galectin-3 levels and LV Ejection Fraction (LVEF) thus proving that Galectin-3 levels are closely correlated with the degree of left ventricular structural and functional changes (remodelling), indicating that Galectin-3 could have been involved in the process of LV remodelling in chronic heart failure (CHF) patients.

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