Research article

Galectin -3: an independent cardiac marker of left ventricular (LV) remodeling in chronic heart failure

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ABSTRACT

Introduction and Aim: Heart failure (HF) with increased morbidity and mortality is a critical condition where the cardiac pumping capacity fails to meet up with the body's demand. Its development is silent due to slow, progressive remodeling presenting with symptoms later. Brain Natriuretic peptides (BNP) denotes ventricular loading status which do not reveal other mechanisms whereas a novel marker Galectin-3 (Gal-3) provides information about cardiac structural changes which includes inflammation, fibrosis, remodeling for guiding treatment. Research studies demonstrated that there is upregulation of Galectin- 3 in both acute and chronic heart failure (CHF) individuals. The objectives of our study were to compare Galectin- 3 levels in moderate and severe LVD CHF patients and determine whether serum Galectin -3 can be used as an independent cardiac marker of ventricular structural remodeling in such HF individuals.

Materials and Methods: 80 patients between 20 - 80 years diagnosed with CHF using Framingham criteria with ejection fraction (EF) of ≤ 45% and classified into two groups:(i) moderate LVD and (ii) severe LVD. Those with abnormal kidney functions were excluded. Comparison was done between serum Galectin - 3 and BNP; Gal- 3 was determined to be an independent marker of structural remodeling of LV between the two categories.

Results: Galectin-3 and BNP were significantly increased in HF with severe LVD than moderate LVD. Multivariate linear regression showed Galectin-3 as an independent predictor of LV remodeling with respect to changes in LV end- diastolic dimension with statistically significant $p < 0.001$ whereas BNP did not show any such significance.

Conclusion: Galectin -3 and BNP levels were elevated in severe LV dysfunction than moderate LVD and concluded that Gal-3 is an independent cardiac biomarker of LV remodeling in Chronic heart failure.

Keywords: Galectin -3 (Gal-3); Brain Natriuretic Peptide (BNP); Chronic Heart failure (CHF); Left Ventricular Dysfunction (LVD); New York Heart Association (NYHA); Left Ventricular Ejection Fraction (LVEF).

INTRODUCTION

Heart failure (HF), is a health pandemic with increased mortality and higher rates of hospitalizations with 64.34 million people affected worldwide (1). It is a pathophysiological condition that results from any structural or functional impairment of ventricular filling or ejection of blood and the pumping capacity of the heart fails to meet up with the body's demand (2).

Innovations in the field of diagnosis and treatment leading to the prolonged life expectancy indirectly increase the risk of HF prevalence. However, the current therapies can only relieve symptoms, without targeting the disease progress since there are varied causes affecting the cardiac structure / functions (3).

Normally cardiac cells age by structural changes as a result of increased cardiomyocyte size, reduction in myocytes, apoptosis, increased collagen deposition and progressive fibrotic remodeling resulting in left ventricular diastolic stiffness leading to impaired diastolic function which is clinically silent presenting with symptoms at the later stages of the disease (4).

Left ventricular (LV) remodeling defines alterations in LV mass, shape, volume and its composition after any cardiac injury and/or abnormal hemodynamic loading state. Increased LV end-diastolic volume causes wall thinning and LV dilatation. Current therapies target only the symptomatic phase of this disease only after the occurrence of extensive remodeling. Hence strategies targeting even before the symptoms appear can prevent the complications (5).

The knowledge of cardiac remodeling is an important determinant of HF progression with poor prognosis and a most challenging disorder, where preventive treatment could be targeted earlier. Medical imaging technologies can detect early changes in the cardiac structure or function; whereas considering feasibility to do imaging procedures in the vast number of diseased patients is highly impractical (6). Hence a biomarker could prove useful to screen such high-risk individuals, who deserves to be referred to higher health care setting for cardiac imaging procedures for early recognition of symptoms to initiate early treatment (7).

Natriuretic peptides (NPs) only select patients with high risk prone for re-hospitalization events with worsening heart failure (8) and they indicate ventricular

loading and other mechanisms causing such failure could not be revealed. But new markers like Galectin-3, provides data regarding cardiac structural changes involving inflammation leading to fibrosis and remodeling, providing guidance for treatment (9).

Galectin -3 (Gal-3) binds to β-galactosides. Activated macrophages and cardiac fibroblasts produce Gal -3 in the failing hearts (10). Myocardium releases Gal-3, via a paracrine effect because of acute or chronic damage causing the inflammatory mediators release, activating fibroblast proliferation and deposits procollagen-I (10,11) in the extracellular matrix causing cardiac fibrosis resulting in ventricular dysfunction (12).

Up-regulated Galectin- 3 is identified in the heart failure -prone hypertrophied heart rats (10) and in blood of both acute and chronic HF patients (13). Studies have shown that pericardial infusion of Gal -3 in normal rats resulted in cardiac remodeling and high Gal-3 levels correlated with highest level of fibrosis (10). All these observations collectively indicate circulating Gal-3 could help us identify high-risk patients prone for left ventricular remodeling leading to poor prognosis (14).

Hence, we aimed to compare the serum levels of BNP and Galectin-3 in cardiac failure of moderate LVD with severe LV dysfunction (LVD) and to determine whether serum Galectin-3 is an independent cardiac marker of structural ventricular remodeling in chronic cardiac failure.

MATERIALS AND METHODS

Selection of patients

With prior Institutional Ethical Committee clearance, 80 patients of 20-80 years, from both sexes, diagnosed as chronic HF using Framingham's HF criteria, admitted in the Department of Cardiology at Sri Ramachandra Medical College and Research Institute were chosen in this cross-sectional study.

Eighty patients included in this study had been diagnosed with chronic HF based on New York Heart Association (NYHA) Class III & IV Classification and ECHO with reduced ejection fraction (EF) of ≤ 45% and/ or diastolic dysfunction having normal kidney functions (serum creatinine < 0.8 -1.3 mg/dL in males; 0.6 - 1.2 mg/dL in females). Those of < 20 and > 80 years, with normal diastolic function and LVEF > 45% and patients with raised serum creatinine levels were excluded.

They were categorized into two groups: (i) HF having moderate LVD (EF > 36% and < 45%) and (ii) HF having severe LVD (EF < 35%). After obtaining written informed consent from each study patient, their complete medical history including age, sex, disease duration, details of hypertension, diabetes, ischemic heart disease (IHD), and other relevant illnesses were obtained from the study participants.

Laboratory measurements

Brain Natriuretic peptide (BNP) was estimated in serum using Abbott Architect instrument by MEIA method. Galectin -3 estimated in serum with Human Galectin-3 ELISA method. Serum creatinine estimated using Siemens EXL 200 by Jaffe's method. Using VIVID 9 GE equipment, left ventricular internal diameter diastole (LVIDD) and systole (LVIDS) in mm and left ventricular ejection fraction (LVEF) in % measured using Transthoracic Echocardiogram, was performed in all the patients by a single technical expert in the same equipment to reduce variation in measurements.

Statistical analysis

Statistical analysis was done using SPSS version 17.0. Parametric data were expressed in mean ± standard deviation and compared using independent sample student t - test to check statistical significance. Non-parametric variables were expressed as percentage. Multivariate linear regression analysis was done to assess the strength of univariate association. $P < 0.05$ was taken to be of statistically significant.

RESULTS

The study population consisting of 80 cardiac failure patients were grouped into two groups: (i) Group 1:- those with EF>36% and ≤ 45% labelled as Moderate LVD and (ii) Group 2:- those with EF ≤ 35% as severe LVD.

Basic characteristics of study participants presented in Table 1. Demographics of the study participants presented in Table 2. Measurements of BNP and Galectin -3 between the two groups were compared in Table 3. Multivariate linear regression analysis with respect to change in LVIDD was shown in Table 4.

Table. 3 showed that the mean values of both BNP and Galectin-3 were statistically significant in both the two study groups with significant P value**.**

Table 1: Basic characteristics of the study participants (n=80)

Characteristics	Variables	No (%)
Sex	Male	57 (71%)
	Female	23 (29%)
NYHA	Class III	31 (39%)
	Class IV	49 (61%)
Hypertension	Present	14 (17.5%)
	Absent	66 (82.5%)
Diabetes	Present	42 (52.5%)
	Absent	38 (47.5%)

Cardiomyopathy	Ischemic Dilated	44 (55%) 36 (45%)
ECHO (EF) % Group 1: Group 2:	 Moderate LVD Severe LVD	 32 (40%) 48 (60%)
Gal -3 (ng/ml)	Low risk (<17.8) Intermediate (17.9-25.9) High risk (>25.9)	26 (32.5%) 27 (33.75%) 27 (33.75%)

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

Table 2: Demographics of the study participants (n=80)

Variables	**Group 1 (n=33)**	**Group 2 (n=47)**
Age (years)	64.32±10.52	59.90±16.48
Sex Male Female	 25 (75.7%) 8 (24.3%)	 31 (66.0%) 16 (34.0%)
NYHA Class III Class IV	 31 (94%) 2 (6%)	 1 (2%) 46 (98%)
Diabetes mellitus Present Absent	 19 (57.6%) 14 (42.4%)	24 (51.1%) 23 (48.9%)
Hypertension Present Absent	 7 (21.2%) 26 (78.8%)	6 (12.7%) 41 (87.2%)
Ischemic cardiomyopathy Dilated cardiomyopathy	23 (69.7%) 10 (30.3%)	22 (46.8%) 25 (53.2%)

Group 1: CHF with moderate LVD; Group 2: CHF with severe LVD

Table 3: Comparison of BNP and Galectin - 3 between the two groups

Parameters	**Group 1 (n=33) (Mean ± SD)**	**Group 2 (n=47) (Mean ± SD)**	**P value**
BNP (pg/mL)	745.00 ± 684.15	1586.63 ± 1366.0	0.002*
Galectin -3 (ng/mL)	18.29 ± 1.54	27.22 ± 3.12	<0.001*

Group 1: CHF with moderate LVD; Group 2: CHF with severe LVD
SD = Standard Deviation; BNP = Brain Natriuretic Peptide; P<0.05* - statistically significant

Table 4: Multivariate linear regression analysis -change in LVIDD (mm)

Variables	**B**	**Standard error**	**Beta**	**P value**
Age	-0.83	0.59	- 0.144	0.164
Sex	0.245	1.946	0.014	0.900
NYHA	-2.263	3.352	- 0.134	0.502
LVEF	-0.204	0.376	- 0.167	0.589
DM	-0.612	1.798	- 0.037	0.735
HT	1.477	2.432	0.61	0.545
BNP	-0.001	0.001	- 0.074	0.527
Galectin-3	0.735	0.162	0.457	**<0.001***

Multivariate linear regression analysis as shown in Table 4 showed Galectin -3 as an independent predictor of LV remodeling about change in LV end- diastolic dimension with p<0.001 which was statistically significant whereas BNP did not show such significance.

DISCUSSION

In this study, as shown in Table 1, total of 80 cardiac failure patients were grouped into 3 risk-groups based on serum Gal -3 levels, of which 32.5% into low-risk group, 33.75% into intermediate risk group and 33.75% into high-risk group. As shown in Table 2, in our study out of the 80 participants, 71% were males and 29% were females similar to the study by Krumholz *et al.*, (15) who showed that men have a higher risk of heart failure than women among all the age groups.

This study showed that cardiac failure patients with severe LVD had significantly elevated Galectin - 3 levels when compared to moderate LVD as shown in Table 3. Milting *et al.*, (16) proved that elevated Galectin -3 levels predicted poor outcome in cardiac failure patients than in controls. As shown in Table 3, mean BNP levels were increased in severe LVD patients than in moderate LVD with P value of 0.002. Variations in BNP in both groups were due to the fact that lower BNP values were seen in HF due to dilated cardiomyopathy, whereas HF due to ischemic cause had higher BNP levels.

In our study, like Chen *et al.,* (17) increased Gal -3 levels were observed in severe LVD group than moderate LVD, concluding raised levels in serum had positive correlation with the disease severity along with varied class III and IV of NYHA. Also, in a study by Tang *et al.,* (18) increased Galectin-3 values correlated with higher NYHA class, poor renal function, and advanced age.

Lok *et al.,* (15) and van Kimmenade *et al*., (19) in their studies clearly demonstrated that the higher prognostic value of galectin-3 than NT-proBNP, making Gal-3 a sole predictor of mortality in moderate and advanced CHF. Natriuretic peptides viewed as 'loading markers', responds to ventricular stress, whilst gal-3 levels respond less to loading and are markers of interstitial fibrosis.

Ventricular remodeling occurring as a compensatory mechanism following any myocardial insult; causes architectural alteration in the ventricular chambers and associated volume increase due to myocyte hypertrophy and apoptosis, myo-fibroblast proliferation proceeding to interstitial fibrosis (20) which ultimately leads to LVD and HF. Galectin-3 is undetectable in myocytes of normal myocardium (21).

Gal-3, a soluble β- galactoside lectin on cardiac fibroblasts, secreted by activated macrophages leading to progressive inflammation and cardiac fibrosis (10) was first identified in rat models. Upregulated Gal -3 expression was observed in endocardial biopsies of rats causing cardiac hypertrophy progressing to failure (9) and in the humans, ventricular myocardial hypertrophy causing depressed systolic function, leading to an increased collagen expression, TGF - β activation, interstitial fibrosis and LV dysfunction (10,21).

Understanding this link of CHF associated with cardiac fibrosis in various animal models, various associations of Galectin-3 concentrations and LV structure and functions were investigated and positively correlated with ventricular internal diameter diastolic and systolic dimensions (LVIDD, LVIDS), end diastolic (LVEDD) and systolic volumes (LVESV) and demonstrated negative correlation with ejection fraction (EF). EF of left ventricles is a critical prognostic determinant in cardiac disorders. Solomon *et al.,* (22) showed baseline ESV, EDV and LVEF, each of them behaved as independent predictors of death or HF hospitalization.

White *et al.,* (23) studied the varied degrees of ventricular dysfunction of post-MI using LVEF, LVESV analysis were used to risk stratify patients, proving it to be a more powerful metric. The LVEDV index of > 120 mL/m^2 and LVESV of > 45 mL/m^2 also correlated with poor prognosis and outcome in CAD.

Hence multivariate linear regression analysis as shown in Table 4 was performed in this study and showed that Galectin-3 acts as an independent cardiac predictor of LV remodeling with regards to change in LV end-diastolic dimension with P <0.001 which was statistically significant whereas BNP did not show any statistical significance. Like our study, Lee *et al*., (24) proved that LVEDD as a sole predictor of survival in decreased LV ejection fraction.

In clinical practice, EF, a parameter which is grossly affected by the degree of remodeling is the most commonly used metric to assess cardiac performance. LV mass and volumes are the precise metrics of ventricular remodeling and relates to prognosis and impact of treatment than LVEF has been focused only on clinical trials. Similarly, Valsartan Heart Failure Trail (Val-HeFT) done in 5,010 patients with cardiac failure showed that changes in the baseline EF and LVEDD index changes over time were able to independently predict patient outcome (25).

Sharma *et al.,* (26) showed Gal-3 initiates proliferation of fibroblast through cyclin D1 activation, increasing collagen I production, an essential component which maintains myocardial structural and functional integrity. In the meantime, fibrosis and stiffening is enhanced by collagen cross- linking along with advanced glycation end products with high expression of MMP-1 tissue inhibitor thus proving that increased collagen deposition impacts both systolic and diastolic cardiac function and the progression from compensatory failure to overt cardiac failure is driven mainly by the over expression of Gal-3, in addition to anti-apoptotic actions.

Hence recognizing failure- prone cardiac status at an earlier stage and intervening with new anti-fibrotic agents could be more beneficial over current treatment strategies. Toprak *et al.,* (27) and Calvier *et al.,* (28) also proved the pathogenic feature of Galecin-3 in the failure progression, clearly suggesting that blocking Gal-3 can slow down the progress and decrease failure associated morbidity and mortality. Hence Galectin-3 can prove valuable for early detection, phenotyping status, risk categorization and therapeutic target in early cardiac failure (10). Various studies have been addressed that Gal -3 has prognostic value in heart failure and therapies which down-regulate the over expression of Gal-3 may serve as a new target in heart failure management.

Thus, targeting on Gal-3 can prove to be an ideal therapeutic guide for all types of cardiac failure but remains uncertain since there is lack of adequate knowledge regarding the transcriptional, translational regulation of Galectin-3. Previous studies on cardiac fibroblasts showed the involvement of TGF-β/Smad pathway. Though inflammatory signals regulate Galectin-3, further pharmacological studies must be explored as cytokines and few more factors involved in the Galectin-3 production remains unclear (10).

Limitations

The limitation was the smaller sample size and patients were not followed up as it was cross-sectional study.

Effect of medications used in cardiac failure treatment on Galectin -3 levels and its effects on LV remodeling must be further studied in a prospective study of larger study population.

CONCLUSION

Both Galectin-3 and BNP were elevated in CHF with severe LVD than moderate LV dysfunction. Multivariate linear regression showed that Gal -3 as an independent cardiac marker of ventricular remodeling in such patients whereas BNP did not show any statistical significance proving the usefulness of Galectin-3 for early detection and therapeutic target for such patients with early heart failure.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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