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Galectin-3 as a Predictor for Left Ventricular Remodeling After Anterior Wall Myocardial Infarction Treated by Primary Percutaneous Coronary Intervention

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Abstract

Background: This is a single center, observational prospective study that aimed primarily to study role of Galectin-3 (as a simple marker of inflammation and fibrosis) in prediction of the occurrence of LV remodeling after anterior ST-elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (pPCI) for Left anterior descending artery (LAD) or left main (LM) as infarct related artery. Patients and methods: The present study protocol yielded 2 groups of patients: First group, consists of patients found to have LVR with high galectin 3 levels at baseline and 6 months follow up after anterior STEMI treated with primary PCI to LAD or LM. Second group consists of patients found to have no LVR with low levels of galectin 3 levels at baseline and 6 months follow up after anterior STEMI treated with primary PCI to LAD or LM. Results: Baseline and 6 months EF were significantly higher in the no LVR (57±8 &55 ±8 respectively) group than the LVR group (44 ±7&37 ±8 respectively), P values were <0.001 for each. At 6-month ESV was significantly higher in the LVR group (94 ml) than the no LVR group (42 ml), P-value was <0.001. The median percent change was significantly higher in the LVR group (88.89 %) than the no LVR (5 %). EDV, the mean at 6 months was significantly higher in the LVR group (150 ml) than the no LVR group (94 ml), P-value was <0. 001.The median percent change was significantly higher in the LVR group (77.78%) than the no LVR (0.94%), P-value was <0.00. As regards gelactin-3, the median at baseline was significantly higher in the LVR group (21.8 ng/ml) than the no LVR group (9.6 ng/ml), P-value was <0.001 Table (8). The median percent change was significantly higher in the no LVR group (8.49%) than the LVR group (-31.4%). Conclusion: Gal-3 serum levels after pPCI were independently associated with LVR in patients with anterior STEMI and inversely related to LVEF after a STEMI. Therefore, this study opens the door for a hard question: could we use Gal-3 as part of a screening strategy to identify patients with anterior STEMI who are at higher risk of developing HF after STEMI.

Keywords: Galectin-3, Left Ventricular Remodeling, Anterior Wall Myocardial Infarction.

1. Introduction

Myocardial infarction (MI) is characterized by cardiomyocyte necrosis and acute loss of myocardium, which leads to structural and biomechanical changes to preserve cardiac function and minimize diastolic and systolic wall stress [4]. These changes include collagen deposition with scar formation, fibrosis, hypertrophy, and modifications in ventricular architecture that encompass changes in the size, shape and composition of the left ventricle. These modifications, often referred to as 'ventricular remodeling', can profoundly affect the function of the ventricle and the patient's prognosis [4].

LV remodeling is the major determinant of survival after recovery from MI and it has been strongly associated with clinical outcomes in numerous heart failure(HF) trials(5).In fact, evidence-based treatments that reduce mortality post MI, as β-blockers and angiotensin converting enzyme (ACE) inhibitors, have been shown to inhibit LV remodeling (1).

Galectin-3 is encoded by a single gene, LGALS3, which is located on chromosome 14, and consists of six exons and five introns (13) It is a β-galactoside-binding lectin with two domains, namely an atypical N-terminal domain and a C-terminal carbohydrate-recognition domain (CRD) [5]. It is predominantly produced by macrophages, but many other cell types that have been described in the setting of myocardial infarction, produce galectin-3 as well, e.g. neutrophils, eosinophils, mast cells (5) as well as fibroblasts [25].

In clinical studies, circulating galectin-3 levels have been shown to identify patients at risk for new onset heart failure and atrial fibrillation [19] . Its level predicts progressive left ventricle dilatation after myocardial infarction that conclude that it is an active player in cardiac remodeling post myocardial infarction (22). Galectin-3 has been extensively studied in HF[7]but only a few clinical studies evaluated its effect on LV remodeling post MI.

The aim of this work is to evaluate the role of Galectin-3 (as a simple marker of inflammation and fibrosis) in prediction of the occurrence of LV remodeling after anterior ST-elevation myocardial infarction treated by primary PCI.

2. Patients and methods

This is a single center, observational prospective study that enrolled 100 consecutive patients admitted for acute anterior STEMI treated by primary percutaneous coronary intervention (pPCI) for Left anterior descending artery or left main as infarct related artery at catheterization laboratory in Benha University Hospital & Mahala cardiac center over a period of 18 months.

Only adult patients (above 18 years) were included in this study with ischemic symptoms since <12 hours (eligible for pPCI) and ECG with ST-segment elevation ≥2 mm in ≥2 adjacent anterior precordial/peripheral leads or new left bundle branch block or new significant Q wave in ≥2 adjacent anterior precordial/peripheral leads. Left anterior descending artery or left main as infarct-related artery.

Patients with previous STEMI / NSTEMI , preexisting LV dysfunction (LV ejection fraction LVEF ≤ 50%), patients on mineralocorticoid receptor antagonists (MRAs may modify the biological activity of galectin-3 and subsequent LV remodeling)[10], or Patients with severe renal dysfunction [plasma creatinine level >220 µmol/L (2.4 mg/dl) and/or creatinine clearance <3mL/ min] were excluded from this study. Also, who with severe illness (Severe liver disease, Child-Pugh Class 3), cancer or life expectancy <6 months, cardiac arrest lasting >10 min or inability or unwillingness to comply with the treatment or follow-up visits) were excluded.

Ethical approval was obtained by Benha University Research Ethics Review Committee. Written informed consent was obtained from each patients of all participants.

Coronary angiograms done in the defined study period were consecutively analyzed by experienced cardiologists (two for each angiogram) at Benha University Hospital. The procedure was done according to the standard technique for coronary angiography and PCI.

Full history taking was collected from all patients including time of ischemic symptom, Killip classification during admission. End Systolic Volume (ESV), End Diastolic Volume (EDV) and Ejection fraction (by Simpson's biplane method) as measured by conventional echocardiography 36-48 after pPCI. Routine baseline laboratory investigations, in addition to cardiac troponin I (cTnI), galectin 3 (Gal-3).

Follow-up after STEMI will include a clinical visit and blood sampling for Gal-3 measurements at 6 months, when a two-dimensional echocardiogram will be again obtained.

2.1. Statistical Analysis

Data management and statistical analysis were done using SPSS vs.25. (IBM, Armonk, New York, United States). Numerical data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. Due to the small number in the LVR group, normality testing may be invalid. So, comparisons between LVR and no LVR groups were done using the Mann-Whitney U test for numerical data. Categorical data were compared using the Chi-square test. ROC analysis was done for gelactin-3 in the prediction of LVR. Area Under Curve (AUC) with 95%, best cutoff point, and diagnostic indices were calculated. P values less than 0.05 were considered significant.

3. Results

The mean age of the whole study population was 60 years. The number of male patients presenting was 55 % (45% were females). Although the LVR was more in male (76.9%) than female (23.1%), but it was statistically non-significant, p value 0.088. 95% patients had anterior STEMI and were included in the study Table (1). Sixty-six percent and 86% were diabetic and hypertensive, respectively. Forty-four percent were smokers. Dyslipidemia and obesity represented 64% and 31%, respectively Table (1).

The commonest clinical presentation among all patients on admission in both groups was chest pain (100%), nighty five percent of the whole patients were anterior (only 5.0% were lateral). The distribution on Killip class of these patients included in the study were more Killip class II (80%) and less in classes III (15%) and IV (4%). Although Killip class II was more in non LVR (85.1%) group than LVR (46.2%), it was statistically non-significant Table (2).

The median total ischemic time was 125 minutes (130 in LVR group vs 120 in non LVR group, p value 0.926) and ranged from 30 to 480 minutes. Mean first medical contact to device time was 72 minutes in LVR vs 63 minutes in non LVR with a standard deviation of 30 minutes, p value 0.275 Table (2).

Among patients proved to have anterior STEMI, 91% had TIMI flow grade 0 before PPCI (84 % in LVR group vs 80 % in non LVR,). After PPCI, the majority were grade III (85.0%) which was significantly higher in no LVR group (78 %) than LVR group (53 %), p value 0.001. Grade II was significantly higher (85.0%) in the LVR group than the no LVR group (53.8%), P-value was 0.001. Multivessel affection was higher in LVR group but statistically was non-significant while GP IIb/IIIa inhibitors' use was significantly

higher in LVR group (38.5% in LVR group vs 4.6% in non LVR, p value <0.001) Table (3).

Baseline and 6 months EF were significantly higher in the no LVR group (57±8 & 55±8 respectively) than the LVR group (44±7 & 37±8), P values were <0.001 for each. The mean EF at baseline for the whole patients was 56%. At 6 months, it was 53%. The median percent change was significantly higher in the no LVR group (-3.43%) than the LVR group (-9.58%), P-value was 0.001001 Table (4). At 6-month ESV was significantly higher in the LVR group (94 ml) than the no LVR group (42 ml), P-value was <0.001. The median percent change was significantly higher in the LVR group (88.89 %) than the no LVR (5%), P-value was <0.001001 Table (4). Regarding EDV, the mean at 6 months was significantly higher in the LVR group (150 ml) than the no LVR group (94 ml), P-value was <0. 001.The median percent change was significantly higher in the LVR group (77.78%) than the no LVR (0.94%), P-value was <0.001 Table (4).

As regards gelactin-3, the median at baseline was significantly higher in the LVR group (21.8 ng/ml) than the no LVR group (9.6 ng/ml), P-value was <0.001. The median percent change was significantly higher in the no LVR group (8.49%) than the LVR group (-31.4%), P-value was 0.02 Table (5).

ROC analysis was done to predict LV remodeling; it revealed an excellent Area Under Curve (AUC) of 0.897 with a 95% confidence interval ranging from 0.818 to 0.976. The best cutoff point was >19.3 at which sensitivity and specificity were 92.3% and 87.2% respectively. P-value was <0.001 Fig. (1).

Table (1) General characteristics in the whole study population.

		Total (n = 100)	LVR (n = 13)	No LVR (n = 87)	P value
Age (years)	**Mean ±SD**	60 ±8	59 ±11	60 ±8	0.817
Gender	**Males n (%)**	55 (55.0)	10 (76.9)	45 (51.7)	0.088
	Females n (%)	45 (45.0)	3 (23.1)	42 (48.3)	
Diabetes mellitus	**n (%)**	66 (66.0)	8 (61.5)	58 (66.7)	0.716
Hypertension	**n (%)**	86 (86.0)	9 (69.2)	77 (88.5)	0.062
Smoker	**n (%)**	45 (45.0)	9 (69.2)	36 (41.4)	0.06
Dyslipidemia	**n (%)**	64 (64.0)	8 (61.5)	56 (64.4)	0.843
Obesity	**n (%)**	31 (31.0)	5 (38.5)	26 (29.9)	0.533

Mann Whitney U test was used for age. Chi-square test was used for categorical data

Table (2) Clinical presentation on admission.

		Total (n = 100)	LVR (n = 13)	No LVR (n = 87)	P value
Location of STEMI	**Anterior n (%)**	95 (95.0)	13 (100.0)	82 (94.3)	NA
	Lateral n (%)	5 (5.0)	0 (0.0)	5 (5.7)	
Killip class on admission	**II n (%)**	80 (80.0)	6 (46.2)	74 (85.1)	
	III n (%)	15 (15.0)	3 (23.1)	12 (13.8)	
Total ischemic time (min.)	**Median (range)**	125 (30 - 480)	130 (60 - 480)	120 (30 - 400)	0.926
First medical contact to device time (min.)	**Mean ±SD**	71±30	72 ±30	63 ±25	0.275

Table (3) STEMI and pPCI procedural characteristics in the whole study population & in those with and without LVR.

		Total (n = 100)	LVR (n = 13)	No LVR (n = 87)	P value
TIMI flow before PPCI	**Grade 0 n (%)**	91 (91.0)	11 (84.6)	80 (92.0)	0.388
	Grade I n (%)	9 (9.0)	2 (15.4)	7 (8.0)	
TIMI flow after PPCI	**Grade II n (%)**	15 (15.0)	6 (46.2)	9 (10.3)	0.001
	Grade III n (%)	85 (85.0)	7 (53.8)	78 (89.7)	

No of vessel diseased	**One n (%)**	67 (67.0)	2 (15.4)	65 (74.7)	NA
	Two n (%)	30 (30.0)	9 (69.2)	21 (24.1)	
	Three n (%)	3 (3.0)	2 (15.4)	1 (1.1)	
Thrombectomy	**n (%)**	12 (12.0)	6 (46.2)	6 (6.9)	<0.001
Stent	**n (%)**	100 (100.0)	13 (100.0)	87 (100.0)	-
Type of the stent	**DES n (%)**	100 (100.0)	13 (100.0)	87 (100.0)	-
Diameter of the stent (mm)	**Mean ±SD**	3.23 ±0.33	3.23 ±0.33	3.23 ±0.33	0.954
Length of the stent (mm)	**Mean ±SD**	31 ±7	30 ±8	31 ±6	0.581
GP IIb/IIIa inhibitors' use	**n (%)**	9 (9.0)	5 (38.5)	4 (4.6)	<0.001

Mann Whitney U test was used for numerical data. Chi-square test was used for categorical data NA = Not applicable.

Table (4) Baseline & 6months Echocardiographic data in the whole study population & in those with and without LVR.

		Total (n = 100)	**LVR (n = 13)**	**No LVR (n = 87)**	**P value**
Ejection fraction					
Baseline	**Mean ±SD**	56 ±9	44 ±7	57 ±8	<0.001
6 months	**Mean ±SD**	53±10	37 ±8	55 ±8	<0.001
% change	**Median (range)**	-3.81 (-52.94– 11.29)	-9.58 (-45.18– 0.78)	-3.43 (-52.94 – 11.29)	0.001
ESV (ml)					
Baseline	**Mean ±SD**	40 ±8	50±7	39 ±8	<0.001
6 months	**Mean ±SD**	49 ±19	94 ±14	42 ±6	<0.001
% change	**Median (range)**	5.51 (-9.80– 144.90)	88.89 (27.59 – 144.90)	5.00 (-9.8–65.38)	<0.001
EDV (ml)					
Baseline	**Mean ±SD**	91± 12	91 ±14	91 ±12	0.0961
6 months	**Mean ±SD**	101 ± 22	150 ±20	94±10	<0.001
% change	**Median (range)**	1.07 (-18.75– 124.36)	77.78 (-2.73 – 124.36)	0.94 (-18.75– 52.54)	<0.001

Mann Whitney U test was used.

Table (5) Baseline & 6months gelactin-3 in the whole study population & in those with and without LVR.

		Total (n = 100)	**LVR (n = 13)**	**No LVR (n = 87)**	**P value**
Gelactin-3 (ng/ml)					
Baseline	**Median (range)**	13.2 (0.29 – 41.3)	21.77 (9.9 – 41.3)	9.85 (0.29 - 38)	<0.001
6 months	**Median (range)**	13.4 (1 – 36.9)	19 (3.8 – 36.9)	13.2 (1 - 33)	0.201
% change	**Median (range)**	-7.84 (-84.13 – 9520.69)	-31.4 (-82.49 – 27.78)	8.23 (-84.13 – 9520.69)	0.022

Mann Whitney U test was used.

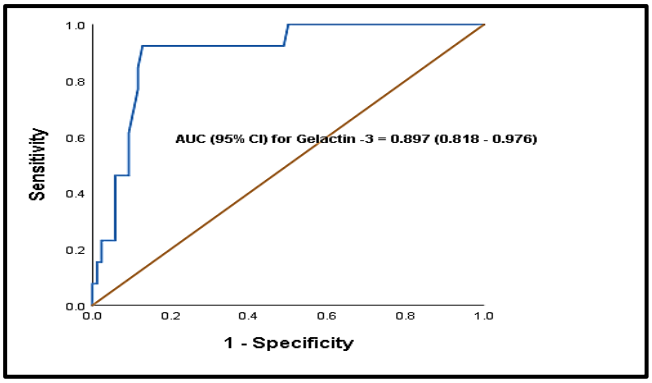

Fig. (1) ROC curve for gelactin-3 in the prediction of LVR.

4. Discussion

Post-MI LVR is a key precursor of the development of overt HF and an important predictor of mortality [12, 17]. LVR is reported to occur frequently after anterior STEMI, despite achievement of early flow in the infarct-related artery [11]. Gal-3, a β-galactoside-binding lectin secreted by activated macrophages, has recently been proposed as a marker of inflammation and fibrosis, both of which are implicated in LVR pathophysiology. After six months, Gal-3 anticipated a minimum 15% rise in LVESV, which is a widely accepted LVR criterion and a powerful predictor of prognosis following MI [24] regardless of LVEF or the size of the infarct.

Only few studies, based on subgroup analyses from randomized controlled trials, described Gal-3 levels in patients with acute MI. These studies were limited to the assessment of Gal-3 relationship with scar extension or LV function. Among 100 patients with reduced LVEF after acute MI [23] found an inverse correlation between baseline Gal-3 and LVEF after 6 months. However, they found no relationships between Gal-3 and LV parameters at baseline or any changes over time in any parameter. In a large, acute STEMI population(n = 247, a GIPS-III sub study) examined by [21] patients with elevated Gal-3 (≥17.8 ng/ml) measured at hospital admission had lower LVEF, higher LV end-systolic volume and larger infarct size evaluated by CMR 4 months after the MI than patients with levels below this limit. They conclude that baseline Gal-3 levels were independent predictors of lower LVEF and bigger infarct-related scars at 4 months. however, no baseline measures of LVEF or LV volumes were available [21].

In a larger cohort comprising 103 STEMI patients treated by pPCI, [4] reported that baseline Gal-3 predict an increase of at least 15% of LVESV after 6 months, which is a validated definition of LVR and a strong predictor of outcome after MI, irrespective of LVEF or infarct size.Gal-3 remained high in their LVR patients 1 month after MI, when it maintained its independent predictive value, but after 6 months no relationship with LVR was observed. So, they suggest that Gal-3 acts its pathophysiological role in pro remodeling pathways early post-MI, when high levels may reflect greater macrophage activation, extracellular matrix turnover and fibrosis and ensuing LVR [4].

This finding is in line with our observation during the 6-month follow-up, the relationship between circulating Gal-3 levels during the early post- STEMI phase and cardiac remodeling at the 6 months post- MI were inversely related to LV function (at baseline) and adverse LVR (an increase of at least 15% of LV ESV at the 6-month follow-up) where 13% of our successfully reperfused patients developed LVR after 6 months. Univariable logistic regression analysis showed that Gal-3 levels were associated with an increased risk of LVR and multivariable analysis adjusted by age, gender, and baseline EDV showed that galectin-3 was an independent prediction factor for LVR (OR was 1.203, with a 95% CI ranged from 1.085 – 1.333, P-value was <0.001).

In contrary to, [16] as they found no association between Gal-3 and LV volumes or infarct size during the first year following successfully revascularized first-time STEMI. In contrast to the acute setting, there was a modest but significant relationship between Gal-3 levels, MI size and LV volumes in patients with old MI. In Prospective study by [2] included 29 STEMI patients treated with pPCI, they found a significant association of serum Gal-3 levels and infarct size, after 4 months, but not statistically significant, correlation of Gal-3 and LVEF.

Galectin-3 was also described as a predictor of 30-day MACE in patients with STEMI who underwent primary percutaneous coronary intervention [20]. This result was confirmed in study with 52 STEMI patients, where increased serum Gal-3 levels were associated with in hospital MACE [15]. This short-term predictive value has also been confirmed in a long follow-up

period After STEMI, early post-intervention levels of Gal-3 were long-term predictors of all-cause death or heart failure hospitalization [3].

Due to short term follow up and the small sample of patients in our study, patients with high Gal-3 levels had no MACE at 6 months. It was similar to [4] where patients with abnormal Gal-3 levels had lower event-free survival rates at 6 months [4, 14]. They stated that **"** because low number of MACE in our study, it was not possible to establish a relationship with prognostic outcomes**"**.

In patients presented with STEMI and heavy thrombus burden in a culprit artery, manual thrombus aspiration has great value in reducing hospitalization and 1-month mortality which improve TIMI flow and left ventricular systolic function [6, 9]. The effects of intracoronary thrombectomy on LV remodeling had been studied in 109 patients with STEMI who underwent PCI plus thrombus aspiration with the Rescue catheter and 86 controls treated with conventional PCI. The incidence of LV remodeling, evaluated by cine angiography, was significantly lower in the thrombectomy group at six months [9].

Thrombectomy use was significantly higher in the LVR group (46.2%) than the no LVR group (6.9%), P-value was <0.001. Also, GP IIb/IIIa inhibitors' use was significantly higher in the LVR group (38.5%) than the no LVR group (4.6%), P-value was <0.001.

It was similar to, The enhanced Myocardial efficacy and recovery by aspiration of liberated debris (EMERALD) trial that failed to show any improvement in microvascular flow, reperfusion success, infarct size, LVR, and event free survival in patients with STEMI undergoing primary PCI with a balloon occlusion and aspiration distal microcirculatory protection system [18].

Anterior STEMI has higher mortality and risk of developing HF than other MI sites [27]. The primary goal is to reduce total ischemia time, which is the time interval from the start of STEMI symptoms and the reperfusion treatment initiation. However, the patients who derive the most benefit are those treated earliest and those at the highest risk, such as those with anterior STEMI [27]. This study focused on the first anterior STEMI, where 95% of the whole patients were anterior. Most of them were admitted with Killip class II (80.0%). The median total ischemic time was 125 minutes. The mean first medical contact to device time was 71 minutes. Regarding TIMI flow before PPCI, most patients were grade 0 (91.0%), and the studied groups showed no significant difference on the univariate level. As regards the LVR group after PPCI, grade II was significantly higher (85.0%) compared to the non-LVR one (53.8%); P-value was 0.001.

This finding was similar to the GALAMI study done by [4] included 103 consecutive patients presented with de novo anterior STEMI, Killip class > I, and symptoms to balloon time of 3 hours (2–4h). The studied groups did not show a significant difference as regards the Killip class. In contrast,[28] reported that 44% showed inferior STEMI, and 86% showed Killip class I. The mean time from the start of symptoms to artery open was 270 minutes. Although patients with no TIMI III flow showed slightly higher levels of Galectin-3 compared to those with TIMI III flow after PPCI, the difference was not statistically significant. The Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI-22) trial included patients with prior MI or HF. Only a third had anterior STEMI, and two-thirds underwent PPCI for the index event [28]. It did not focus on total ischemic time or TIMI flow before or after PPCI.

Up to date, there are no convincing clinical data to suggest a specific treatment driven by elevated Gal-3 levels. [23] reported no significant treatment effect of eplerenone on serum Gal-3 levels over the 24-week study period, while the post-hoc analysis by [21] suggested that MRAs might be used to lower Gal-3 levels and, indirectly, reduce the risk of developing LV dysfunction. In our study, MRA treatment was an exclusion criterion. Our data suggest that patients at risk of LVR with elevated Gal-3 levels might benefit from early therapy with MRA after MI possibly adverse outcomes related to LV dysfunction.

5. Conclusion

Gal-3 serum levels after pPCI were independently associated with LVR in patients with anterior STEMI and inversely related to LVEF after a STEMI. Therefore, this study opens the door for a hard question: could we use Gal-3 as part of a screening strategy to identify patients with anterior STEMI who are at higher risk of developing HF after STEMI

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