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Galectin-3 and Severity of The Coronary Artery Disease in Ischemic Patients Guided by Coronary Angiography

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ABSTRACT

Background: The inflammatory process is actively involved in atherosclerosis and underlies all stages of atherosclerotic plaque development: the beginning, the progression and the plaque rupture. It has been reported that during the inflammatory process the expression of Gal-3 is increased in human atherosclerotic lesions, suggesting its involvement in atherogenesis. **Aim:** In the present study, we tried to evaluate the levels of Gal-3 in patients with chronic stable angina and its relation to the severity of coronary artery disease (CAD) and the CAD risk factors such as Aging, Diabetes, Hypertension, Smoking and Dyslipidemia. **Patients and Methods:** Our study population consisted of 95 chronic stable angina patients who were planned for coronary angiography. All patients had clinical and/or electrocardiographic evidence of significant stable ischemic heart disease**.**
Results: We found a significant positive correlation between CAD and Gal-3 levels (r = 0.207), (p value= 0.045). Patients with multi-vessel (MVD) had significantly higher plasma Gal-3 levels and syntax score than 3 vessel disease (TVD) and single vessel disease (SVD) (P value <0.001)., while Patients with TVD had significantly higher plasma Gal-3 levels and syntax score than SVD, but still lower than MVD Patients (P value <0.001.
Conclusion: Gal-3 plasma levels were significantly correlated with the severity of CAD in chronic stable angina and can be used as a prognostic marker of chronic stable angina patients.
Recommendation: We recommend that the Gal-3 might be useful for risk stratification and outcome prediction of coronary heart diseases.
Keywords: Coronary artery disease, syntax score, chronic stable angina.

INTRODUCTION

The inflammatory process is actively involved in atherosclerosis and all stages of atherosclerotic plaque development: the beginning, the progression and the plaque rupture[1]. In recent years, several studies have been done define the mechanism that leads to acute clinical events, and systemic approaches are pursued to discover serum biomarkers useful to identify patients with plaque at risk of future vascular events[2,3]. Galectin-3 (Gal-3) is a galactosidase-binding protein and a member of the Galectin family which contains more than 10 members. It is expressed in the epithelia of several organs and inflammatory cells such as macrophages, dendritic cells and Kupffer cells[4]. The extracellular Gal-3 has been demonstrated to activate different types of inflammatory cells such as monocytes/macrophages, mast cells, neutrophils, and lymphocytes, and it has been shown to facilitate cell-cell and cell-matrix interaction[5]. It is known that Gal-3 is able to form dimers through the amino-terminal non-lectin domain that allows cross-linking appropriate glycoproteins on the cell surface[6].During the inflammatory process this lectin is up regulated and it has been reported that the expression of Gal-3 is increased in human atherosclerotic plaques, suggesting its involvement in atherogenesis[7]. In the present study, we will try to evaluate the levels of Gal-3 in patients with chronic stable angina and its relation to the severity of CAD and the coronary artery disease risk factors such as Aging, Diabetes, Hypertension, Smoking and Dyslipidemia.

AIM OF THE STUDY

we tried to evaluate the levels of Gal-3 in patients with chronic stable angina and its relation to the severity of CAD and the coronary artery disease risk factors such as Aging, Diabetes, Hypertension, Smoking and Dyslipidemia.

PATIENTS AND METHODS

Our study was conducted from January 2018 to July 2018 at Aswan university hospital. Our study population included 95 chronic stable angina patients who were planned for coronary angiography. All patients had clinical and/or electrocardiographic evidence of significant stable ischemic heart disease. Patients with Prior heart failure, Severe valvular heart diseases, Connective tissue diseases, Coexisting cancers and chemotherapy and radiotherapy, Pericardial disease, Cirrhosis and Atrial fibrillation were excluded from the study.

All the patients were subjected to

A) **Clinical assessment including** (CV risk factors, general and local examination).
B) **Electrocardiography** twelve leads resting ECG done for all patients to exclude non-sinus rhythm and to detect any ischemic changes or arrhythmias.
C) **Echocardiography** done in the left lateral position using Philips IE 33 X51 MHz transducer on outpatient basis, m-mode and 2 D was acquired to evaluate

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systolic and diastolic function, regional wall motion abnormalities and left ventricular ejection fraction, and also to exclude other causes of chest pain[8].

D) **Peripheral Blood samples** to measure the following parameters (random blood glucose, renal function, lipid profile and Plasma Gal-3). Peripheral blood samples and plasma Gal-3 assay were gathered within 24 hours from admission. Peripheral blood samples were collected in test tubes containing Ethylene diamine tetra acetic Acid (EDTA) and heparin. The EDTA blood sample was centrifuged 1000 xg for 15 minutes and plasma was frozen at -20 c. Plasma concentrations of Gal-3 were detected by an enzyme-linked immunosorbent assay kit (Bioscience, American)[9].

E) Coronary angiography for diagnosis of CAD Coronary angiography done using a modified Seldinger's technique; an 18- gage thin-walled needle is inserted at a 30- to 45- degree angle into the femoral artery, and a 0.035 or 0.038 in. J-tip Teflon-coated guide wire is advanced through the needle into the artery[10]. an arterial sheath with proximal one-way valve and side arm is placed over the wire and allows multiple catheter exchanges. Sheath diameter is at least equal to coronary catheter diameter (typically 6 French sheaths are used). The Judkins left 4 (JL4) and JL3.5 were used to engage the left coronary system and The Judkins right 4 (JR4) catheter is used in the majority of cases to access the right coronary artery. After finishing the procedure, manual compression is most commonly used for hemostasis after removal of the indwelling femoral artery sheath[10].Assessment of the severity of the CAD was done by using the syntax score.

SYNTAX score was calculated retrospectively based on diagnostic angiograms obtained before the PCI by two experienced interventional cardiologists using the SYNTAX score calculator (available at http://www.syntaxscore.com). In case of disagreement, the opinion of a third observer was obtained, and the final decision was made by consensus[11].

Statistical analysis

The data were tested for normality using the Anderson-Darling test and for homogeneity variances prior to further statistical analysis. Categorical variables were described by number and percent (N, %), where continuous variables described by mean and standard deviation (Mean, SD). Chi-square test and fisher exact test used to compare between categorical variables where compare between continuous variables by t-test and Independent-Samples T test ANOVA. A two-tailed $p < 0.05$ was considered statistically significant. We are used person and spearman correlation to appear the association between variables. All analyses were performed with the IBM SPSS 20.0 software[12].

RESULTS

Our study included 95 patients that were diagnosed as chronic stable angina and were planned for coronary angiography between 1st January 2018 and 31th July 2018. Their mean age was (57.05±7.77) ranges from 37 to 68 years, 62.1% (59) were males and 37.9 % (36) were females (table 1).

Demographic characteristics of the studied population: (Table 1)

Variables		Patients(n=95)
Age (years)	Mean ±SD	57.05 ± 7.77
Sex	M (n, %) F (n, %)	59 (62.1%) 36 (37.9 %)
Hypertension	Yes (n, %) No (n, %)	59 (62.1%) 36 (37.9 %)
Diabetes	Yes (n, %) No (n, %)	51 (53.7%) 44 (46.3%)
Smoking	Yes (n, %) No (n, %)	59 (62.1%) 36 (37.9 %)
Positive family history for CAD	Yes (n, %) No (n, %)	33 (34.7%) 62 (65.3%)
Dyslipidemia	Yes (n, %) No (n, %)	34 (35.8%) 61 (64.2%)
Total cholesterol, mg/dL	Mean ±SD	206.33 ± 36.75
HDL-C, mg/dL	Mean ±SD	41.85 ± 10.08
LDL-C, mg/dL	Mean ±SD	128.49 ± 33.3

HDL-C=High density lipoprotein cholesterol, LDL-C= low density lipoprotein cholesterol, SD= standard deviation.

Every patient in our study was subjected to clinical, laboratory and echocardiographic evaluation. Table 2 shows the measurement of interest in our study including BMI (kg/m2), creatinine clearance, galectin-3 (ng/mL), LVEF (%). Mean LVEF was (56±70) and the level of Gal-3 ranged from 1.77 to 23.4 ng/ mL, with a median of 7.88 ng/mL (Table 2).

Clinical, Laboratory and echocardiographic data of the studied patients: (Table 2)

Variables		Patients(n=95)
Galectin-3 (ng/mL)	Mean ±SD	10.1 ± 7.08 7.88 (Median)
Syntax score	Mean ±SD	15.97 ± 7.87
LVEF (%)	Mean ±SD	56% ± 70%
Cr. Cl	Mean ±SD	86.32 ± 7.18
BMI (kg/m2)	Mean ±SD	26.95 ± 2

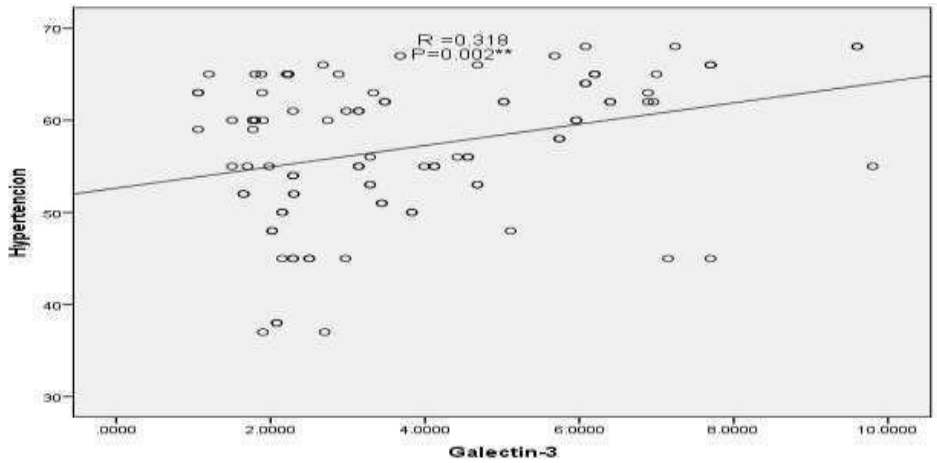
SD = standard deviation, Cr. Cl = creatinine clearance, LVEF = left ventricular ejection fraction, BMI = body mass index.

In the CAD population, Plasma concentrations of Gal-3 levels were positively Correlated with hypertension (Fig1), while showed non-significant correlation with diabetes Mellitus, Cr. Cl, BMI, smoking, age, and LDL-C (Table3).

Correlation between Gal-3 CV risk factors: (table3).

Variables	r	P value
Hypertension	0.318	0.002**
Diabetes	-0.051	0.623
Smoking	0.058	0.574
Age	0.026	0.801
BMI	-0.056	0.589
LDL-C	0.087	0.403
Cr. Cl	-0.014	0.893

*** Statistically significant correlation (p<0.05), ** statistically significant correlation (p<0.01) Cr. Cl = creatinine clearance, BMI = body mass index, LDL-C = low density lipoprotein cholesterol.**



(Fig1) Correlation between Gal-3 and hypertension

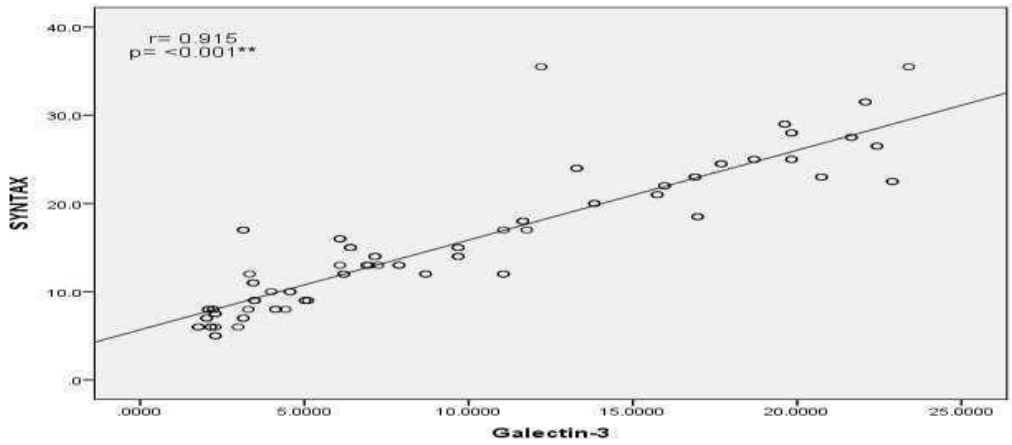
Every patient in our study was subjected to coronary angiographic evaluation. Single vessel disease was present in 31 patients (32.6%), two vessel diseases was present in 24 patients (25.3%) and three vessel diseases was present in 40 patients (42.1%). There was a significant positive correlation between severity of CAD

(assessed by syntax score) and Gal-3 (r = 0.915), (p value <0.001) (Fig2). Patients with MVD had significantly higher plasma Gal-3 levels and syntax score than TVD and SVD, (P value <0.001). Patients with TVD had significantly higher plasma Gal-3 levels and syntax score than SVD, but still lower than MVD, (P value <0.001). (Table4).

Comparison between numbers of coronary vessels affected, Gal-3 and syntax score (Table4)

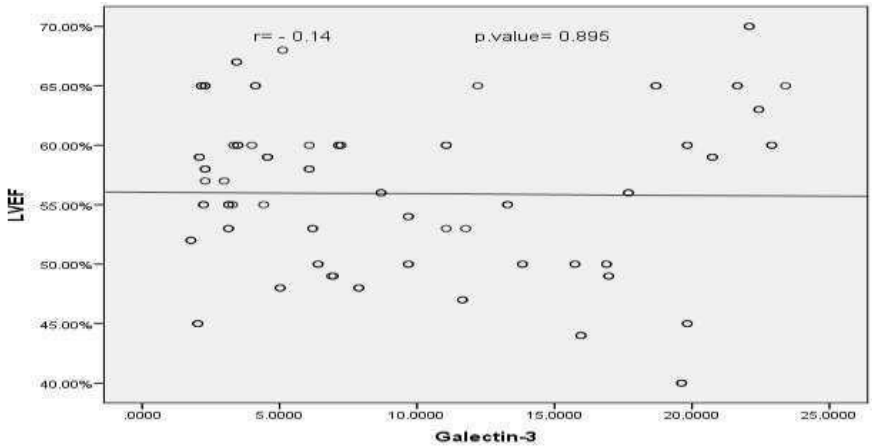
	CAD			P. value
	MVD	SVD	TVD	
	Mean±SD	Mean±SD	Mean±SD	
SYNTAX score	23.68±5.27	8.39±2.89	12.92±2.15	<0.001**
Gal-3	17.5±3.93	2.96±0.95	6.99±1.78	<0.001**
Median	17.690	2.980	6.925	

One-way ANOVA test, * statistically significant difference (p<0.05), ** highly significant difference (p<0.01). SVD = single vessel disease, TVD = two vessel disease, MVD = multi vessel disease, SD = standard deviation, CAD = coronary artery disease.



(Fig2) Correlation between Gal- 3 and syntax score.

In our study LVEF was measured by transthoracic echocardiography using m-mode method and correlated with Gal-3 and we found that there was no significant correlation between Gal-3 and left ventricular ejection fraction (r = -0.14), (p value = 0.895). (Fig3**).**



(Fig3) Correlation between Gal-3 and LVEF

DISCUSSION

Several independent pathways of evidence suggest inflammation as a key regulatory process that links the atherosclerotic risk factors and its complications with altered arterial biology. This new evidence regarding the pathophysiology of atherosclerosis has provided clinical insight and practical tools that may concur in patient management[13]. In the present observational prospective study, we tried to evaluate the levels of Gal-3 in patients with chronic stable angina and its relation with the severity of CAD and the coronary artery disease risk factors such as Aging, Diabetes, Hypertension, Smoking and Dyslipidemia.

Correlation between Gal-3 and CV risk factors:

Our study showed that plasma concentrations of Gal-3 levels was positively correlated with hypertension, while showed non-significant correlation with diabetes Mellitus, Cr. Cl, BMI, age, smoking, and LDL-C in the CAD population[14]. Our findings are in agreement with **Yao** who showed that serum Gal-3levels increase in patients with hypertension; however, it is more obvious in patients with left ventricular hypertrophy. Therefore, Gal-3 is independently correlated with left Ventricular remodeling (LVR) and can be regarded as a valuable biomarker for early Cardiac remodeling[15]. These findings may be explained by the fact that Hypertension is normally a chronic medical condition characterized by elevated arterial blood pressure. Hypertensive cardiac remodeling begins with inflammation, an increased deposition of extracellular matrix proteins, followed by formation of myocardial fibrosis and finally cardiac dysfunction[16].

Correlation between Gal-3 and CAD:

There is a significant positive correlation between CAD and Gal-3 (r = 0.207), (p value= 0.045). Our findings are also in agreement with **Kusaka** who observed that the higher concentrations of galectin-3 in CAD patients[17]. Our findings are also in agreement with **Aksan** who found that the serum Gal-3 level had a positively correlated with the severity of coronary artery stenosis, number of vessels involved and serum C-reactive protein levels[18]. These findings may be explained by the fact that Gal-3, a major inflammatory signal and promoter, can activate reduced-coenzyme, increase neutrophil superoxide production, stimulate outbreak of the respiratory chain and trigger oxidative-stress reactions leading to an increase in uptake of ox-LDL by vascular endothelial cells, macrophages and smooth muscle cells, eventually causing the proliferation of foam cells and promoting atherosclerosis[19].

Comparison between numbers of coronary vessels affected, Syntax score and Gal-3:

Patients with MVD had significantly higher plasma Gal-3 levels and syntax score than TVD and SVD, (P value <0.001). Patients with TVD had significantly higher plasma Gal-3 levels and syntax score than SVD, but still lower than MVD, (P value <0.001)[20].

Our findings are in agreement with **Sanchez-Mas** who found that Patients with three vessel disease had higher levels of Gal-3 than patients with 1- or 2vessel disease. Gal-3 levels were significantly higher in patients diagnosed with MI or CHD compared to control [21,22]. Our findings are in agreement with **Falcone** who found that patients with three vessel disease had higher levels of Gal-3 than patients with 1- or 2-vessel disease[23]. Our findings are also in agreement with **the study of T sail** who observed that multivessel coronary patients had higher level of Gal-3 than control group, and multi vessel disease correlates with higher Gal-3 level and WBC count. There is a significant association between Gal-3 and number of affected coronary blood vessels[24].

Correlation between Gal-3 and left ventricular ejection fraction:

There is no significant correlation between Gal-3 and left ventricular ejection fraction (r = -0.14), (p value = 0.895). These findings may be explained by the fact that Gal-3 has been proposed as a biomarker involved in the pathophysiology of HF and may be of lesser importance during the early stage of disease [25,26]. In HF, Gal-3 concentration is associated with echocardiographic marker of ventricular ejection fraction [28]. The left ventricular ejection fraction in our patients was comprised in normal range and we did not observe a relation between Gal-3 and left ventricular ejection fraction. Recently, other studies have reported the absence of this relation and in particular, no association between LVEF $\geq$ 40% and value of plasma Gal-3 levels was observed [27,28].

CONCLUSION

Gal-3 plasma levels are significantly correlated with the severity of CAD in chronic stable angina and can be used as a prognostic marker of chronic stable angina patients.

RECOMMENDATION

We recommend that the Gal-3 might be useful for risk stratification and outcome prediction of coronary heart diseases.

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