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Original article

Evaluation of galectin-3 levels in acute coronary syndrome

Évaluation des niveaux de la galectine-3 dans le syndrome coronarien aigu

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Abstract

Galectin-3 is a new biomarker that is assumed to reflect fibrogenesis and inflammation. In this study, we aimed to evaluate the levels of galectin-3 in patients with acute coronary syndrome (ACS) and the relation of galectin-3 to the burden of atherosclerosis. Nineteen patients with ACS who underwent coronary angiography and 17 age-matched healthy controls were enrolled. The burden of atherosclerosis was assessed with Gensini score and with the number of involved vessels. Galectin-3 levels were measured on admission by using ELISA. The mean age of the cohort was 62.8 ± 10.6 and 56% of the patients were male. Compared to control group, median galectin-3 levels were significantly higher in ACS patients (0.77 ng/mL [0.50–1.19] vs. 0.51 ng/mL [0.41–0.78], $P = 0.01$). Patients were classified into three groups according to the number of involved vessels. Median galectin-3 levels did not differ significantly among groups (one vessel: 0.68 ng/mL [0.55–0.74], two vessels: 0.67 ng/mL [0.46–1.84], three vessels 0.90 ng/mL [0.53–1.38], $P = 0.62$). There was a strong correlation between galectin-3 levels and Gensini score ($r = 0.625$, $P = 0.004$). In conclusion, galectin-3 levels were elevated in patients with ACS and there was a strong correlation between galectin-3 levels and Gensini score.

Keywords: Acute coronary syndrome; Atherosclerosis; Biomarker; Galectin-3; Gensini

Résumé

La galectine-3 est un nouveau biomarqueur qui est supposé refléter la fibrogenèse et l'inflammation. Dans cette étude, nous avons l'intention d'évaluer les niveaux de la galectine-3 pour les patients avec un syndrome coronarien aigu (SCA) et la relation de la galectine-3 à la charge de l'athérosclérose. Dix-neuf patients avec un SCA qui ont subi une angiographie coronarienne et 17 témoins sains appariés selon l'âge étaient inscrits. La charge de l'athérosclérose a été évaluée avec le score Gensini et le nombre de navires concernés. Les niveaux de la galectine-3 à l'admission ont été mesurés en utilisant le test ELISA. L'âge moyen de la cohorte était de $62,8 \pm 10,6$ et 56 % des patients étaient masculins. Par rapport au groupe témoin, les médianes de la galectine-3 étaient significativement plus élevées pour les patients avec SCA (0,77 ng/mL [0,50–1,19] vs 0,51 ng/mL [0,41–0,78], $p = 0,01$). Les patients ont été classés en trois groupes selon le nombre de navires concernés. Les médianes des niveaux de la galectine-3 n'ont pas différé significativement entre les groupes (un navire : 0,68 ng/mL [0,55–0,74], deux navires : 0,67 ng/mL [0,46–1,84], trois navires : 0,90 ng/mL [0,53–1,38], $p = 0,62$). Il y avait une forte corrélation entre les niveaux de la galectine-3 et le score Gensini ($r = 0,625$, $p = 0,004$). En conclusion, les niveaux de la galectine-3 ont été élevés pour les patients avec un SCA et il y avait une forte corrélation entre les niveaux de la galectine-3 et le score Gensini.

Mots clés : Athérosclérose ; Biomarqueur ; Galectine-3 ; Gensini ; Syndrome coronarien aigu

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1. Introduction

Despite significant improvements in diagnosis and treatment in the recent decades, cardiovascular diseases still remain as the leading cause of mortality and morbidity, with coronary artery disease being the major cause [1]. Acute coronary syndrome (ACS) represents the main concern to the investigators within the spectrum of coronary artery disease. Early diagnosis and risk stratification can alter the course of the disease and improve the survival. There have been a number of studies worldwide to find a useful biomarker in order to make an early and accurate diagnosis, predict prognosis and identify high-risk patients [2].

Galectin-3 is a soluble B-galactoside-binding lectin that mediates different pathways of inflammation and fibrosis [3]. It is expressed by activated macrophages and regulates several inflammatory cells including lymphocytes, neutrophils, monocytes and mast cells [4,5]. Studies have shown that galectin-3 induces the migration of monocytes and macrophages, triggers antioxidant secretion from active phagocytic cells, promotes fibroblasts proliferation and increases collagen synthesis [6–8]. A genetic mutation in galectin-3 has been shown to impede these pathways causing inadequate phagocytosis and impaired immune response [9]. Those properties emphasize the pivotal role of galectin-3 in inflammation and fibrosis, motivating numerous studies evaluating the function of galectin-3 in cardiovascular diseases [10–12]. Although several studies have been conducted to assess the association of galectin-3 in heart failure and remodeling, less is known about the role of galectin-3 in coronary artery disease and in ACS [11,12]. In this study, we aimed to evaluate the galectin-3 levels in patients with ACS and the relation of galectin-3 with the severity of the coronary artery disease.

2. Methods

2.1. Study patients

Nineteen patients with ACS who underwent coronary angiography and 17 age-matched controls without a history of coronary artery disease or heart failure were prospectively enrolled in our study. Patients diagnosed with ST and non-ST elevated myocardial infarction were included as ACS. Non-ST elevated myocardial infarction diagnosis was based on elevated cardiac enzymes with typical chest pain and/or electrocardiographic changes suggestive of myocardial ischemia. ST elevated myocardial infarction diagnosis was based on presence of prolonged chest pain and ST-segment elevation (>1 mm in two or more standard leads or ≥2 mm in two or more contiguous precordial leads), or the presence of new left bundle branch block. Routine treatment was initiated according to current ACS guidelines.

Information regarding risk factors including age, gender, diabetes mellitus, hypertension, hyperlipidemia, and smoking status was obtained. Hypertension was defined as blood pressure >140/90 mmHg on >2 occasions during office measurements or use of antihypertensive treatment. Diabetes mellitus was defined as fasting blood glucose >126 mg/dL or use of antidiabetic treatment. Hyperlipidemia was considered to be present in patients with fasting total cholesterol ≥200 mg/dL or triglyceride ≥150 mg/dL. Body mass index was calculated by dividing weight in kilograms by height in squared meters. Glomerular filtration rates were estimated with the Modification of Diet in Renal Disease equation [13]. Coronary artery disease was defined as documented coronary stenosis of >50%. The severity of the coronary artery disease was assessed by Gensini score and with the number of involved vessels [14]. Transthoracic echocardiography was performed for each patient immediately after hospitalization using a commercially available machine (Vivid 3®, GE Vingmed Ultrasound) with a 3.5-MHz transducer. Simpson's method was used to assess the left ventricular ejection fraction. The Institutional Research Ethics Committee approved the study and informed consent was obtained from each patient.

2.2. Laboratory

Venous blood samples were obtained immediately after index admission. Plasma glucose, aspartate aminotransferase, alanine aminotransferase, creatinine, troponin I, triglyceride, total cholesterol, and high-density lipoprotein cholesterol levels were measured by using standard methods. Low-density lipoprotein cholesterol levels were calculated according to the Friedewald formula [15]. Hemoglobin and white blood cell count values were measured using an automated hematology analyzer. Blood samples were centrifuged within 60 minutes of sampling, serum was isolated and stored at −20 °C for galectin-3 measurement. After collecting all serum samples, galectin-3 was measured by solid phase enzyme linked immunosorbent assay (ELISA) with a commercially available kit (eBioscience, San Diego, USA) at Hacettepe University, School of Sports Sciences Laboratory.

2.3. Statistics

Continuous variables were expressed as mean ± standard deviation or as median with interquartile range; and categorical variables were expressed as number and percentages. A χ^2 test or Fisher's exact test was performed to compare the categorical variables. Student's *t*-test was used for normally distributed continuous variables, and Mann-Whitney U test or Kruskal-Wallis test were used when the distribution was skewed. The optimal cut-off level of galectin-3 to detect ACS was evaluated by using the area under the receiver operating characteristic (ROC) curve. Spearman correlation analysis was performed to evaluate the relationship of galectin-3 with clinical and biochemical parameters. All statistical analyses were performed with SPSS software version 17.0 (SPSS Inc., Chicago, IL). A *P*-value of 0.05 was considered statistically significant.

3. Results

The mean age of the study participants was 62.8 ± 10.6, with men comprising 56% of the cohort. The baseline demographics, risk factors and laboratory findings of the enrolled subjects

Table 1
Demographics, risk factors and laboratory findings of the patients with ACS in comparison with control group.

	Total ($n=36$)	ACS ($n=19$)	Control ($n=17$)	P
Age (years)	62.8 ± 10.6	64.5 ± 7.6	60.9 ± 7.6	0.3
Gender (% female/% male)	44/56	42/58	47/53	1
Diabetes mellitus	5 (14%)	4 (21%)	1 (6%)	0.34
Hypertension	11 (31%)	7 (37%)	4 (23%)	0.38
Hyperlipidemia	10 (28%)	4 (21%)	6 (35%)	0.46
Smoking	12 (33%)	6 (32%)	6 (35%)	0.81
Body mass index (kg/m^2)	25.4 ± 4.3	24.3 ± 3.6	26.6 ± 4.7	0.1
Galectin (ng/mL)	0.67 (0.46–0.84)	0.77 (0.50–1.19)	0.51 (0.41–0.78)	0.01
Glucose (mg/dL)	114.5 (101.7–131.5)	123 (112.4–177)	111 (96–116.5)	0.01
Creatinine (mg/dL)	0.94 (0.73–1.2)	0.87 (0.73–1.74)	0.97 (0.7–1.2)	0.3
Glomerular filtration rate (mL/min)	73.4 ± 22.4	65.8 ± 23.1	82 ± 18.8	0.02
Total cholesterol (mg/dL)	190 (174–240.2)	182 (163–289)	190 (174–220)	0.59
Triglyceride (mg/dL)	98.5 (65–165)	101 (76–158)	96 (59–243)	0.67
High-density lipoprotein (mg/dL)	48.7 (44.1–62.6)	47 (34.5–62.7)	49.4 (474.7–63)	0.64
Low-density lipoprotein (mg/dL)	118 (94.2–153.3)	119 (105–200.5)	113 (80.8–148.5)	0.31
Alanine aminotransferase (IU)	16.9 (13.2–22.3)	19 (12.7–23.1)	16 (12–20.3)	0.4
Aspartate aminotransferase (IU)	19 (17–23.7)	29.5 (19.5–46)	18.6 (16–21.5)	0.004
White blood cell count ($\times 10^3/\mu L$)	6.45 (5.56–7.51)	8.03 (7.02–10.5)	6.2 (5.38–6.9)	0.001
Hemoglobine (g/dl)	13.9 (13.4–15.1)	15.8 (10.7–16.3)	13.9 (13.5–14.3)	0.4

Table 2
Clinical characteristics of the patients with ACS.

Variables	ACS patients ($n=19$)
Previous coronary artery disease	5 (26%)
Heart failure signs and symptoms	3 (16%)
Triple vessel disease	10 (53%)
Gensini score	40 (22–55.5)
ST-segment elevation	7 (37%)
Ejection fraction (%)	51.4 ± 12.5
Ischemic mitral regurgitation	6 (32%)
Troponin level on admission (ng/mL)	8.1 (2.9–17.8)

are summarized in Table 1. The clinical characteristics of the patients with ACS are summarized in Table 2.

In the ACS group, 12 patients had non-ST elevation myocardial infarction and 7 patients had ST elevation myocardial infarction. All patients underwent coronary angiography. Seventeen patients underwent percutaneous coronary intervention ($n=10$) or surgery ($n=7$), and remaining 2 cases received conservative treatment. Compared to control group, median galectin-3 levels were significantly higher in ACS patients (Fig. 1). ROC analysis showed that a galectin-3 value of ≥0.68 ng/mL predicted ACS with 68% sensitivity and 69% specificity (area under curve: 0.74, 95%CI: 0.57–0.90, $P=0.01$).

When patients were classified into three groups according to the number of involved vessels, median galectin-3 levels did not differ significantly among groups (one vessel: 0.68 ng/mL [0.55–0.74], two vessels: 0.67 ng/mL [0.46–1.84], three vessels 0.90 ng/mL [0.53–1.38], $P=0.62$; Fig. 2).

The results of the correlation analysis are shown in Table 3. There was a strong correlation between galectin-3 levels and Gensini score ($r=0.625$, $P=0.004$). Galectin-3 levels were also correlated with glomerular filtration rate ($r=-0.409$, $P=0.01$), left ventricular ejection fraction ($r=-0.479$, $P=0.03$), and with white blood cell count ($r=0.381$, $P=0.02$).

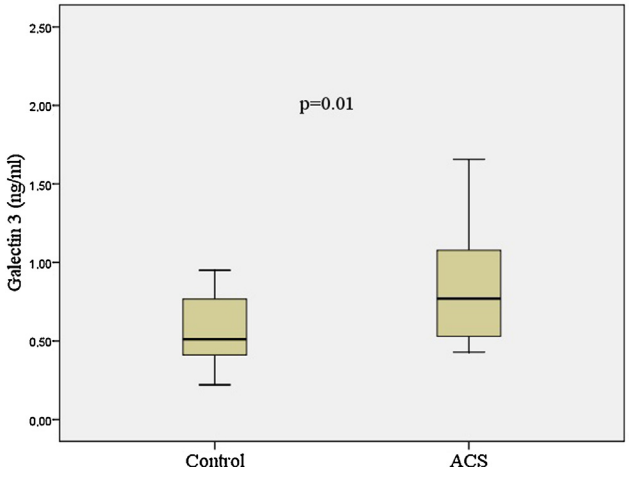

Fig. 1. The comparison of galectin-3 levels in patients with ACS and controls.

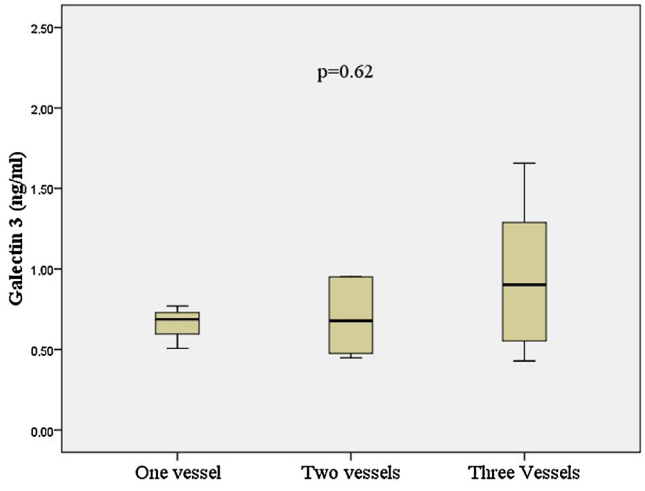

Fig. 2. Galectin-3 levels in ACS subgroups (the patients were classified according to the number of involved coronaries).

Table 3
The correlation analysis of galectin-3 and other variables.

Variables	Correlation coefficient	*P*
Age	0.163	0.35
Body mass index	−0.16	0.33
Gensini score	0.625	0.004
Number of involved vessels	272	0.26
Troponin	−0.07	0.75
Ejection fraction	−0.479	0.03
Glomerular filtration rate	−0.409	0.01
Glucose	0.235	0.18
Creatinine	0.167	0.34
Hemoglobine	−0.09	0.61
White blood cell count	0.381	0.02

4. Discussion

Galectin-3 is a regulator molecule that participates in several pathways throughout inflammation and fibrogenesis [4,5]. Previous studies indicate that galectin-3 interferes with numerous immune reactions such as activation of the neutrophils, migration of the inflammatory cells, apoptosis, and opsonization [16–19]. In case of repetitive injury, galectin-3 becomes a modulator of transition to chronic inflammatory response by inducing fibroblast proliferation and collagen synthesis, resulting in tissue injury and scarring [6–8]. All of these observations suggest that galectin-3 plays a major role in many phases of acute and chronic inflammatory response.

In a study by Arar et al., galectin-3 gene expression was evaluated in animal models by inducing experimental atherosclerosis. The researchers observed activated expression of the galectin-3 gene in the smooth muscle cells of the hypercholesterolemic and artificially injured aorta, suggesting the involvement of the galectin-3 in atherogenesis [20]. In a study by Nachtigal et al., galectin-3 levels were found to be higher in atherosclerotic arteries than umbilical cord arteries [21]. Furthermore, galectin-3 levels and galectin-3 positive cells were increased in the atherosclerotic lesions that were rich in foam cells, whereas fibrotic atherosclerotic lesions had lower galectin-3 levels and fewer galectin-3 positive cells. Galectin-3 positive cells were close to a lipid core, or to the areas with fibrosis, hemorrhage, or thrombosis in the atherosclerotic lesions [21]. In another study, in the absence of galectin-3 expression, the incidence of atheromatous plaques was lower and galectin-3 was strongly expressed in the foam cells of the atheromatous plaques [22]. These findings indicate that galectin-3 may involve in the active phase of the vulnerable atherosclerotic plaques.

We found elevated galectin-3 levels in patients with ACS as compared to control group. There was a positive correlation between galectin-3 levels and white blood cell count. These findings support the role of galectin-3 in ACS and acute inflammation. Previous studies also reported similar findings [23,24]. Papaspyridonos et al. demonstrated elevated galectin-3 expression in unstable atherosclerotic plaques. The expression was positively correlated with age and plaque size, suggesting the role of galectin-3 in progression of the atherogenesis in chronic phase [5]. The positive correlation between Gensini score and galectin-3 in the present study confirms the role of galectin-3 in chronic inflammation and atherogenesis [25]. Also, patients with three-vessel disease tended to have higher levels of galectin-3 but that difference did not reach statistical significance.

The association between Gensini scores and galectin-3 suggests that galectin-3 may predict the severity of the coronary artery disease in clinical practice, and may become an additional tool in identifying high-risk patients. This would be especially useful in patients with non-ST elevated myocardial infarction when there is a debate to proceed with early invasive strategy. Previous work indicated that galectin-3 may become a good predictor of poor outcome. In a study by Tsai et al., elevated galectin-3 levels were found to be independent predictor of early mortality and heart failure development in acute myocardial infarction patients undergoing primary percutaneous coronary intervention [23]. Tuñón et al. assessed the prognostic value of plasma biomarkers in 706 patients with chronic coronary artery disease. They showed that development of heart failure and mortality were independently associated with increased levels of galectin-3 [26]. De Boer et al. evaluated the relationship between galectin-3 and survival in the general population [27]. In 7968 subjects, with a median follow-up of 10 years, baseline galectin-3 levels were associated with all-cause mortality. Additionally, elevated galectin-3 levels were associated with a higher rate of new-onset AF and diuretic treatment during hospitalization in patients with myocardial infarction [28]. Recently, Grandin et al. found that elevated galectin-3 levels were associated with development of heart failure following an event of ACS [29]. Furthermore, higher plasma galectin-3 levels were found to be associated with impaired renal function and poor survival rates in patients with chronic systolic heart failure [30]. We found a reverse correlation between galectin-3 levels and glomerular filtration rate, as well as with left ventricular ejection fraction; both are well-known indicators of poor outcome in patients with ACS [31,32].

Compared with previous research in the literature, we observed lower galectin-3 concentrations in our study cohort [27]. In a study by Falcone et al., in which the researchers analyzed patients with documented coronary artery disease, galectin-3 levels were 27.75 ng/mL and 6.48 ng/mL in unstable and stable patients respectively [24]. Unlike these studies, we used serum instead of plasma and calculated the levels of galectin-3 with a different commercial ELISA kit. Nevertheless, galectin-3 levels were significantly higher in ACS group than those of control group.

5. Limitations

The main limitation of the present study is the small sample size. We did not follow the change in galectin-3 levels overtime. The duration of the symptoms before admission varied from a few hours to a few days. These limitations may have caused wide range of the galectin-3 levels, lowering the sensitivity and specificity rates to detect patients with ACS.

It is unclear whether galectin-3 reflects high-risk patients (lower glomerular filtration rate, lower left ventricular ejection fraction) and therefore correlates with Gensini score, or

galectin-3 itself identifies the burden of atherosclerosis. Higher Gensini scores usually tend to accompany with high-risk patients, but our study sample was too small to adjust the potential confounders with a regression model. Three-vessel disease was prominent in the study population, the median Gensini score was high and there was no patient with unstable angina. Future prospective studies are needed to confirm our findings with a larger patient cohort.

6. Conclusion

According to our findings, galectin-3 may become a promising biomarker and provide complementary information for assessment of early risk stratification in patients with ACS.

Disclosure of interest

The authors declare that they have no competing interest.

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