The relation of endocan and galectin-3 with ST-segment resolution in patients with ST-segment elevation myocardial infarction

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
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Abstract

Background. ST-segment elevation myocardial infarction (STEMI) remains a leading cause of morbidity and mortality around the world. In patients with STEMI undergoing primary percutaneous coronary intervention (PPCI), electrocardiographic measures of ST-segment resolution (STR) may give information about the myocardial perfusion and poor prognosis.

Objectives. To investigate the relation of endocan and galectin-3 levels with STR in STEMI patients.

Material and methods. In this cross-sectional study, 98 consecutive patients undergoing PPCI for STEMI were enrolled. Synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) scores were recorded. Electrocardiograms were assessed at baseline and 60 min after PPCI. According to STR levels, patients undergoing PPCI (n = 98) were divided into complete STR group (≥70%, n = 53) and incomplete STR group (<70%, n = 45).

Results. Serum glucose, total cholesterol, low-density lipoprotein cholesterol, SYNTAX score, endocan and galectin-3 levels were significantly higher and ejection fraction was significantly lower in the incomplete STR (<70%) group (p < 0.05 for all). Body mass index (BMI) (p = 0.046) and galectin-3 (p = 0.037) were independently associated with the SYNTAX score. Endocan (p = 0.044) and galectin-3 (p = 0.017) were independent predictors of incomplete STR.

Conclusions. In patients with STEMI, the levels of endocan and galectin-3 may be helpful in identifying patients with a higher risk of insufficient myocardial perfusion and worse clinical outcome after PPCI.

Key words: ST-segment elevation myocardial infarction, galectin-3, endocan, ST-segment resolution

Introduction

ST-segment elevation myocardial infarction (STEMI) is a form of coronary artery disease (CAD) that requires immediate and adequate attention to avoid deadly consequences. It may occur as a result of coronary thrombosis in an epicardial coronary artery, which is damaged by a chronic and inflammatory process known as atherosclerosis.[1] The high mortality rate of STEMI could be offset by providing sufficient blood flow to the damaged myocardium as quick as possible.[2] Primary percutaneous coronary intervention (PPCI) has become the more preferred treatment option for STEMI, over the past 2 decades, compared to thrombolysis.

Primary percutaneous coronary intervention aims to restore complete blood flow in the infarcted arteries in STEMI patients. However, good blood flow does not always indicate an effective microvasculature perfusion at the myocyte level.[3] In other words, good angiographic blood flow is unfortunately not always accompanied by good clinical outcomes. ST-segment deviations may be good indicators of the myocyte physiology, and thus the preferable option is to determine the success of PPCI electrocardiographically (ECG) by measuring ST-segment resolution (STR).[4] Previous data suggests that a sufficient STR may be predictive for clinical outcomes in STEMI patients undergoing PPCI.[4,5]

Endocan or endothelial cell-specific molecule-1 is synthesized in the vascular endothelium and gives information about angiogenesis and endothelial cell functions.[6] Endocan plays a key role in cell adhesion and is reported to be associated with endothelial dysfunction.[7] In patients with STEMI, higher endocan levels on admission were reported to be associated with a worse cardiovascular outcome and high synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score.[8]

Galectin-3 is a β-galactoside-binding lectin expressed by activated macrophages that regulates inflammation, ventricular remodeling and fibrosis.[9] In addition, galectin-3 was also reported to have a prognostic value in patients with CAD, possibly related to its role in plaque destabilization.[10] Moreover, an association between higher levels of galectin-3 and a lower ejection fraction, as well as higher mortality, was reported in patients diagnosed with acute coronary syndrome.[11]

The specific pathophysiology of endocan and galectin-3's association with negative cardiovascular outcomes remains to be elucidated. The assessment of the predictors of incomplete STR in acute phase might be helpful in identifying the patients at high risk for ineffective coronary reperfusion. Aggressive treatment may be planned for these patients to recover sufficient coronary perfusion.

This study evaluated the concentrations of endocan and galectin-3 in patients with STEMI and determined the relation of these parameters with STR.

Methods

Study population

Ninety-eight patients with STEMI with symptoms for less than 12 h who had underwent coronary angiography and PPCI at the Department of Cardiology of Bozok University in Turkey were prospectively enrolled in this cross-sectional study. ST-segment elevation myocardial infarction diagnosis was based on the presence of prolonged chest pain and ST-segment elevation (in all leads other than V2–V3: ≥1 mm, in leads V2–V3: ≥2 mm in men ≥40 years; ≥2.5 mm in men <40 years, or ≥1.5 mm in women regardless of age).[12] Exclusion criteria were the following: cardiogenic shock, ventricular tachycardia, ventricular fibrillation, thrombolysis within the last 24 h, oral anticoagulant therapy, indication for emergency coronary artery bypass grafting, active severe bleeding, uncontrolled hypertension, severe renal failure, and left bundle branch block. Routine treatment was initiated according to current STEMI guidelines. Information regarding risk factors, including age, gender, diabetes mellitus, hypertension, family history, and smoking status was obtained. Weights and heights of participants were measured. Body mass index (BMI) was calculated as (weight in kilograms)/(height in meters)^2. Transthoracic echocardiography was performed for each patient immediately after admission using a commercially available machine (Philips Logic Affiniti 50G machine; Philips, Amsterdam, Netherlands) with a broadband transducer. The study was conducted according to the Declaration of Helsinki. The ethics committee of Bozok University approved the study and informed consent was obtained from all patients.

Electrocardiogram

A standard 12-lead ECG was recorded in all patients at admission (baseline ECG) and 60 min after the completion of revascularization with PPCI. All ECGs were interpreted by an observer who was unaware of other patient data. ST-segment elevation in millivolt was calculated 20 ms after the J point. The sum of ST-segment elevations in leads I, aVL, and V1–V6 for noninferior infarction and in leads II, III, aVF, V5, and V6 for inferior infarction were calculated separately. ST-segment resolution was calculated by reducing the sum of the ST-segment elevation from the baseline ECG to the 60-min ECG and was expressed as a percentage. A decrease in the sum of ST-segment elevation by at least 70% was categorized as complete STR. Patients were divided into 2 groups according to the degree of STR: <70% (incomplete resolution) and ≥70% (complete resolution).

Coronary angiography

The SYNTAX score is the most commonly used anatomical scoring system worldwide to assess the complexity

of coronary lesions.[13] The baseline coronary angiograms were evaluated to determine the SYNTAX score by an experienced interventional cardiologist unaware of the patients' clinical or laboratory results. The SYNTAX score was determined for all coronary lesions with >50% diameter stenosis in a vessel >1.5 mm based on SYNTAX score calculator 2.1 (www.syntaxscore.com).

Laboratory measurements

Samples were taken from the antecubital vein when the patients were admitted to the hospital. Serum endocan and galectin-3 levels have been shown to be higher in patients with a myocardial infarction than in the healthy population.[14,15] Although the entire study group consisted of patients with an acute myocardial infarction, blood samples were collected as soon as possible at the first admission to the hospital, to minimize possible changes resulting from the myocardial infarction. The venous blood samples were drawn from the patients at admission to the hospital. The blood samples used for endocan and galectin-3 measurements were centrifuged and preserved in the freezer (−80°C). Enzyme-linked immunosorbent assay (ELISA) kit (YH-Biosearch, Shanghai, China) was used for measuring serum endocan and galectin-3 levels.

Statistical analysis

Data was analyzed using PASW Statistics for Windows v. 18.0 (SPSS Inc., Chicago, USA). Continuous variables were reported as mean ± standard deviation (SD) or range (min–max). Normally distributed variables were compared with Student's t-test, whereas non-normally distributed variables were compared with Mann–Whitney U test. Categorical variables were reported as percentages and counts and compared using the χ^2 test. Correlation of the SYNTAX score with study parameters was assessed by Pearson or Spearman's correlation analysis as appropriate.

A multivariate logistic regression analysis was used to identify the predictors of incomplete STR. Furthermore, a linear regression analysis was performed to find predictors of SYNTAX score in the study population. Variables that had $p < 0.2$ in the univariate analysis were included in the multivariable models. For all statistical tests, $p < 0.05$ was considered significant.

Results

Patients' demographic characteristics and baseline clinical data are presented in Table 1. According to STR levels,

Table 1. Demographic and clinical data of the participants

Characteristics	Incomplete STR <70% (n = 45)	Complete STR ≥70% (n = 53)	p-value
Age [years]	62.5 ±10.6	59.1 ±10.3	0.097
Gender, n (female/male)	9/36 (25)	8/45 (18)	0.354
BMI [kg/m²]	28.74 ±4.93	29.15 ±4.62	0.678
Hypertension, n (%)	19/45 (42)	23/53 (47)	0.535
Diabetes mellitus, n (%)	16/45 (35)	15/53 (28)	0.290
Smoking, n (%)	24/45 (53)	25/53 (47)	0.343
Family history, n (%)	17/45 (37)	14/53 (28)	0.228
Systolic blood pressure [mm Hg]	120.6 ±20.2	119.2 ±18.6	0.737
Diastolic blood pressure [mm Hg]	74.3 ±12.6	73.5 ±12.0	0.740
Heart rate [bpm]	75.8 ±12.5	74.1 ±13.1	0.422
Initial troponin level [ng/mL]	13.211 (18–50.000)	9.169 (11–50.000)	0.574
Peak troponin level [ng/mL]	38.843 (19.900–50.000)	33.244 (11.900–50.000)	0.142
Serum glucose [mg/dL]	145 (87–524)	118 (60–557)	0.019
Serum creatinine [mg/dL]	0.91 ±0.21	0.88 ±0.24	0.422
Total cholesterol [mg/dL]	204.9 ±42.2	180.7 ±43.6	0.007
Triglyceride [mg/dL]	141 (73–798)	115 (71–379)	0.063
HDL-C [mg/dL]	37.04 ±7.2	39.68 ±8.1	0.137
LDL-C [mg/dL]	136.3 ±35.2	114.6 ±37.5	0.004
SYNTAX score	16.2 ±7.6	12.04 ±6.6	0.003
Ejection fraction (%)	46.4 ±8.5	49.8 ±6.5	0.039
Endocan [ng/mL]	2.41 ±0.48	1.90 ±0.69	<0.001
Galectin-3 [ng/mL]	5.25 ±1.06	4.46 ±1.00	<0.001

Continuous variables are presented as mean ±SD and range (min–max). Categorical variables are presented as n (%). STR – ST-segment resolution; BMI – body mass index; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol.
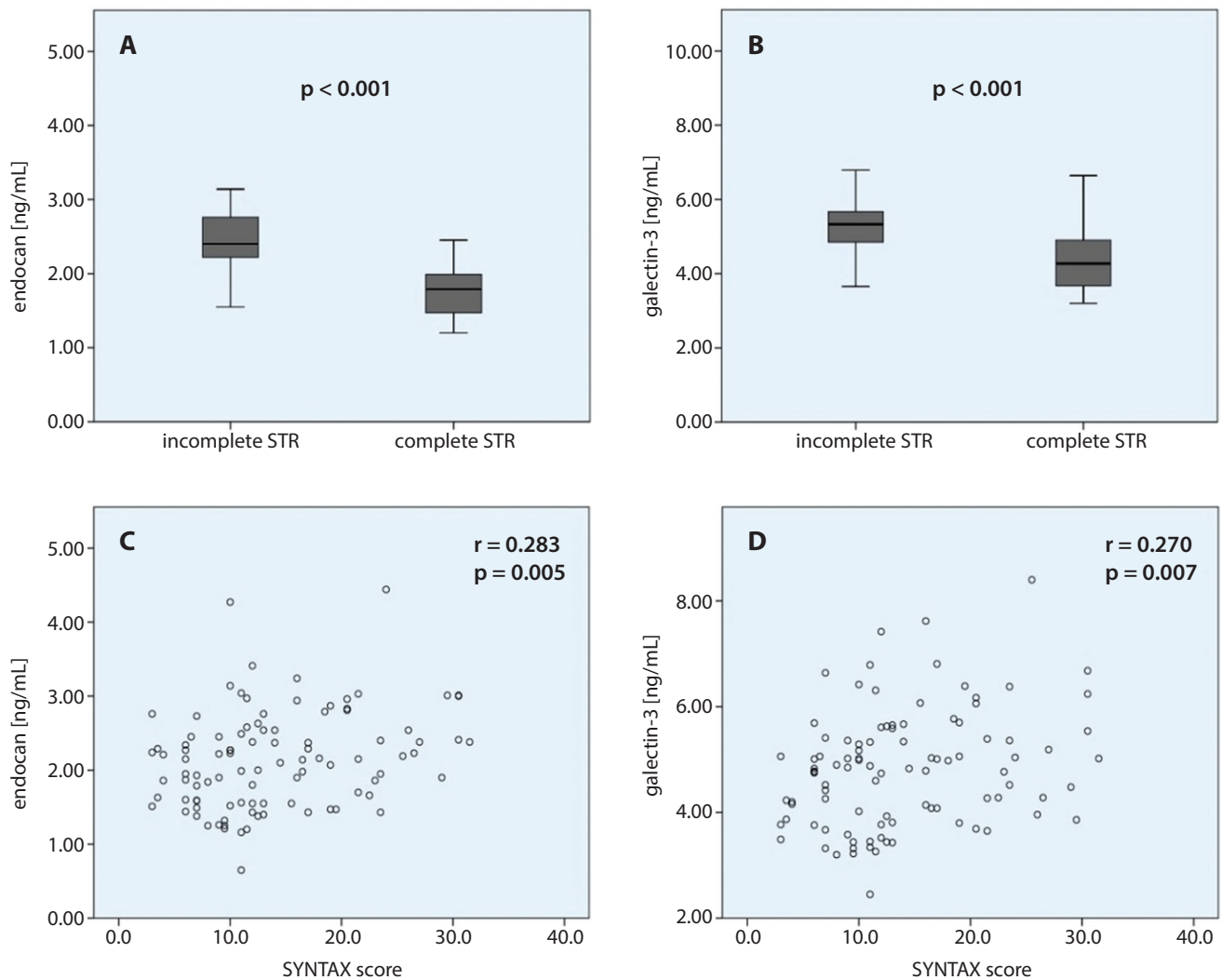
Fig. 1. A – comparison of endocan levels in the incomplete STR and complete STR groups; B – comparison of galectin-3 levels in the incomplete STR and complete STR groups; C – correlation between SYNTAX score and endocan; D – correlation between SYNTAX score and galectin-3

patients undergoing PPCI (n = 98) were divided into a complete STR group (≥70%, n = 53) and an incomplete STR group (<70%, n = 45). Compared with the complete STR group, glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), SYNTAX score, endocan and galectin-3 levels were significantly higher and the ejection fraction (EF) was significantly lower in the incomplete STR group (p < 0.05 for all) (Fig. 1). The 2 groups were similar regarding age, gender, BMI, and CAD risk factors, such as arterial hypertension, diabetes mellitus, family history, and smoking (p ≥ 0.05 for all).

Correlation analysis showed that the SYNTAX score was positively correlated with BMI (r = 0.227, p = 0.025), peak troponin level (r = 0.310, p = 0.03), endocan (r = 0.283, p = 0.005), galectin-3 (r = 0.270, p = 0.007), and negatively correlated with EF (r = −0.145, p = 0.010) (Table 2) (Fig. 1).

Multivariate linear regression analysis revealed that BMI (β = 0.196, p = 0.046) and galectin-3 (β = 0.212, p = 0.037) were significantly associated with the SYNTAX score in patients with STEMI.

The results of multivariate logistic regression showed that in patients with STEMI, endocan (odds ratio (OR) = 0.406; 95% confidence interval (95% CI) = 0.169–0.976; p = 0.044) and galectin-3 (OR = 0.212; 95% CI = 0.084–2.752; p = 0.017) were significant predictors of incomplete STR (<70%) after PPCI.

Discussion

The main finding of the present study was that endocan and galectin-3 were independent predictors of incomplete STR (<70%) after PPCI in patients with STEMI. Furthermore, along with BMI, galectin-3 was an independent predictor of the SYNTAX score.

Vascular inflammation is an important process in the initiation and progression of atherosclerosis. The inflammatory process affects the endothelial functions starting in the early phases of atherosclerosis. Endothelial dysfunction can be interpreted as the early step of cardiovascular disease development. Endocan and galectin-3 have

Table 2. The correlation between SYNTAX score and clinical/demographic variables in STEMI patients

Variables	SYNTAX score	
	r	p-value
Age	0.188	0.064
BMI	0.227	0.025
Waist circumference	0.134	0.189
Heart rate	0.131	0.197
Systolic blood pressure	−0.182	0.075
Diastolic blood pressure	−0.077	0.454
Initial troponin level	0.093	0.370
Peak troponin level	0.310	0.030
Serum glucose	0.029	0.777
Serum creatinine	0.112	0.279
Total cholesterol	0.091	0.372
Triglyceride	0.109	0.284
HDL-C	−0.130	0.203
LDL-C	0.121	0.235
Ejection fraction	−0.145	0.010
Endocan	0.283	0.005
Galectin-3	0.270	0.007

SYNTAX – synergy between percutaneous coronary intervention with taxus and cardiac surgery; BMI – body mass index; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol.

a significant role in the regulation of the inflammatory process and may be interpreted as markers of endothelial activation. Galectin-3 plays an important role in both acute and chronic phases of inflammation by many immune reactions such as neutrophil activation, migration of the inflammatory cells and apoptosis.[15] Endocan causes endothelial dysfunction by promoting adhesion molecules and migration of leukocytes across the damaged endothelium.[16] Later in this cascade, activated adhesion molecules may also secrete chemokines, which are essential for inflammatory reaction and the ultimate outcome is the acceleration of the atherosclerotic process.[17]

There are individual studies suggesting that increased levels of endocan[8] and galectin-3[18] are associated with CAD. In our study, which examined these biomarkers together, the results were consistent with the previous data. Although BMI, endocan and galectin-3 were significantly correlated with the SYNTAX score, only BMI and galectin-3 were independently associated with the SYNTAX score. Body mass index is reported to be a predictor of the extent and severity of coronary atherosclerosis.[19] However, data about galectin-3 and SYNTAX score is relatively scarcer. Although both endocan and galectin-3 are associated with inflammation, galectin-3 has a complex relation with both acute and chronic phases of inflammation. Winter et al. suggested that galectin-3 was significantly related with premature myocardial infarctions, dyslipidemia and markers of inflammation.[20] In this manner,

galectin-3 may affect both plaque formation and plaque destabilization and this mechanism may explain the independent association of galectin-3 with the SYNTAX score. Galectin-3 may be interpreted as a novel biomarker that is independently associated with the complexity of coronary lesions.

The rupture of atherosclerotic plaque is the primary cause of STEMI. Through the complex mechanisms, including inflammation, oxidative stress and endothelial dysfunction, a cascade of events begins, leading to intimal thickening, development of plaque, eventually plaque rupture and clinical consequences.[21] These mechanisms may also contribute to adverse outcomes during the follow-up of patients with a myocardial infarction.[22]

Two types of ischemia induced microvascular damage have been classified based on the pathophysiology.[23] The first type is structural microvascular damage due to myocardial necrosis and the second type is functional microvascular damage in which the microvessels are intact and may be due to increased constriction of microvessels, edema, endothelial dysfunction or obstruction with platelets or neutrophils. Despite angiographically successful PPCI, lack of STR may be a good indicator of compromised tissue perfusion and more extensive myocardial damage.

As a novel finding, our results revealed that endocan and galectin-3 were independent predictors of incomplete STR in patients with STEMI. Besides the role of galectin-3 in inflammation, it also has effects on fibrosis and cardiac remodeling, thus galectin-3 is also reported to be associated with the development and worsening of heart failure.[24] The prognostic role of galectin-3 in CAD is a current issue. In this manner, galectin-3 was reported to be an independent predictor of advanced heart failure and 30-day mortality in patients with STEMI.[11,25] In a prospective study with 1013 CAD patients, Maiolino et al. reported that galectin-3 was a strong independent predictor of cardiovascular mortality.[10] The relation of endocan and worse cardiovascular outcomes after STEMI was reported.[8,26] Ye et al. demonstrated that serum endocan was associated with coronary slow flow.[27] Qui et al. followed up 105 patients with STEMI for 3 months and reported that endocan was a predictor of major adverse cardiac events.[28]

Although the previous data indicates that both endocan and galectin-3 are valuable markers in predicting worse cardiovascular outcomes, to the best of our knowledge, there is no data concerning the association of STR, endocan and galectin-3 levels in STEMI patients. Considering the functional microvascular damage mechanism one can conclude that microvascular endothelial dysfunction and inflammation may explain the poor myocardial perfusion observed after PPCI. Although the pathophysiologic mechanisms by which higher levels of endocan and galectin-3 increase the risk of incomplete STR after PPCI are not clearly understood, possible hypothesis of our findings could be that elevated levels of endocan and galectin-3, as indicators of endothelial dysfunction and inflammation,

may be surrogate markers of insufficient microvasculature perfusion at the myocyte level, which might contribute to incomplete STR.

The mechanism of the relationship between endocan, galectin-3 and cardiovascular mortality and morbidity is still unclear. Considering the association between endocan, galectin-3, endothelial dysfunction and inflammation, it can be proposed that insufficient coronary reperfusion related with elevated endocan and galectin-3 may be a potential pathophysiological mechanism of the adverse cardiovascular outcomes in patients with STEMI.

Our study had some limitations; it was a cross-sectional study with a limited number of patients and there was no control group. It reflects a single center experience and in our laboratory, there was an upper limit for troponin results. The levels of endocan and galectin-3 were evaluated only at admission and they were not evaluated after the acute phase of the myocardial infarction. ST-segment resolution may be helpful, but it cannot be accepted as a definitive parameter for the microvascular impairment like the invasive hemodynamic procedures. Longitudinal studies may be designed to determine the long-term influence of these parameters on cardiovascular outcome.

Conclusions

To our knowledge, ours is the first report describing endocan and independent association of galectin-3 with incomplete STR in patients with STEMI. Based on the relation of endocan and galectin-3 with endothelial dysfunction, oxidative stress and inflammation, it can be proposed that insufficient coronary reperfusion related with elevated endocan and galectin-3 may be a potential pathophysiological mechanism of the adverse cardiovascular outcomes in patients with STEMI. The levels of endocan and galectin-3 may be helpful in identifying patients with a higher risk of insufficient myocardial perfusions and worse clinical outcome.

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