ORIGINAL ARTICLE

Neutrophil gelatinase-associated lipocalin is a predictor of complications in the early phase of ST-elevation myocardial infarction

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ABSTRACT

Aim To evaluate a correlation of serum level of neutrophil gelatinase-associated lipocalin (NGAL) to the risk of the occurrence of complications in patients with the early phase of ST-segment elevation myocardical infarction (STEMI) treated with fibrinolytic therapy prior to percutaneous coronary intervention (PCI).

Methods A total of 54 patients with the diagnosis of STEMI treated with fibrinolytic therapy (alteplase) prior to PCI were included. Patients were admitted to the Intensive Care Unit (ICU) of Clinic for Heart, Blood Vessel and Rheumatic Diseases in the period January to March 2018. All patients underwent coronary angiography and PCI within the maximum of 48 hours delay after fibrinolysis, according to the hemodynamic and electrical stability and PCI availability. Blood samples were taken immediately after admission prior to fibrinolytic administration. Patients were divided into two groups according to NGAL values (less or more than 134.05 ng/mL).

Results Higher values of NGAL have effect on a higher mean systolic and diastolic pressure (p=0.001 and p=0.003, respectively). Patients with higher NGAL values also have higher values of brain natriuretic peptide (p=0.0001) and highly sensitive troponin I (p=0.002). In that group relative risk (RR) for lethal outcome was 6.4 times significantly higher (p=0.002), for the development of heart failure 2.88 times (p=0.0002), for post-myocardial infarction angina pectoris 2.24 times (p=0.0158), and for ventricular rhythm disturbances (ventricular tachycardia, ventricular fibrillation) 1.96 times higher (p=0.0108).

Conclusion Increased NGAL value is related to an unfavourable outcome of patients in the early phase of STEMI treated with fibrinolytic therapy prior to PCI.

Key words: acute coronary syndrome, lipocalin-2, prognosis

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INTRODUCTION

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a 25 kDa siderophore 178 amino acids binding protein, composed of 8 beta sheets that form a shaped structure, and represents an acute renal injury marker (AKI) (1-7). Its advantage is that it can detect AKI after two hours of injury, much earlier than a rise in creatinine concentration (3,4). It is synthetized in renal tubular, intestinal, hepatic, and pulmonary tissue (4). Circulating NGAL is filtered by the glomerulus and reabsorbed in the proximal tubule (NGAL is stored in neutrophils within specific granules) so it can be monitored in both urine and plasma, but also in whole blood and serum (5,7). It is associated with many processes, such as inflammation, infection, intoxication, ischemia, neoplastic transformation, transport of pheromones and with the synthesis of prostaglandin (7,8). It is significant for the prediction of renal dysfunction in patients with chronic heart failure (HF) (9). In acute HF, it can be a predictor of worsening of the renal function and strongly predicts adverse clinical outcomes (10). The prognostic mortality factor is in patients with HF, both with and without chronic kidney disease, and it is superior to estimated glomerular filtration rate (eGFR) and cystatin C values (11). The value of NGAL urine in the early phase of acute myocardial infarction (MI) is associated with NT-pro BNP values, and it can be related with localization of MI (12). It represents an important part of mineralocorticoid-stimulated vascular fibrosis (13). It is found in endothelial cells, smooth muscle cells, and macrophages in atherosclerotic plaques, and could therefore be associated with the development, or progression of, atherosclerotic stable or unstable plaque (via endothelial dysfunction, inflammation and matrix degradation and plaque instability), and it is in relation with anamnestic data, risk factors and medication intake (14-17). Serum NGAL level is strongly predictive for survival to hospital discharge after cardiac arrest (16).

Renal function is one of the most important parameters that contribute to the outcome of a patient with STEMI, so early diagnosis of renal dysfunction may be helpful in the therapeutic modality. The aim of research was to evaluate a correlation of serum level of NGAL with the risk of complications occurrence in patients with the early phase of ST-segment elevation myocardial infarction (STEMI) treated with fibrinolytic therapy prior to PCI.

PATIENTS AND METHODS

Patients and study design

This prospective study included 54 patients with the diagnosis of STEMI treated with fibrinolytic therapy (alteplase) prior to PCI. The patients were admitted to the Intensive Care Unit (ICU) of Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Centre University of Sarajevo in the period January to March 2018. The patients were divided into two groups according to NGAL value (less or more than 134.05 ng/mL). Criteria for inclusion were diagnosis of STEMI, treatment with fibrinolytic therapy prior to PCI and accepted participation in the research. Exclusion criteria were diagnosis of sub-acute myocardial infarction, diagnosis of non-ST segment elevation myocardial infarction (NSTEMI), those who were not treated by fibrinolytic therapy prior to PCI and patients over 85 years of age.

The research was conducted in accordance with basic principles of the Declaration of Helsinki (last revision in 2008) on the rights of patients involved in biomedical research. An informed consent was obtained from all patients included in the study. An ethical approval was obtained from the Ethical Committee of the Clinical Centre of the University of Sarajevo.

Methods

The dose of alteplase was 0.9 mg/kg infused over 60 minutes (not exceeding 90 mg). Patients were followed up for 5 to 7 days (median follow-up time of patients was 6 days). All patients underwent coronary angiography and PCI within maximum of 48 hours delay after fibrinolysis, according to the hemodynamic and electrical stability and PCI availability. Blood samples were taken immediately after the admission prior to fibrinolytic administration. The NGAL value in plasma was measured at the Institute for Clinical Biochemistry and Immunology, Clinical Centre of the University of Sarajevo using Human NGAL Rapid ELISA Kit (BioPorto Diagnostics, Hellerup, Denmark) test. NGAL values were presented as third quartile of laboratory values (it was consider as pathological) (18). Values of low density lipoproteins (LDL), high density lipoproteins (HDL), glycolized haemoglobin (HbA1C), brain natriuretic peptide (BNP), high sensitive Troponin I (hsTnI), urea and creatinine were also taken at admission. Anamnestic data of

comorbidities and risk factors (age, gender, diagnosis of hypertension, diabetes mellitus, dyslipidaemia, previous myocardial infarction, previous coronary artery bypass surgery) and habits (smoking) were collected. Echocardiography was performed on the fifth day of hospitalization, and ejection fraction of left ventricle (EFLV) was assessed by the Simpson method. Complications of STEMI (acute heart failure during hospitalization, post-infarction angina pectoris, ventricular heart rhythm disorders, lethal outcome) were also monitored.

Statistical analysis

The study used $\chi 2$ test, Student's t test and Relative Risk. Receiver operating curve (ROC) analysis was used to determine sensitivity and specificity. The values of monitored laboratory parameters, systolic and diastolic function, as well as the complications of STEMI were all analysed comparing to plasma NGAL values. All analytical results with $p<0.05$ were considered statistically significant. Identity and all personal data of patients are permanently protected in accordance to regulations of protection of identification data. Identification number was assigned to every patient in order to protect personal information and that number was used in statistical analysis.

RESULTS

Patients with high NGAL (above 134.05 ng/mL) had significantly higher mean systolic and diastolic blood pressure compared to patients with low NGAL (p=0.001 and p=0.003, respectively). The significant difference was not proven in other investigated factors (Table 1).

Table 1. Characteristics of patients with ST-segment elevation myocardial infarction (STEMI) according to neutrophil gelatinase-associated lipocalin (NGAL) value

Parameter	NGAL		p
	<134.05 ng/mL	>134.05 ng/mL	
Age (mean) (±SD) (years)	60.6±10.6	66.2±11.3	0.155
Gender (No, %)	18 (56.3)	8 (80.0)	0.165
Diabetes mellitus (No, %)	8 (25.0)	5 (50.0)	0.136
Hypertension (No, %)	24 (75.0)	7 (70.0)	0.524
Dyslipidaemia (No, %)	19 (59.4)	8 (80.0)	0.212
Smoking (No, %)	18 (56.3)	8 (80.0)	0.320
Previous myocardial infarction (No, %)	3 (9.4)	5 (50.0)	0.012
Previous CABG (No, %)	1 (3.1)	3 (30.0)	0.036
SBP (mean) (±SD)	133.5±12.9	152.1±6.7	0.0001
DBP (mean) (±SD)	88.5±7.8	97.6±5.6	0.001

CABG, coronary artery bypass surgery; SBP, systolic blood pressure; DBP, diastolic blood pressure

Patients with high NGAL had significantly higher brain natriuretic peptide (BNP) level (647.06±1001.37 vs. 2249.89±1336.43; p=0.0001), high sensitive troponin I level (14840.85±17965.39 vs. 37313.5±22699.86; p= 0.002), larger left atrial diameter (3.63±0.3 vs. 4.23±0.28; p=0.0001), significantly larger left ventricular internal dimension at end-systole (LVIDs) (4.18±0.34 vs. 3.68±0.47; p= 0.006), larger mitral peak velocity of early filling (E) to mitral peak velocity of late filling (A) (E/A) ratio (0.81±0.25 vs. 1.48±0.89, p=0.001). Patients with high NGAL had significantly reduced ejection fraction (45.16±5.22 vs. 37.3±5.06, p=0.00001). The significant difference was not proven in other investigated factors (cholesterol, triglycerides, high density lipoproteins (HDL), low density lipoproteins (LDL), urea, creatinine, glycolized haemoglobin and left ventricular internal dimension at end-diastole (LVIDd)) (Table 2).

Table 2. Laboratory and echocardiography findings of patients with ST-segment elevation myocardial infarction (STEMI) according to neutrophil gelatinase-associated lipocalin (NGAL) value

Parameter	Reference value	NGAL		p
		<134.05 ng/mL	>134.05 ng/mL	
Cholesterol (mmol/L)	3.1-5.2	5.84±0.83	6.16±0.34	0.244
Triglycerides (mmol/L)	0.11-1.7	2.49±3.13	3.13±1.04	0.180
HDL (mmol/L)	1.06-1.94	1.6±0.69	2.14±0.82	0.049
LDL (mmol/L)	1.4-3.4	3.16±0.69	3.5±0.36	0.145
Urea (mmol/L)	2.0-7.8	7.46±1.69	9.45±2.29	0.005
Creatinine (μmol/L)	63-109	86.88±22.37	102.6±23.16	0.060
HbA1c (%)	4-6.5	6.65±1.55	7.82±2.34	0.075
hsTnI (pg/mL)	5-30	14840.85 ±17965.39	37313.5 ±22699.86	0.002
BNP (pg/mL)	<100	647.06±1001.37	2249.89±1336.43	0.0001
LVIDs (cm)	3.5-5.6	3.68±0.47	4.18±0.34	0.006
LVIDd (cm)	2.0-4.0	5.5±0.46	5.36±2.02	0.694
LAD (cm)	2.0-4.0	3.63±0.3	4.23±0.28	0.0001
EF (%)	>50	45.16±5.22	37.3±5.06	0.0001
E/A	1-2.2	0.81±0.25	1.48±0.89	0.001

LDL, low density lipoproteins; HbA1C, glycolized haemoglobin; BNP, brain natriuretic peptide; hsTnI, high sensitive Troponin I; LVIDd, left ventricular internal dimension at end-diastole; LVIDs, left ventricular internal dimension at end-systole; LAD, left atrial diameter; EF, ejection fraction; E/A, mitral peak velocity of early filling (E) to mitral peak velocity of late filling (A) ratio

Patients with higher NGAL had a relative risk (RR) of lethal outcome 6.4 times significantly higher (CI 1.9466-21.0147; p=0.0022), while for development of HF 2.88 times significantly higher (CI = 1.6552-5.0112; p=0.0002). For post-myocardial infarction angina pectoris it was 2.24 times significantly higher (CI 1.1638-4.3114;

p=0.0158), while for ventricular rhythm disturbances (ventricular tachycardia, ventricular fibrillation) 1.96 times significantly higher (CI = 1.1695-3.3158; p=0.0108) (Table 3).

Table 3. Occurrence of complications of the patients in the early phase of ST-segment elevation myocardial infarction (STEMI)

Complication	No (%) of patients with NGAL		p
	<134.05 ng/mL	>134.05 ng/mL	
Acute HF during hospitalization	10 (31.3)	9 (90.0)	0.002
Post-infarction angina pectoris	10 (31.3)	7 (70.0)	0.036
Ventricular heart rhythm disorders (VT, VF)	13 (40.6)	8 (80.0)	0.033
Lethal outcome	9 (9.4)	6 (60.0)	0.0001

NGAL, neutrophil gelatinase-associated lipocalin; HF, heart failure; VT, ventricular tachycardia; VF, ventricular fibrillation

The ROC curve estimates the best possible sensitivity (90%) and specificity (71.9%) at a certain cut off value (Figure 1). For lethal outcome, optimal sensitivity and specificity for NGAL values occur at cut off values> 362.9 ng/mL, with significant (p=0.0022) area under curve (AUC) of failure or systolic 0.85.

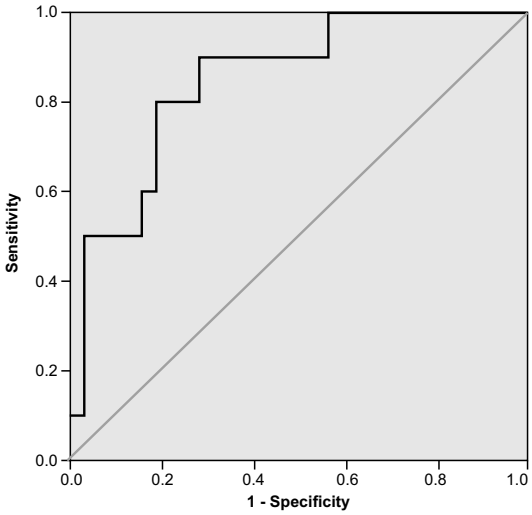

Figure 1. Sensitivity and specificity of the neutrophil gelatinase-associated lipocalin (NGAL) value for the prediction of lethal outcome

DISCUSSION

The research showed higher levels of NGAL in patients with higher systolic and diastolic pressure. Gharishvandi et al. have proven that NGAL concentrations are higher in hypertension, and that they are elevated in hypertensive patients with early stages of renal failure (17). Elrin et al. have found elevated NGAL values in patients with renovascular hypertension (19). In our study patients with elevated NGAL value also had the elevated brain natriuretic peptide (BNP) value, which is followed by echocardiographic changes in the form of a systolic and diastolic dysfunction. Kim et al. established NGAL as independent predictor of left ventricular hypertrophy (LVH) and left ventricular diastolic dysfunction (LVDD) on 332 pre-dialysis chronic kidney disease patients (20). Increased values of BNP are a sign of heart left ventricular dysfunction (20). Elevated NGAL serum levels on admission are associated with a worsening of renal function in patients with acute HF (10), which directly causes the development of complications. Nakada et al. the verified elevated NGAL values in urine as the marker of the prediction of the occurrence of acute HF (21). Although the NGAL increase occurs before the rise of creatinine, the Acute Kidney Injury Neutrophil Gelatinase-Associated Lipocalin Evaluation of Symptomatic Heart Failure Study (AKINESIS) trial did not confirm the superiority of NGAL compared to creatinine in 930 patients for predicting worsening renal function or in-hospital outcomes (22). Al-Afify in 52 patients with STEMI treated with fibrinolytic therapy (reteplase) concluded that death and in-hospital complications were significantly higher in patients with high NGAL than those with low NGAL and that plasma NGAL was a significant predictor of mortality and in hospital complications (23). Serum levels of NGAL are higher in patients with acute coronary syndrome than those with stable angina (24). Akcay et al. in a study of 100 consecutive patients with STEMI found that in-hospital and 1-year major adverse cardiovascular event rates were significantly higher in the high-NGAL group compared to the low NGAL group (25). Neutrophil activation has been reported in unstable angina and acute myocardial infarction but not in patients with stable angina (26). Plasma NGAL is a significant predictor of mortality but is weakly associated with several traditional cardiovascular risk factors including age, systolic blood pressure, hypertension and diabetes (27,28). That is in accordance to results obtained in our research. At cell model of myocardial infarction after percutaneous coronary intervention, NGAL is overexpressed by the heart after MI and blocks cardiac dysfunction and fibrosis in experimental MI, and may represent therapeutic modality (29). Direct effects of NGAL

expression on cardiomyocyte size and number could be related to cardiac hypertrophy and heart failure (30). Plasma level of lipocalin 2 gene is elevated at 1-3 days in patients with ischemic stroke (31) (ischemic stroke is related to the progression of atherosclerotic process).

Although a precise mechanism of plaque rupture is poorly understood, it is generally accepted that the disorder occurs at the site of a fibrous capsule that is highly infiltrated by macrophages and T lymphocytes where the underlying necrotic nucleus is usually large (30,31). Degradation of atherosclerotic plaque and its fibre cap is considered to occur through the extracellular matrix protein degradation of extracted matrix metalloproteinase (MMP), which is directly involved in the plaque rupture process (30,31). Plasma MMP-9 antigen was elevated in unstable plaques (30). An important function of NGAL is the formation of a complex with MMP-9, which slows down the inactivation of MMP-9 by tissue inhibitors of matrix metalloproteinases (TIMP-1) and results in a longer effect of proteolytic activity of MMP-9 (30). NGAL may exist as monomer, dimer and/ or NGAL/ MMP-9 complex forms in humans (32). Furthermore, the NGAL/ MMP-9 complex has also been detected in a variety of tumour tissues and in acute cystitis and plays a role in many inflammatory processes, including chronic inflammatory processes and neoplastic changes (33). The formation of a complex of NGAL and MMP-9 prevents the degradation of MMP-9 and reinforces its proteolytic activity, which can take part in the formation of unstable atherosclerotic plaque (31). Excessive MMP activity can weaken vessels and, more importantly, destabilize plaques leading to increased risk of rupture (34-36). Degradation of MMP-9 has been shown to be significantly inhibited in the presence of NGAL and results in the preservation of MMP-9 enzymatic activity (34). Our research showed that increased NGAL concentration, increased free NGAL, lead to MMP degradation, resulting with plaque rupture. As this plaque rupture is greater, the values of NGAL will be higher, and MI will be more severe with the occurrence of a greater number of complications. Hedmahl et al. proved the same thing in mouse models (36). Helanova et al. proved that increased levels of NGAL were detected in patients with acute myocardial infarction, heart failure or stroke, and were demonstrated to be strong predictors of adverse prognosis (37).

The research presents an importance of NGAL value in the early stage of STEMI, and shows that NGAL can be one additional marker that can be helpful in the prediction of occurrence of complications, and according to that helpful in modification of the therapeutic approach. A larger number of patients, primary PCI and analysis of patients in relation to the characteristics of primary PCI could further establish NGAL as a useful maker in STEMI.

In conclusion, higher concentrations of NGAL correlate with the occurrence of complications in the early phase of STEMI treated with fibrinolytic therapy prior to PCI, and increase mortality risk, correlate with BNP values and predict the origin of acute HF. Also, NGAL is a predictor of post-myocardial infarction angina pectoris as well as ventricular rhythm disturbances. Further research should indicate the importance of NGAL values in the prediction of major adverse cardiovascular events after STEMI.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

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