

Cardiac biomarkers and left ventricular systolic function in acute myocardial infarction with ST- segment elevation in diabetes mellitus type 2 patients

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ABSTRACT

Aim To determine a status of systolic function in patients with diabetes mellitus (DM) type 2 with ST-segment elevation acute myocardial infarction (STEMI), to determine values of cardiac biomarkers in patients with DM type 2 with STEMI and correlate the parameters with ejection fraction of left ventricle (EFLV).

Methods A total of 80 patients were divided into two groups, the study group (group I) consisting of 40 patients admitted with the diagnosis of DM type 2 and STEMI, and a control group (group II) with 40 patients with STEMI without diagnosed DM type 2. Cardiac biomarkers - creatine kinase MB fraction (CKMB), and troponin I were monitored. The EFLV was evaluated echocardiographically (using Simpson method) five days after primary percutaneous coronary intervention (pPCI).

Results In the group I the EFLV five days after pPCI was significantly correlated with troponin values (with a minimum $r = -0.47$; $p=0.002$, a maximum $r = -0.339$; $p = 0.032$, as well as with an average value of $r = -0.389$; $p=0.013$), and with an average CK value ($r = -0.319$; $p=0.045$). In the group II there was a significant negative correlation of EFLV with the maximum value of troponin ($r = -0.309$; $p=0.05$).

Conclusion Troponin values have an effect on the EFLV after STEMI, and thus on the left ventricular status, as well as on the pharmacological modality itself.

Keywords: prognosis, ST elevation myocardial infarction, troponin

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INTRODUCTION

Acute coronary syndrome (ACS) covers unstable angina, non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) (1). Atherosclerosis accounts for about 80% of cardiovascular diseases, and given the large percentage of potentially fatal complications of atherothrombosis (the process progresses through life, before finally manifesting as an acute ischemic event), a proper understanding of the pathogenesis of this disease is of great importance for determining optimal modalities of prophylaxis and therapy (1,2). Biomarkers are measurable and quantitative biological parameters that serve as indicators of health and physiology of assessment, and in 1979, the World Health Organization (WHO) recommended a panel of creatine kinase (CK), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) for the diagnosis of acute myocardial infarction (AMI), while later, troponin was given its place in the diagnosis itself after the introduction of immunoassays into clinical practice in the 1990s (3). The CK enzyme is responsible for the transfer of the phosphate group from ATP to creatine, and consists of two M and or B subunits, and accordingly distinguishes three forms of CK- MM, CK-MB, and CK-MM. The CKMB is considered as sensitive and specific marker for AMI; it begins to grow 3-4 hours after the development of AMI, reaches its peak after 10-24 hours, and returns to normal after 72 hours (3,4). The concentration of troponin in the blood begins to rise 4-6 hours after the onset of symptoms, meaning that blood sample must be taken on admission and again 6-9 hours later. Maximum values of troponin appear 18-24 hours after the onset of the problem (4-6). The only advantage of CK-MB over troponins is fast clearance that helps to detect reinfarction, and therefore serum troponin levels along with the CK-MB fraction level are sensitive and significant for the diagnosis of myocardial infarction (5). Troponin is released from dead cells of the heart muscle and the level of troponin in the blood is related to the size of the affected myocardium, or the size of necrosis (6-8). The AMI is characterized by loss of contractile tissue and changes in left ventricular geometry. This leads to alteration of systolic as well as diastolic function, each of which may separately alter further clinical course of the disease (9). Risk asse-

ssment for major adverse cardiovascular events (MACE) after primary percutaneous intervention (pPCI) is therefore focused on systolic function, and accordingly, there are numerous studies that have shown that the ejection fraction of left ventricle (EFLV) or other closely related parameters are powerful guides for selecting therapy and predicting the risk of future events (1,9).

Cardiovascular risk factors that can be influenced by lifestyle and thus eliminated as possible causes of coronary disease are called preventable-variable risk factors. Variable risk factors include nicotine, dyslipidaemia, obesity, diabetes mellitus (DM), metabolic syndrome, arterial hypertension, increased heart rate and insufficient physical activity (1). DM in early stage of diagnosis has an effect on metabolic imbalance (9-12).

Presence of DM as a comorbidity additionally complicates clinical outcome of patients with the diagnosis of ACS hence it is of critical importance to stratify those patients adequately (12). The combination of DM and cardiovascular disease also has the impact on the gender-independent prevalence of mortality and morbidity (12). It has been clear for 40 years that DM is a risk factor for AMI (13). The existence of silent myocardial ischemia in diabetics, and its early detection, is one of the imperatives of modern cardiology (13,14).

The aim of the study was to determine a status of systolic function in patients with DM type 2 with STEMI, to determine values of serum markers in patients with DM type 2 with STEMI, and to correlate parameters of systolic function and values of the serum markers in patients with DM and AMI. The aim was also to evaluate factors that influence patient stratification, and to answer the question whether such stratification is already possible on initial patient admission. Similar studies have not been conducted in Bosnia and Herzegovina. Also, studies that correlate biomarkers of cardiac necrosis and systolic function after pPCI have not been performed in overall.

PATIENTS AND METHODS

Patients and study design

This prospective study which included 80 patients attended to the Department of Cardiology, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Center of the University of

Sarajevo between January 2018 and June 2018. The patients were divided into two groups, a study group (group I) consisting of 40 patients with DM type 2 admitted and treated under the diagnosis of AMI, and a control group (group II) comprising of 40 patients diagnosed with AMI, without diagnosed DM type 2. Inclusion criteria were: chest pain, electrocardiographic signs according to the STEMI criteria (1), increase in serum CKMB more than double of normal values, increase in troponin I greater than 0.5 ng/mL, patients with DM type 2. Exclusion criteria were previously diagnosed myocardial infarction or already diagnosed cardiomyopathy, diagnosed with DM type 2 during hospitalization, patients who left the clinic before completing the treatment or patients who exited during hospitalization (intra-hospital death).

Ethical approval was obtained from the Ethics Committee of the Clinical Center of the University of Sarajevo.

Methods

Patients on admission had creatine kinase, CKMB, and troponin I values (reference values: 22 to 198 U/L, 0-25 IU/L, and up to 0.5 ng/mL, respectively) analyzed. These analyses were repeated after 8, 16 and 24 hours.

Five days after admission, patients underwent echocardiographic evaluation of EFLV. The EFLV was assessed by Simpson method (1).

All patients underwent pPCI and were previously treated with antiaggregation and anticoagulation therapy. The existence of the diagnosis of arterial hypertension in medical history was analyzed, as well as the existence of the diagnosis of dyslipidemia (elevated cholesterol over 5.8 millimoles per liter (mmol/L) or triglyceride values over 1.85 mmol/L) and smoking habit. Patients in the first group were divided into those with HbA1C values below and above 6.5%.

Statistical analysis

All variables were tested for normal distribution using the Kolmogorof-Smirnov test. All variables are presented descriptively using appropriate measures of central tendency (arithmetic mean and median) and dispersion (standard deviation and interquartile range). Quantitative variables were compared using Student's t-test with correction

for unequal variance where needed. The frequencies of the qualitative variables were compared using a chi-square test with continuity correction for 2x2 tables. Relationships between the variables were tested using the parametric Pearson correlation. All tests were performed with the accuracy level of 95% ($p < 0.05$).

RESULTS

A total of 80 patients with a mean age (SD) of 64 ± 10 years (ranging from 41 to 89 years) were analyzed. No statistical difference was observed regarding the mean age in the study and control group (66 ± 10 and 63 ± 10 years, respectively; $p = 0.19$). In the overall sample, there were 51 (63.7%) male and 29 (36.3%) female patients (the ratio of 1.76:1). In group I there were 20 (50%) male patients versus group II where there were 31 (77.5%) males ($p = 0.02$). In group I of patients with DM type 2 in 90% of cases diagnosis was established within five years. In group I, a total of 27 (67.5%) patients were on oral antidiabetic drugs, 12 (30%) were on insulin, and one patient (2.5%) was on combined treatment. In this group of patients, the average measured value of glucose was 7.05 ± 1.0 mmol/L and the average HbA1c level was $11.71 \pm 3.45\%$. When it comes to risk factors, both hypertension and dyslipidemia were significantly higher in the group I ($p = 0.04$ and $p = 0.00$, respectively). No statistically significant difference was found in the smoking habit between the study groups ($p = 0.50$) as well as family history of heart diseases ($p = 1.0$). There was no significant difference in the frequency of STEMI localisation between the study groups ($p = 0.68$).

No statistically significant difference of average values of EFLV between the study groups was found (44.85 ± 8.82 vs. 45.60 ± 8.62 ; $p = 0.70$). No statistically significant difference of average values of troponin I between the study groups was found for all measured values ($p = 0.64$). Average CK values were higher in the control group of patients ($p = 0.06$). Significantly higher values of CKMB in group I was found (48.63 ± 30.35 vs. 35.15 ± 21.85 ; $p = 0.03$) (Table 1).

There was no statistically significant difference ($p = 0.92$) in comparing the level of troponin values with the localization of infarction. There was no statistically significant difference ($p = 0.10$) in comparing the level of troponin values with

Table 1. Ejection fraction of left ventricle (EFLV) and cardiac enzymes in patients with (group I) and without (group II) diabetes mellitus (DM) type 2

Variable	Group	Mean ±SD
EFLV (%)	I	44.85±8.82
	II	45.60±8.62
Troponin I minimal (ng/mL)	I	8.14±10.49
	II	7.22±6.82
Troponin I maximal (ng/mL)	I	31.88±33.75
	II	21.25±25.53
Troponin I mean (ng/mL)	I	20.01±20.21
	II	14.24±15.25
CK (mean) (IU/L)	I	331.18±229.34
	II	251.73±135.63
CKMB (mean) (IU/L)	I	48.63±30.35
	II	35.15±21.85

SD, standard deviation; CK, creatine kinase; CKMB, creatine kinase MB fraction;

the EFLV to both groups. There was no significant difference in EFLV values between the two subgroups of group of patients with DM type 2 ($p=0.18$). The type of antidiabetic therapy had no effect on EFLV ($p=0.47$). In group I, the EFLV five days after pPCI significantly correlated with all troponin I values (minimum $r = -0.47$; $p=0.002$, a maximum $r = -0.339$; $p=0.032$, and an average value of $r = -0.389$; $p=0.013$), and with an average of CK ($r = -0.319$; $p=0.045$). In group II of the patients there was a marginal significant negative correlation of EFLV with the maximum value of troponin ($r = -0.309$; $p=0.05$) (Table 2).

Table 2. Correlation of left ventricular systolic function (LVSF) and cardiac enzymes in patients with (group I) and without (group II) diabetes mellitus five days after primary percutaneous intervention (pPCI)

Patient's group		Troponin I (ng/mL)			CK	CKMB
		Minimal	Maximal	Mean	(mean) IU/L	(mean) IU/L
I	Correlation coefficient	-0.470	-0.339	-0.389	-0.319	-0.177
	p	0.002	0.032	0.013	0.045	0.275
II	Correlation coefficient	0.125	-0.309	-0.226	0.098	0.121
	p	0.444	0.052	0.162	0.549	0.459

CK, creatine kinase; CKMB, creatine kinase MB fraction

DISCUSSION

Average time between onset of symptoms of Type 1 DM and the diagnosis is 15 days, while this time in Type 2 DM is from 6 to 10 years (15). The Atherosclerosis Risk in Communities Study (ARIC) trial proved that values of HbA1c close to upper normal limit can still be one of the risk factors for the development of cardiovascular diseases, and that HbA1c is a reliable risk factor of all-cause and cardiovascular mortality in both diabetics and non-diabetics (15). When it comes

to prognosis, patients with coronary artery disease and DM usually have worse outcome than patients without DM (16). On the other hand, atherosclerosis itself has vascular manifestations on three levels: coronary arteries, carotid arteries and lower limbs arteries. Abnormal metabolism connected with diabetes is a common cause of arterial disfunction (16,17).

Hyperglycemia, which is common in diabetic patients, inhibits production of nitric oxide (NO) by blocking synthesis of endothelial nitric oxide synthetasis (eNOS) and increases production of reactive oxygen species, above all, superoxide anion in endothelial and vascular smooth muscle cells (18). In the Multiple Risk Intervention Trial (MRFIT) 9.7% (out of 5163 male patients) died due to cardiovascular diseases within the 12-year period (19). A study conducted by Haffner et al. (1373 non-diabetic and 1059 patients previously diagnosed with DM type 2) during a 7-year period found an increase in incidence of AMI in diabetic patients regardless of their medical history of previous myocardial infarction (20). Furthermore, Haffner et al. showed that DM increased the incidence of both, early and late complications in patients with acute coronary syndrome (20).

According to a trial by the Organisation to Assess Strategies for Ischemic Syndromes (OASIS), a 57%-increase of mortality rate was found in patients with unstable angina and AMI due to DM. A poorer long-term prognosis after the myocardial infarction, including recurrent myocardial infarction, heart failure and sudden cardiac death, has been found among patients with DM (21). Feng et al. have found that glycolised haemoglobin concentration affected major adverse cardiovascular events (MACE) in patients with AMI (22). In addition, Lipsic et al. have found that lower levels of haemoglobin are associated with higher short-term mortality in patients with acute MI (23). Our results have failed to show the connection between the glycolised haemoglobin and EFLV five days after STEMI. However, taking in consideration the number of patients in this research, these results can lead to new studies, which could confirm that unregulated DM is likely to affect EFLV. More reliable results could be achieved by following the development of MACE, as well as analysing the coronarography findings. In group 1, the EFLV five days after pPCI was significantly correlated with

minimum troponin values, which are essentially the initial values of troponin I on admission. Maximum values also correlate significantly with EFLV. In patients without the diagnosis of DM, only maximal values of troponin I were significantly correlated. Cubbon et al. have found that the mortality risk rapidly increased among male patients with the growth of glycaemia as compared to female patients (24). Furthermore, a study by Deedwania et al. has found that hyperglycaemia increases the mortality rate among patients with acute coronary syndrome (25). Monterio et al. have confirmed that hyperglycaemia is a bad prognostic marker and strong predictor of intrahospital mortality (26). All patients in their research were treated with metformin and sulphonylurea (SU) with or without insulin therapy (26). It is well known that the derivate of SU, meglitinides and thiazolidinediones have higher risk of new-onset acute coronary syndrome as compared with insulin (27). Contemporary therapy of DM recommends the usage of inhibitors of dipeptidyl peptidase-4, Sodium-glucose co-transporter-2 and glucagon-like peptide-1 agonists in patients with a high cardiovascular risk (28).

Our results have shown the relationship between values of cardiac troponin and systolic function of left ventricle five days after STEMI. A weak negative statistical correlation between EFLV and maximal value of cardiac troponin has been found in non-diabetic patients. On the other hand, a significant correlation between EFLV and all values of troponin, as well as average value of creatinine kinase has been found in diabetes patients. Khan et al. have failed to confirm that the increase in values of cardiac troponin would lead to lower EFLV (29). Furthermore, Shah et al. have found that value of cardiac troponin could lead to remodelling of left ventricle (30). These results are likely to be connected to timing of reperfusion therapy, as well as the patient's profile itself.

Our research has shown the importance of the minimum values of troponin I in patients with DM.

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They could be used as a better predictor of EFLV as compared to the maximum values. A limitation of the study is a relatively smaller sample, and it should be considered as an initial one. Nonetheless, there is no large number of studies that compare the minimum and maximum values of troponin I as a predictor factors of EFLV. Furthermore, total CK values are much better predictor of EFLV for patients with DM as compared to the CKMB values. They could indicate the importance of patient observation and anticipation of new values of troponin after three to four hours in emergency centres, even when troponin itself has borderline values and ECG signs are not convincing. The increase in troponin should be a determinant for the diagnosis of ACS, with mandatory interpretation and correlation with total CK values, which is very important in emergency centers, when the MB fraction is not available. It is necessary to emphasize that the only advantage of CK-MB over troponin is in detecting reinfarction after surgical revascularization, while in all other cases troponin should be used as the main determinant. Some authors have also suggested using CK-MB to CK ratio to improve specificity, however this approach significantly reduces sensitivity (31).

In the conclusion, we have failed to show the connection between the values of glycolised haemoglobin and the modality of treatment of DM and the EFLV after the diagnosis of MI. Values of troponin affect EFLV after STEMI. Optimized pharmacological treatment is an imperative in preventing future cardiovascular incidents and better control of DM and its complications. More extensive research is needed.

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TRANSPARENCY DECLARATION

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