

Dynamics and correlation of serum matrix metalloproteinase levels in patients with myocardial infarction with ST-segment elevation

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Abstract: The title “Dynamics and correlation of serum matrix metalloproteinase levels in patients with ST-segment elevation myocardial infarction” implies the study of changes in blood matrix metalloproteinase (MMP) concentrations in patients who have undergone ST-segment elevation myocardial infarction. This may include assessing the dynamics of MMP levels over time from the onset of infarction and analysing the correlation of these levels with clinical parameters such as blood glucose levels, measures of diabetic compensation and other risk factors or complications. Such a study aims to unravel the possible relationships between MMP levels and the course of the disease and to identify their potential value as biomarkers for diagnosis, prognosis and evaluation of the effectiveness of therapy in patients with STEMI.

Keywords: dynamics, correlation, serum matrix, metalloproteinase

Although mortality and disability due to cardiovascular disease (CVD) have decreased in developed countries in recent years, CVD is still a common problem in morbidity statistics. Patients with type 2 diabetes (T2DM) are known to have an increased risk of cardiovascular complications such as myocardial infarction (MI), stroke and sudden cardiac death. About 20-25% of patients with acute coronary syndrome (ACS) also have DM2. These patients are at increased risk of adverse outcomes such as death or recurrent myocardial infarction, both in the early and distant periods.

Previous studies have shown that patients with ACS and DM2 have a decreased activity of tissue inhibitors of matrix metalloproteinases, which is associated with a high risk of complications. The use of new biomarkers for the diagnosis and treatment of CVDs is being actively investigated, which may help to better understand the mechanisms of these diseases. However, despite the potential of new methods, their clinical application is limited.

New therapeutic approaches for patients with DM2 are being explored to reduce inflammation in the vascular wall and decrease the concentration of inflammatory

markers and matrix metalloproteinases in the blood. However, there are still no unequivocal data on the effect of DM2 on the activity of matrix metalloproteinases.

The aim of this study was to evaluate the relationship between matrix metalloproteinase activity and glycaemic levels in patients with ST-segment elevation MI, depending on the presence or absence of DM2.

MATERIALS AND METHODS: 175 patients with ST-segment elevation MI were included in the study. They developed symptoms within 48 hours of hospitalisation. Appropriate diagnostic procedures were performed in all patients to exclude other clinical conditions that might have affected the results.

Data on blood concentrations of matrix metalloproteinases and glycaemic levels were collected and analysed. Statistical processing of the data was performed using standard methods of analysis. The mean age of the patients was 61.3 years, most of whom were male. Frequent diseases in the history were arterial hypertension, angina pectoris and heart failure.

Table 1.

Clinical and anamnestic characteristics of patients with STEMI

Signs	Meaning
Men, n(%)	116 (66.3)
Women, n(%)	59 (33.7)
Age, years	62 (33; 87)
Smoking, n (%)	69 (39.2)
History of type 2 diabetes, n(%)	34 (19.4)
Obesity (BMI \geq 30 kg/m ²), n (%)	55 (31.4)
History of hypertension, n (%)	133 (76.0)
PICS, n (%)	36 (20.6)
History of angina pectoris, n (%)	94 (53.7)
ONMC, n (%)	15 (8.6)
CHF, n (%)	88 (50.3)
MI of anterior localization, n (%)	90 (51.4)
LVEF, %	49 (23; 68)
Class OCH according to Killip II-IV, n (%)	31 (17.7)

Note: AH - arterial hypertension; BMI - body mass index; PICS - postinfarction cardiosclerosis; AMI - acute cerebral circulatory failure; CHF - chronic heart failure; MI - myocardial infarction; LVEF - left ventricular ejection fraction; ARF - acute heart failure.

The control group consisted of 87 healthy volunteers aged 59 (43 to 68 years), who had not previously suffered from arterial hypertension, coronary heart disease, diabetes mellitus or other clinically significant pathology. There were 52 (59.8%) males and 35 (40.2%) females. All study participants were divided into two groups according to the presence or absence of a diagnosis of type 2 diabetes mellitus according to the 2011 WHO criteria. Serum MMP-1, -3 and -9 concentrations were studied in all participants. The group of patients with STEMI type 2 myocardial infarction consisted of 34 (18.2%) patients, including 25 (73.53%) males and 9

(26.47%) females, with a mean age of 69 years (43 to 81 years). There were no significant differences between the groups in the presence of comorbidities (COPD, CPN, peptic ulcer disease). Comparative analysis of clinical data showed that the presence of type 2 diabetes mellitus was significantly associated with cardiovascular risk factors such as arterial hypertension and obesity. In addition, the mean age of patients with myocardial infarction and type 2 diabetes mellitus was significantly higher than that of patients without type 2 diabetes ($p = 0.02$).

In addition, patients with coronary heart disease and type 2 diabetes had a markedly increased risk of previous stroke of 20.6% and 5.7%, respectively. However, there were no notable differences in other clinical characteristics or medical history between these groups (see Table 2).

Clinical and anamnestic characteristics of patients with STEMI depending on the presence of T2DM in history

Signs	With T2DM (n=34)	Without T2DM (n=141)	P
Men, n(%)	25 (26.5)	107 (75.9)	P=0.01
Women, n(%)	9 (73.5)	34 (34.1)	P=0.01
Age, years	69 (43; 81)	31 (33; 87)	P=0.02
Smoking, n(%)	7 (20.6)	62 (44.0)	P=0.02
Obesity(BMI \geq 30kg/m ²)	18 (52.9)	37 (26.2)	P=0.003
History of hypertension, n(%)	31 (91.2)	102 (72.3)	P=0.02
PIX, n(%)	8 (23.5)	28 (19.9)	P0.05>
History of angina pectoris, n(%)	19 (55.9)	75 (53.2)	P0.05>
ACVA, n(%)	7 (20.6)	8 (5.7)	P0.005=
CHF, n(%)	19 (55.3)	69 (48.9)	P0.05>
LVEF, %	50.0 (28.0; 50.0)	13 (23.0; 68.0)	P0.05>
Class OCH according to Killip II-IV, n(%)	5 (14.7)	26 (18.4)	P0.05>

When analysing the level of metalloproteinases (MMPs) in serum, the median values of these parameters on the 1st and 12th day after ST-segment elevation myocardial infarction (STEMI) were found to be higher than in healthy individuals. Specifically, MMP-1 concentration was 1.7 times higher on the first day and 2.7 times higher by the twelfth day than in the control group. MMP-3 also showed elevated values, by 1.2-fold and 1.4-fold, respectively. All serum MMP levels were 1.1 to 1.6 times higher by day twelve after BMIST. Patients with STEMI showed significantly elevated levels of MMP-1, -3 and -9 throughout the hospitalisation period compared to controls, and levels of these markers continued to increase by day 12. In addition, significantly elevated fasting blood glucose, HbA1c and blood glucose levels were seen on admission in patients with ST-segment elevation myocardial infarction and type 2 diabetes compared to other patients. Patients with ST-segment elevation myocardial infarction without type 2 diabetes mellitus had 1.3 times higher MMP-9 concentrations on day 1 than those with type 2 diabetes ($p=0.0001$). Further analysis of MMP levels according to hypoglycaemic therapy showed the following:

Patients who followed only a low-carbohydrate diet had MMP-3 concentrations 1.9 times higher on the first day of hospitalisation than those on other forms of hypoglycaemic therapy and remained elevated on day 12 ($p=0.02$). MMP concentrations were also 1.3-fold higher ($p=0.04$) in patients using oral hypoglycaemic agents compared to those taking them. However, the highest MMP-3 concentrations were observed in patients who received insulin together with other hypoglycaemic therapy in the preclinical phase compared to those who took oral antidiabetic agents, both on the first and twelfth day of hospitalisation.

Discussion of results:

The presented study results are in line with previous *in vitro* and *in vivo* studies that confirm the important role of certain metalloproteinases (MMPs) in destabilising atherosclerotic plaques, which can lead to thrombosis and therefore contribute to the development of acute coronary syndrome (ACS).

Experimental and clinical data also support an increase in MMP expression after a heart attack within hours of onset. Previous studies also indicate a significant increase in plasma concentrations of MMP-1, -2 and -9 in patients with ACS. Our study confirms these findings by showing a significant increase in MMP-1, -3 and -9 levels in patients with STEMI throughout the hospitalisation period compared to healthy patients. This is in agreement with previous studies showing increased concentrations of MMP-1, -2 and -9 during the first weeks after IMSPT.

Thus, the data of our study confirm previously published results and contribute to the understanding of the role of MMPs in the pathogenesis of the acute phase of myocardial infarction. Currently, the possibility of using some metalloproteinases (MMPs) not only as independent predictors of atherosclerotic plaque destabilisation, but also as markers for determining early and late adverse course of myocardial infarction is actively discussed.

One of the possible causes of increased MMP expression in patients with myocardial infarction but without coronary heart disease may be concomitant type 2 diabetes. However, the results of studies on the relationship between patients' glycaemic status and MMP concentration have been mixed.

Some have focused on patients with myocardial infarction and chronic hyperglycaemia in type 2 diabetes mellitus, as well as those with 'stress' hyperglycaemia resulting from an acute increase in the production of catecholamines, glucagon, cortisol and growth hormone. In such cases, there was an increase in creatine kinase activity and myocardial necrosis area.

Other studies indicate that more than half of patients without type 2 diabetes experience elevated blood glucose levels during the acute phase of myocardial infarction.

Conclusion

This study confirmed that patients with type 2 diabetes mellitus hospitalised due to ST-segment elevation myocardial infarction (STEMI) had significantly higher concentrations of MMP-3 and MMP-9. A statistically significant correlation was found between blood glucose levels and MMP-3 and MMP-9 levels on the first day of STEMI, which may indicate a possible effect of hyperglycaemia on MMP expression, regardless of medical history. Also, the findings on the relationship between HbA1c and MMP-3, -9 concentrations may indicate that MMP levels are dependent on the degree of diabetes compensation. However, there is no evidence that MMP concentrations in patients with type 2 diabetes reflect the severity of the process.

Increased matrix degradation may be a sign not only of chronic hyperglycaemia but also of other processes associated with the course of acute myocardial infarction and diabetes mellitus. This fact emphasises the need for further studies of the potential prognostic value of high MMP concentrations in patients with type 2 diabetes mellitus.

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