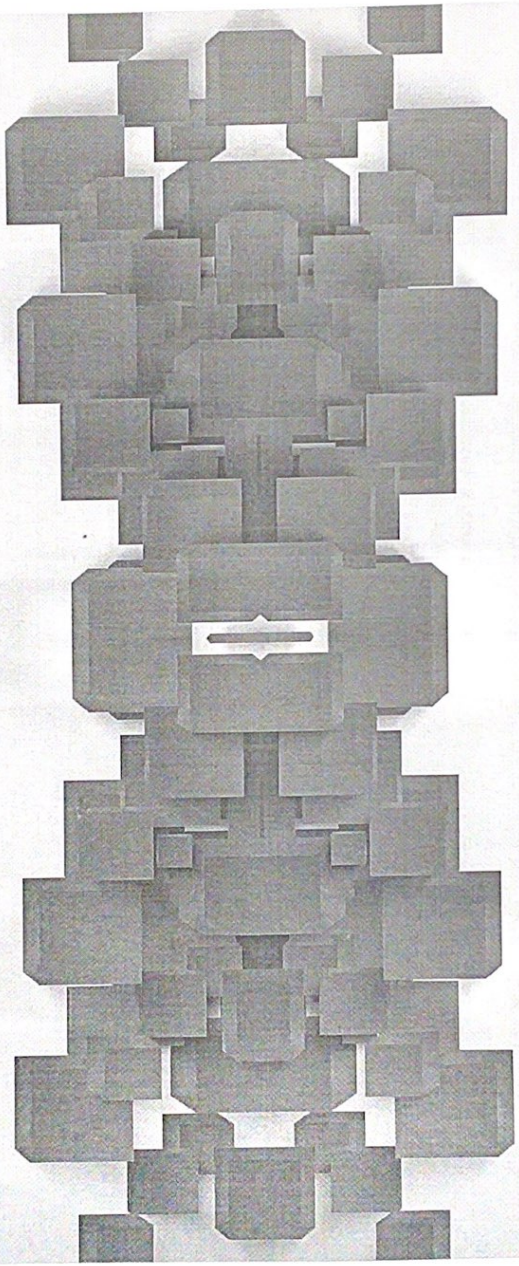

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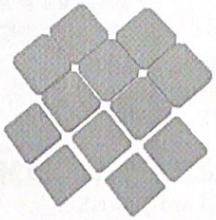

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THE PLASMA LEVELS OF MATRIX METALLOPROTEINASE-9 IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND 2 TYPE DIABETES

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Abstract

This study was aimed to assess the plasma levels of matrix metalloproteinase-9 (MMP-9) in patients with acute coronary syndrome (ACS) and with or without type 2 diabetes mellitus (T2DM). In this observational cohort trial we observed of 124 patients with ACS. All patients were randomized into two groups: 1st group - 93 patients with ACS and DM; 2nd group – 31 patients with ACS without 2 type DM. 30 apparently healthy persons were included into control group. We studied of MMP-9 levels in blood at admission by ELISA method. The mean age of all observed patients with ACS was (67.3±10.4) years; 63 (50.8%) were males and 61 (49.2%) females among them. The plasma levels of MMP-9 in patients with ACS without DM was for 2.24 times higher versus control group: (93.27±7.77) ng/ml, versus (41.57±8.34) ng/ml ($p<0.001$). Our study result showed that the MMP-9 levels were significantly higher among patients with ACS who also had DM: (123.41±9.58) ng/ml. **Conclusion.** In patients with acute coronary syndromes with 2 type diabetes the higher MMP-9 levels were observed, which is an independent predictor of in-hospital death in acute MI.

Keywords: acute coronary syndrome, diabetes mellitus, matrix metalloproteinase-9.

Introduction. Due modern epidemiological data cardiovascular diseases (CVD) cause, approximately, one-third of all deaths worldwide: nearly 7.5 million deaths are estimated to be due to coronary artery diseases (CAD), more than twice that caused by cancer [1]. The cardiovascular deaths account for nearly 50% of all deaths in Europe, over 4 million each year [2]. Acute coronary syndromes (ACS) and sudden death cause most CAD-related deaths, which represent 1.8 million deaths per year, with similar numbers of men and women dying from CAD [1]. In the United States, it is estimated that each year approximately 660,000 individuals have a new coronary attack, over 300,000 persons have a recurrent attack, and that 160,000 silent myocardial infarctions occur [3].

Diabetes mellitus (DM) is one of the important and independent predictors of mortality in CAD. Irrespective of the type of DM, patients with ACS are categorized as having a very high risk of recurrent cardiovascular events, translating into a doubled risk of premature death [4]. The recent meta-analysis of 10 European registries provided data in a systematic manner on ACS patients with DM (total 28 899 persons), and without DM (total 97 505 persons) showed: in the DM population, the proportion of patients with ST-Segment Elevation Myocardial Infarction (STEMI) ranged from 22.1% to 64.6% (other patients had non-ST-Segment Elevation Myocardial Infarction (NSTEMI-ACS) or unstable angina) [4]. In most, but not all, registries, event rates in DM patients were higher than in patients without DM. Pooled risk ratios comparing cohorts with DM vs. no DM were in-hospital significantly higher in DM for all-cause death (1.66; 95% CI 1.42–1.94), for cardiovascular death (2.33; 1.78 - 3.03), and for major bleeding (1.35; 1.21–1.52) [4].

Matrix metalloproteinases (MMPs) are proteolytic enzymes that break down extracellular matrix (ECM) components and have shown to be highly active in the myocardial infarction (MI) landscape. In addition to breaking down ECM products, MMPs modulate cytokine signaling and mediate leukocyte cell physiology. MMP-2, -7, -8, -9, -12, -14, and -28 are well studied as effectors of cardiac remodeling after MI [5].

This study was aimed to assess the plasma levels of matrix metalloproteinase-9 in patients with acute coronary syndrome and with or without type 2 diabetes mellitus (T2DM).

Material and Methods. In this observational cohort trial we observed of 124 patients with ACS in period from 1 January 2020 to 30 July 2020, which were hospitalized at Ivano-Frankivsk Regional Cardiology Center, Ivano-Frankivsk Central City Hospital and Kyiv National Institute of Cardiovascular Surgery (Ukraine). The diagnosis of ACS was verified by laboratory and instrumental methods according to European Society of Cardiology guidelines (2017, 2020) [6, 7]. The diagnosis of DM was verified by laboratory and instrumental methods according to American Diabetes Association guidelines (2020) [8]. All patients were randomized into two groups: 1st group - 93 patients with ACS and DM; 2nd group – 31 patients with ACS without 2 type DM. 30 apparently healthy persons were included into control group.

We studied of MMP-9 levels in blood at admission by ELISA method. The study was performed in accordance with the Helsinki Declaration and Good Clinical Practice Guideline. The study was approved by the local ethics committee (decision from 20 December 2019) and written informed consent was obtained from all patients. Categorical variables are presented as percentages, whereas continuous variables are presented as mean (M) and standart error of mean (m) if normally distributed, or as median and interquartile range (Me [IQR]), if not. Categorical variables were compared by the χ^2 test and continuous variables by the t test or the Mann–Whitney U test. A p value of <0.05 was considered statistically significant. All tests were 2-sided. Analyses were performed with Statistica system software, version 12.0.

Results and Discussion. The mean age of all observed patients with ACS was (67.3±10.4) years; 63 (50.8%) were males and 61 (49.2%) females among them. ACS without persistent ST segment elevation was diagnosed in 24 (19.4%) cases; instead ACS with persistent ST segment elevation – in 100 (80.6%) cases. 47 (37.9%) patients were identified as current smokers, mostly – males (31 (65.9%) persons).

Cigarette smoking is an important modifiable risk factor for cardiovascular and cerebrovascular disease in a general population. The risk for ACS and total mortality associated with smoking is high in type 2 diabetes patients. Due results of the longitudinal study involved 13 087 female and male patients with type 2 diabetes from the Swedish National Diabetes Register with no previous MI or stroke at baseline, aged 30-74 years, and with data available for all analysed variables, followed up for mean 5.7 years, showed adjusted hazard ratios (HRs) for smoking and first-incident fatal/nonfatal MI, stroke and total mortality were 1.7 [95% confidence interval (CI): 1.4-2.0; p<0.001], 1.3 (95% CI: 1.1-1.6; p = 0.006) and 1.8 (95% CI: 1.5-2.2; P<0.001), respectively, by Cox regression analysis, adjusted for age, sex, diabetes duration, hypoglycaemic treatment, haemoglobin A1c, blood pressure, body mass index, microalbuminuria, antihypertensive and lipid-lowering drugs. Adjusted HR was higher for fatal MI, 2.1 (95% CI: 1.7-2.7; p<0.001), than for nonfatal MI, 1.4 (95% CI: 1.2-1.7; p<0.001). The highest HRs were observed in more frequently smoking (22%), middle-aged patients (age <60 years) for fatal/nonfatal MI, 2.3 (95% CI: 1.8-3.1; p<0.001) and for total mortality, 2.5 (95% CI: 1.6-3.8, p<0.001), whereas lower HRs were observed in older and less smoking patients [9].

The plasma levels of MMP-9 in patients with ACS without DM was for 2.24 times higher versus control group: (93.27±7.77) ng/ml, versus (41.57±8.34) ng/ml (p<0.001) (see fig. 1). Our study result showed that the MMP-9 levels were significantly higher among patients with ACS who also had DM: (123.41±9.58) ng/ml.

There is strong evidence that the prognosis of ACS is associated with various factors, including dyslipidemia, smoking status, hypertension, DM, age, male gender, and plasma levels of B-type natriuretic peptide (BNP) and MMP-9 [10]. Among these biomarkers, MMP-9 is unique because it is closely associated with the development of atherosclerosis and instability of plaques [11].

Several studies showed the closed relation between MMP-9 levels in blood and in-hospital fatality in patients with ACS. First, coronary atherosclerotic plaques are the pathological basis of coronary heart disease. Acute MI is usually initiated by rupture of atherosclerotic plaque, leading to intracoronary thrombosis and clinical sequelae. Human coronary atherectomy specimens revealed uniform and active synthesis of MMP-9 by macrophages and smooth muscle cells in lesions from patients with unstable versus stable angina, found that MMP-9 is play a pathogenic role in the development of acute coronary ischemia, because it promoted the basement membrane rupture, resulting in smooth muscle cell migration and proliferation in the plaque, MMP - 9 at the same time promote the accumulation of mononuclear cells and macrophages, and these cells gradually turn into foam cells thus formed fatty nuclei of atherosclerotic plaques, moreover those precursor cells can secrete inducer and inflammation factors, it can stimulate activation of MMP-9 [12]. Second, a greater infarct size is associated with a higher the risk of mortality after AMI. Some studies showed that increases in value of MMP-9 levels were associated with increased left ventricle wall motion score index (WMIS), which is closely related to the area of acute MI [12]. Third, in association with extracellular matrix degradation during left ventricle remodeling. Left ventricular remodeling after MI is a leading cause of congestive heart failure, and the degree of remodeling predicts morbidity and mortality [13].

Recent study has provided evidences that in patients with type-2 diabetes mellitus, circulating MMP-9 levels were more affected by chronic hyperglycemic condition rather than by acute hyperglycemia. The linear correlation between HbA1c and MMP-9 levels were showed [14]. In recent cross-sectional study, conducted in Indonesia, showed a relationship between MMP-9 levels and hyperglycemia occurring in ACS. Patients with hyperglycemia had a prevalence ratio of 2.88 for having high MMP-9 levels while suffering from acute coronary syndrome. High MMP-9 levels may mediate the detrimental effects of hyperglycemia in acute coronary syndrome. Acute hyperglycemia exacerbates oxidative stress and RAGE production with subsequent MMP overexpression in the vascular wall. Moreover, on-admission hyperglycemic state alone is also associated with worse outcomes in acute coronary syndromes. In combination with increased MMP-9 levels, these patients may have additional risk and burden for developing adverse events during hospitalization [15].

Conclusion. In patients with acute coronary syndromes with 2 type diabetes the higher MMP-9 levels were observed, which is an independent predictor of in-hospital death in acute MI.

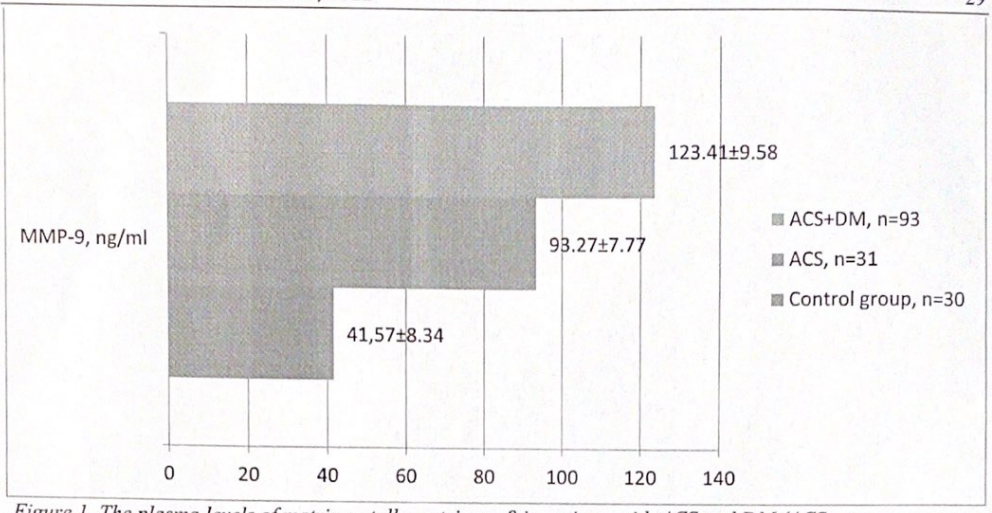

Figure 1. The plasma levels of matrix metalloproteinase-9 in patients with ACS and DM (ACS – acute coronary syndrome, DM – diabetes mellitus)

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