DYNAMICS OF FABP4 AND CTRP3 BIOMARKERS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND TYPE 2 DIABETES MELLITUS

Mariia Koteliukh

The aim of the work was to study the characteristics of adipokine metabolism based on the analysis of fatty acid binding protein 4 (FABP4) and C1q/tumour necrosis factor-related protein-3 (CTRP3) levels and their dynamics in non-diabetic and diabetic patients with cardiovascular (CV) complications of acute myocardial infarction (AMI).

Materials and methods. The study was carried out between 2018 and 2020 and involved 134 AMI patients with or without type 2 diabetes mellitus (DM) aged 59.00 [52.75; 66.00] years. The control group consisted of 20 healthy individuals with the mean age of 56.50 [48.50; 61.75] years. The serum levels of FABP4 and CTRP3 were measured by enzyme-linked immunosorbent assay on days 1 and 10 of hospital stay.

Results. The mean levels of FABP4 were elevated on day 1 in AMI patients with type 2 DM (group II) compared to those in AMI patients (group I) and the control individuals (p<0.05). The FABP4 concentrations on day 10 were 7.68 [6.42; 8.42] ng/ml and 8.31 [6.92; 9.63] ng/ml (p<0.05) in groups I and II, respectively. The CTRP3 levels were lower in group II on day 1 as compared to those in group I and the control group patients (p<0.001). After 10 days, the levels of CTRP3 were 287.56 [271.48; 300.58] ng/ml and 262.01 [225.32; 288.84] ng/ml (p<0.001) in groups I and II, respectively. In the presence of early AMI complications in diabetic patients, the levels of FABP4 remained elevated on day 10, and the levels of CTRP3 were low compared to those in diabetic patients without AMI complications (p<0.05).

Conclusions. The characteristics of adipokine metabolism in AMI patients have been revealed: the worsened imbalance in adipokine metabolism in type 2 DM due to the difference in FABP4 and CTRP3 levels. Special mention should be made of severely deteriorated adipokine metabolism in diabetic patients with CV complications.

Keywords: markers, adipokine metabolism, acute myocardial infarction, adverse course, diabetes mellitus

1. Introduction

According to the World Health Organization, cardiovascular disease (CVD) and diabetes mellitus (DM) are among the top ten diseases worldwide. Mortality rates associated with coronary heart disease in 2019 was 8.9 million cases of the world population [1]. The global prevalence of type 2 DM in 2017 was 8.8 % and scientists expect an increase in type 2 DM cases to 9.9 % by the year 2045 [2]. In 2019, 1.5 million deaths due to DM were recorded [3]. Cardiovascular (CV) complications of acute myocardial infarction (AMI) have been found to be more common in diabetic patients than in non-diabetic individuals [4]. The influence of metabolic markers on the development and course of AMI is currently studied in modern medicine. Proinflammatory fatty acid binding protein 4 (FABP4) and anti-inflammatory C1q/tumour necrosis factor-related protein-3 (CTRP3 or cartonectin) are adipokines involved in the regulation of carbohydrate and lipid metabolism and associated with unfavourable course of AMI [5, 6] through the indirect proinflammatory signalling pathway influence on the myocardium. Therefore, the study on metabolic markers which provide an opportunity to better understand the mechanisms of development and unfavourable course of AMI in diabetic and non-diabetic patients is relevant and one of the priority areas of research.

The aim of the research was to study the characteristics of adipokine metabolism based on the analysis of FABP4 and CTRP3 levels and their dynamics in non-diabetic and diabetic patients with CV complications of AMI.

2. Materials and methods

The study was carried out between 2018 and 2020 in the Government Institution “L. T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine” and the Kharkiv Railway Clinical Hospital No. 1 of the branch “Center of Healthcare” of Public Joint Stock Company “Ukrainian Railway”. The study involved 134 participants with ST-segment elevation AMI (STEMI) in the absence or presence of type 2 DM aged 59.00 [52.75; 66.00] years.

The patients were divided according to CV AMI complications absence or presence (acute heart failure (AHF), acute aneurysm of the apex and interventricular septum of the left ventricle (LV), recurrent AMI, parox-
The nonparametric Mann-Whitney rank test and test was applied to compare the frequency of signs in the (Me), 25th and 75th percentiles [Q1; Q3]. The Pearson bibles were shown as the following parameters: median software package IBM SPPS version 27.0. Qualitative diograph “Fukuda” FX was recorded with the help of a three-channel electrocar-
Pro30 (Ukraine). Standard 12-lead electrocardiography formed with an ultrasound scanner Radmir ULTIMA.
On the 1st day of inpatient treatment, the serum CTRP3 concentrations were low among nondiabetic (I) and diabetic (II) patients who later developed early CV complications and did not differ between patients without CV complications (p>0.05) (Table 1). On day 10 of treatment, the CTRP3 levels in nondiabetic (I) and diabetic (II) patients with early CV complications were reduced low 8.64 % and 7.64 %, respectively, as compared to those in patients without CV complications (p<0.05). During inpatient treatment, the serum CTRP3 levels in group I patients without early CV complications were significantly increased (13.84 %) compared to day 1 of hospital stay (p<0.05). Group I and II patients with early CV complications demonstrated an upward tendency in the concentrations of CTRP3, but it was statistically insignificant compared to day 1 of hospital stay (p>0.05). In group II patients without early AMI complications, the levels of CTRP3 were significantly increased 14.07 % increased as compared to those on 1 day (p<0.05). In nondiabetic patients with and without early CV complications on the 10th day, the CTRP3 concentrations were 6.11 % and 14.22 % lower, respectively, compared to the threshold value of this marker 315.85 [287.06; 371.02] ng/ml (p<0.05). The levels of CTRP3 on the 10th day of treatment in diabetic patients without early CV complications remained low 8.64 % and 7.64 %, respectively, as compared with those in the controls (p>0.05).

It is worth noting that on the 10th day of treatment, the levels of CTRP3 in diabetic patients without early AMI complications were 11.65 % reduced compared with those in non-diabetic patients (p<0.05), while in diabetic patients with the presence of early AMI complications, that was a decline of 10.69 % (p<0.05). Importantly, the lowest concentrations of CTRP3 were found in type 2 DM patients with complicated AMI.

So, there was a dynamic increase in the serum CTRP3 levels during treatment in all patients. Despite the dynamics of CTRP3, the levels of this marker remained low. Also, worth noting is the prevalence of the lowest CTRP3 levels on the 10th day of treatment among diabetic patients with early CV complications, indicating a metabolic shift in the adipokine balance in this cohort of patients.

### 4. Discussion

The use of modern treatments such as PCI and intensive antithrombotic therapy still leaves the group of DM patients in a zone of high risk for AMI CV complications [11]. Identifying and studying the metabolic markers are important for understanding their pathophysiological effects in the development and progression of early AMI complications in non-diabetic and diabetic patients.

Elevated serum FABP4 levels were detected from the first hours of AMI development, especially if this marker was examined in AMI patients resuscitated from out-of-hospital cardiac arrest caused by VF 130.2 [51.8; 243.9] ng/ml compared with individuals without it 26.1 [17.1; 43.4] ng/ml [5]. Serum FABP4 may be in terms of an excessively adrenergic signal that accompanies acute CVD, including AMI. Previous study showed significantly higher circulating FABP4 in patients who developed adverse cerebrovascular (stroke) and CV events (34 cardiac deaths and 3 unclear deaths, recurrent myocardial infarction) during 30-day follow-up as compared to control patients without any event: 39.9 ng/ml [5th – 95th percentile range, 15.0–307.7] versus 26.4 ng/ml [5th – 95th percentile range, 13.8–97.9] [12]. Indeed, FABP4 plasma levels were associated with higher rates of CVD mortality in men with type 2 DM [13]. Scientists’ results revealed a close association between A-FABP and heart failure and suggested a probability of causal relations between increased A-FABP and pathogenesis of heart dysfunction in humans [14]. Prolonged hyperglycemia and insulin resistance were found to stimulate the release of cartonectin [15]. Besides that, patients with acute coronary syndrome demonstrated decreased cartonectin levels [16]. Patients with persistent AF had lower plasma CTRP3 levels than patients with paroxysmal AF [17]. A model of ventricular tachycardia (VT) prognosis was constructed based on cartonectin levels, where the borderline CTRP3 value was 200 ng/ml and it predicted the development of VT with sensitivity of 88.1 % and specificity of 80.2 % [18].

### Study limitations

Several limitations to this study need to be considered. First, this study had a relatively small sample size. Second, an estimation of the STEMI adverse course in both non-diabetic and diabetic patients based on the levels of FABP4 and CTRP3 needs a longer duration of follow-up. Third, the FABP4 and CTRP3 levels need to be examined in both non-diabetic and diabetic patients with early NSTEMI complications.

### Table 1

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Consequences</th>
<th>No complications</th>
<th>Early CV complications</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Group I</td>
<td>Group II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Me [Q25; Q75]</td>
<td>Me [Q25; Q75]</td>
</tr>
<tr>
<td>FABP4, ng/ml</td>
<td></td>
<td></td>
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<td>On admission to the hospital</td>
<td></td>
<td>9.71</td>
<td>10.72</td>
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<td></td>
<td></td>
<td>[8.84; 10.77]</td>
<td>[9.24; 12.12]</td>
</tr>
<tr>
<td>On the 10th day of treatment</td>
<td></td>
<td>6.77</td>
<td>7.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[5.91; 8.42]</td>
<td>[6.70; 8.79]</td>
</tr>
<tr>
<td>CTRP3, ng/ml</td>
<td></td>
<td>260.51</td>
<td>229.69</td>
</tr>
<tr>
<td>On admission to the hospital</td>
<td></td>
<td>[241.75; 294.26]</td>
<td>[194.30; 267.67]</td>
</tr>
<tr>
<td>On the 10th day of treatment</td>
<td></td>
<td>296.56</td>
<td>262.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[283.54; 308.16]</td>
<td>[225.89; 288.09]</td>
</tr>
</tbody>
</table>

Note: * – p<0.05 – differences between groups without and with early CV complications; # – p<0.05 – differences between groups on admission and on the 10th day of the inpatient treatment; ● – p<0.05 – differences between groups.
Prospects for further research. Our further study will involve the measurement of adipokine metabolism markers (FABP 4 and CTRP3) in type 2 DM patients 1 year after myocardial infarction.

5. Conclusions
The serum levels of FABP4 and CTRP3 were changed on the 10th day of follow-up in AMI patients with or without type 2 DM. Significantly high concentrations of FABP4 and low levels of CTRP3 in diabetic patients on days 1 and 10 of hospital stay should be noted.

In the dynamics of treatment, the elevated levels of FABP4 and particularly low levels of CTRP3 were identified in diabetic patients with early CV complications of AMI on day 10.

These findings provide insights into FABP4 and CTRP3 levels in diabetic and non-diabetic patients, which may help to develop a new approach to correcting metabolic shifts in unfavourable course of AMI.

Conflict of interest
The author has no conflicts of interest to declare.

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