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

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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*

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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 pro-inflammatory 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-

ysm of atrial fibrillation (AF) or ventricular fibrillation (VF), atrioventricular (AV) block, reduced LV ejection fraction (EF) < 40 %). Among 60 patients with AMI (group I), 41 patients without early AMI complications and 19 patients with unfavourable course of AMI were identified. There were 48 patients without early AMI complications and 26 patients with unfavourable course of AMI out of 74 patients with AMI and type 2 DM (group II). Diagnosis of AMI and its early complications including AV block, AF, VF, AHF Killip classes II, III, IV, acute left ventricular aneurysm of the apex and interventricular septum, reduced LV EF <40 % was based on the clinical-laboratory and instrumental methods of examination according to the European Society of Cardiology guidelines [7]. All the patients underwent percutaneous coronary intervention (PCI). Therapy for type 2 DM was prescribed according to the American (2018) and European (2018, 2019) Associations for the Study of DM joint recommendations and the International Diabetes Federation criteria (2019) [8–10]. Patients diagnosed with type 1 DM, non-ST-segment elevation myocardial infarction (NSTEMI), COVID-19, autoimmune diseases, pituitary and hypothalamic diseases, thyroid disease, symptomatic hypertension, valvular heart disease, chronic heart failure IV FC to myocardial infarction, chronic obstructive pulmonary disease, liver and renal dysfunction, severe anemia, malignancy were excluded from the study.

The control group consisted of 20 healthy individuals aged 56.50 [48.50; 61.75] years.

The study was conducted following the requirements of the World Medical Association Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine, Good Clinical Practice and approved by the Bioethics Commission of Kharkiv National Medical University (Protocol No. 2 dated April 2, 2018). Participants were only included in the study after signing the voluntary informed consent.

Diagnostic testing was carried out in the Biochemical Department of the Central Research Laboratory of Kharkiv National Medical University. Blood samples were taken on the 1st and the 10th day. Serum FABP4 and CTRP3 levels were measured by enzyme-linked immunosorbent assay using an analyzer "Labline-90" (Austria) with a commercial test system “Human FABP4” (Elabscience, USA) and “Human CTRP3” (Aviscera Bioscience, USA), respectively, following the standard manufacturer instructions. The method of FABP4 and CTRP3 level quantification uses the sandwich technique principle based on an antibody pair of the capture antibody and biotin-labelled detection antibody binding to the captured analyte.

Conventional Doppler echocardiography was performed with an ultrasound scanner Radmir ULTIMA Pro30 (Ukraine). Standard 12-lead electrocardiography was recorded with the help of a three-channel electrocardiograph “Fukuda” FX-326U (Japan).

The findings were analyzed statistically using the software package IBM SPPS version 27.0. Qualitative data were presented as percentages; quantitative variables were shown as the following parameters: median (Me), 25th and 75th percentiles [Q1; Q3]. The Pearson χ^2 test was applied to compare the frequency of signs in the groups. The nonparametric Mann-Whitney rank test and Wilcoxon test were used to compare quantitative variables for independent and dependent samples, respectively. The nonparametric Kruskal-Wallis test was used to compare indicators between three groups. The results were considered significant at a level of $p<0.05$.

3. Results

On admission, mean FABP4 serum levels were increased in patients with AMI and type 2 DM 10.68 [9.26; 12.00] ng/ml (II) compared with those in AMI patients 9.83 [9.25; 10.79] ng/ml (I) and the controls 4.25 [3.46; 6.16] ng/ml ($p<0.05$). On day 10 of hospital stay, the serum levels of FABP4 declined to 8.31 [6.92; 9.63] ng/ml (II) and 7.68 [6.42; 8.42] ng/ml (I), making the statistically significant difference ($p<0.05$) between the two groups of patients.

On admission to the hospital, the serum CTRP3 levels of patients with AMI and type 2 DM showed declining trends – 218.32 [191.95; 268.68] ng/ml (II) compared to those in AMI patients 260.50 [240.08; 295.96] ng/ml (I) and the control group 315.85 [287.06; 371.02] ng/ml ($p<0.001$). After 10 days of treatment, the mean levels of CTRP3 were increased in both group I – 287.56 [271.48; 300.58] ng/ml and group II – 262.01 [225.32; 288.84] ng/ml) ($p<0.001$).

On day 1 of inpatient treatment, the serum FABP4 concentrations were low in both non-diabetic (I) and diabetic (II) patients, who later showed early CV complications, and that indicator did not differ among patients without CV complications ($p>0.05$) (Tab. 1). On day 10 of treatment, the FABP4 levels in both non-diabetic (I) and diabetic (II) patients with early CV complications were increased by 19.20 % and 22.13 %, respectively, compared to those in patients without CV complications ($p<0.05$). During inpatient treatment, the serum FABP4 levels in group I and II patients without early complications were almost equally declined by 30.28 % and 29.2 % ($p<0.05$), respectively, and with the presence of CV AMI complications – by 19.14 % and 13.12 %, respectively, compared with those on day 1 of hospital stay. In non-diabetic patients (group I) with and without early CV complications, the FABP4 concentrations were 1.59 and 1.9 times increased on day 10, respectively, compared with the threshold value of this marker 4.25 [3.46; 6.16] ng/ml) ($p<0.05$). The levels of FABP4 on the 10th day of treatment in diabetic patients (group II) with and without early CV complications remained 1.79 and 2.18 times increased, respectively, compared with those in the control group ($p<0.001$). It is worth noting that on day 10 of treatment, the FABP4 levels in diabetic patients without early AMI complications tended to increase compared to those in non-diabetic patients, but the difference was not significant ($p>0.05$). The FABP4 serum levels in diabetic patients with early AMI complications on day 10 of follow-up were 14.87 % greater compared with those in non-diabetic patients with AMI complications ($p<0.05$).

Thus, the serum FABP4 levels remain elevated in both groups during inpatient treatment. Nevertheless, on day 10 of treatment, the FABP4 levels in diabetic patients were significantly increased regardless of presence or absence of early AMI complications, unlike in non-diabetic patients.

Table 1

Mean values of FABP4 and CTRP3 in groups I and II

Indicators / Consequences	No complications		Early CV complications	
	Group I	Group II	Group I	Group II
	Me [Q25; Q75]			
FABP4, ng/ml				
On admission to the hospital	9.71 [8.84; 10.77]	10.72 [9.24; 12.12]	9.98 [9.34; 10.95]	10.67 [9.26; 11.95]
On the 10th day of treatment	6.77 [5.91; 8.42]*#	7.59 [6.70; 8.79]*#	8.07 [7.46; 8.44]#●	9.27 [8.49; 10.41]#
CTRP3, ng/ml				
On admission to the hospital	260.51 [241.75; 294.26]●	229.69 [194.30; 267.67]	255.50 [225.77; 308.11]●	227.52 [189.63; 254.87]
On the 10th day of treatment	296.56 [283.54; 308.16]*#●	262.01 [225.89; 288.09]*#	270.95 [247.80; 279.45]●	241.99 [204.84; 272.11]

*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.*

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) (Tab. 1). On day 10 of treatment, the CTRP3 levels in nondiabetic (I) and diabetic (II) patients with early CV complications were remained 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 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 with and without early CV complications remained 17.05 % and 23.38 % reduced, 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.

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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References

1. WHO Newsletter: 10 leading causes of death in the world (2020). Available at: https://www.who.int/ru/news-room/fact-sheets/detail/the-top-10-causes-of-death

2. Standl, E., Khunti, K., Hansen, T. B., Schnell, O. (2019). The global epidemics of diabetes in the 21st century: Current situation and perspectives. European journal of preventive cardiology, 26 (2), 7–14. doi: http://doi.org/10.1177/2047487319881021

3. WHO Newsletter: Diabetes. November 10, 2021. https://www.who.int/ru/news-room/fact-sheets/detail/diabetes

4. Khalid, S. H., Liaqat, I., Mallhi, T. H., Khan, A. H., Ahmad, J., Khan, Y. H. (2020). Impact of diabetes mellitus on clinico-laboratory characteristics and in-hospital clinical outcomes among patients with myocardial infarction. The Journal of the Pakistan Medical Association, 70 (12 (B)), 2376–2382. doi: https://doi.org/10.47391/JPMA.370

5. Obokata, M., Iso, T., Ohyama, Y., Sunaga, H., Kawaguchi, T., Matsui, H. et. al. (2018). Early increase in serum fatty acid binding protein 4 levels in patients with acute myocardial infarction. European heart journal. Acute cardiovascular care, 7 (6), 561–569. doi: http://doi.org/10.1177/2048872616683635

6. Wu, D., Lei, H., Wang, J. Y., Zhang, C. L., Feng, H., Fu, F. Y. et al. (2015). CTRP3 attenuates post-infarct cardiac fibrosis by targeting Smad3 activation and inhibiting myofibroblast differentiation. Journal of molecular medicine, 93 (12), 1311–1325. doi: http://doi.org/10.1007/s00109-015-1309-8

7. Ibanez, B., James, S., Agewall, S., Antunes, M. J., Bucciarelli-Ducci, C., Bueno, H. et al. (2018). 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European heart journal, 39 (2), 119–177. doi: http://doi.org/10.1093/eurheartj/ehx393

8. Online version of IDF Diabetes Atlas: Nineth edition, 2019. https://www.diabetesatlas.org/en/

9. Davies, M. J., D'Alessio, D. A., Fradkin, J., Kernan, W. N., Mathieu, C., Mingrone, G. et. al. (2018). Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia, 61 (12), 2461–2498. doi: http://doi.org/10.1007/s00125-018-4729-5

10. Cosentino, F., Grant, P. J., Aboyans, V., Bailey, C. J., Ceriello, A., Delgado, V. et. al. (2020). 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. European heart journal, 41 (2), 255–323. doi: http://doi.org/10.1093/eurheartj/ehz486

11. Simek, S., Motovska, Z., Hlinomaz, O., Kala, P., Hromadka, M., Knot, J. et. al. (2020). The effect of diabetes on prognosis following myocardial infarction treated with primary angioplasty and potent antiplatelet therapy. Journal of clinical medicine, 9 (8), 2555. doi: http://doi.org/10.3390/jcm9082555

12. Reiser, H., Klingenberg, R., Hof, D., Cooksley-Decasper, S., Fuchs, N., Akhmedov, A. et al. (2015). Circulating FABP4 is a prognostic biomarker in patients with acute coronary syndrome but not in asymptomatic individuals. Arteriosclerosis, thrombosis, and vascular biology, 35 (8), 1872–1879. doi: http://doi.org/10.1161/atvbaha.115.305365

13. Liu, G., Ding, M., Chiuve, S. E., Rimm, E. B., Franks, P. W., Meigs, J. B. et. al. (2016). Plasma levels of fatty acid-binding protein 4, retinol-binding protein 4, high-molecular-weight adiponectin, and cardiovascular mortality among men with type 2 diabetes: a 22-year prospective study. Arteriosclerosis, thrombosis, and vascular biology, 36 (11), 2259–2267. doi: http://doi.org/10.1161/atvbaha.116.308320

14. Liu, M., Zhou, M., Bao, Y., Xu, Z., Li, H., Zhang, H. et. al. (2013). Circulating adipocyte fatty acid-binding protein levels are independently associated with heart failure. Clinical science, 124 (2), 115–122. doi: http://doi.org/10.1042/cs20120004

15. Liang, W., Ye, D. D. (2019). The potential of adipokines as biomarkers and therapeutic agents for vascular complications in type 2 diabetes mellitus. Cytokine & growth factor reviews, 48, 32–39. doi: http://doi.org/10.1016/j.cytogfr.2019.06.002

16. Choi, K. M., Hwang, S. Y., Hong, H. C., Choi, H. Y., Yoo, H. J., Youn, B. S. et. al. (2014). Implications of C1q/TNF-related protein-3 (CTRP-3) and progranulin in patients with acute coronary syndrome and stable angina pectoris. Cardiovascular diabetology, 13 (1). doi: https://doi.org/10.1186/1475-2840-13-14

17. Chen, L., Liu, S., Xu, W., Zhang, Y., Bai, J., Li, L., et al. (2020). Association of plasma C1q/TNF-related protein 3 (CTRP3) in patients with atrial fibrillation. Mediators of inflammation, 2020, 8873152. doi: http://doi.org/10.1155/2020/8873152

18. Yildirim, A., Sumbul, H. E., Koca, H., Kucukosmanoglu, M., Kemal Icen, Y., Koc, M. (2021). Complement C1q/tumor necrosis factor-related protein-3 (CTRP3) is significantly decreased in patients with heart failure and closely related with ventricular tachycardia. Acta Cardiologica Sinica, 37 (3), 278–285. doi: https://doi.org/10.6515/ACS.202105_37(3).20201019B

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