UDC 616.127-005.8+616.379-008.64]-078:57.083.3:[577.125+577.122]
DOI https://doi.org/10.32782/2415-8127.2022.65.3

Koteliukh Mariia Yuriivna,
PhD, postdoctoral researcher at the Department of Internal Medicine No. 2 and Clinical Immunology and Allergology named after academician L. T. Malaya, Kharkiv National Medical University,
koteliukh@gmail.com
https://orcid.org/0000-0001-6090-4835
Kharkiv, Ukraine

Relationship between parameters of adipokine and lipid profiles in patients with acute myocardial infarction and type 2 diabetes mellitus

Introduction. Nowadays, it becomes topical to search for methods of diagnosis and treatment for polymorbid patients. The importance of the study on pathophysiological mechanisms of acute myocardial infarction (AMI) in patients with type 2 diabetes mellitus (DM) has been shown.

The aim of the study: to examine the relationship between adipokine and lipid profiles in AMI patients with the presence or absence of type 2 DM.

Material and methods. The study was conducted over a period from September 1, 2018 to December 31, 2020. A total of 134 patients with ST-segment elevation AMI in the presence or absence of type 2 DM aged 58.97 ± 7.92 years hospitalized in the intensive care unit of Government Institution "L. T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine" and Kharkiv Railway Clinical Hospital No. 1 of the branch "Center of Healthcare" were enrolled in the study. Group 1 included 74 patients with AMI and type 2 DM aged 59.42 ± 7.66 years. Group 2 (comparison group) comprised 60 patients with AMI without type 2 DM aged 58.42 ± 8.25 years. The control group consisted of 20 otherwise healthy individuals. Serum concentrations of fatty acid-binding protein 4 (FABP4) and C1q/TNF-related protein 3 (CTRP3) of patients were measured by enzyme-linked immunosorbent assay. Serum total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol were analyzed by peroxidase enzymatic method. Triglyceride (TG) levels were measured by enzymatic colorimetric method. The atherogenic index was calculated by the A.M. Klimov formula. The levels of very low-density lipoprotein (VLDL) cholesterol and low-density lipoprotein (LDL) cholesterol were estimated by the Friedewald formula.

Results and discussion. The patients in Group 1 were found to have higher levels of serum TG in comparison with Group 2 patients ($p<0.05$). In groups 1 and 2, there was an upward tendency in the levels of TC and LDL ($p>0.05$), as well as a significant 4.04 and 2.92 times increase in VLDL, respectively, as compared to the control group ($p<0.05$). The serum levels of FABP4 were significantly increased, while CTRP3 levels were decreased in AMI patients compared to those in otherwise healthy individuals ($p<0.05$). In AMI patients with type 2 DM (group 1), an inverse correlation was found between FABP4 and VLDL ($r = 0.502$, $p<0.05$), TG ($r = 0.596$, $p<0.001$); between CTRP3 and TC ($r = -0.507$, $p<0.05$), LDL ($r = -0.512$, $p<0.05$). In patients with AMI (group 2), an inverse correlation was revealed between FABP4 and VLDL ($r = 0.453$, $p = 0.006$), TG ($r = 0.439$, $p = 0.009$); between CTRP3 and TC ($r = -0.413$, $p = 0.001$), LDL ($r = -0.429$, $p = 0.01$).

Conclusions. The characteristics of changes in the FABP4 and CTRP3 serum levels are evidence of an adipokine metabolism imbalance in AMI with the presence or absence of type 2 DM, indicating a metabolic shift in this patient category. The relationship between lipid profile markers and FABP4 and CTRP3 may indicate the influence of the latter on lipid metabolism.

Key words: adipokines, biomarkers, lipids, comorbidity, metabolism.

Котелюх Марія Юріївна, кандидат медичних наук, докторант кафедри внутрішньої медицини № 2 і клінічної імунології та алергології імені академіка Л.Т. Малої, Харківський національний медичний університет, koteliukh@gmail.com, https://orcid.org/0000-0001-6090-4835, м. Харків,Україна

Взаємозв'язок між показниками адипокінового та ліпідного профілю у пацієнтів на гострий інфаркт міокарда та цукровий діабет 2 типу

Вступ. Сьогодні ведуться наукові пошуки щодо діагностики та лікування хворих із поліморбідним фоном. Доведено важливість дослідження патофізіологічних механізмів гострого інфаркту міокарда (ГІМ) у хворих із цукровим діабетом (ЦД) 2 типу.

Мета дослідження: дослідити взаємозв'язок між ліпідним та адипокіновим профілем у хворих на ГІМ за умов наявності та відсутності ЦД 2 типу.

Матеріал та методи. Дослідження проведено з 1 вересня 2018 року по 31 грудня 2020 року. На базі відділення інтенсивної терапії Державної установи «Національному інституті терапії імені Л.Т. Малої Національної академії медичних наук України» та Харківської клінічної лікарні на залізничному транспорті № 1 філії «Центр охорони здоров'я» Публічного акціонерного товариства «Українська залізниця» було обстежено 134 пацієнтів на ГІМ з елевацією сегменту ST за умов наявності та відсутності ЦД 2 типу віком 58,97±7,92 років. Першу групу склали 74 хворих на ГІМ та ЦД 2 типу віком 59,42±7,66 років. До другої групи (група порівняння) увійшло 60 пацієнтів на ГІМ без ЦД 2 типу віком 58,42±8,25 років. Контрольну групу склали 20 практично здорових осіб. Визначення вмісту білка, що зв'язує жирні кислоти 4 (FABP4) and C1q/TNF – асоційованого білка 3 (CTRP3) у сироватці крові пацієнтів проведено імуноферментним методом. Визначення у сироватці крові загального холестерину (ЗХС) та ліпопротеїдів високої щільності відбувалося пероксидазним методом. Вміст тригліцеридів (ТГ) визначено ферментативним колориметричним методом. Коефіцієнт атерогенності розраховано за формулою А.М. Клімова. Рівень ліпопротеїдів дуже низької щільності (ЛПДНЩ) та ліпопротеїдів низької щільності (ЛПНЩ) визначено за формулою Фрідевальда.

Результати досліджень та їх обговорення. Було встановлено, що хворі 1 групи відрізнялись більш високими рівнями в сироватці крові ТГ у порівнянні з хворими 2 групи ($p<0,05$). У групі 1 та 2 відзначалася тенденція до зростання ЗХС та ЛПНЩ ($p>0,05$) та

достовірне збільшення у 4,04 та 2,92 рази ЛПДНЩ порівняно із групою контролю (p<0,05). Встановлено вірогідне збільшення FABP4 та зниження CTRP3 у крові хворих на ГІМ на фоні ЦД 2 типу в порівнянні з хворими на ГІМ без ЦД (p<0,05). У пацієнтів із ГІМ та ЦД 2 типу (1 група) була виявлена зворотня кореляція між FABP 4 та ЛПДНЩ (r = 0,502, p<0,05), ТГ (r = 0,596, p<0,001); між CTRP 3 та ЗХС (r = -0,507, p<0,05), ЛПНЩ (r = -0,512, p < 0,05). У пацієнтів із ГІМ (2 група) була виявлена зворотня кореляція між FABP 4 та ЛПДНЩ (r = 0,453, p = 0,006), ТГ (r = 0,439, p = 0,009); між CTRP 3 та ЗХС (r = -0,413, p = 0,001), ЛПНЩ (r = -0,429, p = 0,01).

Висновки. Особливості змін вмісту FABP 4 та CTRP 3 говорять про дисбаланс в адипокіновому обміні при ГІМ за наявності та відсутності ЦД 2 типу, що свідчить про метаболічний зсув у даної категорії хворих. Взаємозв'язок між FABP 4, CTRP 3 та показниками ліпідного профілю може стверджувати про вплив цих маркерів та ліпідний обмін.

Ключові слова: адиопокіни, біомаркери, ліпіди, коморбідність, метаболізм.

Introduction. The prevalence of non-communicable diseases such as cardiovascular disease (CVD) and type 2 diabetes mellitus (DM) has reached epidemic proportions and is continuing to grow worldwide. Nowadays, comorbid and polymorbid patients need an integrated approach to diagnosis and treatment. Significantly increasing levels of type 2 DM are driving a global incidence which is set to increase of 9.9% from its present level by 2045 [1]. Acute myocardial infarction (AMI) is one of the leading causes of death in patients with type 2 DM. The mortality rate from coronary heart disease (CHD) was 8.9 million cases around the world in 2019 according to the World Health Organization [2].

Atherosclerotic lesions of the coronary arteries coupled with lipid profile dysregulation are the main cause of AMI. Hyperlipidemia is known to develop in type 2 DM [3]. A 20-fold increase in the probability of heart attack among diabetic patients has been reported in the presence of high levels of triglycerides (TG) and low levels of high-density lipoprotein (HDL) cholesterol [4].

Fatty acid-binding protein 4 (FABP4) and C1q/TNF-related protein 3 (CTRP3) are state of the art biomarkers of adipokine profile involved in the regulation of carbohydrate and lipid metabolism [5; 6]. There data that elevated levels of circulating FABP4 was associated with type 2 DM and CVD as well as higher rates of CVD-related mortality [7]. FABP4 serum levels were significantly greater in patients with progressive subclinical atherosclerosis compared with those in individuals without it [8]. Serum CTRP3 concentrations were significantly lower in patients with acute coronary syndrome (ACS) or stable angina compared to those in control subjects [9]. In an experimental model of type 2 DM, globular C1q-like domain serum levels of CTRP3 and endothelial function were significantly lower as compared to those in controls [10]. CTRP3 may promote the phenotypic conversion of monocytes into anti-inflammatory macrophages post-AMI [11]. But nonetheless, the effect of energy homeostasis markers on lipid metabolism in AMI patients with the presence of type 2 DM is the matter to be addressed.

It is known that impaired metabolism associated with type 2 DM induces considerable shifts in metabolic pathways in AMI patients, and it becomes evident that levels of various biologically active compounds, including adipokines, are affected in the human body, that needs to be further studied.

The aim of the study: to examine the relationship between adipokine and lipid profiles in AMI patients with the presence or absence of type 2 DM.

This study is a part of the scientific-research works of the Department of Internal Medicine No. 2 and Clinical Immunology and Allergology named after academician L. T. Malaya "Ischemic heart disease in polymorbidity: pathogenetic aspects of development, course, diagnostic and improvement of treatment", No. 0118U000929, valid term 2017 – 2019 and "Prediction of the course, improvement of diagnosis and treatment of ischemic heart disease and arterial hypertension in patients with metabolic disorders",. No. 0120U102025, valid term 2020 – 2022.

Material and methods. The study was conducted over a period from September 1, 2018 to December 31, 2020. A total of 134 patients with ST-segment elevation AMI (STEMI) in the presence or absence of type 2 DM aged 58.97 ± 7.92 years hospitalized in the intensive care unit of Government Institution "L. T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine" and Kharkiv Railway Clinical Hospital No. 1 of the branch "Center of Healthcare" of Public Joint Stock Company "Ukrainian Railway" were enrolled in the study.

The main group (group 1) included 74 patients with AMI and type 2 DM with a mean age of 59.42 ± 7.66 years. The comparison group (group 2) comprised 60 patients with AMI without type 2 DM aged 58.42 ± 8.25 years. The control group consisted of 20 otherwise healthy individuals.

All the studies were carried out after members consented to take part in the study (a written informed consent to relevant diagnostic and treatment procedures was obtained from all the patients), and methods for that were in accordance with the Helsinki Declaration of 1975, as revised in 1983, the Convention on Human Rights and Biomedicine developed by the Council of Europe and Ukrainian legislation.

STEMI was diagnosed based on clinical, instrumental and laboratory data, according to the criteria proposed by the Expert Consensus of the European Society of Cardiology [10]. Diagnosis and management of type 2 DM were performed following the recommendations of the American Diabetes Association and the European Association for the Study of Diabetes (2018, 2019) [11; 12].

The inclusion criteria were the presence or absence of type 2 DM in patients with STEMI.

The exclusion criteria were 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 (CHF) FC IV to myocardial infarction, chronic obstructive pulmonary disease, severe liver and renal dysfunction, severe anemia, malignancy.

All diagnostic tests were performed in the Biochemical Department of the Central Research Laboratory of Kharkiv

National Medical University. Blood serum samples were collected from the patients on 1 day and stored at -80 ºC. Serum concentrations of FABP4 and CTRP3 of patients were measured by enzyme-linked immunosorbent assay using an analyzer "Labline-90" (Austria) with commercial test-systems "Human FABP4" (Elabscience, USA) and Human CTRP3 (Aviscera Bioscience Inc, USA) following the manufacturers' instructions, respectively. Serum total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol were analyzed by peroxidase enzymatic method with assay kits "Human Cholesterol Liquicolor" (Germany) and "HDL Cholesterol liquicolor" (Germany), respectively. Triglyceride (TG) levels were measured by enzymatic colorimetric method using an assay kit "Triglycerides GPO" produced by "Human" company (Germany). The atherogenic index (AI) was calculated by the standard A.M. Klimov formula. The levels of very low-density lipoprotein (VLDL) cholesterol and low-density lipoprotein (LDL) cholesterol were estimated by the Friedewald formula.

The results of patient examination were analyzed and assessed using a statistical software suite IBM SPPS, version 27.0, (IBM Inc., USA, 2020) and employing parametric methods to calculate the results obtained. Significant differences between the means of normally distributed numerical parameters were compared statistically using one-way analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons. Correlations between parameters were quantified by the Pearson correlation coefficient (r). A value of $p \leq 0.05$ was considered statistically significant.

Results and discussion.

For achieving the aim of this study, the parameters of lipid and adipokine profiles in diabetic and non-diabetic patients in the presence of AMI were assessed and compared with the control group (Fig. 1 and 2). There was an upward tendency in the lipid profile (TC, LDL), except for HDL, among both group 1 and 2 patients as compared with the control group ($p>0.05$). Hypertriglyceridemia was dominated among patients with AMI and concomitant type 2 DM ($p <0.05$). In groups 1 and 2, there was a significant 4.04 and 2.92 times increase in VLDL, respectively, in comparison to the control group ($p <0.05$).

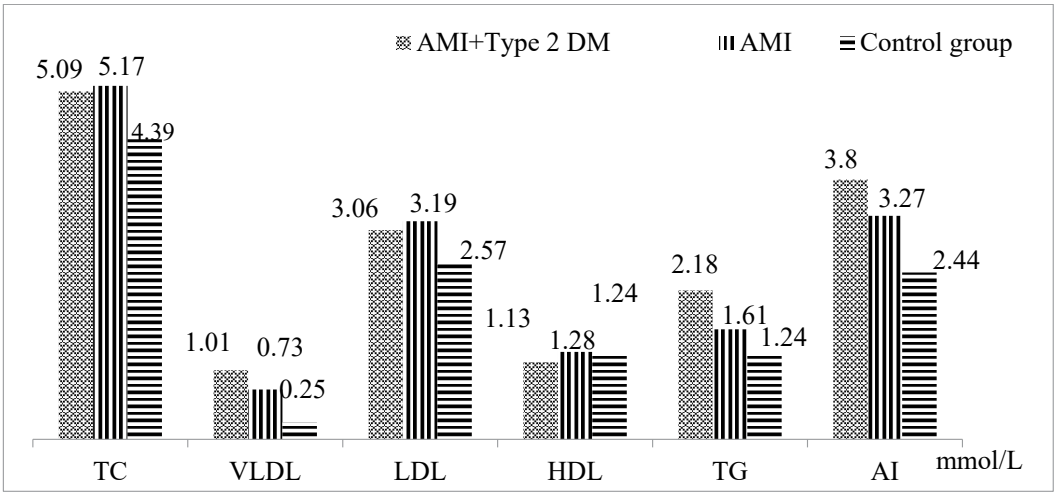

Fig. 1. Parameters of blood lipid profile

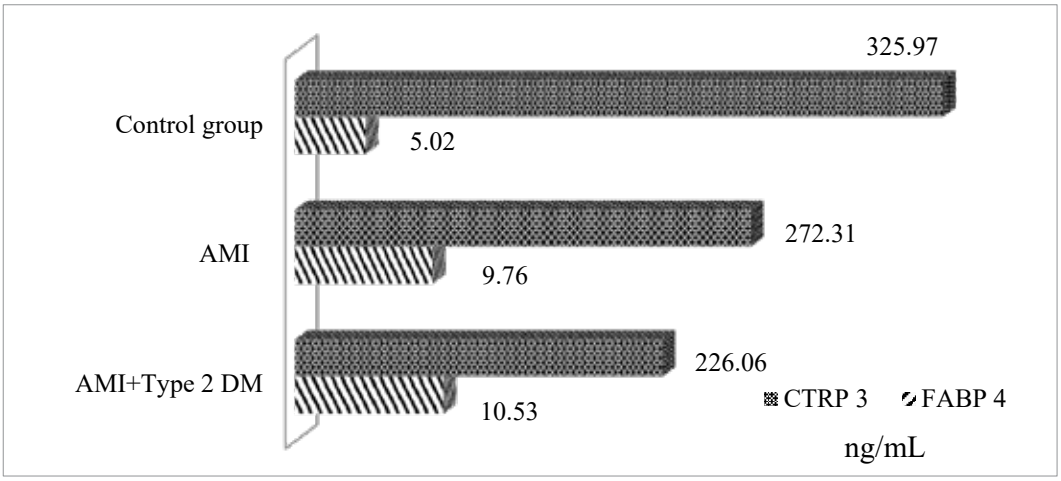

Fig. 2. Parameters of adipokine profile markers

In groups 1 and 2, the serum levels of FABP4 were 2.1 and 1.94 times increased, respectively, compared to those in otherwise healthy individuals ($p <0.001$) (Fig. 2). Meanwhile, there were no significant differences in FABP4 serum

levels between groups 1 and 2 (p>0.05). The CTRP3 serum levels were 30.65% and 16.46% lower in groups 1 and 2, respectively, as compared to those in the control group (p <0.001). AMI patients with type 2 DM were revealed with 16.98% lower CTRP3 concentrations compared with patients without type 2 DM (p <0.001).

In AMI patients with type 2 DM (group 1), an inverse correlation was found between FABP4 and VLDL (r = 0.502, p <0.05), TG (r = 0.596, p <0.001); between CTRP3 and TC (r = -0.507, p <0.05), LDL (r = -0.512, p <0.05).

In patients with AMI (group 2), an inverse correlation was revealed between FABP4 and VLDL (r = 0.453, p = 0.006), TG (r = 0.439, p = 0.009); between CTRP3 and TC (r = -0.413, p = 0.001), LDL (r = -0.429, p = 0.01).

There is also some evidence pointing out that FABP4 serum levels are significantly elevated during the early hours after onset of AMI and are robustly increased in out-of-hospital cardiac arrest survivors, probably due to rapid lipolytic release of FABP4 from epicardial fat owing to adrenergic overdrive which is characteristic of acute CVD [14]. Significantly lower plasma CTRP3 concentrations were observed in patients with coronary artery disease (CAD) and type II DM in comparison with nonCAD controls [15].

Conclusions. The significant difference has been found in adipokine profile parameters between groups of patients with AMI in the presence or absence of type 2 DM and the control group. There were signs of affected lipid and adipokine metabolism in the group with comorbidity, which were evidenced by the upward tendency in serum VLDL, TG, FABP4 and decreased CTRP3. Deterioration of adipokine metabolism markers was revealed in the group of patients with AMI. These facts may indicate the influence of FABP4 and CTRP3 on lipid profile both in the presence and absence of type 2 DM.

A better understanding of the potential mechanisms of AMI development and course with comorbid conditions may suggest important prospective therapeutic targets for AMI treatment.

Conflicts of interest: the author reports no conflict of interest in the study conduction and this paper preparation.

Funding information. The author has no any form of rewards influencing the results of the work to declare.

Personal contribution of the author: M.Yu. Koteliukh – idea, purpose, collection of research material, analysis of the results, preparation of the text of the article.

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