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DYNAMICS OF ADROPIN AND IRISIN BIOMARKERS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND TYPE 2 DIABETES MELLITUS

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SUMMARY. A pressing concern of modern medicine is the search for new biomarkers that can influence the development and course of acute myocardial infarction (AMI) in patents with type 2 diabetes mellitus (DM).

The aim – To examine the dynamics of adropin and irisin serum levels in diabetic patients with or without AMI complications.

Materials and Methods. In total, 134 AMI patients were enrolled. Among 60 examined AMI patients (group I), 41 patients were identified without early cardiovascular (CV) complications of AMI and 19 patients – with complicated AMI. Among 74 AMI patients with type 2 DM (group II), there were 48 patients without early AMI complications and 26 patients with early AMI complications. The control group consisted of 20 otherwise healthy persons. Serum levels of adropin and irisin were measured by enzyme-linked immunosorbent assay.

Results. The adropin and irisin serum levels on day 1 of treatment was low in both nondiabetic (I) and diabetic patients (II) compared with those in the control group ($p<0.05$). On the 10th day of treatment, the levels of adropin in group II patients without early AMI complications were reduced by 13.91 % compared with those in group I ($p<0.05$). Group II with the presence of early AMI complications showed a reduction of 17.34 % in adropin levels on day 10 compared with group II ($p<0.05$). On day 10 of treatment, the irisin levels in group II without early AMI complications were reduced by 18.94 % compared with those in group I ($p<0.05$). In group II with the presence of early AMI complications on the 10th day, the irisin levels were reduced by 23.87 % compared with those in group I ($p<0.05$).

Conclusions. The concentrations of adropin and irisin were significantly low in group II on day 1 and 10 of hospital stay. In the dynamics of treatment on day 10, the levels of adropin and irisin remained low in group II with early CV complications of AMI.

KEY WORDS: biomarkers; energy metabolism; myocardial infarction; diabetes mellitus.

Introduction. Cardiovascular disease and diabetes mellitus (DM) are globally common health problems and the leading causes of death. According to the World Health Organization, the coronary heart disease (CHD) mortality in 2019 was 8.9 million cases worldwide [1]. Adverse course of acute myocardial infarction (AMI) can be fatal in the population. In 2017, the prevalence of type 2 DM accounted for 8.8 % of the world population, and it is projected to increase to 9.9 % by 2045 [2; 3]. In 2019, diabetes was the ninth out of ten-leading cause of death with an estimated 1.5 million deaths in the world [4]. Researchers have found that MI patients with DM experienced higher prevalence of adverse cardiovascular events as compared to non-diabetic individuals [5; 6]. Metabolic markers that affect the development and course of early cardiovascular (CV) complications in diabetic patients are still inconclusive. Understanding the pathophysiological effects of metabolic markers would identify a diabetic patient at high risk for unfavorable outcome after AMI.

Adropin and irisin are recently identified proteins that may play a role in the development and progression of acute and chronic diseases, including AMI and type 2 DM [7; 8]. They may be important components in the pathophysiological pathways underlying these diseases. Today, the potential mechanisms of adropin and irisin action in cardiac energy metabolism in comorbid conditions have not been studied enough. Understanding of the adropin and irisin metabolic effects would not only provide diagnostic tools for early detection of AMI complications in the presence of type 2 DM but would also help develop new treatments to regulate metabolic disorders in adverse CV events in AMI.

The aim – to examine the dynamics of adropin and irisin serum levels in diabetic patients with or without AMI complications as a means to increase the understanding of metabolic disorders in this group of patients.

Material and Methods. In total, 134 participants with ST-segment elevation AMI (STEMI) in the presence or absence of type 2 DM aged 59.00 (52.75; 66.00) years with male dominance – 106 (79 %) were examined. All the patients received a treatment course 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" between 01 September 2018 and 31 December 2020. The control group consisted of 20 otherwise healthy persons aged 56.50 (48.50; 61.75) years.

Depending on the disease course, the patients were divided into 2 groups during the hospital stay: patients with uncomplicated AMI and patients who developed AMI complications such as acute heart failure (HF), acute aneurysm of the apex and inter-

ventricular septum of the left ventricle (LV), recurrence of AMI, paroxysmal atrial fibrillation (AF), ventricular fibrillation (VF), atrioventricular block, decreased LV ejection fraction <40 %. Among 60 patients with AMI (group I), 41 patients with no early CV AMI complications and 19 patients with complicated AMI were identified. Among 74 patients with AMI and type 2 DM (group II), there were 48 patients without early AMI complications and 26 patients with CV complications.

All the patients were diagnosed with AMI, early complications were examined, and a treatment was prescribed as recommended by the European Society of Cardiology guidelines [9]. The concept of early complications of AMI involved the presence of atrioventricular block, AF, VF, AHF of Killip classes II, III, IV, acute aneurysm of the apex and interventricular septum of the LV, reduced <40 % LV ejection fraction. All the patients underwent percutaneous coronary intervention (PCI). Diagnosis and treatment of type 2 DM was provided according to the American (2018) and European (2018, 2019) Associations for the Study of DM joint recommendations and the International Diabetes Federation criteria (2019) [10; 11; 12].

The inclusion criterion was STEMI in patients with the presence or absence of type 2 DM.

Exclusion criteria were type 1 DM, non-ST-segment elevation acute myocardial infarction (NSTEMI), COVID-19, autoimmune diseases, pituitary and hypothalamic diseases, thyroid disease, secondary hypertension, valvular heart disease, IV functional class chronic heart failure to myocardial infarction, chronic obstructive pulmonary disease, liver and kidney dysfunction, severe anemia, malignancy.

The purpose of each examination was explained in detail, and a written informed consent was signed by all participants. The study protocol was approved by the Bioethical Committee of Kharkiv National Medical University (Protocol No. 2 dated April 2, 2018), and patient data were analyzed following the 6th version (2008) of the 1975 Helsinki Declaration.

Diagnostic testing was performed on the basis of the Biochemical Department of the Central Research Laboratory of Kharkiv National Medical University. Blood samples were collected on days 1 and 14. Serum levels of adropin and irisin were measured by enzyme-linked immunosorbent assay with the help of a "Labline-90" (Austria) analyzer using commercial test systems "Human Adropin" and "Human Fibronectin type III domain-containing protein 5" (Elabscience, USA), respectively, in accordance with the manufacturer instructions. To quantify the adropin and irisin serum levels, the method used was based on the principle of the sandwich technique for detecting an antibody pair of the capture antibody and biotin-labeled detection antibody binding to captured analyte.

Conventional Doppler echocardiographic images were obtained with an ultrasound scanner Radmir ULTIMA Pro30 (Ukraine). A three-channel electrocardiograph "Fukuda" FX–326U (Japan) was used to record standard 12-lead electrocardiograms.

The data obtained were statistically processed with IBM SPPS software version 27.0 (IBM Inc., USA, license No. L-CZAA-BKKMKE, 2020). Prism version 9.0.2 (GraphPad software, USA, Serial No. GPS-2050439-TCSZ-2EDFF, 2021) helped to display the statistical results graphically. The normality of the quantitative data distribution was determined by the Shapiro-Wilk test. Statistical analysis involved both quantitative and qualitative variables. Qualitative data were presented as percentages. Quantitative variables were described by the following parameters: median (Me), 25th and 75th percentiles (Q1; Q3). The nonparametric Mann-Whitney rank test was used to compare quantitative variables for independent samples, while the Wilcoxon test was performed for dependent samples. When comparing the indicators between three groups, the nonparametric Kruskal-Wallis test was used. The intergroup comparisons of sign frequency were performed with the Pearson χ^2 test. To test statistical hypotheses, the critical level of significance in this study was 0.05.

Results. The AMI patients with type 2 DM were found to have lower mean adropin levels on admission (14.12 (9.44; 16.94) pg/ml (II)) (Fig. 1B) compared with those in AMI patients without type 2 DM (17.85 (10.42; 20.90) pg/ml (I)) (Fig. 1A) and in the control group (23.58 (20.86; 26.29) pg/ml) ($p<0.001$). On day 10 of hospital stay, the serum adropin levels were elevated to 19.97 (16.35; 20.99) pg/ml (II) and 22.11 (20.45; 22.49) pg/ml (I) and the difference between the two groups was statistically significant ($p<0.001$).

Upon admission to the hospital, the serum irisin levels in AMI patients with type 2 DM demonstrated declining trends – 1.89 (1.49; 2.21) ng/ml (II) (Fig. 1, B) compared with those in AMI patients without type 2 DM – 2.05 (1.49; 2.35) ng/ml (I) (fig. 1A), but there were no statistically significant differences between the two groups ($p>0.05$). When comparing the irisin levels in groups I and II with those in the control group – 6.59 (3.91; 7.92) ng/ml, differences were found to be statistically significant ($p<0.001$). After 10-day treatment, the mean irisin levels were increased in group I – 3.21 (2.40; 3.48) ng/ml and group II – 2.10 (1.67; 2.42) ng/ml) ($p<0.001$).

On day 1 of inpatient treatment, the serum adropin concentrations among both nondiabetic (I) and diabetic (II) patients, who later showed early CV complications, were low and did not differ from

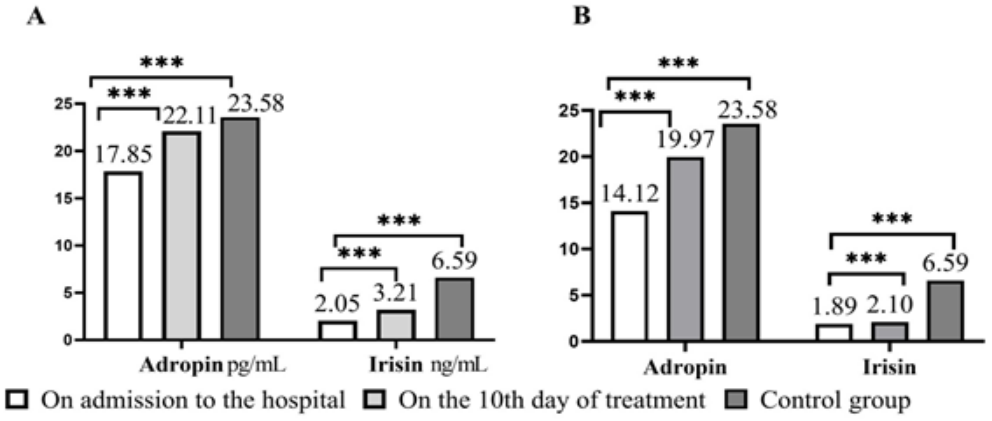

Fig. 1. Adropin and irisin levels in nondiabetic (A) and diabetic (B) AMI patients.

those among patients without CV complications (p>0.05) (Table 1). On day 10 of treatment, the levels of adropin in nondiabetic (I) and diabetic (II) patients with early CV complications was 15.09 % and 18.47 % lower, respectively, as compared to those in patients without CV complications (p<0.05). During inpatient treatment, the serum adropin levels in groups I and II with or without the presence of early CV complications tended to increase compared to day 1 of hospital stay (p<0.05). In nondiabetic patients (group I) with the absence or presence of early CV complications, the adropin concentrations on day 10 were 6.11 % and 20.27 % reduced, respectively, compared with the threshold value of this marker (23.58 (20.86; 26.29) pg/ml) (p<0.01). The levels of adropin on day 10 of treatment in diabetic patients (group II) with or without early CV complications remained reduced by 19.17 % and 34.1 %, respectively, compared with those in the control group (p<0.001). It is worth noting that on the 10th day of treatment, the levels of adropin in diabetic patients with no early AMI complications represented a 13.91 % reduction compared with those in nondiabetic patients (p<0.05). Furthermore, the adropin levels in diabetic patients with the presence of early AMI complications were reduced by 17.34 % on the 10th day of observation compared with those in nondiabetic patients (p<0.05).

Table 1. Mean values of adropin and irisin in groups I and II, Me (Q25; Q75)

Indicators / **Consequences**	**No complications**		**Early CV complications**	
	Group I	**Group II**	**Group I**	**Group II**
Adropin, pg/ml				
On admission to the hospital	17.21 (10.59; 21.19)	14.28 (11.14; 17.20)	16.53 (12.60; 19.19)	12.87 (8.76; 16.84)
On the 10th day of treatment	22.14 (20.63; 22.62)*# •	19.06 (17.85; 20.90)*#	18.80 (18.17; 19.68)# •	15.54 (11.89; 18.14)
Irisin, ng/ml				
On admission to the hospital	2.12 (1.50; 2.34)	1.86 (1.49; 2.25)	2.13 (1.59; 2.31)	1.71 (1.67; 2.16)
On the 10th day of treatment	3.22 (2.53; 3.58)*# •	2.61 (2.37; 3.04)*#	2.43 (2.29; 3.04)# •	1.85 (1.66; 2.09)

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 – significant differences between groups.

Thus, the serum adropin levels remained low in both groups during inpatient treatment. However, on day 10 of treatment, adropin levels were significantly decreased in diabetic patients regardless of the AMI course as compared to those in nondiabetic patients.

On day 1 of inpatient treatment, the serum irisin concentrations were low among nondiabetic (I) and diabetic (II) patients, who later showed early CV complications, and did not differ among patients without CV complications (p>0.05) (Table 1). On day 10 of treatment, irisin levels in nondiabetic (I) and diabetic (II) patients with early CV complications was lower by 24.53 % and 29.12 %, respectively, than those in patients without CV complications (p<0,05). During inpatient treatment, the serum irisin levels in group I in the absence or presence of early CV complications were significantly increased by 51.89 % and 14.08 % (p<0.05), respectively, compared with

those on day 1 of hospital stay. The same trend was observed in group II without early AMI complications, where the irisin levels were significantly elevated by 40.32 % ($p<0.05$). In group II, in the presence of early CV complications, the irisin concentrations tended to increase, but the difference was statistically insignificant compared to day 1 of hospital stay ($p>0.05$). In nondiabetic patients with or without early CV complications, the irisin concentrations were 2.05 and 2.71 times lower, respectively, than the threshold value for this marker (6.59 (3.91; 7.92) ng/ml) ($p<0.05$). The irisin levels on day 10 of treatment in diabetic patients with or without the presence of early CV complications remained 2.52 and 3.56 times reduced, respectively, compared with those in the control group ($p<0.05$). It should be mentioned that on day 10 of treatment, the irisin levels in diabetic patients without early AMI complications were reduced by 18.94 % compared with those in nondiabetic patients ($p<0.05$). Meanwhile, in diabetic patients with the presence of early AMI complications, the irisin levels were reduced by 23.87 % on day 10 of observation compared with those in nondiabetic patients ($p<0.05$).

Therefore, the serum irisin levels dynamically increased in all patients during treatment. Nevertheless, there were low irisin levels despite the dynamics of this marker. It is important to note that the lowest irisin levels on the 10th day of treatment prevailed in diabetic patients with early CV complications, indicating a critical level of energy balance in the body of this patient cohort.

Discussion. Early AMI complications in diabetic patients pose a serious threat to life and require a rapid response to prevent death among this category of persons. Despite current medical care using PCI, intensive antithrombotic therapy, DM still seriously negatively affects the prognosis of AMI [13]. The importance of further study on the development and progression of early AMI complications and understanding their pathophysiological mechanisms would improve the diagnosis and treatment of high-risk diabetic patients. In patients with type 2 DM, in contrast to patients without it, there is a significant left-sided heart dilatation [14].

According to Zheng J. et al. [15] and Yu H. Y. et al. [16], serum adropin levels in patients with CHD were significantly lower, especially if this marker was examined in the presence of AMI. Previous study reported that significantly reduced serum adropin concentrations were found in AF patients. In addition, patients with persistent AF had decreased serum adropin concentrations as compared to patients with paroxysmal AF [17]. Askin L. et al. [18] showed a protective role of adropin in HF and hypertension. Adropin regulates energy metabolism in the heart through a number of reactions, such as insulin signaling, glucose and fat oxidation. Such regulation of energy metabolism may be a source of alternative therapies for DM with obesity. Kalkan A. K. et al. [19] demonstrated an association between adropin and irisin levels and the severity of HF and can serve as HF diagnostic markers.

Khorasani Z. M. et al. [20] found that serum irisin levels were lower in DM patients with CV complications compared with uncomplicated diabetic patients. Aydin S. et al. [21] revealed low irisin levels in AMI patients. And according to Berezin A. E. et al. [22], irisin as a myokin may be involved in the pathogenesis and course of HF. Low irisin levels were identified in patients with AMI and HF in the study by Abd El-Mottaleb N. A. et al. [23]. The finding of Anaszewicz M. et al. [24] are indicative of low irisin levels in patients with paroxysmal or persistent AF. However, some limitations associated with this study could not be avoided. First, given the adverse effects of STEMI in diabetic and nondiabetic patients, it would be interesting to examine CV complications in diabetic and nondiabetic patients with NSTEMI. Second, it would be useful to study the dynamics of energy homeostasis markers during a one-year follow-up including this cohort of patients.

Conclusions. The adropin and irisin levels were different on the 10th day of observation in AMI patients with the presence or absence of type 2 DM. It is worth noting that concentrations of adropin and irisin were significantly low in diabetic patients on days 1 and 10 of hospital stay. In the dynamics of treatment on day 10, the levels of adropin and irisin remained low in diabetic patients with early CV complications of AMI. These findings provide insights into adropin and irisin levels in adverse AMI course in diabetic and nondiabetic patients, which would help to develop a new approach to the correction of metabolic disorders in these conditions.

Prospects for further research. A study on energy metabolism markers in type 2 DM patients 1 year after myocardial infarction is planned.

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

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ДИНАМІКА БІОМАРКЕРІВ АДРОПІНУ Й ІРИСИНУ У ХВОРИХ НА ГОСТРИЙ ІНФАРКТ МІОКАРДА ТА ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ

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РЕЗЮМЕ. Актуальною проблемою сучасної медицини є пошук нових біомаркерів, які можуть впливати на розвиток та перебіг гострого інфаркту міокарда (ГІМ) із цукровим діабетом (ЦД) 2-го типу.

Мета – дослідити динаміку рівнів адропіну й ірисину в сироватці крові у пацієнтів із ЦД 2-го типу за умов наявності та відсутності ускладненого перебігу ГІМ.

Матеріал і методи. У дослідженні брали участь 134 пацієнти із ГІМ. Обстежено 60 хворих із ГІМ (I група) та виявлено 41 пацієнта без ранніх кардіоваскулярних ускладнень ГІМ та 19 пацієнтів із ускладненим перебігом ГІМ. Серед 74 хворих із ГІМ та ЦД 2-го типу (II група) визначено 48 пацієнтів без ранніх ускладнень ГІМ та 26 хворих із несприятливим перебігом ГІМ. Контрольну групу склали 20 практично здорових осіб. Вміст адропіну й ірисину визначали імуноферментним методом.

Результати. Вміст адропіну й ірисину на 1 день лікування був низький у хворих із відсутністю (I) та наявністю (II) ЦД 2-го типу, порівняно із групою контролю ($p<0,05$). На 10 добу лікування вміст адропіну в групі II без ранніх ускладнень ГІМ був знижений на 13,91 %, порівняно із групою I ($p<0,05$). У групі II із наявністю ранніх ускладнень ГІМ на 10 добу рівень адропіну був знижений на 17,34 %, порівняно з групою II ($p<0,05$). На 10 добу лікування вміст ірисину у групі II та відсутністю ранніх ускладнень ГІМ був знижений на 18,94 %, порівняно з групою I ($p<0,05$). У групі II із наявністю ранніх ускладнень ГІМ на 10 добу рівень ірисину був знижений на 23,87 %, порівняно з групою I ($p<0,05$).

Висновки. Визначено значно нижчий вміст адропіну та ірисину у групі II на 1 та 10 добу перебування у стаціонарі. У динаміці лікування на 10 добу вміст адропіну та ірисину залишався низьким у пацієнтів групи II з ранніми кардіоваскулярними ускладненнями ГІМ.

КЛЮЧОВІ СЛОВА: біомаркери; енергетичний обмін; інфаркт міокарда; цукровий діабет.

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