https://doi.org/10.37436/2308-5274-2022-1 ISSN 2308-5274

МІЖНАРОДНИЙ МЕДИЧНИЙ ЖУРНАЛ

МЕЖДУНАРОДНЫЙ МЕДИЦИНСКИЙ ЖУРНАЛ
INTERNATIONAL MEDICAL JOURNAL

ЩОКВАРТАЛЬНИЙ НАУКОВИЙ ЖУРНАЛ

Том 28, № 1(109)'2022

Заснований 14.03.1995 р. під назвою «Харківський медичний журнал», перейменований 09.07.1997 р.

ЗАСНОВНИКИ

Харківська медична академія післядипломної освіти

Інститут проблем кріобіології і кріомедицини Національної академії наук України

Харківське медичине товариство

ВИДАВЕЦЬ

Харківська медична академія післядипломної освіти

Журнал
представлений на порталі Національної бібліотеки України ім. В. І. Вернадського (з індексуванням), зареєстрований у міжнародних каталогах наукових видань та наукометричних базах даних: CrossRef, Scholar Google (з індексуванням), Index Copernicus.

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Свідоцтво про державну реєстрацію друкованого засобу масової інформації серії КВ № 7355 від 29.05.2003 р.

Згідно з додатком 5 до наказу Міністерства освіти і науки України 24.09.2020 р. № 1188 журнал внесено до Переліку наукових фахових видань України з медичних спеціальностей: 222 «Медицина», 228 «Педіатрія», 224 «Технології медичної діагностики та лікування».

Рекомендовано до друку вченою радою Харківської медичної академії післядипломної освіти 28.12.2021 р. (протокол № 10).

Підписано до друку 05.01.2022 р. Формат 60×84/8. Умовн. друк. арк. 10,23
Замовлення № 10-01. Тираж 1000.

При роздрукуванні матеріалів посилання на «Міжнародний медичний журнал» обов'язкове.

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МІЖНАРОДНИЙ МЕДИЧНИЙ ЖУРНАЛ
Щоквартальний науковий журнал
Том 28, № 1(109), 2022

Заснований 14.03.1995 р.
під назвою «Харківський медичний журнал», перейменований 09.07.1997 р.

Засновники
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Надруковано в друкарні ПП Цуварєва Н. М.
Свідоцтво суб'єкта видавничої справи АЄ № 147899
просп. Науки, 26, Харків, 61166, Україна

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UDC 616.127-005.8-056.25-078:616.132.2-089.819.5 https://doi.org/10.37436/2308-5274-2022-1-1

FEATURES OF CONTENT OF ENERGY AND ADIPOKINE METABOLIC INDICATORS IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION AND COMORBIDITIES AFTER PRIMARY STENTING OF CORONARY ARTERIES

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The study involved determination of the content of adropin, irisin, fatty acid binding protein 4 and C1q/ TNF-related protein 3 in the patients with acute myocardial infarction and comorbidities following primary stenting of coronary arteries. Changes in energy and adipokine profile may be considered as a prognostic marker for the effectiveness of treatment of acute myocardial infarction in the presence of comorbidity.

Key words: *energy and adipokine exchange, myocardial infarction, obesity, stenting.*

ПОКАЗНИКИ ЕНЕРГЕТИЧНОГО ТА АДИПОКІНОВОГО ОБМІНУ У ПАЦІЄНТІВ ІЗ ІНФАРКТОМ МІОКАРДА ТА КОМОРБІДНОЮ ПАТОЛОГІЄЮ ПІСЛЯ ПЕРВИННОГО СТЕНТУВАННЯ КОРОНАРНИХ АРТЕРІЙ

М. Ю. КОТЕЛЮХ, П. Г. КРАВЧУН, М. І. КОЖИН

Визначено вміст адропіну, ірисину, білка, що зв'язує жирні кислоти 4, та C1q/TNF-асоційованого білка 3 у пацієнтів із гострим інфарктом міокарда та коморбідною патологією за умов застосування первинного стентування коронарних артерій. Зміна енергетичного та адипокінового профілів у пацієнтів може бути прогностичним маркером ефективності лікування гострого інфаркту міокарда за наявності коморбідності.

Ключові слова: енергетичний і адипокіновий обмін, інфаркт міокарда, ожиріння, стентування.

Cardiovascular disease (CVD) is an immense problem of humanity, which causes global socio-economic losses. According to the World Health Organization (WHO), the first place in the list of ten leading reasons of deaths is still occupied by ischemic heart disease (IHD). In 2019 the CVD mortality increased by more than 2 million cases compared to 2000 and reached 8.9 million cases worldwide [1]. An acute myocardial infarction (AMI) is the main reason of mortality in IHD. Obesity is one of the risk factors of the AMI development. According to the WHO data for 2016, 39 % of adults older 18 years (39 % of men and 40 % of women) were overweight [2].

Primary stenting of coronary arteries (CA) improves a prognosis in the patients with AMI, affecting the left ventricular (LV) remodeling and improving diastolic function, which further prevents the development of chronic heart failure [3]. Topical issue of today is the researchers' reports on the role of energy and adipokine system in the AMI development and course [4, 5]. Of interest is investigating the dependence of the state of coronary vessels on indicators of energy and adipokine exchange in the patients with AMI and the presence and absence of obesity.

The purpose of this study was to determine the content of energy and adipokine exchange indicators in the patients with ST-segment elevation myocardial infarction (STEMI) depending on the obesity presence and absence in hospital period after primary stenting of CA.

The study involved 60 patients with STEMI (group 1) and 60 patients with STEMI and obesity (group 2). The first and second groups were divided into subgroups depending on the CA primary stenting presence and absence. The group 1 was divided into 20 patients with STEMI without the myocardium revascularization (1st subgroup) and 40 patients with percutaneous coronary interventions (PCI) (2^{nd} subgroup). The group 2 consisted of 30 patients with STEMI and obesity without the myocardium revascularization (1^{st} subgroup) and 30 patients with PCI and obesity (2^{nd} subgroup). The control group included 20 apparently healthy individuals. All the patients were diagnosed with STEMI, diagnostic measures were conducted to identify the AMI early complications and treatment in accordance with European recommendations of cardiologists [6]. The obesity signs according to the European recommendations were examined by the body weight index (BMI) using the following formula: weight (kg) / height (m^2) and determined if BMI was equal to or exceeded 30 kg/m^2 [7, 8].

The patients with AMI (group 1) amounted to 91.67 % of men, 8.33 % of women, mean age was 59.00 (53.00; 65.00) years and the patients with AMI and obesity (group 2) comprised 76.67 % of men, 23.33 % of women, mean age made 59.00 (49.25; 65.75) years. Risk factors in the first group comprised hypertensive disease (HD) as 100 %, 25 % for tobacco smoking, 65 % for hypercholesterolemia, and BMI averaged 23.7 kg/m^2. In the second group, similar risk factors were revealed as follows: 100 % HD, 16.7 % tobacco smoking, 75 % hypercholesterolemia, BMI averaged 32 kg/m^2. All the patients of groups 1 and 2 underwent coronography with the following decision on the possible revascularization of myocardium. Patients who had not undergone myocardial revascularization, were loaded with 300 mg acetylsalicylic acid and 300 mg clopidogrel. An additional loading dose of 300 mg clopidogrel in the case of PCI was applied in 25.8 % of patients and 180 mg ticagrelor was used in 74.2 % of cases. All the patients received 100 % statins and 41.7 % nitrates. In addition, all the patients received low molecular weight anticoagulants during the first 8 days and in 58.3 % PCI was performed. No vascularization of myocardium was done in 41.7 % of the patients because of anatomical difficulties to monitor the coronary artery, admission of patients within the period of the lost «reperfusion window» more than 24 hours from the moment of myocardial infarction and with no signs of pain syndrome at the time of admission, refusal of patients from stent implantation.

The level of adropin, irisin, fatty acid binding protein 4 (FABP 4) and C1q / TNF-related protein (CTRP 3) was determined in both groups on day 1 before PCI and 14 days after admission to the hospital by means of enzyme immunoassay using reagents “Human Adropin”, “Human Fibronectin type III domain-containing protein 5”, “Human FABP 4” manufactured by Elabscience, Houston, USA and “Human CTRP 3” manufactured by Aviscera Bioscience Inc., Santa Clara, USA. SYNTAX Score (SS) was used to assess the severity of coronary atherosclerotic lesions and was severity-rated [9, 10].

The obtained data were statistically processed using the IBM SPPS Version 27.0 (2020) (IBM Inc., USA, License No. L-CZAA-BKKMKE). The studied parameters relative to the normality of distribution were assessed with the Shapiro — Wilk test. Statistical analysis involved quantitative and qualitative variables. Qualitative data were presented as percentage shares; quantitative as a median and interquartile range (25 and 75 percentile). A nonparametric Mann-Whitney rank was used to compare the quantitative indices between the two groups. Nonparametric Kruskal — Wallis criterion was applied for comparison of the indices between three groups. The frequency of features in the groups was compared with the χ^2 Pearson criterion. The relationship between indices was determined by Spearman correlation. The critical level of significance for checking statistical hypotheses in the research was 0.05.

As Table 1 shows, all the patients did not have a significant difference ($p > 0.05$) by myocardial infaction localization. As coronography showed, in the first group, the frequent damage to the anterior interventricular branch (AIVB) was found in 20 (33.33 %) of persons, in group 2 of the left coronary artery (LCA) in 17 (28.33 %) patients, while the right coronary artery (RCA) was equal in each group in 25 individuals (41.67 %). Following the coronography on the severity of CA lesion, the patients of the first group predominantly had multivascular lesions in 30 (50 %) patients ($p > 0.05$), and monovascular lesion in 35 persons (58.33 % ($p = 0.03$) in the 2nd group. As for the SS, there was no significant difference in the CA lesion severity in both groups ($p > 0.05$). Before primary stenting of CA the patients underwent evaluation of coronary flow by the thrombolysis in myocardial infarction (TIMI) flow grade: in both groups, TIMI-0 flow was found, while in group 1 TIMI-1 flow was more common in 25 %, and in group 2 TIMI-2 blood flow in 26.67 %. Consequently, there was no significant difference between the groups according to angiographic data.

In group 1, the levels of adropin, irisin, CTRP3 were significantly reduced by 24.3 %, by 68.9 %, by 16.17 % compared to the control group ($p < 0.05$). On the contrary, FABP 4 content significantly increased compared to the control group ($p < 0.05$). In group 2, the concentration of adropin, irisin, CTRP3 was significantly reduced by 36.22 %, by 75.49 %, by 25.44 % compared to the control group ($p < 0.05$), and FABP 4 content increased strongly compared to the control group ($p < 0.05$) (Table 2).

Levels of adropin, irisin, CTRP3 on day 1 were significantly reduced in the patients with AMI and obesity (group 2) compared to the patients with AMI (group 1) ($p < 0.05$). On the contrary, FABP 4 content increased in group 2 as compared to group 1 ($p < 0.05$). This indicates an appropriate imbalance in energy and adipokine metabolism.

In the time course of observation for 14 days in groups 1 and 2, an increase in the concentration of adropin by 23.87 % and 29.79 %, irisin by 56.59 % and 43.34 %, CTRP3 by 11.59 % and 17.07 % was recorded as compared to day 1 ($p < 0.05$). However, the level of these indices in both groups for 14 days remained low as compared to the control group ($p < 0.05$). On the contrary, FABP 4 content decreased by 19.69 % and 22,17 % in groups 1 and 2 as compared with day 1 ($p < 0.05$). The level of FABP 4 for 14 days was high in both groups compared to the control group ($p < 0.05$).

The energy and adipokine exchange indicators was compared considering the presence or absence of CA stenting in groups 1 and 2 (Table 3). In group 1 and 2, during the myocardium revascularization there was a rise in the level of adropin by 4.41 % and 20.14 %, the content of irisin increased by 6.19 % and by 28.29 %, concentration of CTRP3 by 4.74 % and 25.96 %, and the FABP 4 content had a tendency

Table 1

Localization of myocardial infarction and coronary indicators

MI localization	Group 1	Group 2	*p*
Anterior wall	28 (46.67)	29 (48.33)	0.89
Inferior wall	11 (18.33)	11 (18.33)	1.00
Posterior wall	21 (35)	20 (33.33)	0.88
Infarction-dependent artery			
LCA trunk	9 (15)	17 (28.33)	0.12
LCA AIVB	20 (33.33)	14 (23.33)	0.30
Left circumflex artery	6 (10)	4 (6.67)	0.53
RCA	25 (41.67)	25 (41.67)	1.00
Monovascular lesion	19 (31.67)	35 (58.33)	0.03
Two-vascular lesion	11 (18,33)	6 (10)	0.23
Multivascular lesion	30 (50)	19 (31.67)	0.12
Angiographic features: SS, in %			
Low < 22	31 (51.67)	26 (43.33)	0.51
Moderate — 23–32	22 (36.67)	27 (45)	0.50
Severe > 32	7 (11.67)	7 (11.67)	1.00
TIMI blood flow prior to myocardial revascularization			
TIMI-0	38 (63.33)	36 (60)	0.82
TIMI-1	15 (25)	8 (13.33)	0.14
TIMI-2	7 (11.67)	16 (26.67)	0.06

Table 2

Energy and adipokine metabolism indicators

Indicator, *p* value	Group 1		Group 2		Control group
	day 1	day 14	day 1	day 14	
Adropin, pg/mL	17.85 (10.42; 20.90)	22.11 (20.45; 22.49)	15.04 (8.77; 18.06)	19.52 (16.84; 22.21)	23.58 (20.86; 26.29)
p value		<0.001**	<0.01#	<0.001** # <0.001	<0.001*
Irisin, ng/mL	2.05 (1.49; 2.35)	3,21 (2.40; 3.48)	1.62 (1.28; 2.12)	2.32 (1.97; 2.66)	6.59 (3.91; 7.92)
p value		<0.001**	<0.01#	<0.001** <0.001#	<0.001*
FABP 4, ng/mL	9.65 (8.36; 10.92)	7.75 (6.27; 8.62)	10.96 (9.25; 12.65)	8.53 (6.85; 10.67)	4.25 (3.46; 6.16)
p value		<0.001**	<0.001#	<0.001** <0.01#	<0.001*
CTRP 3, ng/mL	264.78 (240.20; 302.20)	295.48 (282.45; 305.11)	235.50 (204.47; 268.63)	275.69 (231.56; 302.12)	315.85 (287.06; 371.02)
p value		<0.001**	<0.001#	<0.001** <0.01#	<0.001*

* Comparing the indices with the control group.
** Comparing the indices between days 1 and 14.
# Between group 1 and group 2.

Table 3

Determination of energy and adipokine metabolism indicators on day 14 day as for the percutaneous coronary interventions presence or absence

Indicator, *p* value	Group 1		Group 2	
	subgroup 1	subgroup 2	subgroup 1	subgroup 2
Adropin, pg/mL	21.32 (15.69; 22.41)	22.26 (21.26; 22.70)	17.53 (15.65; 20.15)	21.06 (19.14; 22.72)
p value	0.02* 0.01#	0.143#	<0.001*	
Irisin, ng/mL	3.07 (2.17; 3,50)	3.26 (2.58; 3.73)	2.05 (1.77; 2.25)	2.63 (2.33; 2.75)
p value	0.198* <0.01#	<0.001#	<0.001*	
FABP 4, ng/mL	6.96 (6.05; 8.58)	7.87 (7.19; 8.65)	10.16 (7.29; 11.72)	7.82 (6.48; 8.86)
p value	0.196* <0.001#	0.767#	<0.01*	
CTRP 3, ng/mL	288.19 (278.14; 301.39)	301.84 (298.62; 318.03)	233.69 (203.27; 271.98)	294.35 (285.97; 317.78)
p value	0.097#	<0.001*	* <0.001	0.94#

* Between presence and absence of stent.
# Comparison between group 1 and group 2.

to decrease in the group 1, but it was not significant ($p > 0.05$), and in group 2, FABP 4 was likely to decrease by 23.03 % compared to patients without stent implantation ($p < 0.05$) (Table 4). That is, in both groups during stent implantation in the time course of observation, the results of the content of adropin, irisin and CTRP3 probably improved compared to the patients without the myocardium revascularization. This allows an assumption that timely PCI affects the state of energy and adipokine exchange in patients with AMI.

If myocardial revascularization was performed, the comparison of groups 1 and 2 showed that the concentration of adropin and CTRP3 had a tendency to increase, but was not significant ($p > 0.05$). The content of FABP 4 almost did not change when comparing both groups ($p > 0.05$). In addition, the level of irisin in group 1 was significantly different and increased by 23.95 % ($p < 0.001$) compared to group 2. On the contrary, the level of adropin in the patients with AMI without stenting (group 1) increased by 21.56 % on day 14, irisin by 49.76 %, CTRP3 by 23.32 % and FABP 4 content decreased by 31.49 % ($p < 0.05$) compared to group 2. That is, in the patients with AMI, the energy and adipokine indicators exchange were better than in comorbidity. The study showed that the time course of irisin content was statistically different in both groups ($p < 0.05$). Consequently, the myocardium revascularization did not affect the changes in the concentration of irisin and the increase in this index occurs not by implantation of the stent.

Group 1 patients were found to have correlation between the energy metabolism indicators and the SS (adropin ($r = -0.432$, $p = 0.01$), irisin ($r = -0.478$, $p < 0.01$)) as well as between the adipokine system indicators and SS (FABP 4 ($r = 0.436$, $p < 0.05$), CTRP 3 ($r = -0.473$, $p < 0.01$)). Also, in group 2 there was relationship between energy metabolism indicators and SS (adropin ($r = -0.412$, $p < 0.05$), irisin ($r = -0.475$, $p < 0.05$)), between the adipokine system indicators and SS (FABP 4 ($r = 0.428$, $p < 0.05$), CTRP 3 ($r = -0.427$, $p < 0.05$)).

The study showed that when comparing the groups 1 and 2, low levels of adropin, CTRP 3 and increased FABP 4 levels were found in the patients with severe CA lesion ($p < 0.05$) (Table 4). It is important to note that the patients with AMI and comorbidities were noted to have a decreased adropin content, CTRP 3 and a significant increase in the concentration of FABP 4 ($p < 0.05$). The level of irisin remained lowered in both groups ($p < 0.05$), but did not have a strong difference between the values of the CA lesion severity.

According to the results of observations, the patients with AMI had varying degrees of CA lesion severity, in some patients it might be quite favorable, while in other patients it might be unfavorable, requiring careful monitoring of this cohort of patients [11]. Therefore, it is important to determine the indicators associated with moderate and severe lesions of the CA. According to the findings of E. A. Gktuğ et al. [12], adropin is one of the predictors, playing a role in the development of atherosclerotic load in the patients with NSTEMI. Adropin levels were found to be lower in the patients with severe CA lesion versus moderate CA lesion. These data suggest that adropin may be an alternative indicator for predicting the IHD severity. M. Ozturk et al. [13] reported about low adropin levels in the patients

Table 4

Comparative characteristics of energy and adipokine metabolic indicators by CA lesion degree on day 1

Indicator	Group 1			Group 2		
	Low	Moderate	Severe	Low	Moderate	Severe
Adropin, pg/mL	21.49 (19.23; 24.14)	19.16 (13.42; 22.85)	16.53 (9.58; 9.95)#	15.31 (8.57; 18.25)	14.92 (9.36; 17.75)	10.84 (6.47; 7.17)
Irisin, ng/mL	1.94 (1.08; 2.22)	2.22 (1.96; 3.04)#	3.03 (2.92; 3.98)#	1.66 (1.27; 2.11)	1.44 (1.24; 1.93)	2.46 (2.08; 2.70)
FABP 4, ng/mL	9.34 (7.71; 10.55)#	9.77 (9.18; 10.77)	11.60 (9.07; 14.05)#	10.96 (9.16; 12.52)	10.78 (8.83; 12.08)	23.37 (13.49; 24.86)
CTRP 3, ng/mL	282.10 (253.76; 315.28) #	244.87 (221.58; 288.78)	247.41 (222.38; 299.76)#	247.82 (208.33; 274.39)	219.08 (192.38; 254.22)	183.59 (132.36; 216.52)

# $p < 0.05$ — comparison between group 1 and group 2.

with STEMI. This biomarker negatively correlated with the SS, that indicated the IHD severity in the patients with STEMI. Therefore, myocardial homeostasis may worsen further due to the increased severity of IHD in these patients.

The findings of J.-A. Pan et al. [14] demonstrate, that the lowest irisin content was noted in the patients with AMI and was associated with the severity of CA lesion compared with patients with stable IHD. When comparing mild and moderate CA lesions in the patients with IHD, a significantly reduced irisin level was found in patients with moderate CA lesions [15].

Concentration of FABP 4 was known to be increased in the patients with AMI compared with stable IHD [16]. According to M. Kajiya et al. [17], the patients with stable IHD and complicated coronary lesions had significantly higher serum FABP 4 levels compared to simple CA lesions, and serum FABP 4 was a significant predictor of angiographically complex coronary lesions regardless of the degree of coronary lesions. Natriuretic peptide correlates with the number of stenosed vessels.

M. Sawicka et al. [18] reported that the content of CTRP 3 decreases in the patients with AMI. M. Shanaki et al. [19] revealed that the CTRP3 attenuates post-infarction cardiac fibrosis and inhibits myofibroblast differentiation through the AMPK and Akt signaling pathways.

This study was subjected to several limitations as follows. First, the sample size was relatively small (n = 120), which should be increased in the future to confirm the findings. Second, since he study included only the patients with STEMI depending on the obesity presence and absence, the assessment of the extent of CA lesion requires further testing among the patients with NSTEMI in the obesity presence and absence, demanding additional investigations.

The research discovered that the patients with AMI (group 1) had better energy and adipokine metabolism indicators than patients with comorbidity (group 2). In groups 1 and 2, it was found that low levels of adropin, CTRP 3 and increased levels of FABP 4 were associated with severe CA lesion. Irisin content was associated with the lesion severity by SS in groups 1 and 2, but no significant difference was found between the degrees of CA lesions.

After PCI, the concentration of adropin and CTRP 3 increased, and the content of FABP 4 decreased compared with those in the patients with no stent implanted in groups 1 and 2. Myocardial revascularization did not affect changes in irisin concentration and the increase in the content of this indicator was not due to stent implantation.

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Accepted on 26.11.2021