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CONNECTIONS BETWEEN PLATELETS AMINO ACIDS PROFILE AND KNOWN CARDIOMETABOLIC RISK FACTORS IN PATIENTS WITH CORONARY ARTERY DISEASE AND ATRIAL FIBRILLATION

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Ключові слова: ішемічна хвороба серця, фібриляція передсердь, амінокислоти, тромбоцити, кардіометаболічні фактори ризику

Abstract. Connections between platelets amino acids profile and known cardiometabolic risk factors in patients with coronary artery disease and atrial fibrillation. Melnychuk I.O. The aim of our work was to identify the relationship between platelet amino acid profile and cardiometabolic risk factors in patients with coronary heart disease and atrial fibrillation. 300 patients were examined, who were divided into 3 groups: the first (I) – 149 patients with coronary artery disease (CAD) and without arrhythmias, the second (II) – 123 patients with CAD and paroxysm of atrial fibrillation (AF) and the control group (CG) – 28 patients without CAD and arrhythmia. The platelets amino acid (AA) profile was determined by ion exchange liquid column chromatography. Cardiometabolic risk factors studied: total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), lipoprotein a (Lp α), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), C-reactive protein (CRP), interleukin-6 (IL-6), trimethylamine (TMA) and trimethylamine-N-oxide (TMAO). Significant increase of isoleucine (10.73%), leucine (12.63%) and decrease of threonine (23.05%), serine (5.06%), glycine (32.21%), valine (30.83%) levels in platelet AA profile was observed in patients with CAD and AF compared to patients with CAD without arrhythmias, $p < 0.05$. Also, significant increase of apolipoprotein B (29.91%), CRP (40.93%), IL-6 (22.93%), TMA (16.13%) and TMAO (57.54%) and decrease of TMA/TMAO ratio (26.16%) was found in CAD with AF patients compared to CAD patients without arrhythmia, $p < 0.05$. The highest number of correlations was found between platelets AA profile and TMA/TMAO ratio (total number = 7), TC (total number = 7) and fibrinogen levels (total number = 6). In addition, most correlations were found between glycine (total = 12), threonine (total = 6), glutamate (total = 6), valine (total = 6), and cardiometabolic risk factors. The level of glycine in platelets is correlated with most cardiometabolic risk factors, such as: age ($r = -0.305$), BMI ($r = -0.351$), TC ($r = -0.304$), LDL ($r = -0.348$), ApoA1 ($r = 0.373$), ApoB ($r = -0.347$), IL-6 ($r = -0.315$), TMAO ($r = -0.654$), TMA/TMAO ratio ($r = 0.688$), prothrombin index ($r = 0.317$), activated partial thromboplastin time ($r = -0.365$) and fibrinogen level ($r = -0.396$), $p < 0.05$. So, in our work, the relationship between platelets AA profile and cardiometabolic risk factors in patients with CAD with AF was revealed. According to the results of the correlation analysis with known cardiometabolic risk factors, an important pathogenetic role of the glycine, threonine, valine and glutamate platelets levels in CAD and AF patients was revealed.

Реферат. Взаємозв'язки між амінокислотним профілем тромбоцитів та відомими кардіометаболічними факторами ризику у хворих на ішемічну хворобу серця та фібриляцію передсердь. Мельничук І.О. Метою нашої роботи є виявити зв'язок між амінокислотним профілем тромбоцитів і кардіометаболічними факторами ризику в пацієнтів з ішемічною хворобою серця та фібриляцією передсердь. Було обстежено 300 пацієнтів, які розподілені на 3 групи: перша (I) – 149 пацієнтів з ішемічною хворобою серця (ІХС) та без аритмій, друга (II) – 123 хворих з ІХС та пароксизмом фібриляції передсердь (ФП) та контрольна група (КГ) – 28 пацієнтів без ІХС та аритмій. Амінокислотний (АК) профіль тромбоцитів визначали методом іонообмінної рідинної колонкової хроматографії. Кардіометаболічні фактори ризику, які досліджувалися: загальний холестерин (ТС), тригліцериди (ТГ), ліпопротеїни низької щільності (LDL), ліпопротеїни високої щільності (HDL), ліпопротеїн α (Lp α), аполіпопротеїн А1 (АроА1), аполіпопротеїн В (АроВ), С-реактивний білок (CRP), інтерлейкін-6 (ІЛ-6), триметиламін (ТМА) і триметиламін-N-оксид (ТМАО). В АК-профілі тромбоцитів значне

підвищення рівня ізолейцину (10,73%), лейцину (12,63%) і зниження рівня треоніну (23,05%), серину (5,06%), гліцину (32,21%), валіну (30,83%) спостерігалось у пацієнтів з ІХС та ФП порівняно з пацієнтами з ІХС без аритмій, $p < 0,05$. Також виявлено значне підвищення рівнів аполіпопротеїну В (29,91%), СРБ (40,93%), ІЛ-6 (22,93%), ТМА (16,13%) і ТМАО (57,54%) і зниження співвідношення ТМА/ТМАО (26,16%) при ІХС із ФП порівняно з пацієнтами з ІХС без аритмій, $p < 0,05$. Найбільшу кількість кореляцій було виявлено між АК-профілем тромбоцитів і співвідношенням ТМА/ТМАО (загальна кількість = 7), ТС (загальна кількість = 7) і рівнями фібриногену (загальна кількість = 6). Крім того, більшість кореляцій виявлено між гліцином (загальна кількість = 12), треоніном (загальна кількість = 6), глутаматом (загальна кількість = 6), валіном (загальна кількість = 6) і кардіометаболічними факторами ризику. Рівень гліцину в тромбоцитах корелює з більшістю кардіометаболічних факторів ризику, таких як: вік ($r = -0,305$), ІМТ ($r = -0,351$), ТС ($r = -0,304$), LDL ($r = -0,348$), ApoA1 ($r = 0,373$), ApoB ($r = -0,347$), ІЛ-6 ($r = -0,315$), ТМАО ($r = -0,654$), співвідношення ТМА/ТМАО ($r = 0,688$), протромбіновий індекс ($r = 0,317$), активованій частковий тромбопластиновий час ($r = -0,365$) та рівнями фібриногену ($r = -0,396$), $p < 0,05$. Отже, у нашій роботі виявлено зв'язки між АК-профілем тромбоцитів і кардіометаболічними факторами ризику у хворих на ІХС з ФП. За результатами кореляційного аналізу з відомими кардіометаболічними факторами ризику виявлена важлива патогенетична роль рівня гліцину, треоніну, валіну та глутамату тромбоцитів у хворих на ІХС та ФП.

Atrial fibrillation (AF) is the most widely spread arrhythmia all over the world. The former is connected with increasing mortality and cases hospitalization of: stroke, heart failure, dementia, depression and impaired life quality are the well-known AF complications. AF presence is directly connected with thrombosis risk. Anticoagulation treatment is the one of the bases in AF management. Coronary artery (CAD) is the most common cardiovascular disease. It is also characterized by prothrombotic state. Moreover, CAD is the independent AF risk factor and vice versa. Together they worsen course of each other [1, 2].

Amino acids (AA) play the crucial role in platelets activation. Branched chain AA (BCAA) have a prothrombotic properties by increasing levels of trombosmodulin-3 and integrin $\alpha\text{IIb}\beta\text{3}$. Valine catabolite – α -ketoisovaleric acid has the strong promotion effect on platelets activation [3]. At the same time taurine and glycine have antithrombotic potential. Glycine can block the calcium flow into platelets by hyperpolarization of chlorine channels of platelets membrane. Taurine decreases platelets activation by inhibition of platelets derived growth factor BB [4, 5]. Platelets amino acids spectrum in patients with AF is still uninvestigated. But it is changed in some metabolic diseases, as diabetes mellitus, etc., which are known AF risk factors [1, 6].

Factors which contribute to cardiovascular diseases and diabetes are called cardiometabolic risk factors (CMRF). Obesity, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, rise of low-density lipoprotein (LDL), apolipoprotein B (ApoB), lipoprotein α ($\text{Lp}\alpha$), inflammatory markers as C-reactive protein (CRP) levels and interleukin-6 (IL-6) levels, also decrease in high-density lipoproteins (HDL), apolipoprotein A1 (ApoA1) are well known CMRF [7, 8, 9]. Role of the gut microbiota metabolites in cardiovascular diseases pathogenesis is still under discussion. But, by the latest data, trimethyl-

amine (TMA) and trimethylamine-N-oxide (TMAO) levels are directly connected with CAD and AF development [10].

So, platelets AA profile and its connections with known CMRF is an interesting pathogenetic question in AF paroxysm pathogenesis in CAD patients. This can help us find the new biochemical risk factors of AF development in CAD patients.

Aim: to find connections between platelets amino acids profile and cardiometabolic risk factors in coronary artery disease patients with atrial fibrillation.

MATERIALS AND METHODS OF RESEARCH

We investigated 300 patients divided into 3 groups: first (I) – 149 patients with CAD and without arrhythmias, second (II) – 123 patients with CAD and AF paroxysm and control group (CG) – 28 patients without CAD and arrhythmias. CAD and AF diagnosis were based on latest ESC guidelines [1, 2]. CAD diagnosis was confirmed by history of coronary arteries stenotic changes during invasive coronary angiography. AF paroxysm was checked by electrocardiography in 12 leads at least. Exclusion criteria were: reported malignancies, chronic kidney disease (glomerular filtration rate, $\text{GFR} < 60 \text{ mL/min}$), valvular AF, heart failure Class III-IV (by New York Heart Association), thyroid pathology, inflammatory bowel disease, irritable bowel syndrome, vegetarians and vegans, pregnancy, taking probiotics and antibiotics for a month before the study. No significant difference in risk factors at baseline level were seen between investigated groups. The study was conducted at the base and was approved by the ethical commission of the Kyiv City Clinical Hospital No. 12 (protocol No. 8 from 22/08/2018). Informed consent was obtained from all subjects in accordance with the Declaration of Helsinki. Baseline characteristics of study sample are shown in Table.

Baseline characteristics of study sample, mean ± standard error

Characteristic /group	I	II	CG	p1-2	p2-3	p1-3
Age (years)	67.71±3.90	67.96±0.94	56.25±2.18	p>0.05	p>0.05	p>0.05
Men (%)	48.99	47.97	48.15	p>0.05	p>0.05	p>0.05
BMI (kg/m ²)	27.02±0.33	26.93±0.43	28.12±2.10	p>0.05	p>0.05	p>0.05
Uric acid (mmol/l)	380.5±28.16	404.9±36.11	310.2±29.12	p>0.05	p<0.05	p<0.05
Total bilirubin (mmol/l)	11.3±0.09	12.4±0.08	11.7±0.11	p>0.05	p>0.05	p>0.05
GFR (ml/min)	62.03±2.31	67.73±1.98	84.01±5.48	p>0.05	p<0.05	p<0.05
PI, %	82.10±0.78	77.16±0.69	81.08±1.82	p>0.05	p<0.05	p>0.05
Ht, %	43.93±0.48	45.17±0.64	43.08±1.05	p>0.05	p>0.05	p>0.05
aPTT, s	29.33±0.40	30.29±0.62	27.30±0.56	p>0.05	p<0.05	p>0.05
Fibrinogen, mg/dl	2.89±0.08	3.21±0.09	2.65±0.11	p<0.05	p<0.05	p>0.05
Fibrin, mg	17.26±0.46	16.73±0.47	17.54±1.81	p>0.05	p>0.05	p>0.05

Platelets AA level was detected by method of ion exchange liquid column chromatography, such AA were identified: lysine, histidine, arginine, ornithine, taurine, asparagine acid, threonine, serine, glutamine acid, proline, glycine, alanine, cysteine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, glutamine, ammonia. Blood sampling from patients was performed on an empty stomach from the cubital vein on the first day of hospitalization, before treatment. Citrated blood is centrifuged for 10 minutes at a speed of 1500 revolutions per minute. The middle layer is collected with a Pasteur pipette – the plasma is saturated with platelets. The obtained material is again centrifuged for 20 minutes at a speed of 3000 revolutions per minute. The upper supernatant liquid was collected with a Pasteur pipette, and the lower layer was washed with buffer (pH 6.2). Washed platelets are resuspended in buffer (pH 7.4) [11].

Cardiometabolic risk factors explored: total cholesterol (TC), triglycerides (TG), LDL, HDL, Lp α , apolipoprotein A1 (ApoA1), ApoB, CRP, IL-6, TMA and TMAO. Also, ApoB/ApoA1 and TMA/TMAO ratios were checked. The level of TMAO, TMA plasma was determined by gas chromatography with mass electron detection. They were extracted from blood plasma into acid by adding internal standards. Patient's blood sampling was performed on an empty stomach from the cubital vein on the day of hospitalization. Hymalyzer 2000 was used for detection of TC, TG, HDL, LDL (reagent produced by HUMAN GmbH), ApoA1, ApoB, Lp α and CRP (reagent

produced by Dialab) by flow cytometry method [12]. Hymareader 2106 (ELISA) was used for detection of IL-6 – reagents produced by Vector Best [13].

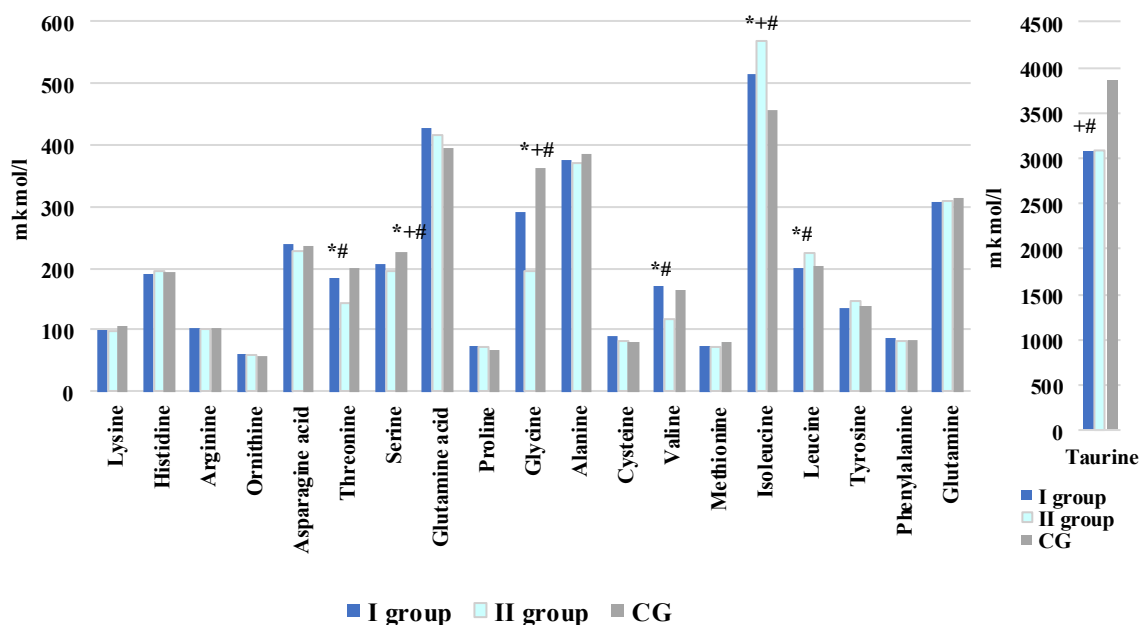
Results were presented as mean ± standard error for continuous variables. Variables distribution for normality were checked by the Pearson criterion. Data were compared by Scheffe's multiple comparison method with two critical regions for variables distribution respectively; Spearman's rank correlation coefficient was detected [14]. All calculations were done in MATLAB R2014a (License number 271828).

RESULTS AND DISCUSSION

In our study we investigated platelets AA spectrum in CAD patients with AF. Results are shown in Figure 1.

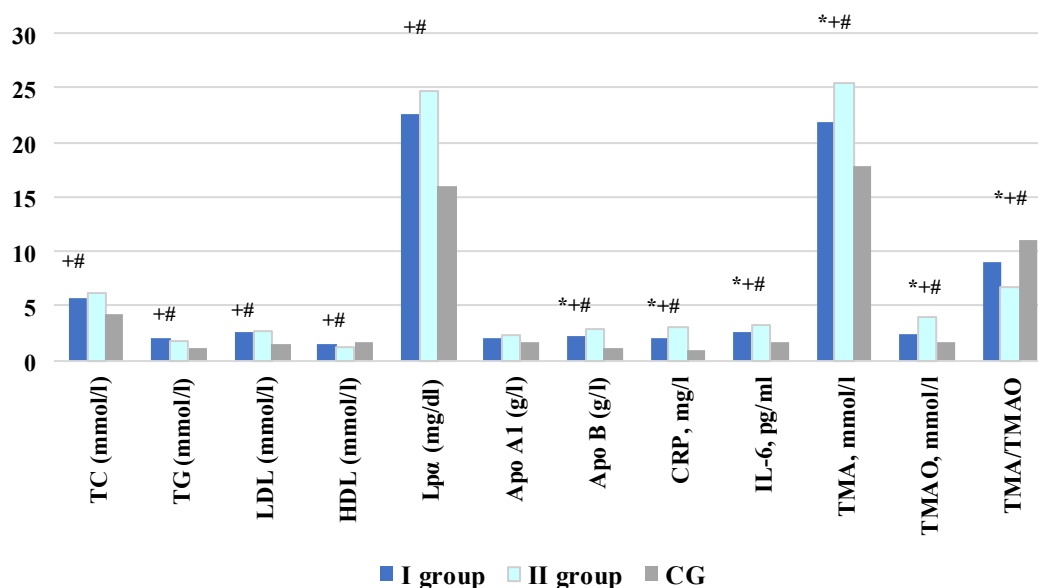
In patients with CAD and without arrhythmias significant increase of isoleucine (12.41%) and decrease of taurine (20.26%), serine (9.31%) and glycine (19.73%) levels was reveled in comparison with CG, p<0.05. In patients with CAD and AF a significant elevation of isoleucine (24.47%), leucine (10.20%) and descent of taurine (19.84%), threonine (29.37%), serine (13.90%), glycine (45.59%) and valine (27.87%) levels in comparison with CG, p<0.05 was found. Moreover, in CAD patients with AF in comparison with CAD patients without arrhythmias significant increase of isoleucine (10.73%), leucine (12.63%) and decrease of threonine (23.05%), serine (5.06%), glycine (32.21%), valine (30.83%) levels was revealed, p<0.05.

CMRF were investigated in CAD patients with AF as well. Results are shown in Figure 2.



*- p<0.05 I-II groups; +- p<0.05 I group - CG; # - p<0.05 II group - CG.

Fig. 1. Platelets amino acids profile in investigated groups, mkmol/l



* - p<0.05 I-II groups; +- p<0.05 I group - CG; # - p<0.05 II group - CG.

Fig. 2. Cardiometabolic risk factors of investigated groups

Significant increase in TC (32.64% and 43.06% respectively), TG (80.36% and 55.36% respectively), LDL (70.78% and 72.73% respectively), Lpa (41.17% and 54.95% respectively), ApoB (85.12% and 140.50% respectively), CRP (136.26% and 232.97% respectively), IL-6 (65.22% and 103.11%

respectively), TMA (22.50% and 42.25% respectively), TMAO (50.00% and 136.31% respectively) and decrease in HDL (16.09% and 29.31% respectively), TMA/TMAO ratio (18.59% and 39.89% respectively) was found in CAD patients with and without AF compared with CG (p<0.05). Significant

elevation of ApoB (29.91%), CRP (40.93 %), IL-6 (22.93%), TMA (16.13%), TMAO (57.54%) levels and decrease in TMA/TMAO ratio (26.16%) were revealed in CAD patients with AF in comparison with CAD patients without arrhythmia, $p < 0.05$.

The correlation analysis between platelets AA profile and cardiometabolic risk factors was done in investigated groups. All correlations are shown in Figure 3.

Platelets AA/CMRF	Age	BMI	TC	TG	LDL	HDL	Lpα	ApoA1	ApoB	AIP	CRP	IL-6	TMA	TMAO	TMA/TMAO	PI	Ht	aPTT	Fibrinogen	Fibrin
Lysine									■											
Histidine				■																■
Arginine												■								
Ornithine	■									■										
Taurine		■	■										■	■	■					
Asparagine acid																■				
Threonine	■		■				■								■			■	■	
Serine														■	■				■	
Glutamine acid			■				■	■							■			■	■	
Proline		■																	■	■
Glycine	■	■	■		■			■	■			■		■	■	■		■	■	
Alanine	■				■				■								■			
Cysteine															■					
Valine	■				■				■			■		■	■					
Methionine		■	■																	
Isoleucine													■	■						
Leucine								■	■			■	■						■	
Tyrosine						■														
Phenylalanine			■														■			
Glutamine			■	■									■			■				

- – moderate positive correlation, $0.3 < r < 0.7$;
- – strong positive correlation, $r > 0.7$;
- – no significant correlations;
- – moderate negative correlation, $-0.3 > r > -0.7$;

Fig. 3. Correlations heatmap between platelets amino acids and cardiometabolic risk factors, $p < 0.05$

The largest number of correlations was revealed between platelets AA profile and such characteristics as TMA/TMAO (total number =7), TC (total number =7) and fibrinogen (total number =6) levels. The largest number of correlations was found between glycine (total number =13), threonine (total number =6), glutamate (total number =6), valine (total number =6) and CMRF.

Significant elevation of ApoB, CRP, IL-6, TMA, TMAO levels and decrease in TMA/TMAO ratio were revealed in CAD patients with AF in comparison with CAD patients without arrhythmia. These data are matched with results of different previous studies [7, 8, 9, 10].

Significant BCAA platelets spectrum changes in CAD patients with AF were found in our work: increase of isoleucine, leucine and decrease of valine levels. Valine is an important resource for valine/ α -ketoisovaleric acid metabolic pathway that plays an important role in platelets activation [3]. Moreover, BCAA promotes megakaryocytes differentiation and platelets biogenesis [15]. Leucine, isoleucine and valine can have different metabolic effects. For example, in lipogenesis valine decreases odd-chain fatty acids level, that is associated with lower risk of diabetes mellitus type 2. At the same time, leucine provides fatty acids transport and regulates their intake with food. Also, leucine can promote platelets activation through mTOR signaling pathway by rise of S6 ribosomal protein phosphorylation [16]. Increase of leucine and isoleucine is associated with cardiac fibrosis development, which is one of the important pathogenetic mechanism of AF paroxysm development [17].

On the other hand, by our results decrease of threonine, serine and glycine levels in platelets AA profile due to CAD in AF patients was present. Biochemically threonine, glycine and serine metabolism are closely linked. Threonine and glycine also take part in mTOR metabolic pathway regulation through protein synthesis modulation. Moreover, threonine stimulates anti-inflammatory cytokines production, modulates gut microbiota condition and normalizes intrahepatic triglycerides metabolism [18]. Glycine inhibits platelets aggregation through the activation of glycine-gated chloride channels in platelets, this hyperpolarizes platelets membrane and leads to calcium channels blockage [4]. Serine metabolism promotes intrahepatic lipogenesis, decreases triglycerides production, has anti-inflammatory action [19].

For example, platelets AA profile changes in patients with diabetes mellitus type 2 are characterized by an increase in isoleucine and decrease in alanine, threonine, and taurine levels [6]. In this study, in CAD patients an increase in isoleucine and decrease in taurine levels compared to CG was also

found. As was mentioned, BCAA have proved prothrombotic properties [15] and impact on lipids and glucose exchange [16, 17]. This can explain the pathogenetic role of isoleucine in cardio-metabolic disorders. According to literature review taurine has strong antithrombotic, anti-inflammatory and anti-lipidemic effects [5], which can be disturbed in case of its decrease. According to obtained data platelets threonine level decreased in CAD and AF. Threonine takes an important place in lipids exchange, it increases hepatic triglycerides accumulation, improves fatty acids oxidation and triglycerides transport, binds apolipoprotein D, modulates adiponectin transcription factors. Moreover, decreased circulating threonine levels correlate with proatherogenic state [18]. So, low platelets threonine level also can be a potential marker of cardiometabolic disorders. At the same time, probably a decrease in platelets glycine and serine levels is a special feature in CAD and AF patients. Nevertheless, decrease in circulating glycine is mentioned as a marker of myocardial ischemia [20]. At the same time, glycine, serine and threonine exchange is closely linked [18].

The role of glycine, threonine and valine exchange in cardiometabolic risks formation is shown by a huge number of significant correlations between known CMRF and platelets glycine, threonine and valine levels.

CONCLUSIONS

Connections between platelets amino acids profile and cardiometabolic risk factors in coronary artery disease patients with atrial fibrillation were investigated in our work. Obtained results:

1. Increase in isoleucine (10.73%), leucine (12.63%) and decrease in threonine (23.05%), serine (5.06%), glycine (32.21%), valine (30.83%) levels in platelets amino acids profile was checked in coronary artery disease patients with atrial fibrillation in comparison with coronary artery disease patients without arrhythmias, $p < 0.05$;

2. Significant elevation of apolipoprotein B (29.91%), C-reactive protein (40.93%), interleucine-6 (22.93%), trimethylamine (16.13%) and trimethylamine-N-oxide (57.54%) levels and decrease in trimethylamine/trimethylamine-N-oxide ratio (26.16%) was revealed in coronary artery disease patients with atrial fibrillation in comparison with coronary artery disease patients without arrhythmias, $p < 0.05$;

3. The largest number of correlations was checked between platelets amino acids profile and trimethylamine/trimethylamine-N-oxide ratio (total number =7), total cholesterol (total number =7) and fibrinogen (total number =6) levels. Also, majority of correlations was found between glycine (total

number =12), threonine (total number =6), glutamate (total number =6), valine (total number =6) and cardiometabolic risk factors.

4. Platelets glycine level correlates with majority of cardiometabolic risk factors: age ($r=-0.305$), BMI ($r=-0.351$), total cholesterol ($r=-0.304$), low-density lipoproteins ($r=-0.348$), apolipoprotein A1 ($r=0.373$), apolipoprotein B ($r=-0.347$), interleucine-6 ($r=-0.315$), trimethylamine-N-oxide ($r=-0.654$), trimethylamine/trimethylamine-N-oxide ratio ($r=0.688$), prothrombin index ($r=0.317$), activated partial thromboplastin time ($r=-0.365$) and fibrinogen ($r=-0.396$), $p<0.05$.

Perspectives of further scientific research: Platelets amino acids profile changes, as a new cardiometabolic risk factors, correction ways will be interesting topic for further investigations.

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Conflict of interests. The author declare no conflict of interest.

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