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Proinflammatory biomarkers and platelet aggregation activity in patients with coronary artery disease

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ABSTRACT

Aim. To determine concentrations and identify the relationship of biomarkers (endocan / cell-specific molecule-1, fatty acid binding protein 4 (FABP 4), placental growth factor (PlGF), oncostatin M), with parameters of collagen-induced platelet aggregation in patients with coronary artery disease (CAD).

Materials and methods. In patients with CAD (n = 51), serum levels of endocan, FABP 4, PlGF, oncostatin M, and platelet aggregation indices (collagen at concentrations of 2 and 10 mmol / l) were determined. Patients were divided into groups with and without high residual platelet reactivity (HRPR). Correlation coefficients between concentrations of proinflammatory biomarkers and platelet aggregation indices were determined in patients of both groups.

Results. In patients with HRPR, the concentrations of endocan and PlGF were significantly higher, and the concentrations of FABP4 and oncostatin M were lower than in the first group. In patients with HRPR, a correlation was found between the concentration of endocan and the degree of platelet aggregation in the presence of 2 mmol / l of collagen ($\rho = 0.48$; $p = 0.01$), between the concentration of PlGF and the degree of platelet aggregation in the presence of 10 mmol / l of collagen ($\rho = 0.58$; $p = 0.01$), as well as between the concentration of FABP 4 and the size of aggregates at both collagen concentrations ($\rho = 0.42$; $p = 0.03$) and ($\rho = 0.70$; $p = 0.01$) and the degree of platelet aggregation in the presence of 10 mmol / l of collagen ($\rho = 0.43$; $p = 0.01$).

Conclusion. In all examined CAD patients, regardless of the residual platelet reactivity, the levels of endocan and FABP 4 increased compared to the reference values. In patients with HRPR, the content of parameters (endocan, PlGF) contributing to plaque growth was elevated, and in patients without HRPR, the levels of platelet-activating factors (FABP 4, oncostatin M) were increased, which determines a personalized approach to prescribing therapy for these groups of patients. In patients with CAD, platelet aggregation indices were associated with concentrations of proinflammatory biomarkers (endocan, PlGF, and FABP 4), which contribute to the development of endothelial dysfunction.

Keywords: aggregation, platelet, collagen, coronary artery disease, biomarkers

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the Ethics Committee at Cancer Research Institute of Tomsk NRMC (Protocol No. 139 of 18.11.2015).

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Провоспалительные биомаркеры и агрегационная активность тромбоцитов у пациентов с ишемической болезнью сердца

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РЕЗЮМЕ

Цель: определить концентрации и выявить связь биомаркеров (эндокана-1, белка, связывающего жирные кислоты, 4 (FABP 4), плацентарного фактора роста (PLGF), онкостатина М с показателями коллаген-индуцированной агрегации тромбоцитов у пациентов с ишемической болезнью сердца (ИБС).

Материалы и методы. У пациентов с ИБС (n = 51 человек) определяли сывороточную концентрацию эндокана-1, уровень FABP 4, PLGF, онкостатина М и показатели агрегации тромбоцитов (коллаген в концентрации и 10 мкмоль/л). Пациенты разделены на группы с высокой остаточной реактивностью тромбоцитов (ВОРТ) и без нее. Определялись коэффициенты корреляции между концентрациями провоспалительных биомаркеров и показателями агрегации тромбоцитов.

Результаты. У всех обследованных пациентов с ИБС вне зависимости от остаточной реактивности тромбоцитов повышена концентрация эндокана-1 и FABP 4 по сравнению с референсными значениями. У пациентов с ВОРТ концентрация эндокана-1 и PLGF значимо выше, а концентрации FABP 4 и онкостатина М ниже, чем в первой группе. У пациентов с ВОРТ выявлена корреляция между концентрацией эндокана-1 и степенью агрегации тромбоцитов в присутствии 2 мкмоль/л коллагена (ρ = 0,48; p = 0,01), концентрацией PLGF и степенью агрегации в присутствии 10 мкмоль/л коллагена (ρ = 0,58; p = 0,01), а также между концентрацией FABP 4 и размерами агрегатов при обеих концентрациях коллагена (ρ = 0,42; p = 0,03) и (ρ = 0,70; p = 0,01) и со степенью агрегации в присутствии 10 мкмоль/л коллагена (ρ = 0,43; p = 0,01).

Заключение. У пациентов с ВОРТ увеличено содержание факторов (эндокан-1, PLGF), способствующих росту бляшки, а у пациентов без таковой – факторов активации тромбоцитов (FABP 4, онкостатин М), что обусловливает персонифицированный подход к назначению терапии для больных этих групп. У пациентов с ИБС показатели агрегации тромбоцитов ассоциированы с концентрациями провоспалительных биомаркеров, которые способствуют развитию эндотелиальной дисфункции.

Ключевые слова: агрегация, тромбоцит, коллаген, ишемическая болезнь сердца, биомаркеры

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Despite the ongoing therapeutic and preventive measures, coronary artery disease (CAD) remains the most common cardiovascular pathology in Russia. High residual platelet reactivity (HRPR) in the context of broad-spectrum antiplatelet therapy in patients is associated with the development of ischemic complications, which has been proven by numerous studies and data of the meta-analysis [1–3]. The main causes of CAD development are coronary stenosis and microvascular endothelial dysfunction [4]. It is known that endocan acts as a marker of endothelial dysfunction; its release is one of the earliest pathogenetic events observed in atherosclerosis, thrombosis, and chronic heart failure [5]. Researchers discuss the role of platelets as primary factors in the pathogenesis of cardiovascular diseases through modulation of immune responses, which are currently considered to be the driving force in atherogenesis. Proinflammatory cytokines promote the expression of enzymes that lead to atherosclerotic plaque destabilization (APD), followed by plaque rupture [6]. After the atherosclerotic plaque rupture, macrophages and smooth muscle cells produce a tissue factor that triggers a coagulation cascade leading to thrombosis. Platelets are activated due to their interaction with collagen in the extracellular matrix of the plaque. It has been shown that oncostatin M can contribute to the development of atherosclerosis and vascular destabilization [7, 8]. Quite often, thrombosis develops at the site of hemodynamically insignificant stenosis in the coronary arteries [4]. Thus, the development of arterial and venous thrombosis was associated with an increase in the content of placental growth factor (PlGF) in patients with antiphospholipid syndrome [9].

Biochemical markers are the most important tool for timely diagnosis and prediction of a risk of developing cardiovascular pathology [10]. Both clinical and experimental data have shown that fatty acid binding protein type 4 (FABP4) plays an essential role in the development of atherosclerosis and CAD, and it is directly associated with left ventricular hypertrophy and cardiac dysfunction [11, 12]. The multi-marker approach should more accurately reflect the key links in the pathogenesis and biochemical interactions compared to the use of individual markers. In this regard, there is a growing interest in the development and use of combinations of biomarkers.

In this work, concentrations of proinflammatory biomarkers (endocan, FABP4, PlGF, and oncostatin M) will be determined in patients with CAD in the presence and absence of HRPR, and their relationship with the parameters of collagen-induced platelet aggregation will be evaluated. Knowledge in this area of research is relevant for both clinical and fundamental medicine.

The aim of the study was to determine concentrations and identify the relationship of proinflammatory biomarkers (endocan / cell-specific molecule-1, FABP 4, PlGF, oncostatin M) with parameters of collagen-induced platelet aggregation in patients with CAD.

MATERIALS AND METHODS

A single-stage, simple comparative study was conducted. The study included 51 patients with CAD (75% of them were men). The recruitment of patients was performed at the Cardiology Research Institute in accordance with the principles of the Declaration of Helsinki. The study included patients aged 41–83 years. All examined patients received combined basic therapy in accordance with the guidelines for CAD treatment.

Criteria for inclusion in the study: stable CAD and continuous antiplatelet therapy for 6 months (cardiomagnil, 75mg). Exclusion criteria from the study: combined antiplatelet therapy, acute vascular complications within less than 6 months before the inclusion in the study; severe concomitant pathology; clinical and laboratory signs of acute inflammation; refusal to participate in the study.

To obtain blood serum, whole peripheral blood of patients stabilized with 3.8% sodium citrate was centrifuged at 3,000 rpm for 15 minutes at room temperature. The obtained serum samples were stored at –40 °C. Concentrations of proinflammatory biomarkers endocan, FABP 4, PlGF, and oncostatin M were determined in the samples. The study was conducted at the Medical Genomics Collective Use Center of Tomsk NRMC by the multiplex immunoassay (Luminex FLEXMAP 3D platform, USA) using the Human Cardiovascular Disease Panel 1 (Merck KGaA, Darmstadt, Germany). The parameters of collagen-induced platelet aggregation were determined by the Born's method in the modification of Z.A. Gabbasov on the two-channel laser analyzer (220 LA Research and Production Company Biola, Russia).

To isolate the platelet suspension, blood was drawn into test tubes with 3.8% sodium citrate as an anticoagulant. All samples were examined using a standard approach (hereinafter referred to as Method 1), as well as by the authors' own patented

methodology (hereinafter referred to as Method 2). In Method 1, the aggregation inductor (collagen) was introduced once at a final concentration of 2 mmol / l at 10 seconds of measurement. According to Method 2, aggregation parameters were determined 5 times when adding 2 mmol / l of collagen at 10 seconds, 1, 2, 3, and 4 minutes of the platelet aggregation evaluation with the final concentration of collagen in the sample being 10 mmol / l [3].

The degree of platelet aggregation (%) was evaluated by the maximum amount of light transmission, and the size of the aggregate was evaluated by the average aggregate size curve (rel. units). The examined patients were divided into two groups. Group 1 ($n = 27$) included patients who had no HRPR. The degree of collagen-induced aggregation measured by both methods did not exceed 60%, and the size of aggregates was less than 4 rel. units. Group 2 included patients ($n = 24$) whose degree of platelet aggregation was ≥ 60%, and the size of aggregates was ≥ 4 rel. units according to at least one of the methods. The parameters were determined by both methods. According to [3], patients of the second group corresponded to a group of individuals with HRPR.

Statistical data processing was carried out using the SPSS (version 19) and STATISTICA 10.0 software packages. To assess the distribution of quantitative variables, the Shapiro – Wilk test was used. The statistical significance of differences for two independent samples was assessed using the Mann – Whitney *U*–test. For comparison with a given value of one parameter, the Student's *t*–test was used, after applying the Box – Cox data transformation method. The Spearman's rank correlation coefficient (ρ) was used to evaluate the relationships between the variables. The data were presented as the median and the interquartile range ($Me\ (Q_1; Q_3)$). The results of the comparative and correlation analysis were considered statistically significant at $p < 0.05$.

RESULTS

Platelet aggregation indices in patients assigned to groups 1 and 2 significantly differed, according to [3]. The groups of patients were comparable by gender, age, duration of CAD, the number of prior myocardial infarctions, and concomitant pathology. Drug therapy did not differ significantly between the groups of patients (aspirin, calcium antagonists, statins, diuretics, nitrites, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors).

The concentrations of endocan and FABP 4 in both groups of patients significantly exceeded the maximum reference values. Thus, the concentration of FABP 4 increased by 10 times compared to the reference values (Table). The concentrations of endocan and PlGF were significantly increased in the group of patients with HRPR compared to patients of group 1, and the levels of FABP 4 and oncostatin M, on the contrary, were reduced (Table).

Table

Concentrations of biomarkers in patients with coronary artery disease and their reference values

Parameter	Group 1, $n = 27$, Me (Q_1; Q_3)	Group 2, n = 24, $Me\ (Q_1; Q_3)$	p value between the groups	Reference values Mean (Min.; Max.)
Endocan, ng / ml	2.13 ($p = 0.02$) (1.89; 2.66)	2.61 ($p = 0.01$) (2.07; 2.96)	0.03	0.94 (0.65; 1.72)
PlGF, pg / ml	4.22 (2.86; 12.19)	9.51 (5.48; 18.73)	0.01	8.72 (0.0; 39.98)
FABP 4, ng / ml	68.74 ($p = 0.01$) (45.60; 75.44)	51.52 ($p = 0.01$) (25.59; 55.47)	0.02	5.34 (0.0; 11.83)
Oncostatin M, pg / ml	26.12 (5.02;45.68)	14.93 (2.98; 28.45)	0.04	22.73 (4.07; 53.83)

Note: p is the level of significance of differences between the groups of CAD patients and in comparison with the reference values.

The correlation analysis revealed the following. In group 1 (patients without HRPR), a positive correlation was found between the concentration of PlGF and the size of aggregates according to both aggregation methods ($r = 0.39$; $p = 0.01$) and ($r = 0.62$; $p = 0.02$). In addition, a correlation was found between the concentration of oncostatin M and the degree of aggregation determined in the presence of 10 mmol / l of collagen ($r = 0.82$; $p = 0.01$).

In group 2 (patients with HRPR), correlations were found between the concentration of endocan and the degree of aggregation determined in the presence of 2 mmol / l of collagen ($r = 0.48$; $p = 0.01$), as well as between the concentration of PlGF and the degree of aggregation measured in the presence of 10 mmol / l of collagen ($r = 0.58$; $p = 0.03$). In addition, correlations were found between the concentration of FABP 4 and the size of aggregates measured in the presence of

two concentrations of collagen (r = 0.42; p = 0.04), (r = 0.70; p = 0.01), as well as the degree of aggregation determined in the presence of 10 mmol / l of collagen (r = 0.43; p = 0.01).

DISCUSSION

The present work was an open, single-center, cross-sectional study. In the present study, we found that in patients of group 2 (with HRPR), the concentration of endocan and PlGF increased, which can contribute to the growth of atherosclerotic plaques, and in patients of group 1 (without HRPR), FABP 4 and oncostatin M, factors contributing to the activation of platelets, were elevated. In addition, we showed that in patients with CAD, platelet aggregation indices are associated with concentrations of proinflammatory biomarkers (endocan, PlGF, and FABP 4), which may contribute to the development of endothelial dysfunction.

In the present study, the levels of endocan and FABP 4 were significantly increased in patients with CAD in both groups compared to reference values, which indicates the development of endothelial dysfunction in patients with CAD [13]. As is known, endothelial dysfunction is one of the earliest pathogenetic events in the development of atherosclerosis, hypertension, and thrombosis [14]. An increase in the level of endocan, which is a potential marker of inflammation and cardiovascular diseases [6, 15], found in this study, confirms this theory. In addition, the revealed correlation between the concentration of endocan and platelet aggregation in patients with HRPR (group 2) indicates endothelial dysfunction leading to increased thrombosis. Platelet activation products promote endocan release by endothelial cell culture *in vitro*, which was pronounced in patients with transfusion complications [5].

A ten-fold increase in the concentration of FABP 4 in patients of both groups confirms the proatherogenic and prothrombotic effects of this marker. FABP 4 has been shown to mediate inhibition of the peroxisome proliferator-activated receptor (PPAR)γ [16]. The latter, in turn, inhibits the activation of platelets and the release of active mediators from them [17]. FABP 4 plays an important role in the development of atherosclerosis and CAD and is associated with left ventricular hypertrophy and cardiac dysfunction [11, 12]. The prothrombotic role of FABP 4 in this study is also confirmed by the revealed correlations between its concentration and the size of aggregates in patients with HRPR.

In the group of patients with HRPR, an elevated concentration of PlGF was found compared to group 1. PlGF promotes neoangiogenesis in CAD, which is considered as an adaptive response aimed at improving perfusion of the ischemic myocardium by increasing the number and size of collateral arteries [9, 18].

At the same time, the study established correlations of PlGF with platelet aggregation parameters in both groups. PlGF is a placental growth factor capable of stimulating angiogenesis and inducing atherosclerosis by binding and activating its membrane-bound receptor, soluble fms-like tyrosine kinase-1. Expression of PlGF in atherosclerotic lesions activates monocytes and macrophages, which subsequently produce inflammatory and angiogenic mediators, leading to an increasing risk of plaque rupture. Conversely, inhibition of PlGF reduces the size of atherosclerotic plaques [8]. The development of thrombosis is associated with an increase in the content of PlGF in patients with antiphospholipid syndrome [9]. The relationship between platelet aggregation parameters and PlGF is shown in women with preeclampsia [19], however, the molecular mechanisms that may underlie this relationship are unknown and require further study.

It is possible that the associations of platelet aggregation parameters in CAD patients of group 1 with the levels of oncostatin M and PlGF revealed in this study prove the modulating effect of platelets on the inflammatory response in the endothelium.

In this study, a correlation was established between the concentration of oncostatin M and the degree of platelet aggregation in group 1. Oncostatin M is known to contribute to the development of atherosclerosis and vascular destabilization [20, 21]. In addition, oncostatin M is considered as a megakaryocyte colony-forming factor that promotes thrombocytopoiesis [7]. There is evidence that under the influence of oncostatin M, activation of the signal transducer and activator of transcription (STAT)3 occurs, which plays an important role in collagen-mediated aggregation [8].

The role of platelets in the atherosclerosis and pathogenesis of cardiovascular diseases is very significant, since platelets, in addition to their contribution to thrombosis and hemostasis, modulate inflammatory and immune responses [22]. One of the first signals for platelet activation is collagen, the main protein of connective tissue that is exposed when a vessel is damaged. In addition to vascular damage, various proinflammatory mediators activate platelets

[11, 21]. The study revealed multiple correlations between platelet aggregation and the levels of serum biomarkers of cardiovascular diseases. In this study, it was revealed that the levels of endocan and FABP 4 were increased in patients of both groups, which points to the possible inflammatory damage of the vascular endothelium and platelet activation. At the same time, the differences in the concentration of some biomarkers were found in patients of both groups. Thus, in patients without HRPR, the concentrations of FABP 4 and oncostatin M were elevated, and in patients with HRPR, the concentrations of endocan and PlGF were increased. Based on this, it can be assumed that in group 1, the increase in thrombus formation is mainly associated with platelet activation, and in group 2, it may be associated with plaque growth. All of the above creates opportunities for a personalized approach to the prevention and treatment of patients with CAD. In particular, antiplatelet therapy requires certain adjustments in the group of patients with HRPR, namely, prescription of additional anti-atherosclerotic drugs or an increase in the dose of antiplatelet agents.

CONCLUSION

It was found that in patients with CAD, the levels of proinflammatory biomarkers (endocan 1 and FABP 4) were elevated compared to the maximum reference values. It was revealed that the concentrations of endocan 1 and PlGF were significantly increased in patients with collagen -induced HRPR. The study revealed the presence of correlations between the increased size of aggregates, the degree of platelet aggregation and the concentrations of proinflammatory biomarkers (endocan 1, PlGF, and FABP 4). At the same time, in patients with HRPR, the concentrations of endocan 1 and PlGF, contributing to plaque growth, were increased, and in patients without HRPR, platelet activation factors FABP 4 and oncostatin M were elevated, which determines various adjustments in therapy for patients of these groups.

REFERENCES

1. Stone G.W., Witzenbichler B., Weisz G., Rinaldi M.J., Neumann F.-J., Metzger D.C. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet*. 2013;382(9892):614–623. DOI: 10.1016/S0140-6736(13)61170-8.
2. Mirzaev K.B., Andreev D.A., Sichev D.A. The evaluation of platelet aggregation in clinical practice. *Rational Pharmacotherapy in Cardiology*. 2015;11(1):85–91 (in Russ.). DOI: 10.20996/1819-6446-2015-11-1-85-91.
3. Trubacheva O.A., Suslova T.E., Gusakova A.M., Kologrivova I.V., Shnaider O.L., Zavadovskij K.V., Petrova I.V. High residual platelet reactivity in patients with coronary heart disease: a new methodological approach to detection. *Bulletin of Siberian Medicine.* 2021;20(2):113–119 (in Russ.). DOI: 10.20538/1682-0363-2021-2-113-119.
4. Barbarash O.L., Komarov A.L., Panchenko E.P., Staroverov I.I., Shakhnovich R.M., Yavelov I.S. Eurasian clinical guidelines for the diagnosis and treatment of acute coronary syndrome without ST elevation. *Eurasian Journal of Cardiology.* 2021;(4):6–59 (in Russ.). DOI: 10.38109/2225-1685-2021-4-6-59.
5. Tariket S., Sut C., Arthaud C.A., Eyraud M.A., Meneveaux A., Laradi S.et al. Modeling the effect of platelet concentrate supernatants on endothelial cells: focus on endocan/ESM-1. *Transfusion.* 2018;58(2):439–445. DOI: 10.1111/trf.14450.
6. Sviridova S.P., Somonova O.V., Kashiya Sh.R., Obukhova O.A., Sotnikov A.V. The role of platelets in inflammation and immunity. *Research'n Practical Medicine Journal.* 2018;5(3):40–52. DOI: 10.17709/2409-2231-2018-5-3-4.
7. Wallace P.M., MacMaster J.F., Rillema J.R., Peng J., Burstein S.A., Shoyab M. Thrombocytopoietic properties of oncostatin M. *Blood.* 1995;86(4):1310–1315. DOI: 10.1182/blood.V86.4.1310.bloodjournal8641310.
8. Fossey S.L., Bear M.D., Kisseberth W.C., Pennell M., London C.A. Oncostatin M promotes STAT3 ctivation, VEGF production, and invasion in osteosarcoma cell lines. *BMC Cancer.* 2011;11:125. DOI: 10.1186/1471-2407-11-125.
9. Smadja D., Gaussem P., Roncal C., Fischer A.M., Emmerich J., Darnige L. Arterial and venous thrombosis is associated with different angiogenic cytokine patterns in patients with antiphospholipid syndrome. *Lupus.* 2010; 19(7):837–843. DOI: 10.1177/0961203309360985.
10. Sharma A., Hijazi Z., Andersson U., Al-Khatib S.M., Lopes R.D., Alexander J.H. Use of biomarkers to predict specific causes of death in patients with atrial fibrillation insights: From the ARISTOTLE trial. *Circulation.* 2018;138(16):1666–1676. DOI: 10.1161/ CIRCULATIONAHA.118.034125.
11. Liu G., Ding M., Chiuve S.E., Rimm E.B., Franks P.W., Meigs J.B. et al. 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.* 2016;6(11):2259–2267. DOI:nm10.1161/ATVBAHA.116.308320.
12. Rodríguez-Calvo R., Girona J., Alegret J., Bosquet A., Ibarretxe D., Masana L. Role of the fatty acid-binding protein 4 in heart failure and cardiovascular disease. *Journal of Endocrinology.* 2017;233(3):173–184. DOI: 10.1530 /JOE-17-0031.
13. Balta S., Balta I., Mikhailidis D. Endocan: a new marker of endothelial function. *Curr. Opin. Cardiol.* 2021; 36(4):462–468. DOI: 10.1097/HCO.0000000000000867.
14. Kral J.B., Schromaier W.C., Salzmann M., Assinger A. Platelet Interac on with Innate Immune Cells. *Transfus Med Hemother.* 2016; 43(2):78–88. DOI: 10.1159/000444807.
15. Abdurahmanov Z.M., Umarov B.Ja., Abdurahmanov M.M. Modern biomarkers of endothelial dysfunction in cardiovascular diseases. *Rational Pharmacotherapy in Cardiology.*

2021;17(4):612-618 (in Russ.). DOI: 10.20996/1819-6446-2021- 08-08.
16. Trojnar M., Patro-Małysza J., Kimber-Trojnar Ż., Leszczyńska-Gorzelak B, Mosiewicz J. Associations between Fatty Acid-Binding Protein 4–A Proinflammatory Adipokine and Insulin Resistance, Gestational and Type 2 Diabetes Mellitus. *Cells.* 2019; 8(3):227. DOI: 0.3390/cells8030227.
17. Ray D.M., Spinelli S.L., O'Brien J.J., Blumberg N., Phipps R.P. Platelets as a novel target for PPARgamma ligands: implications for inflammation, diabetes, and cardiovascular disease. *Bio. Drugs.* 2006; 20(4):231-41. DOI: 10.2165/00063030-200620040-00004.
18. Tulikov M.V., Shevchenko O.P., Shevchenko A.O., Gagaev A.V., Pavlov V.V., Ginzburg L.M. Placental growth factor in the diagnosis and prognosis of the course of coronary heart disease. *Bulletin of Pirogov National Medical and Surgical Center*. 2012; 7(3):86-89 (in Russ.). DOI: 10.17650/1818-8338-2012-3-4-28-32.
19. Li Y., Sun L., Zheng X., Liu J., Zheng R., Lv Y. The clinical value of platelet parameters combined with sFlt-1/PlGF in predicting preeclampsia. *Ann Palliat Med*. 2021; 10(7):7619-7626. DOI:10.21037/apm-21-1244.
20. Feng Y., Ye D., Wang Z., Pan H., Lu X., Wang M. et al. The role of interleukin-6 family members in cardiovascular diseases. *Front. Cardiovasc. Med.* 2022;9:818890. DOI: 10.3389/fcvm.2022.818890.
21. Huo Y., Schober A., Forlow S.B., Smith D.F., Hyman M.C., Jung S. et al., Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein e. *Nat. Med*. 2003;9(1):61–67. DOI: 10.1038/nm810.
22. Klingenberg R., Aghlmandi S., Räber L., Gencer B., Nanchen D., Heg D. et al. Improved risk stratification of patients with acute coronary syndromes using a combination of hsT-nT, NT-proBNP and hsCRP with the GRACE score. *Eur. Heart J. Acute Cardiovasc. Care.* 2018;7(2):129–138. DOI: 10.1177/2048872616684678.

Authors' contribution

Petrova I.V., Kovalev I.V. – critical revision of the manuscript for important intellectual content, approval of the manuscript for publication. Trubacheva O.A., Vasiliev V.N. – conception and design, interpretation and analysis of the data, drafting of the manuscript. Yakimovich I.Yu., Kologrivova I.V. – justification of the manuscript. Trubacheva O.A., Schneider O.L – carrying out of the experiment.

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