ЭОТАКСИН И СЕРДЕЧНО-ЛОДЫЖЕЧНЫЙ СОСУДИСТЫЙ ИНДЕКС У ПАЦИЕНТОВ ВЫСОКОГО И ОЧЕНЬ ВЫСОКОГО СЕРДЕЧНО-СОСУДИСТОГО РИСКА

Кравченко Е.С., Суслова Т.Е., Кологривова И.В., Кошельская О.А.

Научно-исследовательский институт кардиологии – филиал ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия

Резюме. Эотаксин – хемокин, который является хемоаттрактантом преимущественно для эозинофилов, а также базофилов и Th2-лимфоцитов. По данным исследований, сверхэкспрессия эотаксина обнаружена в эндотелиальных и гладкомышечных клетках сосудов в области атеросклеротической бляшки. В клинической медицине широко используется сердечно-лодыжечный сосудистый индекс (CAVI) как индикатор артериосклероза и предиктор сердечно-сосудистых событий. В немногочисленных исследованиях показана взаимосвязь содержания эотаксина с наличием коронарного атеросклероза, тогда как в других исследованиях не было установлено ассоциации содержания в крови эотаксина с атеросклерозом, инфарктом миокарда и скоростью пульсовой волны. Целью настоящего исследования является оценка уровня эотаксина в крови и сердечно-лодыжечного сосудистого индекса и их ассоциация с основными кардиоваскулярными факторами риска у пациентов высокого и очень высокого сердечно-сосудистого риска. Было обследовано 65 пациентов высокого и очень высокого сердечно-сосудистого риска, обусловленного документированной ишемической болезнью сердца, сахарным диабетом 2-го типа или сочетанием кардиоваскулярных факторов риска, и находящихся на общепринятой кардиоактивной, сахароснижающей и липидснижающей терапии. Всем пациентам выполнено исследование эластических свойств сосудистой стенки методом объемной сфигмографии с оценкой индекса CAVI. В крови определяли концентрацию эотаксина, высокочувствительного С-реактивного белка, гликозилированного гемоглобина и показателей липидного спектра. Все обследованные были разделены на две группы: с нормальным значением CAVI (менее 8) и повышенным. Пациенты с повышенным CAVI имели более высокие концентрации эотаксина ($p = 0,013$), общего холестерина ($p = 0,009$), холестерина липопротеинов низкой плотности ($p = 0,016$), а также были старше ($p < 0,0001$) и реже принимали статины ($p = 0,002$). У всех обследованных были выявлены корреляции между концентрацией эотаксина в сыворотке крови и CAVI ($r_s = 0,34$; $p = 0,005$), а также возрастом ($r_s = 0,32$; $p = 0,006$). Возраст пациентов коррелировал с CAVI ($r_s = 0,35$; $p = 0,007$). Таким образом, в нашем исследовании мы впервые показали взаимосвязь высоких концентраций эотаксина с повышенным сердечно-лодыжечным сосудистым индексом у пациентов высокого и очень высокого сердечно-сосудистого риска. Сердечно-лодыжечный сосудистый индекс был ассоциирован

Адрес для переписки:

Кравченко Елена Сергеевна
Научно-исследовательский институт кардиологии
634012, Россия, г. Томск, ул. Киевская, 111а.
Тел.: 8 (923) 412-00-64.
E-mail: nikonovaes@gmail.com

Address for correspondence:

Elena S. Kravchenko
Research Institute of Cardiology
111a Kievskaya St
Tomsk
634012 Russian Federation
Phone: +7 (923) 412-00-64.
E-mail: nikonovaes@gmail.com

Образец цитирования:

Е.С. Кравченко, Т.Е. Суслова, И.В. Кологривова, О.А. Кошельская «Эотаксин и сердечно-лодыжечный сосудистый индекс у пациентов высокого и очень высокого сердечно-сосудистого риска» // Медицинская иммунология, 2023. Т. 25, № 4. С. 971-976.
doi: 10.15789/1563-0625-EAC-2768

For citation:

E.S. Kravchenko, T.E. Suslova, I.V. Kologrivova, O.A. Koshelskaya "Eotaxin and cardio-ankle vascular index in patients with high and very high cardiovascular risk", Medical Immunology (Russia)/Meditsinskaya Immunologiya, 2023, Vol. 25, no. 4, pp. 971-976.
doi: 10.15789/1563-0625-EAC-2768

DOI: 10.15789/1563-0625-EAC-2768

с возрастом, с показателями липидного обмена и наличием липиднижающей терапии. Полученные результаты позволяют рассматривать эотаксин как фактор, связанный с атерогенезом и артериальной жесткостью.

Ключевые слова: эотаксин, хемокины, артериальная жесткость, сердечно-лодыжечный сосудистый индекс, атеросклероз, факторы риска сердечно-сосудистых заболеваний

EOTAXIN AND CARDIO-ANKLE VASCULAR INDEX IN PATIENTS WITH HIGH AND VERY HIGH CARDIOVASCULAR RISK

Kravchenko E.S., Suslova T.E., Kologrivova I.V., Koshelskaya O.A.

Research Institute of Cardiology, Branch of Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russian Federation

Abstract. Eotaxin is a chemokine, which is a chemoattractant mainly to eosinophils, as well as basophils and Th2 lymphocytes. According to studies, overexpression of eotaxin is found in endothelial and smooth muscle cells of blood vessels in the area of atherosclerotic plaque. In clinical medicine, cardio-ankle vascular index (CAVI) is widely used as an indicator of arteriosclerosis and a predictor of cardiovascular events. Few studies have shown the relationship of eotaxin with coronary atherosclerosis; in other studies, the relationship of eotaxin with atherosclerosis, myocardial infarction and pulse wave velocity was not revealed. The aim of the present study was to assess blood level of eotaxin and cardio-ankle vascular index and their association with major cardiovascular risk factors in patients with high and very high cardiovascular risk. We examined 65 patients with high and very high cardiovascular risk, due to documented coronary artery disease, type 2 diabetes mellitus, or combination of cardiovascular risk factors and who were undergoing generally accepted cardioactive, hypoglycemic therapy and lipid-lowering therapy. All patients were examined for the elastic properties of the vascular wall by volumetric sphygmography with assessment of CAVI. In the blood, the concentrations of eotaxin, high-sensitivity C-reactive protein, glycosylated hemoglobin and lipid spectrum indicators were determined. All examined were divided into two groups: with a normal value of CAVI (less than 8) and elevated. Patients with elevated CAVI had higher concentrations of eotaxin ($p = 0.013$), total cholesterol ($p = 0.009$), low-density lipoprotein cholesterol ($p = 0.016$), were older ($p < 0.0001$) and less likely to take statins ($p = 0.002$). In all those examined, correlations were found between serum eotaxin concentration and CAVI ($r_s = 0.34$; $p = 0.005$), as well as age ($r_s = 0.32$; $p = 0.006$). The age of the patients correlated with CAVI ($r_s = 0.35$; $p = 0.007$). Thus, in our study, we for the first time showed the relationship between higher concentrations of eotaxin and an increased cardio-ankle vascular index in patients with high and very high cardiovascular risk. Cardio-ankle vascular index was associated with age, lipid metabolism and lipid-lowering therapy. The obtained results allow us to consider eotaxin as a factor associated with atherogenesis and arterial stiffness.

Keywords: eotaxin, chemokines, arterial stiffness, cardio-ankle vascular index, atherosclerosis, risk factors for cardiovascular disease

The work was conducted within the framework of fundamental scientific research No. 122020300043-1 "Molecular cellular mechanisms of development of cardiovascular diseases of ischemic and non-ischemic genesis. Fundamental aspects of the implementation of organoprotective effects of therapeutic interventions".

Introduction

Chemokines are a class of low-molecular cytokines that can induce directed chemotaxis of immune system cells, smooth muscle cells, fibroblasts, and other body cells in response to the activation of receptors associated with G-protein. However, the biological activity of chemokines is not limited to the stimulation of chemotaxis. Stimulation of chemokine receptors can affect proliferation, differentiation, degranulation, respiratory burst in cells; has an effect on vascular permeability and angiogenesis [5]. Eotaxin (CC chemokine ligand 11, CCL11) is a chemokine of class CC, which is a chemoattractant predominantly to eosinophils, as well as basophils and Th2 lymphocytes, activating CCR3 receptors [2, 7]. The detected overexpression of CCR3 and eotaxin mRNA in human atherosclerotic plaques indicates the role of this chemokine in vascular inflammation and atherosclerotic process [4].

In mouse smooth muscle cell culture, eotaxin has been shown to be a potent chemotactic factor for smooth muscle cells, capable of regulating their migration to the atherosclerotic plaque region [7]. Eotaxin has also been found to stimulate the calcification of smooth muscle cells [9]. On the other hand, other studies have found no association between eotaxin levels and the presence of coronary atherosclerosis or prior myocardial infarction [1, 8]. The relationship of eotaxin with such risk factors for cardiovascular diseases as obesity and smoking has been established [3, 10, 14]. Cell culture studies show that increased expression of eotaxin plays a role in vascular inflammation and atherosclerotic process by increasing endothelial permeability, migration and calcification of smooth muscle cells in the presence of reactive oxygen intermediates [10].

At the present time, the importance of assessing vascular stiffness as an indicator of arteriosclerosis and a predictor of cardiovascular events has been demonstrated. For the past fifteen years, cardio-ankle vascular index (CAVI) has been widely used in clinical medicine to assess the risk of cardiovascular disease. As a marker of arterial stiffness, CAVI has a number of advantages over other methods, namely, it is easy to measure, has high reproducibility, reflects the stiffness of the entire aorta, femoral, popliteal and tibial arteries, allows you to assess the vascular age, to control the dynamics of treatment and the effectiveness of lifestyle changes, and to evaluate the severity of atherosclerotic process, and it is less dependent on blood pressure than pulse wave velocity [6, 12, 13].

Few studies have shown the relationship of eotaxin with coronary atherosclerosis; in the other studies, the relationship of eotaxin with atherosclerosis, myocardial infarction and such a marker of vascular stiffness as pulse wave velocity was not revealed.

The aim of the present study was to assess blood level of eotaxin and cardio-ankle vascular index and their association with major cardiovascular risk factors in patients with high and very high cardiovascular risk.

Materials and methods

We examined 65 patients aged 41-70 years, 29 men and 36 women. 86% of the surveyed were diagnosed with coronary artery disease, 97% were diagnosed with arterial hypertension, and 54% were diagnosed with type 2 diabetes mellitus. At the time of the study, all patients were undergoing generally accepted cardioactive and hypoglycemic therapy. Statins were taken by 62% of those examined. The study did not include patients with acute coronary syndrome, persistent atrial fibrillation, acute infectious diseases, allergic and autoimmune diseases, or oncological diseases. All the procedures and tests were conducted in accordance with the guidelines of the Declaration of Helsinki and "Rules of Clinical Practice in the Russian Federation", approved by the Order of the Ministry of Health of the Russian Federation. The study's protocol was approved by the Biomedical Ethics Committee of Cardiology Research Institute, Tomsk NRMC (protocol No. 210 from February 18, 2021). All the patients recruited into the study signed an informed consent.

All patients underwent a study of the elastic properties of the vascular wall by volumetric sphygmography on the VaSera VS-1000 device (Fukuda Denshi, Japan) with an assessment of cardio-ankle vascular index on the right and on the left and calculation of the average cardio-ankle index. In whole blood, the concentration of glycosylated hemoglobin A_{1C} (HbA_{1C}) was determined by the immunoturbidimetric method (DiaSys, Germany). The concentration of total cholesterol (TCH) and triglycerides (TG) was determined by the colorimetric enzymatic method (DiaSys, Germany). To determine the cholesterol of high-density lipoproteins (HDL), a combined method without precipitation was used (DiaSys, Germany); the concentration of low-density lipoprotein (LDL) cholesterol was calculated using Friedwald's formula. High-sensitivity C-reactive protein (hsCRP) was determined in the blood serum by enzyme-linked immunoassay (Vector-Best, Russia).

Eotaxin concentration was measured with Human Cytokines/Chemokines-38 kit using multiplex instrument FLEXMAP 3D (Luminex Corporation) and MILLIPLEX Analyst 5.1 software (Merck KGaA, Milliplex; Darmshdadt), the Core Facility "Medical genomics", Tomsk NRMC.

All examined were divided into two groups: with a normal value of cardio-ankle vascular index (less than 8) and elevated (more than 8).

The results were statistically processed using the STATISTICA 10.0 software package (StatSoft Inc., USA). The compliance of the law of distribution of variables with the normal one was checked using the Shapiro-Wilk test. Since the distributions of all variables were non-normal, the results are presented as median and interquartile interval: Me ($Q_{0.25}$-$Q_{0.75}$). Qualitative variables are presented as absolute and relative frequencies. The Mann–Whitney test was used to compare the groups. Qualitative variables were compared using Fisher's exact test. Correlation relationships were assessed using the Spearman rank coefficient (r_s). The critical significance level (p) was assumed to be 0.05.

Results and discussion

Patients with elevated CAVI were older. Higher concentrations of total cholesterol and low-density lipoprotein cholesterol in patients with elevated CAVI were consistent with rarer statin intake (Table 1).

TABLE 1. CHARACTERISTICS OF THE EXAMINED PATIENTS DEPENDING ON THE LEVEL OF CARDIO-ANKLE VASCULAR INDEX

Indicator	CAVI < 8 n = 23	CAVI ≥ 8 n = 42	p
CAVI	7.3 (6.90-7.45)	9.1 (8.6-9.8)	0.000
Eotaxin, pg/mL	60.84 (46.28-98.66)	93.09 (63.19-139.43)	0.013
Age, years	54 (50-59)	65 (56-67)	0.000
Men, n (%)	10 (43.5)	19 (45.2)	0.550
Smoking, n (%)	7 (30.4)	14 (33.3)	0.519
Patients with coronary artery disease, n (%)	19 (82.6)	37 (88.1)	0.397
Coronary artery disease, years	1 (0.5-4.0)	2 (0.5-5.0)	0.169
Patients with hypertension, n (%)	22 (95.7)	41 (97.6)	0.586
Hypertension duration, years	10 (5-20)	10 (5-17)	0.951
Patients with diabetes mellitus type 2, n (%)	12 (52.2)	23 (54.8)	0.523
Duration of diabetes mellitus type 2, years	0.5 (0-9)	1 (0-10)	0.995
Body mass index, kg/m^2	30.4 (29.1-34.7)	30.9 (28.3-33.3)	0.600
Waist-to-hip ratio	0.95 (0.88-0.98)	0.97 (0.93-1.02)	0.259
Systolic blood pressure, mm Hg	120 (110-130)	129 (120-140)	0.061
Diastolic blood pressure, mm Hg	80 (75-80)	80 (70-82)	0.433
Statin intake, n (%)	20 (86.9)	20 (47.6)	0.002
HbA_{1C}, %	6.0 (5.2-7.7)	6.8 (5.7-7.7)	0.195
TCH, mmol/L	3.85 (3.24-5.03)	5.08 (4.33-5.44)	0.009
TG, mmol/L	1.40 (1.03-1.96)	1.37 (1.13-1.92)	0.908
LDL, mmol/L	2.21 (1.77-2.90)	3.06 (2.29-3.74)	0.016
hsCRP, mg/L	2.37 (1.35-3.61)	1.92 (1.01-3.94)	0.802

In all those examined, correlations were found between serum eotaxin concentration and CAVI, as well as age (Figure 1). The age of the patients correlated with CAVI ($r_s = 0.35$; $p = 0.007$).

Of all the cardiovascular risk factors studied, the eotaxin in the present study was associated only with age and the arterial stiffness score, CAVI. CAVI, in turn, was associated with age, the state of lipid metabolism and lipid-lowering therapy, which is consistent with other studies [6, 11, 12, 13].

Age is a significant predictor of cardiovascular risk. Depending on the ratio of chronological age and biological age, the concept of early vascular aging (EVA) and normal (healthy) vascular aging was proposed [12]. In 2019, leading experts in the study of vascular stiffness confirmed the hypothesis that

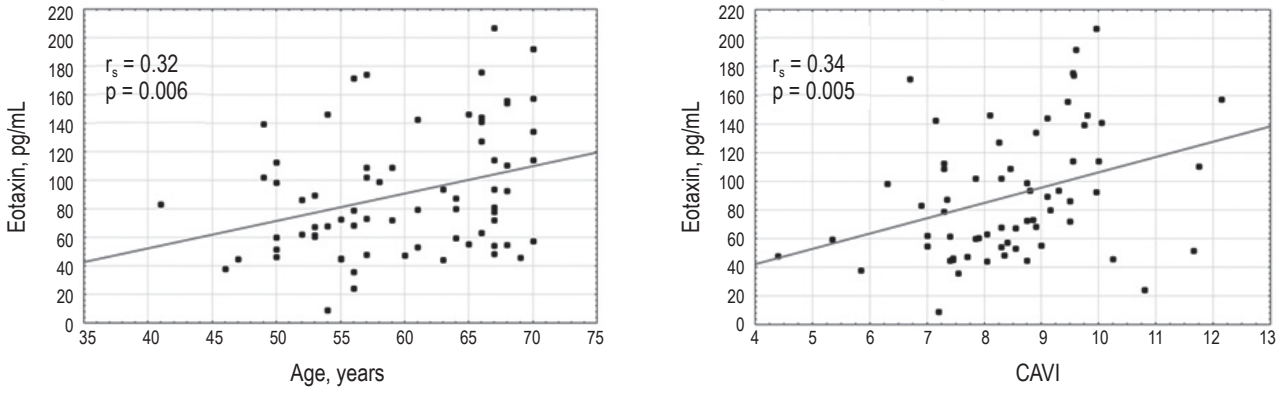

Figure 1. Correlations of eotaxin concentration in the blood with age and cardio-ankle vascular index

arterial stiffness is the best indicator of the combined action of known and unknown risk factors for damage to the arterial wall, and proposed to express very high and very low arterial stiffness in terms of EVA and SUPERNOVA (supernormal vascular aging). Patients with the SUPERNOVA phenotype have extremely low vascular stiffness for their age and sex. The plasticity of vascular smooth muscle cells plays an important role in increasing blood pressure not only by regulating the interaction of actomyosin for contraction, but also by participating in the homeostasis of the cell-extracellular matrix and is very important for the physiology of normal and early vascular aging [11].

The activation of CCR3 receptors and increased expression of eotaxin in case of injury can stimulate the migration of vascular smooth muscle cells from the media of the artery to the intima. This migration and subsequent proliferation of smooth muscle cells in the intima leads to intimal hyperplasia and narrowing of the clearance [7]. Eotaxin promotes the formation of reactive oxygen intermediates through the activation of NADPH oxidase, which leads to transdifferentiation of vascular smooth muscle cells and an increase in the rate of calcification [9]. As chemokine, eotaxin can not only promote inflammation, but also maintain it, due to its chemotactic effect on the endothelial cells of human vessels [2]. As a result, influencing the cells of all layers of the artery wall, eotaxin can affect arterial stiffness.

Conclusion

Thus, in our study, we showed the relationship between higher concentrations of eotaxin and an increased cardio-ankle vascular index in patients with high and very high cardiovascular risk. Cardio-ankle vascular index was associated with age, lipid metabolism and lipid-lowering therapy. The obtained results allow us to consider eotaxin as a factor associated with atherogenesis and arterial stiffness.

References

1. Castillo L., Rohatgi A., Ayers C.R., Owens A.W., Das S.R., Khera A., McGuire D.K., de Lemos J.A. Associations of four circulating chemokines with multiple atherosclerosis phenotypes in a large population-based sample: results from the dallas heart study. *J. Interferon Cytokine Res., 2010, Vol. 30, no. 5, pp. 339-347.*

2. Emanuele E., Falcone C., D'Angelo A., Minoretti P., Buzzi M.P., Bertona M., Geroldi D. Association of plasma eotaxin levels with the presence and extent of angiographic coronary artery disease. *Atherosclerosis, 2006, Vol. 186, no. 1, pp. 140-145.*

3. Grievink H.W., Smit V., Huisman B.W., Gal P., Yavuz Y., Klerks C., Binder C.J., Bot I., Kuiper J., Foks A.C., Moerland M. Cardiovascular risk factors: The effects of ageing and smoking on the immune system, an observational clinical study. *Front. Immunol., 2022, Vol. 13, 968815.* doi:10.3389/fimmu.2022.968815.

4. Haley K.J., Lilly C.M., Yang J.H., Feng Y., Kennedy S.P., Turi T.G., Thompson J.F., Sukhova G.H., Libby P., Lee R.T. Overexpression of eotaxin and the CCR3 receptor in human atherosclerosis: using genomic technology to identify a potential novel pathway of vascular inflammation. *Circulation, 2000, Vol. 102, no. 18, pp. 2185-2189.*

5. Hughes C.E., Nibbs R.J.B. A guide to chemokines and their receptors. *FEBS J., 2018, Vol. 285, no. 16, pp. 2944-2971.*

6. Kaveshnikov V.S., Trubacheva I.A., Serebryakova V.N. Analysis of factors associated with arterial stiffness in the general working-age population. *Russian Journal of Cardiology, 2022, Vol. 27, no. 5, pp. 64-70.* (In Russ.)

7. Kodali R.B., Kim W.J., Galaria I.I., Miller C., Schecter A.D., Lira S.A., Taubman M.B. CCL11 (Eotaxin) induces CCR3-dependent smooth muscle cell migration. *Arterioscler. Thromb. Vasc. Biol., 2004, Vol. 24, no. 7, pp. 1211-1216.*

8. Mosedale D.E., Smith D.J., Aitken S., Schofield P.M., Clarke S.C., McNab D., Goddard H., Gale C.R., Martyn C.N., Bethell H.W., Barnard C., Hayns S., Nugent C., Panicker A., Grainger D.J. Circulating levels of MCP-1 and eotaxin are not associated with presence of atherosclerosis or previous myocardial infarction. *Atherosclerosis, 2005, Vol. 183, no. 2, pp. 268-274.*

9. Raghuraman G., Hsiung J., Zuniga M.C., Baughman B.D., Hitchner E., Guzman R.J., Zhou W. Eotaxin augments calcification in vascular smooth muscle cells. *J. Cell. Biochem., 2017, Vol. 118, no. 3, pp. 647-654.*

10. Rastogi T., Girerd N., Lamiral Z., Bresso E., Bozec E., Boivin J.M., Rossignol P., Zannad F., Ferreira J.P. Impact of smoking on cardiovascular risk and premature ageing: Findings from the STANISLAS cohort. *Atherosclerosis, 2022, Vol. 346, pp. 1-9.*

11. Rotar O.P., Tolkunova K.M. EVA and SUPERNOVA concepts of vascular aging: ongoing research on damaging and protective risk factors. *Arterial Hypertension, 2020, Vol. 26, no. 2, pp. 133-145.* (In Russ.)

12. Saiki A., Ohira M., Yamaguchi T., Nagayama D., Shimizu N., Shirai K., Tatsuno I. New horizons of arterial stiffness developed using Cardio-Ankle Vascular Index (CAVI). *J. Atheroscler. Thromb., 2020, Vol. 27, no. 8, pp. 732-748.*

13. Sumin A.N., Shcheglova A.V. Assessment of arterial stiffness using the cardio-ankle vascular index – what we know and what we strive for. *Rational Pharmacotherapy in Cardiology, 2021, Vol. 17, no. 4, pp. 619-627.* (In Russ.)
14. Vasudevan A.R., Wu H., Xydakis A.M., Jones P.H., Smith E.O., Sweeney J.F., Corry D.B., Ballantyne C.M. Eotaxin and obesity. *J. Clin. Endocrinol. Metab., 2006, Vol. 91, no. 1, pp. 256-261.*

Авторы:

Кравченко Е.С. *— младший научный сотрудник отделения клинической лабораторной диагностики, Научно-исследовательский институт кардиологии — филиал ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия*

Суслова Т.Е. *— к.м.н., руководитель отделения клинической лабораторной диагностики, Научно-исследовательский институт кардиологии — филиал ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия*

Кологривова И.В. *— к.м.н., старший научный сотрудник отделения клинической лабораторной диагностики, Научно-исследовательский институт кардиологии — филиал ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия*

Кошельская О.А. *— д.м.н., профессор, ведущий научный сотрудник отделения атеросклероза и хронической ишемической болезни сердца, Научно-исследовательский институт кардиологии — филиал ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия*

Authors:

Kravchenko E.S., *Junior Research Associate, Department of Clinical Laboratory Diagnostics, Research Institute of Cardiology, Branch of Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russian Federation*

Suslova T.E., *PhD (Medicine), Head, Department of Clinical Laboratory Diagnostics, Research Institute of Cardiology, Branch of Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russian Federation*

Kologrivova I.V., *PhD (Medicine), Senior Research Associate, Department of Clinical Laboratory Diagnostics, Research Institute of Cardiology, Branch of Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russian Federation*

Koshelskaya O.A., *PhD, MD (Medicine), Professor, Leading Research Associate, Department of Atherosclerosis and Coronary Artery Disease, Research Institute of Cardiology, Branch of Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russian Federation*

Поступила 14.04.2023
Отправлена на доработку 18.04.2023
Принята к печати 20.04.2023

Received 14.04.2023
Revision received 18.04.2023
Accepted 20.04.2023