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Association of Metabolic and Inflammatory Molecule Levels and Post-COVID Syndrome of Varying Severity

Karaseva A.A., Afanaseva A.D., Garbuzova E.V., Kashtanova E.V., Polonskaya Ya.V., Stakhneva E.M., Shramko V.S., Shcherbakova L.V., Logvinenko I.I., Ragino Yu.I.

Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences
175/1 Boris Bogatkov St., 630089 Novosibirsk, Russian Federation

ABSTRACT

Aim. To study the associations of the levels of metabolic and inflammatory molecules and the severity of post-COVID syndrome (PCS) in COVID-19 convalescents.

Materials and methods. The observational cross-sectional study included 270 individuals aged 18–84 who were COVID-19 convalescents, including 191 patients with PCS of whom 97 patients had mild PCS and 94 had moderate PCS. Serum concentrations of metabolic and inflammatory molecules were determined using enzyme-linked immunosorbent assay (ELISA), including: alpha interferon (IFN-α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), interleukin 8 (IL-8), monocyte chemoattractant protein 1 (MCP-1), insulin, C-peptide, and high-sensitivity C-reactive protein (hs-CRP).

Results. In COVID-19 convalescents with PCS of varying severity, the level of IL-6 was 1.3 times higher than in individuals without PCS. Among men with PCS, the levels of IL-6, MCP-1, and hs-CRP were 1.5, 1.2 and 1.9 times higher, respectively, compared with men without PCS. In men with moderate PCS, the level of IL-6 was 1.9 times higher and hs-CRP was 1.7 times higher than in men without PCS. The risk of having moderate PCS in COVID-19 convalescents was directly associated with the concentration of C-peptide in the blood. In men, the risk of having PCS was directly associated with the concentration of hs-CRP in the blood.

Conclusion. In COVID-19 convalescents, the risk of having moderate PCS is directly associated with the level of C-peptide in the blood. In men, the risk of having PCS is directly associated with the level of hs-CRP in the blood.

Keywords: post-COVID syndrome, interleukin-6, C-peptide, high-sensitivity C-reactive protein

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest associated with the publication of this article.

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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 local Ethics Committee of the Research Institute of Internal and Preventive Medicine, a branch of the Institute of Cytology and Genetics (Minutes No. 10 dated November 10, 2020).

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✉ *Karaseva Alexandra A.,* Sas96@bk.ru

Ассоциации уровней метаболических и воспалительных молекул и постковидного синдрома разной степени тяжести

Карасева А.А., Афанасьева А.Д., Гарбузова Е.В., Каштанова Е.В., Полонская Я.В., Стахнёва Е.М., Шрамко В.С., Щербакова Л.В., Логвиненко И.И., Рагино Ю.И.

Научно-исследовательский институт терапии и профилактической медицины – филиал Федерального исследовательского центра «Институт цитологии и генетики Сибирского отделения Российской академии наук» (НИИТПМ – филиал ИЦиГ СО РАН)
Россия, 630089, г. Новосибирск, ул. Бориса Богаткова, 175/1

РЕЗЮМЕ

Цель. Изучить ассоциации уровней метаболических и воспалительных молекул и постковидного синдрома (ПКС) разной степени тяжести у реконвалесцентов коронавирусной инфекции (COVID-19).

Материалы и методы. В обсервационное одномоментное исследование были включены 270 человек, возраст 18–84 года, являющихся реконвалесцентами COVID-19, в том числе с наличием ПКС – 191 пациент, из которых с легкой степенью тяжести ПКС – 97 человек, а со средней степенью тяжести ПКС – 94 человека. У всех пациентов в сыворотке крови методом иммуноферментного анализа (ИФА) определяли концентрации метаболических и воспалительных молекул: интерферона альфа (ИФН-α), интерлейкина 1бета (ИЛ-1β), интерлейкина 6 (ИЛ-6), интерлейкина 8 (ИЛ-8), моноцитарного хемотаксического фактора 1 (МСР-1), инсулина, С-пептида, высокочувствительного С-реактивного белка (вчСРБ).

Результаты. У реконвалесцентов COVID-19 с ПКС разной степени тяжести уровень ИЛ-6 был выше в 1,3 раза, чем у лиц без ПКС. Среди мужчин с ПКС уровень ИЛ-6 был выше в 1,5 раза, МСР-1 – в 1,2, вчСРБ – в 1,9 раза, чем у мужчин без ПКС. Среди мужчин с ПКС средней степени тяжести уровень ИЛ-6 был выше в 1,9 раза, уровень вчСРБ – в 1,7 раза, чем у мужчин без ПКС. Шанс наличия ПКС средней степени тяжести у реконвалесцентов COVID-19 прямо ассоциирован с концентрацией в крови С-пептида. У мужчин шанс наличия ПКС прямо ассоциирован с концентрацией в крови вчСРБ.

Заключение. У реконвалесцентов COVID-19 шанс наличия ПКС средней степени тяжести прямо ассоциирован с уровнем в крови С-пептида. У мужчин шанс наличия ПКС прямо ассоциирован с уровнем вчСРБ в крови.

Ключевые слова: постковидный синдром, интерлейкин-6, С-пептид, высокочувствительный С-реактивный белок

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

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INTRODUCTION

After an acute period of novel coronavirus infection (COVID-19), 41.7% of patients [1] develop various symptoms. In October 2021, the World Health Organization (WHO) developed a definition characterizing this condition, known as post-COVID condition or post-COVID syndrome (PCS): a condition after COVID-19 that occurs in individuals with a history of suspected or confirmed SARS-CoV-2 infection, usually starting 3 months after the initial COVID-19 infection, with symptoms that last at least 2 months that cannot be explained by another diagnosis [2]. PCS is characterized by multiple organ damage of varying severity and can lead to serious complications. In clinical practice, this category of patients is increasingly experiencing both the development of new diseases and the progression of existing chronic diseases after infection.

Chronic inflammation is a hallmark of PCS and is believed to contribute to many symptoms. The study of the exact mechanisms that cause long-term inflammation after COVID-19 is a matter of scientific interest. Currently, it is believed that several factors play a role in the development of chronic inflammation in PCS: immune dysregulation, impaired hemostasis, prolonged persistence of the virus after convalescence, and autoimmune reactions.

Existing data indicate the high prognostic value of certain cytokines, inflammatory and metabolic markers in the acute phase of COVID-19 determining the risk of severe disease and death in patients. It is likely that the mechanisms underlying the development of long-term manifestations of the post-COVID period lead to chronic inflammation due to a long-term increase in the level of pro-inflammatory molecules with aberrant immunity.

Studies of metabolic and inflammatory molecules in the context of PCS are relevant and important, since it is necessary to understand whether they retain their high predictive significance regarding both the development of PCS and the severity of its course. The study of changes in the levels of metabolic and inflammatory molecules and their associations with PCS opens up opportunities for the development of new methods for the prevention and treatment of patients with long-term symptoms in the post-COVID period.

The aim of this study was to investigate the associations of levels of metabolic and inflammatory molecules and PCS of varying severity in COVID-19 convalescents.

MATERIALS AND METHODS

The single-stage observational study was conducted at the Research Institute of Internal and Preventive Medicine in 2020–2021. The study included 270 people (48.1% men, average age 53.2±13.2 years) who were convalescents of COVID-19. Inclusion criteria were as follows: the presence of COVID-19, confirmed by a positive analysis of SARS-CoV-2 coronavirus RNA by polymerase chain reaction (PCR) during the disease and/or the presence of IgG antibodies to SARS-CoV-2 coronavirus; two months after convalescence.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee of the Research Institute of Internal and Preventive Medicine, a branch of the Institute of Cytology and Genetics (Minutes No. 10 dated November 10, 2020). All patients gave their informed consent to participate in the study.

All patients were divided into four groups based on the presence or absence of PCS and its severity (mild or moderate), which were determined according to the criteria published earlier in a systematic review [3].

Group 1 included 79 people without PCS, group 2 included 191 people with PCS, group 3 included 97 people with mild PCS, and group 4 included 94 people with moderate PCS. The enzyme-linked immunosorbent assay (ELISA) with Vector-Best kits (Russia) was used to determine the levels of metabolic and inflammatory molecules, interferon alpha (IFN-a), interleukin 1beta (IL-1beta), interleukin 6 (IL-6), and interleukin 8 (IL-8), monocyte chemotactic factor 1 (MCP-1), insulin, C-peptide, high-sensitivity C-reactive protein (hs-CRP) in blood serum.

Statistical processing of the obtained results was performed using the SPSS software package. The normality of the distribution of continuous features was checked using the Kolmogorov–Smirnov test. Due to the nonparametric distribution of quantitative data, the median interquartile range $Me\ [Q_{25};\ Q_{75}]$ was used. The statistical significance of the differences in quantitative indicators in the two groups was assessed using the nonparametric Mann–Whitney test. In cases where the number of groups was more than two, the Kruskal–Wallis test and Dunn's test, a nonparametric multiple-comparison procedure, were used. Associative relationships were studied using univariate and multifactorial logistic regression models. The results are presented as the odds ratio (OR) and the 95% confidence interval (CI) for OR. When testing statistical hypotheses, the critical level

of significance was at $p < 0.05$.

RESULTS

A comparative analysis of the concentrations of the studied metabolic and inflammatory molecules in patients of four groups is presented in Table 1. In patients with both mild and moderate PCS, the blood level of IL-6 was 1.3 times higher than in people without PCS.

Among men with PCS, the blood level of IL-6 was 1.5 times higher, MCP-1 was 1.2 times higher, and hs-CRP was 1.9 times higher than in men without PCS (Table 2). In men with moderate PCS, the blood levels of IL-6 and hs-CRP were 1.9 and 1.7 times higher than in men without PCS, respectively. The level of hs-CRP was also statistically significantly 2.1 times higher in men with mild PCS compared with men without PCS.

A similar analysis in women showed no statistically significant differences in the levels of the studied metabolic and inflammatory molecules in these subgroups.

Table 1

Variability of the Levels of Studied Metabolic and Inflammatory Molecules in COVID-19 Convalescents Depending on the PCS Presence and Severity, *Me* [Q_{25}; Q_{75}]

Parameter	Group 1, no PCS $n = 79$	Group 2, with PCS $n = 191$	Group 3, mild PCS $n = 97$	Group 4, moderate PCS $n = 94$	p
IFN-a, pg/mL	0.82 [0.34;4.06]	1.05 [0.27;4.80]	1.09 [0.27;4.08]	1.05 [0.41;5.03]	$p_{1-2} = 0.312$ $p_{1-3} = 0.383$ $p_{1-4} = 0.333$
IL-1b, pg/mL	2.06 [1.28;3.27]	2.42 [1.41;3.51]	2.56 [1.38;3.76]	2.11 [1.51;3.26]	$p_{1-2} = 0.507$ $p_{1-3} = 0.273$ $p_{1-4} = 0.977$
IL-6, pg/mL	2.10 [1.35;3.08]	2.76 [1.73;4.43]	2.80 [1.79;4.87]	2.72 [1.66;4.24]	**$p_{1-2} = 0.016$** **$p_{1-3} = 0.027$** **$p_{1-4} = 0.032$**
IL-8, pg/ml	7.19 [5.26;11.45]	8.81 [5.84;12.15]	8.55 [5.29;12.22]	9.06 [6.44;12.11]	$p_{1-2} = 0.180$ $p_{1-3} = 0.452$ $p_{1-4} = 0.080$
MCP-1, pg/mL	302.55 [211.27;402.67]	342.68 [258.42;433.39]	339.78 [263.15;415.90]	353.24 [256.48;441.55]	$p_{1-2} = 0.085$ $p_{1-3} = 0.134$ $p_{1-4} = 0.101$
Insulin, mME/L	3.34 [0.76;8.25]	3.71 [1.31;9.83]	4.14 [1.34;10.19]	3.62 [1.11;9.10]	$p_{1-2} = 0.136$ $p_{1-3} = 0.138$ $p_{1-4} = 0.230$
C-peptide, pmol/L	98.21 [50.27;280.17]	143.27 [50.80;377.14]	128.85 [54.46;312.57]	172.97 [45.75;411.88]	$p_{1-2} = 0.294$ $p_{1-3} = 0.417$ $p_{1-4} = 0.264$
hs-CRP, mg/L	2.70 [1.36;8.93]	3.76 [1.90;9.31]	3.60 [1.71;9.31]	3.80 [2.42;9.27]	$p_{1-2} = 0.138$ $p_{1-3} = 0.238$ $p_{1-4} = 0.105$

Table 2

Variability of the Levels of the Studied Metabolic and Inflammatory Molecules in Men, Convalescents of COVID-19, Depending on the PCS Presence and Severity, *Me* [Q_{25}; Q_{75}]

Parameter	Group 1, no PCS $n = 29$	Group 2, with PCS $n = 75$	Group 3, mild PCS $n = 46$	Group 4, moderate PCS $n = 29$	p
IFN-a, pg/mL	0.54 [0.00;4.68]	1.28 [0.51;5.03]	2.30 [0.51;5.05]	1.09 [0.14;5.93]	p_{1-2}=0.178 p_{1-3}=0.140 p_{1-4}=0.432
IL-1b, pg/mL	2.63 [1.35;4.15]	2.47 [1.11;3.79]	2.49 [0.99;4.03]	2.31 [1.71;3.58]	p_{1-2}=0.679 p_{1-3}=0.840 p_{1-4}=0.549
IL-6, pg/mL	1,82 [1,35;2,90]	2,77 [1,64;4,59]	2,36 [1,59;4,80]	3,52 [1,98;4.34]	**p_{1-2}=0.018** p_{1-3}=0.089 **p_{1-4}=0.008**
IL-8, pg/ml	7.02 [5.01;10.59]	8.03 [5.57;11.98]	7.67 [5.31;11.66]	8.54 [6.13;12.01]	p_{1-2}=0.413 p_{1-3}=0.652 p_{1-4}=0.266

End of table 2

Parameter	Group 1, no PCS $n = 29$	Group 2, with PCS $n = 75$	Group 3, mild PCS $n = 46$	Group 4, moderate PCS $n = 29$	p
MCP-1, pg/mL	310.19 [215.85;392.50]	361.11 [281.48;420.83]	351.14 [254.65;415.39]	376.39 [288.29;436.45]	**p_{1-2}=0.042** p_{1-3}=0.095 p_{1-4}=0.047
Insulin, mME/L	4.77 [0.88;8.26]	7.19 [1.86;11.86]	7.38 [1.91;11.18]	6.39 [1.70;12.54]	p_{1-2}=0.087 p_{1-3}=0.105 p_{1-4}=0.176
C-peptide, pmol/L	123.08 [29.58;335.04]	198.08 [67.57;434.57]	189.42 [66.89;425.78]	198.08 [66.57;536.64]	p_{1-2}=0.140 p_{1-3}=0.213 p_{1-4}=0.166
hs-CRP, mg/L	2.32 [1.36;7.44]	4.41 [2.59;10.68]	4.78 [2.43;10.65]	4.03 [2.74;11.43]	**p_{1-2}=0.011** **p_{1-3}=0.028** **p_{1-4}=0.020**

At the next stage of statistical processing, the metabolic and inflammatory molecules we studied were sequentially included in a univariate logistic regression analysis model with standardization by gender and age (Table 3). It was found that the chance of moderate PCS in COVID-19 convalescents is directly associated with the concentration of C-peptide in the blood.

Univariate logistic regression analysis in men shows that the chance of PCS and mild PCS is directly associated with the hs-CRP level (Table 4).

Table 3

Univariate Logistic Regression Analysis of the Chance of Moderate-Grade PCS in COVID-19 Convalescents (with Standardization by Gender and Age)

Parameter	Univariate analysis		
	Exp B	95% CI	p
IFN-a, pg/mL	1.004	0.928–1.086	0.921
IL-1b, pg/mL	0.780	0.901–1.081	0.780
IL-6, pg/mL	1.162	0.936 –1.442	0.173
IL-8, pg/ml	1.015	0.942 –1.094	0.701
MCP-1, pg/mL	1.001	0.998 –1.003	0.695
Insulin, mME/L	1.027	0.972 –1.085	0.339
C-peptide, pmol/L	1.001	1.000 –1.003	**0.048**
hs-CRP, mg/L	1.015	0.979 –1.052	0.425

Table 4

Univariate Logistic Regression Analysis of the Chance of Having PCS and Mild PCS in Men with Standardization by Age)

Parameter	Univariate analysis of the chance of PCS			Univariate analysis of the chance of mild PCS		
	Exp B	95% CI	p	Exp B	95% CI	p
IFN-a, pg/mL	1.002	0.901–1.114	0.970	1.012	0.907–1.129	0.834
IL-1b, pg/mL	0.973	0.804–1,178	0.781	1.000	0.822–1.216	0.996
IL-6, pg/mL	1.309	0.982–1.745	0.067	1.257	0.943–1.676	0.118
IL-8, pg/ml	1.020	0.929–1.120	0.679	1.025	0.935–1.123	0.598
MCP-1, pg/mL	1.002	0.998–1.006	0.308	1.001	0.997–1.006	0.511
Insulin, mME/L	1.050	0.971–1.136	0.219	1.051	0.963–1.148	0.262
C-peptide, pmol/L	1.001	0.999–1.003	0.217	1.001	0.999–1.003	0.316
hs-CRP, mg/L	1.113	1.005–1.223	0.040	1.127	1.008–1.260	0.036

When the metabolic and inflammatory molecules were included in the multivariate logistic regression analysis, which showed a statistically significant difference between the subgroups (IL-6, MCP-1, C-peptide, hsCRP), simultaneously, in COVID-19 convalescents and, separately, in men and women, there were no associative links with the chance of having PCS and its severity.

DISCUSSION

The study of pathophysiological changes and the mechanisms that cause the occurrence of both ongoing and *de novo* PCS symptoms continues. Considering the existing data on the presence of higher levels of metabolic and inflammatory molecules (in particular, IL-1b, IL-6, IL-8, MCP-1, insulin, C-peptide, and hs-CRP) in patients infected with SARS-CoV-2 in the acute period and their associations with the risk of severe coronavirus infection course [4–6], we evaluated this profile in the blood serum of COVID-19 convalescents.

In study of Schultheiß et al., it was shown that there were significantly higher serum levels of IL-1b and IL-6 in the group of patients with PCS compared with those without PCS. The authors also demonstrated data reflecting the positive correlation of the molecules both with each other and with the presence of PCS [7]. Zhdanova et al. provided similar data revealing that the median levels of IL-1b and IL-6 were 1.3 and 4.5 times higher, respectively, in the group of patients with PCS compared with healthy individuals [8]. The PHOSP-COVID study demonstrated elevated IL-6 level 5 months after hospitalization for COVID-19 in a group of convalescents with mild cognitive impairments [9]. Our findings are consistent with the literature data: the level of IL-6 was 1.3 times higher in COVID-19 convalescents with PCS compared with those without PCS. We also found an increased IL-6 content in the blood serum of individuals with PCS of varying severity. It is reported that IL-6 is a key inflammatory factor in the immunopathogenesis of the new coronavirus infection, which is reflected in its use as a marker of severity in COVID-19 [10]. Taking into account the hypothesis of long-term persistence of the virus in the post-COVID period [11], an increase in the level of pro-inflammatory molecules, in particular IL-6, may be explained by ongoing immune reactions against viral antigens.

According to research data, MCP-1 (proinflammatory chemokine) is a key mediator involved in the pathogenesis of COVID-19, its level was higher in critically ill patients and correlated with respiratory failure, acute renal failure and death from COVID-19 [5, 12, 13]. In our study, the median MCP-1 level was significantly higher in men only in the group of patients with PCS compared with those without PCS. This may probably be due to the fact that male sex is a risk factor for severe COVID-19 [14, 15].

Of particular interest are the results that demonstrate the bidirectional relationship of carbohydrate metabolism disorders and COVID-19. According to some data, diabetes mellitus was found to be associated with the severity of COVID-19 and mortality [17]. Man et al. study reported that PCS is the main risk factor for changes in the metabolic status of patients, leading to insulin resistance [18]. According to the results of a subanalysis of the joint registers ACTIV and ACTIV 2, it was found that one year after the infection, patients with type 2 diabetes mellitus and newly diagnosed hyperglycemia are more likely to have symptoms characteristic of post-COVID syndrome [19]. Several mechanisms underlie the pathological interaction of the SARS-CoV-2 virus and carbohydrate metabolism disorders. Since diabetes mellitus is characterized by chronic inflammation, this could contribute both to the development of a more severe course of the disease in the acute period and to increased systemic inflammation observed during follow-up. On the other hand, exposure to an acute inflammatory process leads to insulin resistance in the body. Probably, these data altogether can determine our findings regarding the direct association of the chance of moderate severity PCD with the blood level of C-peptide.

The study of the level of hs-CRP has acquired additional significance in the post-COVID period. Monitoring of hs-CRP as one of the inflammatory markers is included in the guidelines "Features of Long-COVID Infection Clinical Course. Therapeutic and Rehabilitation Measures" [20]. Castro et al. compared patients ($n = 277$) who were hospitalized in 2020 during the first wave of COVID-19 in Brazil, depending on the absence or presence of advanced PCS. An extensive profile of biomolecules in the blood serum was examined 6–12 months after discharge, and a higher level of hs-CRP was noted in the group of patients with PCS compared with those without PCS [16].

The study of Maamar et al. reported that men with hs-CRP levels in the range of low intense inflammation (>0.3 mg/dl and <1.0 mg/dl) had a 10–17-fold increased risk of developing post-COVID syndrome [21]. The results obtained regarding the direct association of the chance of the presence of PCS with the hs-CRP level are consistent with the literature data. The advantage of this inflammatory marker over others (for example, ferritin and IL-6) is that it is readily available and widely used in clinical practice.

CONCLUSION

In COVID-19 convalescents, the chance of moderate PCS is directly associated with the blood level of C-peptide. In men, the chance of having

PCS is directly associated with the level of hs-CRP in the blood. The data obtained during the study demonstrate specific changes in the cytokine profile in patients with PCS. It indicates the need for further in-depth research, enabling to develop methods for personalized management of this patients category.

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Author contribution

Karaseva A.A. – collection, analysis, interpretation of data, drafting of the manuscript. Afanaseva A.D., Garbuzova E.V. – verification of intellectual content, translation of the article. Kashtanova E.V., Polonskaya Ya.V., Stakhneva E.M., Shramko V.S. – performing

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Author information

Karaseva Alexandra A. – Junior Researcher, Laboratory of Genetic and Environmental Determinants of the Human Life Cycle, Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, Novosibirsk, Sas96@bk.ru, http://orcid.org/0000-0002-0423-5021.

Afanaseva Alena D. – Cand. Sc. (Medicine), Head of the Laboratory of Genetic and Environmental Determinants of the Human Life Cycle, Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, Novosibirsk, alene.elene@gmail.com, http://orcid.org/0000–0001–7875–1566.

Garbuzova Evgeniia V. – Cand. Sc. (Medicine), Researcher, Laboratory of Genetic and Environmental Determinants of the Human Life Cycle, Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, Novosibirsk, stryukova.j@mail.ru, http://orcid.org/0000-0001-5316-4664.

Kashtanova Elena V. – Dr. Sc. (Biology), Associate Professor, Head of the Laboratory of Clinical Biochemical and Hormonal Studies of Internal Diseases, Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, Novosibirsk, elekastanova@yandex.ru, http://orcid.org/0000-0003-2268-4186.

Polonskaya Yana V. – Dr. Sc. (Biology), Senior Researcher, Laboratory of Clinical Biochemical and Hormonal Studies of Internal Diseases, Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, Novosibirsk, yana-polonskaya@yandex.ru, http://orcid.org/0000-0002-3538-0280.

Stakhneva Ekaterina M. – Cand. Sc. (Biology), Senior Researcher, Laboratory of Clinical Biochemical and Hormonal Studies of Internal Diseases, Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, Novosibirsk, stahneva@yandex.ru, http://orcid.org/0000-0003-0484-6540.

Shramko Victoria S. – Cand. Sc. (Biology), Researcher, Laboratory of Clinical Biochemical and Hormonal Studies of Internal Diseases, Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, Novosibirsk, nosova@211.ru, http://orcid.org/0000-0002-0436-2549.

Shcherbakova Lilia V. – Senior Researcher, Laboratory for Clinical, Population and Preventive Research of Internal and Endocrine Diseases, Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, Novosibirsk, 9584792@mail.ru, http://orcid.org/0000-0001-9270-9188.

Logvinenko Irina I. – Dr. Sc. (Medicine), Professor, Senior Researcher, Laboratory of Preventive Medicine, Deputy Head of the Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, Novosibirsk, 111157@mail.ru, http://orcid.org/0000-0003-1348-0253.

Ragino Yulia I. – Dr. Sc. (Medicine), Professor, Corresponding Member of RAS, Head of the Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, Novosibirsk, ragino@mail.ru, http://orcid.org/0000-0002-4936-8362.

(✉) **Karaseva Alexandra A.,** sas96@bk.ru

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