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Reseach article

Relationship of the myostatin level and secondary sarcopenia in patients undergoing programmed hemodialysis

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ABSTRACT

The role of myostatin in the development of sarcopenia in patients receiving programed hemodialysis and the severity of the relationship with other risk factors, particularly between the myostatin level in the blood and skeletal muscle indicators, were analyzed. A single-stage prospective non-interventional study was conducted among 196 patients (97 women and 99 men, aged 54–66 years) receiving programed hemodialysis. After signing the informed consent form, all patients underwent a series of examinations consisting of the assessment of anthropometric data, measurement of vital signs, determination of the state of the muscular system for the diagnosis of sarcopenia, including bioimpedance, and laboratory tests (clinical and biochemical blood tests). The level of myostatin in the blood serum of patients was determined once 10 min before the next hemodialysis session. A statistically significant negative correlation of myostatin level with age (ρ = –0.361; $p < 0.001$), skeletal muscle strength (ρ = –0.140; $p = 0.05$), and walking speed (ρ = –0.245; $p < 0.001$) was observed. High myostatin levels were more often detected in men ($U = 2633$, $z = –5.462$; $p < 0.001$). A positive correlation between the levels of myostatin and interleukin-6 was found (ρ = 0.410; $p < 0.001$). The use of myostatin for the diagnosis of sarcopenia had a sensitivity of 71.4%, specificity of 71.4%, cut-off point of 5.01 ng/mL, and area under the curve of 0.714 (95% confidence interval: 0.632–0.795; $p < 0.001$). An increase in myostatin levels above 5.01 ng/mL increases the likelihood of sarcopenia by 6.25 times (95% confidence interval: 3.314–11.788; $\chi 2 = 34.639$; $p < 0.001$). The chances of an increase in myostatin above the threshold value by 2,196 times according to the results of a short international questionnaire for determining physical activity (95% confidence interval: 1.209–3.988; $\chi 2 = 6.78$; $p = 0.009$) were higher in patients with reduced physical activity than in patients with normal physical activity. In general, in patients with chronic kidney disease receiving programed hemodialysis, along with the determination of myostatin level, a positive statistically significant association of myostatin level with interleukin-6, male sex, age, and decreased physical activity was noted, and myostatin could be used as a predictor of sarcopenia.

Keywords: hemodialysis; myostatin; sarcopenia; chronic kidney disease; terminal renal failure; secondary anemia; ubiquitin-proteasome pathway; metabolic acidosis.

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Научная статья

Связь уровня миостатина и вторичной саркопении у пациентов, находящихся на программном гемодиализе

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АННОТАЦИЯ

Анализируется роль миостатина в развитии саркопении у пациентов, получающих программный гемодиализ, и степень выраженности взаимосвязи с другими факторами риска, в частности, между уровнем миостатина в крови и показателями скелетной мускулатуры. Работа выполнена в виде одномоментного проспективного неинтервенционного исследования среди 196 пациентов (97 женщин и 99 мужчин в возрасте от 54 до 66 лет), получающих программный гемодиализ. После подписания информированнного согласия всем пациентам выполнен комплекс обследований, состоящий из оценки антропометрических данных, измерения жизненно важных показателей, определения состояния мышечной системы для диагностики саркопении, в том числе биоимпедансометрия, лабораторные исследования (клинический и биохимический анализы крови). Уровень миостатина в сыворотке крови пациентов определяли однократно за 10 мин до очередного сеанса гемодиализа. Выявлены статистически значимые отрицательные корреляционные связи уровня миостатина с возрастом ($\rho = -0{,}361$; $p < 0{,}001$), силой скелетной мускулатуры ($\rho = -0{,}140$; $p = 0{,}05$), скоростью ходьбы ($\rho = -0{,}245$; $p < 0{,}001$). Повышенные уровни миостатина чаще выявлялись у мужчин ($U = 2633$, $z = -5{,}462$; $p < 0{,}001$). Выявлена положительная корреляционная связь уровня миостатина с уровнем интерлейкина 6 ($\rho = 0{,}410$; $p < 0{,}001$). Использование миостатина для диагностики саркопении имеет чувствительность 71,4 %, специфичность 71,4 %, точка отсечения 5,01 нг/мл, площадь под кривой 0,714 (95 % доверительный интервал: 0,632–0,795; $p < 0{,}001$). Повышение уровня миостатина выше 5,01 нг/мл увеличивает вероятность развития саркопении в 6,25 раз (95 % доверительный интервал: 3,314–11,788) ($\chi^2 = 34{,}639$; $p < 0{,}001$). Шансы повышения миостатина выше порогового значения в 2,196 раз по результатам короткого международного опросника для определения физической активности (95 % доверительный интервал: 1,209–3,988; $\chi^2 = 6{,}78$; $p = 0{,}009$) были выше у пациентов со сниженной физической активностью по сравнению с пациентами с нормальной физической активностью. В целом у пациентов, страдающих хронической болезнью почек, получающих программный гемодиализ, наряду с определением уровня миостатина отмечена положительная статистически значимая связь уровня миостатина с интерлейкином 6, мужским полом, возрастом, снижением физической активности, а также определена возможность использования миостатина в качестве предиктора саркопении.

Ключевые слова: гемодиализ; миостатин; саркопения; хроническая болезнь почек; терминальная почечная недостаточность; вторичная анемия; убиквитин-протеасомный путь; метаболический ацидоз.

Как цитировать

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ЭКО•ВЕКТОР

BACKGROUND

Azotemia, electrolyte disorders, acidosis, and secondary anemia, which are characteristic of end-stage renal failure, have negative effects on almost all systems and organs of patients with chronic kidney disease (CKD) [1]. Skeletal muscles are also affected, which is manifested by a decrease in muscle mass, strength, and endurance. Pathological conditions such as sarcopenia further decrease the quality of life and increase the risk of disability and mortality in patients with CKD [1, 2]. The incidence of sarcopenia is estimated to be 12%–29%, resulting in a significant medical and financial burden [3, 4].

In healthy adults, the level of muscle mass remains constant because of the balance between signaling pathways, namely, (1) insulin-like growth factor-1/Akt protein kinase B (IGF-1/Akt), which triggers protein synthesis and recruitment of muscle satellite cells, and (2) myostatin, which leads to protein cleavage by activating the ubiquitin–proteasome pathway and caspase-3 and inhibits the recruitment of satellite cells [5, 6]. These pathways are highly regulated and interconnected, and muscle loss occurs because of an imbalance between their functions [7]. Understanding the functioning of this system in CKD-associated sarcopenia is extremely important. Specifically, Bataille S., Chauveau P., Fouque D., et al. [8], highlighted the potential therapeutic role of myostatin and emphasized the feasibility of developing appropriate therapeutic molecules, which opens promising prospects for future treatments.

Muscle cells produce myostatin in the form of pre-pro-myostatin, which is then secreted as promyostatin into the intercellular space and blood. After two-step cleavage of the pro-domain, also known as latent-associated protein, myostatin is converted to its active form and acts as an effective autocrine, paracrine, and endocrine inhibitor of muscle growth [9]. Myostatin interacts with its receptor, activin receptor type II B, on the surface of muscle cells, which leads to the activation and phosphorylation of the transcription factors Smad-2 and Smad-3. Smad-2 and Smad-3 are then transported to the nucleus where they modulate the transcription of E3 ubiquitin ligases such as atrogin-1 (also known as MAFbx) and muscle ring-finger protein-1 (MuRF-1), which enhances protein cleavage via the ubiquitin–proteasome system. In addition, Smad-2 and Smad-3 inhibit Akt phosphorylation and the Janus kinase/Stat pathway [10].

In CKD, the decrease in muscle mass is regulated not only by myostatin but also by other factors, such as metabolic acidosis, endogenous glucocorticoids, and inflammation, particularly interleukin (IL)-6. Both metabolic acidosis and endogenous glucocorticoids suppress phosphoinositide 3-kinase activation and Akt phosphorylation [11, 12]. Moreover, in the case of inflammation, IL-6 suppresses muscle protein synthesis through Stat3 activation and probably causes an increase in myostatin transcription [13, 14].

Satellite cells are dormant, partially differentiated stem cells located at the periphery of muscle fibers. When muscle fibers are damaged, growth factors activate these satellite cells, which undergo proliferation, differentiation, and fusion to form new muscle fibers. However, the disruption of IGF-1/Akt pathway or interaction of myostatin with satellite cells suppressed their proliferation and differentiation [15].

An increase in myostatin production during chronic CKD is facilitated by a combination of low physical activity, progression of the inflammatory process and concomitant oxidative stress, accumulation of uremic toxins, angiotensin II, metabolic acidosis, and glucocorticoids [10]. However, the role of myostatin regulation in changes in skeletal muscle mass in patients with CKD is still underinvestigated, and data about it are limited. Most of the available data are obtained from findings in animal models, with only a few data obtained from human studies [17]. Thus, more studies are needed to fully understand the potential renal influence on myostatin excretion.

This study aimed to trace the relationship between blood myostatin levels and skeletal muscle parameters in patients undergoing hemodialysis.

MATERIALS AND METHODS

This study was conducted as a one-stage, prospective, non-interventional study from February 2020 to May 2023. Patients were selected and examined at the Kupchinsky Center for Outpatient Dialysis. In total, 196 patients (97 women and 99 men aged >18 years; median age, 61 [54; 66] years) with stage 5 CKD undergoing hemodialysis for at least 1 year were examined. At the time of study enrolment, all patients were receiving treatment with hemodialysis on devices for extracorporeal blood purification (B.Braun Dialog+, B.Braun, Germany) using water subjected to deep purification by reverse osmosis (Water Purification System Lauer, B.Braun) and on synthetic dialyzers Diacap Pro and Xevonta (B.Braun). The median duration of hemodialysis was 11.6 [8.6; 14.2] years.

After signing the informed consent form, the patients were selected according to the inclusion/non-inclusion criteria. The patients underwent a set of examinations that consisted of assessing anthropometric data, recording vital signs, and determining the state of the muscular system for the diagnosis of sarcopenia, including bioimpedance measurements and laboratory tests (clinical and biochemical blood tests and determination of myostatin level). In addition, all patients completed a short international questionnaire on physical activity (IPAQ).

The exclusion criteria were as follows: diabetes mellitus; positive test results for markers of viral hepatitis B and C and human immunodeficiency virus; hospitalization in the previous 6 months or diagnosis of an acute illness within a month before study inclusion; any malignant neoplasms at the time of the study; continuous therapy with glucocorticosteroids;

chronic heart failure of grades III or IV according to the New York Heart Association classification; chronic obstructive pulmonary disease; and the presence of other diseases that significantly affect the daily physical activity of patients.

The database was generated using Microsoft Office 2016 software. Statistical analysis was performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). For variables measured quantitatively, the Kolmogorov – Smirnov test was used to test the normality of distribution. Data with non-normal distribution are presented in tables as a median and interquartile range (between the first and third quartiles; *Me* [Q1; Q3]). The Mann – Whitney U test was used to compare two independent samples of data that were not normally distributed. Differences between samples were considered statistically significant at $p < 0.05$. To study the relationship between two variables, correlation analysis was applied using the Spearman method, and Pearson's χ^2 method was used to analyze qualitative variables.

RESULTS AND DISCUSSION

According to the results of the IPAQ, 127 patients demonstrated a decrease in physical activity, impaired functioning of skeletal muscles, and physical inactivity as possible predictors of sarcopenia. Based on skeletal muscle parameters, patients were diagnosed with sarcopenia according to the second revision criteria of the European Working Group on Sarcopenia in Older People (EWGSOP 2). Normal values of the appendicular skeletal muscle mass index were registered in 52 (26.5%) patients based on the results of bioimpedancemetry, skeletal muscle strength determined using dynamometry, and walking pace assessed in the 4-m test. Moreover, 25 (12.8%) patients had a decrease in hand strength with normal indicators of mass and performance of skeletal muscles (possible sarcopenia). Sarcopenia was observed in 119 (60.7%) patients, of which 49 cases had a severe course.

Anthropometric indicators, muscular indicators, and clinical and biochemical blood test results are presented in Table 1.

The median myostatin level was 5.13 [3.92; 5.975] ng/mL. A negative correlation was observed between age and myostatin level ($\rho = -0.361$; $p < 0.001$) (Fig. 1). Moreover, myostatin levels were higher in men than in women ($U = 2633.0$, $z = -5.462$; $p < 0.001$) (Fig. 2).

Table 2 presents the results of assessing myostatin levels based on the severity of sarcopenia.

According to the results of a correlation analysis of the relationship between myostatin and skeletal muscle parameters in patients receiving long-term hemodialysis, a low but statistically significant correlation coefficient was obtained with skeletal muscle strength (correlation coefficient $\rho = -0.140$; $p = 0.05$) and walking pace ($\rho = -0.245$; $p < 0.001$). A moderate positive correlation was observed between myostatin and IL-6 ($\rho = 0.410$; $p < 0.001$).

To determine the possibility of using myostatin for diagnosing sarcopenia, receiver operating characteristic (ROC) analysis was performed. A graphical representation of the ROC curve is shown in Fig. 3.

Results of the ROC analysis revealed that myostatin can be used to diagnose sarcopenia because it had an area under the curve of 0.714 (95% confidence interval (CI) 0.632–0.795; $p < 0.001$), sensitivity of 71.4%, and specificity of 71.4% when the cutoff point was 5.01 ng/ml. An increase in myostatin levels >5.01 ng/mL increases the probability of sarcopenia by 6.25 times (95% CI 3.314–11.788) ($\chi^2 = 34.639$; $p < 0.001$).

Moreover, the probability of detecting a myostatin level above the threshold value among patients with identified physical inactivity according to the completed IPAQ was 2.196 times higher (95% CI 1.209–3.988; $\chi^2 = 6.78$, $p = 0.009$) than that in patients with normal physical activity.

Along with peer-reviewed publications, the presented data may be useful in assessing the importance of myostatin as part of the regulatory and signaling mechanisms

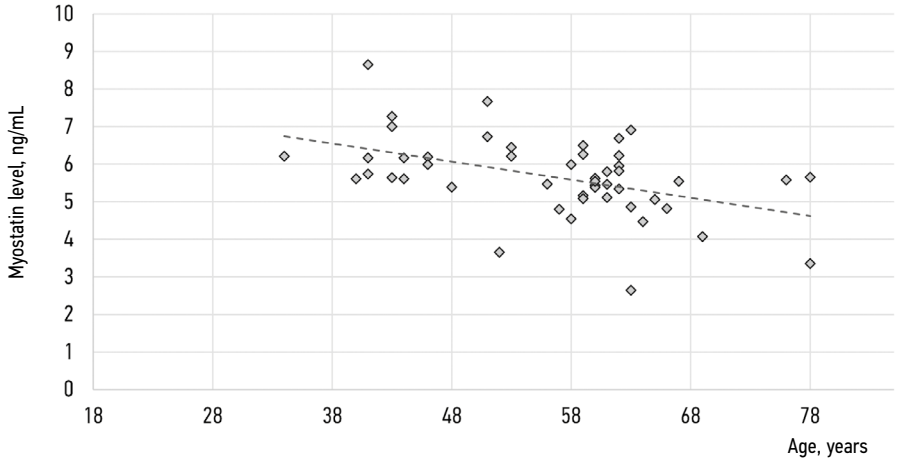

Fig. 1. Correlation between myostatin levels and age (scattering)
Рис. 1. Корреляционная взаимосвязь между уровнем миостатина и возрастом (рассеяние)

Table 1. Main indicators of patients included in the study, *Me* [Q1; Q3]
Таблица 1. Основные показатели пациентов, включенных в исследование, *Me* [Q1; Q3]

Indicator	Value
Age, years	61 [54; 66]
Women, *n* (%)	97 (49.5)
BMI, kg/m^2	24.08 [22.19; 26.75]
Red blood cells, ×10^{12}/L	3.5 [2.9; 4]
Hemoglobin, g/L	103 [92.25; 115]
Leukocytes, ×10^9/L	5.95 [4.8; 7.5]
Platelets, ×10^9/L	218 [187.25; 264.25]
Total protein, g/L	66.6 [64; 69]
Albumin, g/L	38.2 [34.6; 39.5]
Transferrin, g/L	1.85 [1.62; 2.09]
Total cholesterol, mmol/L	4.56 [3.83; 5.28]
Creatinine, μmol/L	788 [649.5; 934.5]
ALT, U/L	13 [9; 21]
AST, U/L	13.5 [9; 21]
Alkaline phosphatase, U/L	94 [68.25; 132]
Total bilirubin, μmol/L	8.9 [7.2; 11.8]
Sodium, mmol/L	137.8 [136; 140]
Potassium, mmol/L	5.4 [5.0; 5.9]
Phosphorus, mmol/L	1.90 [1.56; 2.31]
Calcium, mmol/L	2.27 [2.14; 2.40]
Parathyroid hormone, pg/mL	172.5 [96.325; 273]
Skeletal muscle mass(kg)	21.91 [20.2; 25.08]
Appendicular skeletal muscle mass, kg	15.76 [13.96; 18.78]
Skeletal muscle appendicular mass index, kg/m^2	5.78 [5.18; 6.44]
Shoulder muscle circumference, cm	22.6 [21.1; 25.7]
Walking pace, m/s	0.84 [0.79; 0.88]

Note: ALT — alanine aminotransferase; AST — aspartate aminotransferase; BMI — body mass index.
Примечание: ИМТ — индекс массы тела; АЛТ — аланинаминотрансфераза; АСТ — аспартатаминотрансфераза.

Table 2. Myostatin level depending on the severity of sarcopenia, ng/mL (*Me* [Q1; Q3])
Таблица 2. Уровень миостатина в зависимости от степени тяжести саркопении, нг/мл (*Me* [Q1; Q3])

Indicator	Myostatin level	$p < 0.001$ compared with normal skeletal muscle indicators
No sarcopenia	3.685 [3.2175; 4.405]	–
Possible sarcopenia	5.96 [4.615; 7.045]	$U = 132.5$; $z = -5.63$
Sarcopenia	5.43 [4.4175; 5.9825]	$U = 610$; $z = -6.264$
Severe sarcopenia	5.62 [5.135; 6.21]	$U = 232$; $z = -7.081$

responsible for the control of skeletal muscle mass through secreted proteins of the transforming growth factor-β superfamily [16]. In patients with CKD C5, along with determining the myostatin level, other possible predictors of sarcopenia were studied. Specifically, a positive statistically significant relationship was noted between the myostatin level and IL-6, male sex, age, and decreased physical activity. These results require further systematic analysis and the development of possible mathematical models for assessing the degree of risk of sarcopenia in patients undergoing hemodialysis. The positive results of preclinical studies, which were freely available at the time of publication of this study, have led to the development of several biological drugs aimed at disrupting the myostatin signaling

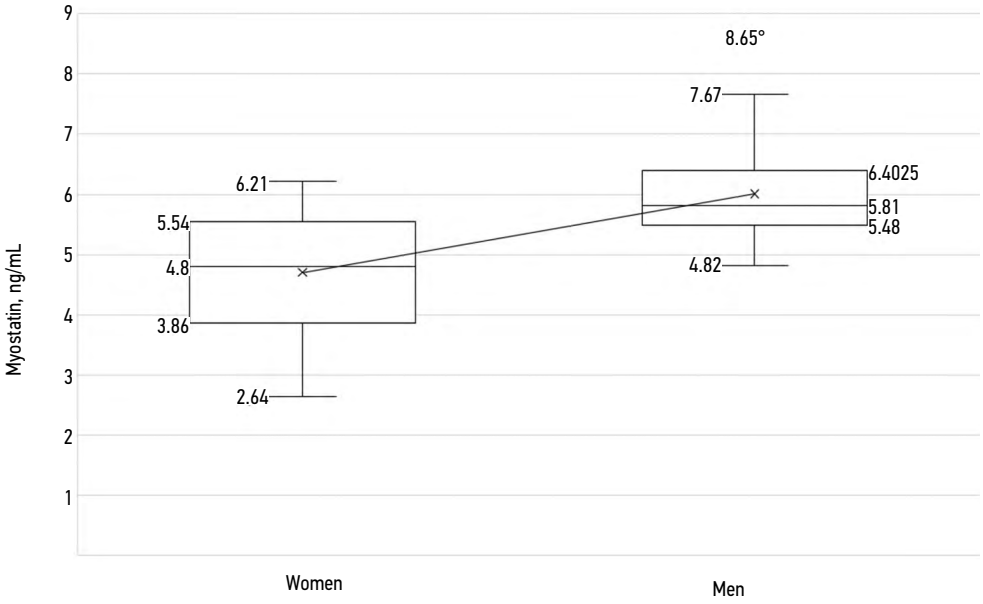

Fig. 2. Level of myostatin in the blood serum, depending on sex
Рис. 2. Уровень миостатина в сыворотке крови в зависимости от пола

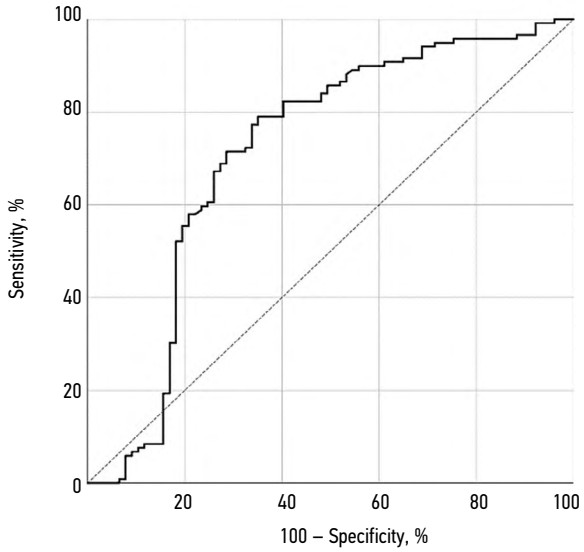

Fig. 3. Graphical result of the ROC analysis for the diagnosis of sarcopenia using myostatin
Рис. 3. Графический результат ROC-анализа для диагностики саркопении с помощью миостатина

pathway and promoting an increase in muscle mass and functionality of skeletal muscles [17]. Clinical trials of these biopharmaceuticals have demonstrated increases in muscle volume and/or appendicular body mass in various diseases associated with muscle loss and excess fat deposition. However, the registered increase in lean body mass of 3%–8% was significantly lower than that in mouse studies where increases in muscle mass reached 25%–50% [18]. This raises questions about the potential for muscle growth in humans and mice and whether these biopharmaceuticals have fulfilled their full potential in humans. Future research should address these issues, and myostatin inhibitors can improve metabolic parameters by increasing muscle mass, making them a promising candidate for the treatment of metabolic disorders [16, 19].

CONCLUSION

Myostatin, a member of the TGF-β superfamily, is important in the regulation of skeletal muscles. However, very few studies are currently evaluating the role of myostatin and examining its association with secondary sarcopenia in CKD. This study was based on data on myostatin levels in 196 patients undergoing chronic hemodialysis. To identify the presence of skeletal muscle disorders and assess their severity, complaints were assessed, the IPAQ results were

considered, dialysis duration and presence of concomitant diseases were taken into account, anthropometric measurements and clinical and biochemical blood tests were performed, IL-6 levels were measured, and dynamometry and bioimpedance measurements were performed. For the first time, the relationship between myostatin level and the above indicators was assessed using the Spearman correlation method, and groups were compared using the Mann–Whitney *U* test. Significant correlations were revealed with skeletal muscle strength ($\rho = -0.140$; $p = 0.05$), walking pace ($\rho = -0.245$; $p < 0.001$), IL-6 level ($\rho = 0.410$; $p < 0.001$), and age ($\rho = -0.361$; $p < 0.001$). In addition, myostatin levels are higher in men than in women and in patients with severe physical inactivity.

The data obtained demonstrate the possibility of using myostatin as a marker of sarcopenia. The threshold level of myostatin based on the results of the ROC analysis was 5.01 ng/mL; levels above this threshold increase the probability of detecting sarcopenia by 6.25 times. The results of this study indicate the feasibility of clinical trials of myostatin antagonists for the correction of skeletal muscle parameters.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

The contribution of each author. V.N. Tsygan — general concept development, research design; O.L. Boriskina — article writing, data analysis; A.A. Yakovenko — material collection, data processing; A.P. Tutin — material collection, statistical data processing.

Competing interests. The authors declare that they have no competing interests.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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Вклад каждого автора. В.Н. Цыган — разработка общей концепции, дизайн исследования; О.Л. Борискина — написание статьи, анализ данных; А.А. Яковенко — сбор материала, обработка данных; А.П. Тутин — сбор материала, статистическая обработка данных.

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

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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