RUSSIAN BIOMEDICAL RESEARCH

2023, VOLUME 8, N 3 SCIENTIFIC AND PRACTICAL JOURNAL FOR DOCTORS

Рецензируемый научно-практический журнал
RUSSIAN BIOMEDICAL RESEARCH
РОССИЙСКИЕ БИОМЕДИЦИНСКИЕ ИССЛЕДОВАНИЯ

Основан в 2016 году в Санкт-Петербурге

ISSN 2658-6584 eISSN 2658-6576

Выпускается 4 раза в год

Журнал реферируется РЖ ВИНИТИ

*Журнал входит в **Перечень ведущих научных журналов и изданий ВАК**, в которых должны быть опубликованы основные результаты диссертаций на соискание ученых степеней кандидата и доктора наук (Распоряжение № 435-р от 15.11.2021).*

Издатели, учредители:
Федеральное государственное бюджетное образовательное учреждение высшего образования «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России (адрес: 194100, Санкт-Петербург, Литовская ул., д. 2),
Фонд НОИ «Здоровые дети — будущее страны» (адрес: 197371, Санкт-Петербург, ул. Парашютная, д. 31, к. 2, кв. 53).

Журнал зарегистрирован Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (РОСКОМНАДЗОР)
ПИ № ФС77-74228 от 02 ноября 2018 г.

Журнал индексируется в РИНЦ. Договор на включение журнала в базу РИНЦ: № 538-10/2016 от 06.10.2016, страница журнала в Российской научной электронной библиотеке http://elibrary.ru/title_about.asp?id=62014.

Проект-макет: Титова Л.А.

Электронная версия — http://www.gpmu.org/science/pediatrics-magazine/Russian_Biomedical_Research, http://elibrary.ru

Титова Л.А. (выпускающий редактор)
Варламова И.Н. (верстка)

Адрес редакции: Литовская ул., 2, Санкт-Петербург, 194100; тел./факс: (812) 295-31-55; e-mail: lt2007@inbox.ru.

Address for correspondence:
2, Litovskaya St., St. Petersburg, 194100, Russia.
Tel/Fax: +7 (812) 295-31-55.
E-mail: lt2007@inbox.ru.

Статьи просьба направлять по адресу: avas7@mail.ru
Please send articles to: avas7@mail.ru

Формат 60 × 90/8. Усл.-печ. л. 10. Тираж 100 экз. Распространяется бесплатно. Оригинал-макет изготовлен ФГБОУ ВО СПбГПМУ Минздрава России.

Format 60 × 90/8. Cond.-printed sheets 10. Circulation 100. Distributed for free. The original layout is made Saint Petersburg State Pediatric Medical University.

Отпечатано ФГБОУ ВО СПбГПМУ Минздрава России
Литовская ул., 2, Санкт-Петербург, 194100.
Заказ 117. Дата выхода 27 .09.2023.

Printed by Saint Petersburg State Pediatric Medical University.
Lithuania 2, Saint Petersburg, Russian Federation, 194100.
Order 117. Release date 27.09.2023.

2023, ТОМ 8, № 3 НАУЧНО-ПРАКТИЧЕСКИЙ ЖУРНАЛ ДЛЯ ВРАЧЕЙ

РОССИЙСКИЕ БИОМЕДИЦИНСКИЕ ИССЛЕДОВАНИЯ

СОДЕРЖАНИЕ CONTENT

ОРИГИНАЛЬНЫЕ СТАТЬИ

ОБЗОРЫ

ORIGINAL PAPERS

REVIEWS

КЛИНИЧЕСКИЙ СЛУЧАЙ

ИНФОРМАЦИЯ

CLINICAL CASE

INFORMATION

UDC 616.5-001.17-082-07-089+57.085.1+616.5-003.93+591.169.2+612.085.1
DOI: 10.56871/RBR.2023.37.44.001

EVALUATION OF THE EFFICACY OF TREATMENT OF 3RD DEGREE BURNS WITH HLDF6 PEPTIDE AND SILVER NANOPARTICLES IN CARBOPOL 2020 GEL *IN VIVO* EXPERIMENT

© Anton S. Shabunin[1], Evgeniy V. Zinoviev[2], Sergey V. Vissarionov[1], Marat S. Asadulaev[1], Alexander Yu. Makarov[1], Andrey M. Fedyuk[1], Timofey S. Rybinskikh[1], Polina A. Pershina[2], Denis V. Kostyakov[2], Alexander V. Semiglazov[2], Svetlana N. Pyatakova[2]

[1] National Medical Research Center for Pediatric Traumatology and Orthopedics named after G.I. Turner. Parkovaya st., 64–68, Saint Petersburg, Pushkin, Russian Federation, 196603
[2] Saint Petersburg institute of emergency care named after I.I. Dzhanelidze. Budapeshtskaya st., 3, Saint Petersburg, Russian Federation, 192242

Contact information: Evgeniy V. Zinoviev — Doctor of Medical Sciences, Professor, Head of the Department of Thermal Injuries.
E-mail: evz@list.ru ORCID ID: 0000-0002-2493-5498

For citation: Shabunin AS, Zinoviev EV, Vissarionov SV, Asadulaev MS, Makarov AYu, Fedyuk AM, Rybinskikh TS, Pershina PA, Kostyakov DV, Semiglazov AV, Pyatakova SN. Evaluation of the efficacy of treatment of 3rd degree burns with HLDF6 peptide and silver nanoparticles in Carbopol 2020 gel *in vivo* experiment // Russian biomedical research (St. Petersburg). 2023; 8(3): 4-11. DOI: https://doi.org/10.56871/RBR.2023.37.44.001

Received: 15.06.2023 **Revised: 05.07.2023** **Accepted: 21.09.2023**

Abstract. ***Introduction.*** Between 250 and 280 thousand victims of deep thermal burns of the skin are registered annually in the territory of the Russian Federation; in every 6 cases the victims are underage patients. The lethality rate in case of thermal trauma is 7.2%, but in case of extensive deep burns it reaches 13–14%. Early surgical treatment of patients with severe thermal burns is an accepted standard and therefore the search for wound healing agents reducing the period of treatment and the risk of infectious complications is essential. ***Objective.*** To evaluate the efficacy of carbopol hydrogel with injected silver nanoparticles and HLDF6 peptide in the treatment of thermal burns of grade III skin in vivo. ***Materials and methods.*** The structure of the work is represented by an experimental study. The work was performed on 50 male Wistar rats, with an average weight of 230–250 g. The animals were divided into 5 groups depending on the applied concentration of HLDF6 peptide in Carbopol 2020 gel. Carbopol ETD 2020 hydrogel samples (0.5%) containing 0,00015% nano-silver and HLDF6 peptide with concentrations of 0%, 0,01%, 0,001%, 0,0001% and 0,00001% were used to evaluate efficacy. A planimetric method was used to assess the dynamics of wound healing. The obtained data were subjected to statistical analysis using the Mann–Whitney U-parameter. ***Results.*** Application of 0,0001 and 0,00001% doses of the peptide HLDF6 demonstrated activation of the healing processes on the 14th day of the experiment by 45,8% and 31,7% correspondingly ($p < 0,01$), and also reduced the incidence of purulent complications by 62,5% ($p < 0,05$). The peptide concentration of 0,01% shows an increase in the duration of treatment, and 0,001%, no significant differences in comparison with the control and experimental groups. ***Conclusion.*** The use of low doses of the HLDF6 peptide (volume concentration in the range of 10^{-4}–10^{-5}%) in gel preparations in the treatment of deep thermal burns of the skin shows high efficacy. Small concentrations of HLDF6 peptide allow significant activation of wound healing processes.

Key words: skin burn; human leukemia differentiation factor-6; silver nanoparticles; combustiology; reparative regeneration; experimental study; traumatology-orthopedics; skin repair.

ОЦЕНКА ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ ОЖОГОВ III СТЕПЕНИ ПЕПТИДОМ HLDF6 И НАНОЧАСТИЦАМИ СЕРЕБРА В ГЕЛЕ CARBOPOL 2020 В ЭКСПЕРИМЕНТЕ *IN VIVO*

© Антон Сергеевич Шабунин[1], Евгений Владимирович Зиновьев[2], Сергей Валентинович Виссарионов[1], Марат Сергеевич Асадулаев[1], Александр Юрьевич Макаров[1], Андрей Михайлович Федюк[1], Тимофей Сергеевич Рыбинских[1], Полина Андреевна Першина[2], Денис Валерьевич Костяков[2], Александр Владимирович Семиглазов[2], Светлана Николаевна Пятакова[2]

[1] Национальный медицинский исследовательский центр детской травматологии и ортопедии им. Г.И. Турнера. 196603, г. Санкт-Петербург, г. Пушкин, ул. Парковая, 64–68
[2] Санкт-Петербургский научно-исследовательский институт скорой помощи им. И.И. Джанелидзе. 192242, г. Санкт-Петербург, Будапештская ул., 3
Контактная информация: Евгений Владимирович Зиновьев — д.м.н., профессор, руководитель отдела термических поражений ГБУ СПб НИИ СП им. И.И. Джанелидзе. E-mail: evz@list.ru ORCID ID: 0000-0002-2493-5498

Для цитирования: Шабунин А.С., Зиновьев Е.В., Виссарионов С.В., Асадулаев М.С., Макаров А.Ю., Федюк А.М., Рыбинских Т.С., Першина П.А., Костяков Д.В., Семиглазов А.В., Пятакова С.Н. Оценка эффективности лечения ожогов III степени пептидом HLDF6 и наночастицами серебра в геле Carbopol 2020 в эксперименте *in vivo* // Российские биомедицинские исследования. 2023. Т. 8. № 3. С. 4–11. DOI: https://doi.org/10.56871/RBR.2023.37.44.001

Поступила: 15.06.2023 **Одобрена: 05.07.2023** **Принята к печати: 21.09.2023**

Резюме. ***Введение.*** На территории Российской Федерации ежегодно регистрируется от 250 до 280 тысяч пострадавших с глубокими термическими ожогами кожи, в каждом шестом случае травмированными являются несовершеннолетние пациенты. Летальность при термическом поражении составляет 7,2%, но при обширных глубоких ожогах может достигать значения 13–14%. Признанным стандартом лечения является раннее начало хирургического вмешательства у пациентов с глубокими термическими ожогами, что делает актуальным поиск ранозаживляющих средств, позволяющих сократить сроки стационарного лечения и снизить риски развития инфекционных осложнений. ***Цель*** — оценить эффективность гидрогеля Карбопола с введенными наночастицами серебра и пептида HLDF6 в лечении термических ожогов кожи III степени *in vivo.* ***Материалы и методы.*** Структура работы представлена экспериментальным исследованием. Работа выполнена на 50 самцах крыс линии Wistar, средней массой 230–250 г. Животные были разделены на 5 групп в зависимости от применяемой концентрации пептида HLDF6 в геле Carbopol 2020. Для оценки эффективности применяли образцы гидрогеля Carbopol ETD 2020 (0,5%), содержащие наносеребро 0,00015% и пептид HLDF6 с концентрациями 0%, 0,01%, 0,001%, 0,0001% и 0,00001%. В процессе работы применяли планиметрический метод оценки динамики заживления ран. Полученные данные подвергали статистическому анализу с применением U-параметра Манна–Уитни. ***Результаты.*** В ходе исследования установлено, что применение геля с содержанием 0,0001 и 0,00001% доз пептида HLDF6 демонстрирует активизацию процессов заживления на 14-е сутки на 45,8% и 31,7% соответственно ($p < 0,01$), а также снижает частоту развития гнойных осложнений на 62,5% ($p < 0,05$). Концентрация пептида 0,01% демонстрирует увеличение сроков лечения, а 0,001% — отсутствие достоверных различий относительно контрольной и экспериментальных групп исследования. ***Заключение.*** Применение малых доз пептида HLDF6 (объемной концентрацией в пределах 10^{-4}–10^{-5}%) в составе гелевых препаратов при лечении глубоких термических ожогов кожи показывает высокую эффективность. Малые концентрации пептида HLDF6 позволяют существенно активизировать процессы ранозаживления и снизить частоту инфекционных осложнений.

Ключевые слова: ожог кожи; человеческий лейкозный фактор дифференцировки-6; наночастицы серебра; комбустиология; репаративная регенерация; экспериментальное исследование; травматология-ортопедия; восстановление кожного покрова.

INTRODUCTION

Skin injuries caused by thermal and chemical burns remain an important and topical issue of modern medicine, and in particular of combustiology and traumatology [1, 2]. Between 250 and 280 thousand victims of deep thermal burns of the skin are registered annually in the territory of the Russian Federation; in every 6 cases the victims are underage patients [14]. The lethality rate in case of thermal trauma is 7.2%, but in case of extensive deep burns it reaches 13–14% [1]. In the emerging socio-political situation, associated with an increase in the number and scale of armed conflicts [3], it is possible to assume an increase in the number of different wound healing agents [21], which are convenient to use both inside and outside the hospital [7]. Modern tactics of treatment of patients with burn wounds is a multidisciplinary task and is carried out taking into account the features of the pathogenesis of burn and its complications [11, 12, 17]. Thanks to the progress of medical science, pathogenetically substantiated methods of antibacterial therapy [9], immunocorrection [8, 19, 20] and local treatment of wounds [18] have been introduced. The accepted standard of early necrectomy of deep thermal skin burns makes it necessary to search for new means that can activate wound healing

processes and reduce their overall treatment time [1, 13]. The most promising new methods of treating superficial and deep burns are biotechnological [10], including stem cell use [24], complex tissue-engineered constructs based on biopolymer matrices [23], populated with allogeneic and autologous cell cultures [13].

One of the promising ways to improve the effectiveness of treatment of patients with extensive deep skin burns involves the use of growth stimulants and regeneration factors [4, 22]. In particular, this refers to epidermal, fibroblast, platelet-derived, and vascular endothelial growth factors [15, 16]. This principle is also true for the development of tissue-engineered constructs [1, 13]. Growth factors and bioactive molecules are introduced into the polymer matrix and onto its surface in these constructs [4, 12].

One possible biologically active substance to be used may be a peptide — human leukemia differentiation factor (HLDF) [2, 4]. It was isolated from the culture medium of the HL-60 promyelocytic leukemia cell line in 1994 [5, 6]. It was found that the HLDF factor induces differentiation along the granulocytic pathway [6]. As a result of this factor, a six-membered peptide fragment human leukemia differentiation factor-6 (HLDF6) was discovered. HLDF6 peptide provides the ability of the full-length factor to differentiate and inhibit cell proliferation, including HL-60 [4, 5]. HLDF6 is also able to interact with membrane lipids, enhancing the activity of cytokines, which participate in the cell proliferation and differentiation [2]. One study showed that HLDF6 also increases the activity of oxidation-reduction processes and enhances the metabolic activity of macrophages [4–6].

For effective delivery and control of the localization of the HLDF6 peptide on the wound surface, it is proposed to use a hydrogel of sparsely cross-linked acrylic polymers (carbopols), in particular, easy-to-disperse (ETD) Carbopol 2020 [2]. They form stable hydrogels that are thermally and chemically stable. The work studied the use of a gel with various concentrations of the target peptide [2]. High efficiency of wound healing was revealed, which was expressed in the improvement of planimetric and histological parameters. However, despite this, a fairly high number of purulent complications in the wound defect zone was also noted in all the studied groups [2, 4]. In the study we plan to carry out, the samples used were additionally modified with antibacterial agents, namely nanodispersed silver, in order to create antibacterial properties in them.

AIM

The aim of the study is to evaluate the efficacy of carbopol hydrogel with injected silver nanoparticles and HLDF6 peptide in the treatment of third-degree thermal burns *in vivo.*

MATERIALS AND METHODS

The structure of the work is represented by a prospective experimental study. The work was performed on 50 male Wistar rats, with an average weight of 230–250 g. Laboratory animals were divided into 5 groups, 10 animals respectively to study samples in each group.

Carbopol ETD 2020 hydrogel samples (0.5%) containing 0,00015% nano-silver and HLDF6 peptide with concentrations of 0%, 0,01%, 0,001%, 0,0001% and 0,00001% were obtained by reducing dissolved $AgNO_3$ in Carbopol ETD 2020 hydrogel solution containing HLDF6 peptide at a temperature of 70 °C. Glucose was used as a reducing agent.

Description of the manipulations performed

Sevoflurane inhalation anesthesia was used in the study. The animal was anesthetized by putting it in a special induction chamber with sevoflurane vaporized at concentrations of 4%. The surgical anesthesia stage developed over 5–10 minutes. After the animal was removed from the induction chamber, anesthesia was maintained by inhalation of concentration of 3% sevoflurane.

The animal was fixed to the operating table with ligatures to simulate the defect. Surgical field preparation included: depilation of the back area and marking a square in this area measuring 4x4 cm. The area of the intervention zone was 16 cm^2. After preparation, the surgical field was treated three times with an alcohol-based antiseptic solutions. Then, the temperature of the skin and the metal plate heated through a resistive heating element were determined using an electrothermocouple sensor of the Electroline multimeter (China). Exposure time was 10 seconds at a skin surface temperature of 95–97 °C. Next, radical necrectomy to the fascia was performed under aseptic conditions. An abdominal surgical scalpel blade was used to make an incision 1.5–2 mm deep. Then, using surgical tweezers and curved surgical scissors, the dermis with a small thickness of the subcutaneous fat was separated from the thoracolumbar fascia adjacent to it. Large-diameter bleeding vessels were coagulated using a coagulator. The resulting defect was washed with 0.9% sodium chloride solution at room temperature. After that, surgical sutures that involve the skin and muscle were applied to fix the wound edges. This was done in order to preserve the lesion area, as well as to prevent premature closure of the wound due to primary intension due to the anatomical and physiological features of the structure of the skin and subcutaneous fat of rats. Suturing was performed using atraumatic suture material Monocryl 3–0 (Bbraun). A needle holder and surgical tweezers were used for suturing. Sutures were applied at a distance of 1 cm from each other.

After suturing, the affected area on the back of the experimental animal was treated with the target agent. 1 ml of gel

was applied to the wound as standard. Repeated application of the gel was performed on the 7th, 14th and 21st days.

Maintenance and withdrawal of animals from the experiment

The maintenance of experimental animals was carried out on the basis of the vivarium of the National Medical Research Center for Pediatric Traumatology and Orthopedics named after G.I. Turner, and it fully complied with GOST 33215-2014 and GOST 33216-2014.

High demands were placed on the cleanliness of the conditions of maintenance, caused by the presence of massive skin injuries. Cleaning, washing and treatment of the cages of experimental animals with disinfectant solutions were carried out daily.

The animals were removed from the experiment on the 28th day after surgery. The withdrawal procedure was developed in accordance with paragraph 6.11 of GOST 33215-2014 and the Recommendations for euthanasia of experimental animals of the European Commission. It was an intravenous injection of 1 ml of lidocaine solution, carried out under deep anesthesia, which led to sudden cardiac arrest.

Disposal of laboratory animals and vivarium waste was carried out within the framework of standard procedures for disposal of Class B waste.

Evaluating treatment effectiveness

The effectiveness of the proposed treatment methods and the general appearance of wounds were assessed by photographing them once every 7 days. Visual examination of wounds was performed daily. The nature of the exudate, the presence and type of granulation, the time of scab rejection and healing of wound surfaces were recorded. The wound area was determined using planimetric method of L.N. Popov. This method involved applying a special film material to the wound surface, outlining the wound edges and then calculating the area either by transferring it to graph paper or using technical means.

In addition, the wound healing index was calculated using the following formula (Fenchin K.I., 1979):

$$\frac{(S-S_n)\cdot 100}{S\cdot T},$$

where S is the wound area at the previous measurement, mm^2; S_n is the wound area at the current measurement, mm^2; T is the interval between measurements, days.

This index allowed us to quantitatively assess the dynamics of the wound healing process based on the planimetric evaluation data.

The reliability of the differences in the obtained results was assessed using nonparametric analysis, namely the Mann–Whitney U-parameter. On its basis, the value of the reliability parameter p was determined. This method was used because of the impossibility of applying a normal distribution and Student's t-distribution due to the small number of groups, caused by requirements of GOST ISO 10993-2014 Part 2 and ethical standards.

Statistical data processing and its visualization were performed using the MS Excel, OriginR 2016 and Wolfram Mathematica 11.0 software packages.

RESULTS

During the experimental work, the survival rate of animals was 100% in all groups studied. The number of purulent complications during the entire treatment period was 4 cases in the control group, 1 observation in the group of gel-carrier with the addition of silver nanoparticles. No significant changes in body weight in experimental animals were detected throughout whole period of the experiment.

The results of the planimetric assessment of the wound surface area are represented in Table 1.

Based on the results obtained, a reliable difference was established between the groups of target gels (with the presence of the peptide in the range of 0.001 and 0.0001%) on the 14th day compared to the control group. In addition, the study revealed a reliable difference between the groups with the minimum peptide content (0.0001 and 0.00001%) and the gel group with 0.01% peptide content on the 14th day ($p < 0.05$). The best treatment effect from the standpoint of planimetry was shown by the gel with silver particles and a peptide content of 0.00001%, both in comparison to control group and other gels ($p < 0.05$).

It should be noted that the moment of increasing the efficiency of the gel with a decrease in the peptide concentration was identified. These changes were most pronounced by day 14, amounting to 84.3% of the wound area reduction

Table 1

Median values and interquartile ranges for the obtained samples

Group	Value	7th day	14th day	21th day	28th day
Gel + HLDF6 0,01%	Median, cm^2	11,39	6,2	3,26	1,32
	IQR, cm^2	4,59	3,59	2,97	2,17
Gel + HLDF6 0,001%	Median, cm^2	9,36	3,46	1,93	1,33
	IQR, cm^2	1,58	1,61	1,09	1,26
Gel + HLDF6 0,0001%	Median, cm^2	9,86	3,16	1,68	0,92
	IQR, cm^2	2,57	1,12	1,76	0,76
Gel + HLDF6 Peptide 0,00001%	Median, cm^2	8,28	2,51	1,61	1,19
	IQR, cm^2	1,41	1,33	1,03	0,89
Gel (without HLDF6)	Median, cm^2	10,5	4,63	1,9	1,985
	IQR, cm^2	3,075	3,12	1,48	1,49

over 14 days in the group with the gel containing 0.00001% peptide. In the control group, the wound area decreased by 58.7%, in the group with the gel containing 0.01% peptide — by 61.3%, and in the group with the gel containing 0.0001% peptide — by 78.4%, over the same period ($p < 0.05$) (Fig. 1).

There was no significant difference between the two groups with the lowest peptide content. Both groups showed a significant improvement in the wound healing dynamics on the 14th day, both when compared with the control group without the addition of the peptide and in the group with its maximum content.

At the same time, it is necessary to note the effect of increasing the wound surface area on 28th day in the group with a peptide content of 0.01% This is especially clearly observed in the graph of the dynamics of the wound healing indices (Fig. 2).

It is also possible to noted extremely high values of this indicator for the period between the 7th and 14th days for the groups with the lowest peptide content in the graph of the dynamics of the wound healing indices. It should be emphasized that the group with the highest peptide content showed the worst wound healing index values among all the groups studied and had a peak only on the 21st day. At the same time, the groups with a lower peptide content demonstrated this peak on the 14th day of the study.

FINDINGS

1. The use of low doses of the HLDF6 peptide tested proved to be the most effective for activating healing processes on the 14th day. Gels containing 0.0001 and 0.00001% of the peptide studied had the most reliable ($p < 0.05$ relative to the control gel group without the peptide) and pronounced differences on the 14th day of treatment.

2. Application of a gel with the highest peptide content (0.01%) led to an increase in the treatment period and a significant deterioration in the final results of the therapy. This suggests a high degree of immunogenicity of such concentrations of the peptide tested. The gel containing 0.001% HLDF6 peptide did not show reliable differences relative to either the control group or other gels with the studied substance.

CONCLUSION

According to the results of the study, it is possible to state the prospects of using low doses of the HLDF6 peptide (volume concentration in the range of 10^{-4}–10^{-5}%) in gel preparations in the treatment of full-layer wounds. Small concentrations of HLDF6 peptide allow significant activating of wound healing processes in the early period and reducing the incidence of infectious complications.

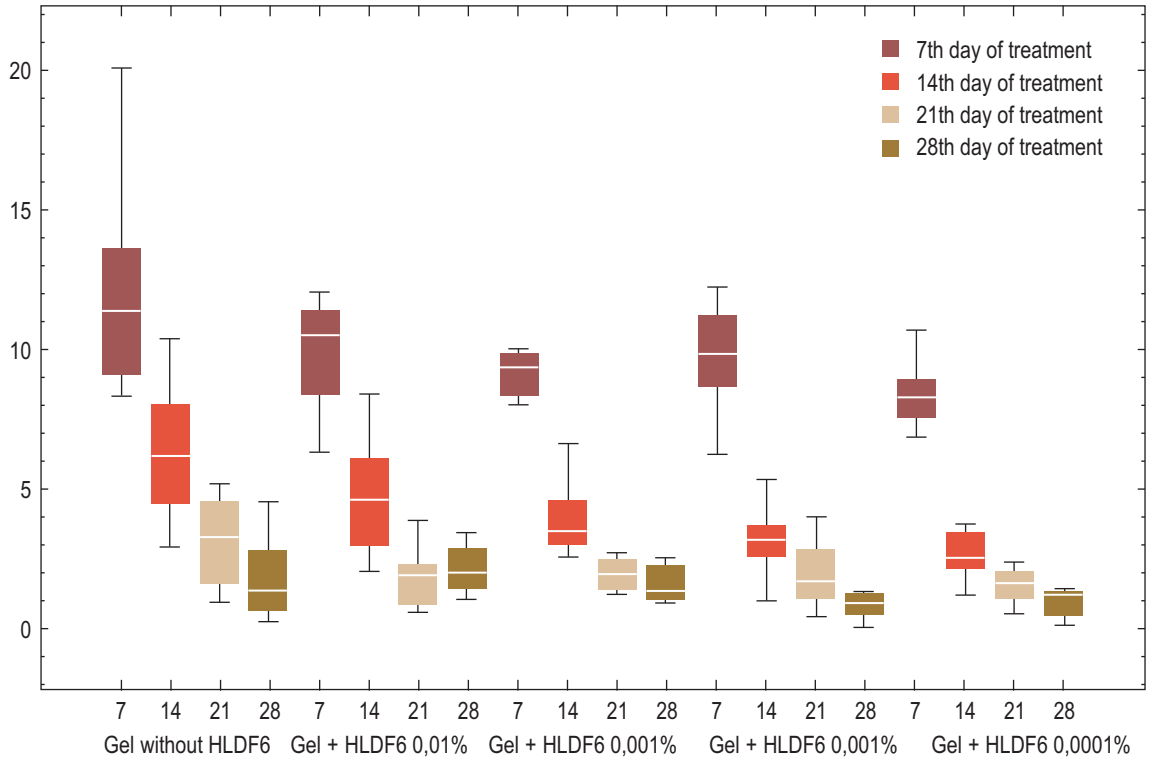


Fig. 1. Diagram comparing the areas of wound surfaces in all studied groups

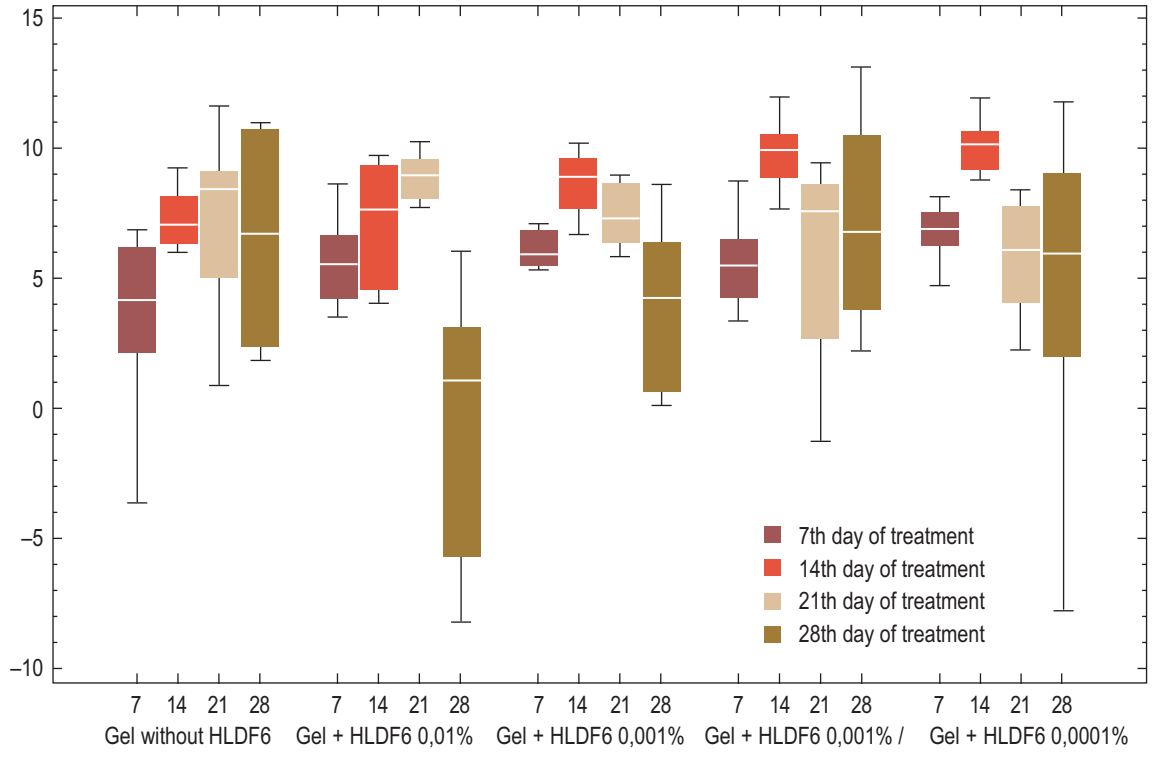


Fig. 2. Graph of the dynamics of wound healing indices in experimental groups

ADDITIONAL INFORMATION

Author contribution. Shabunin A.S. — formulation of the goal and development of the design of the study, writing all sections of the article, statistical processing of the data obtained; Zinoviev E.V. — stage editing of the text of the article; Vissarionov S.V. — final editing of the text of the article; Asadulaev M.S. — writing the "Introduction" section, step-by-step editing of the text of the article; Makarov A.Yu. — conducting experimental studies, collecting and analyzing the data obtained; Fedyuk A.M. — conducting experimental studies, studying histological preparations; Rybinskikh T.S., Kostyakov D.V., Semiglazov A.V., Pyatakov S.N. — conducting experimental studies, analysis of the obtained data; Pershina P.A. — step-by-step editing of the text of the article, translation of the text into English.

Competing interests. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

Source of funding. None.

Ethical review. The study was approved by the ethics committee of the National Research Center for Pediatric Traumatology and Orthopedics named after G.I. Turner of the Ministry of Health of Russia.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Шабунин А.С. — формулировка цели и разработка дизайна исследования, написание всех разделов статьи, статистическая обработка полученных данных; Зиновьев Е.В. — этапное редактирование текста статьи; Виссарионов С.В. — финальное редактирование текста статьи; Асадулаев М.С. — написание раздела «Введение», этапное редактирование текста статьи; Макаров А.Ю. — проведение экспериментальных исследований, сбор и анализ полученных данных; Федюк А.М. — проведение экспериментальных исследований, изучение гистологических препаратов; Рыбинских Т.С., Костяков Д.В., Семиглазов А.В., Пятакова С.Н. — проведение экспериментальных исследований, анализ полученных данных; Першина П.А. — этапное редактирование текста статьи, перевод текста на английский язык.

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

Источник финансирования. Отсутствует.

Этическая экспертиза. Исследование одобрено этическим комитетом ФГБУ «НМИЦ детской травматологии и ортопедии им. Г.И. Турнера» Минздрава России.

REFERENCES

1. Alekseev A.A. Kompleksnoye lecheniye glubokikh ozhogov na osnove primeneniya khirurgicheskoy nekrektomii I sovremennykh biotekhnologicheskikh metodov. [Comprehensive treatment of deep burns based on the use of surgical necrectomy and modern biotechnological methods]. Annaly khirurgii. 2012; 6: 41–5. (in Russian).
2. Zinoviev E.V., Tsygan V.N., Artsimovich I.V. i dr. Eksperimental'naya otsenka effektivnosti mestnogo lecheniya ozhogov kozhi gidrogelem legkodispergiruyemogo karbopola 2020 s peptidom chelovecheskogo leykoznogo faktora differentsirovki-6. [Experimental evaluation of the effectiveness of local treatment of skin burns with easily dispersed carbopol 2020 hydrogel with human leukemic differentiation factor-6 peptide]. Vestnik rossiyskoy voyenno-meditsinskoy akademii. 2020; 3(63): 48–152. (in Russian).
3. Kopichev O.A., Nikolaev A.E. Sovremennyye voyny: analiz tendentsiy razvitiya mezhgosudarstvennogo protivoborstva, klassifikatsiya form i sposobov bor'by, formirovaniye priznakov I kriteriyev voyennogo konflikta. [Modern wars: analysis of trends in the development of interstate confrontation, classification of forms and methods of struggle, formation of signs and criteria of a military conflict]. Sistemy upravleniya, svyazi i bezopasnosti. 2021; 32(1): 1–32. (in Russian).
4. Lagvilava T.O., Zinoviev E.V., Ivakhnyuk G.K. i dr. Ranozazhivlyayushchiye sredstva na osnove karbopolov. [Wound healing agents based on carbopols] Izvestiya Sankt-Peterburgskogo Gosudarstvennogo Tekhnologicheskogo Instituta (Tekhnicheskogo Universiteta). 2013; 18(44): 47–52. (in Russian).
5. Sosnina A.V., Mikhailova E.S., Autenshlyus A.I. i dr. Klassy I subklassy antitel k faktoru dif-ferentsirovki HLDF I peptidam gaponina, vzaimosvyaz' ikh urovnya s patogistologicheskimi parametrami adenokartsinom tolstoy kishki. [Classes and subclasses of antibodies to the differentiation factor HLDF and gaponin peptides, the relationship of their level with pathohistological parameters of colon adenocarcinomas]. Immunologiya. 2012; 2: 92–3. (in Russian).
6. Sysoeva G.M., Danilenko E.D., Masycheva V.I. i dr. Vliyaniye peptida HLDF-6 na proliferativnuyu aktivnost' splenotsitov v kul'ture kletok na fone vvedeniya agonistov opiatnykh retseptorov. [The effect of HLDF-6 peptide on the proliferative activity of splenocytes in cell culture against the background of the administration of opiate receptor agonists]. Sibirskiy meditsinskiy zhurnal. 2009; 4: 55–9. (in Russian).
7. Uskov V.M., Uskov M.V. Osnovnyye zadachi sluzhby meditsiny katastrof v usloviyakh chrezvychaynykh situatsiy mirnogo I voyennogo vremeni. [The main tasks of the disaster medicine service in emergency situations of peacetime and wartime]. Vestnik Voronezhskogo gosudarstvennogo tekhnicheskogo universiteta. 2010. Available at: https://cyberleninka.ru/article/n/osnovnye-zadachi-sluzhby-meditsiny-katastrof-v-usloviyah-chrezvychaynyh-situatsiy-mirnogo-i-voennogo-vremeni (accessed 06/07/2023). (in Russian).
8. Ali Y., Ali T. Nandrolone decanoate safely combats catabolismin burned patients: A new potential indication after recall. Burns. 2022; 48(1): 59–68.
9. Bakadia B.M., Lamboni L., Abeer A.Q. Antibacterial silk sericin/poly (vinyl alcohol) hydrogel with antifungal property for potential infected large burn wound healing: Systemic evaluation. Smart Mater. Med. 2023; 4: 37–58.
10. Behshood P., Rezaei M. A glimpse into the use of silver-nanoparticles as a promising treatment for burn wounds Burns. 2023; 49(1): 241–3.
11. Cao Y.L., Liu Z.C., Chen X.L. Efficacy of hydrosurgical excision combined with skin grafting in the treatment of deep partial-thickness and full-thickness burns: A two-year retrospective study. Burns. 2022. Available at: https://www.researchgate.net/publication/362350344_Efficacy_of_hydrosurgical_excision_combined_with_skin_grafting_in_the_treatment_of_deep_partial-thickness_and_full-thickness_burns_a_two-year_retrospective_study (accessed 07.06.2023).
12. Cenkey A., Hargitai E., Pakai E. et al. Effectiveness of four topical treatment methods in a rat model of superficial partial-thickness burn injury: the advantages of combining zinc-hyaluronan gel with silver foam dressing. Injury. 2022; 53(12): 3912–9.
13. Dobrovolskaya I.P., Yudin V.E., Popryadukhin P.V., Lebedeva I.O. In vivo study of the nanofiber-based composite wound dressing intended for treatment of deep skin wounds. J. Appl. Cosmetol. 2016; 34(1): 1–8.
14. Evdokimov V.I., Kourov A.S. Genesis of research on burn injury (analysis of domestic articles in 2005–2017). Medico-Biological Socio-Psychological Issues Saf. Emerg. Situations. 2019; 6(4): 108–20.
15. Baassiri M., Dosh L., Haidar H. et al. Nerve growth factor and burn wound healing: Update of molecular interactions with skin cells. Burns. 2022. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0305417922002820?via%3Dihub (accessed 07.06.2023).
16. Gragnani A., Tonarelli E., Chomiski V. et al. Fibroblast growth factor in the treatment of burns: A systematic review. Burns. 2022; 48(1): 104–10.
17. Haik J., Segalivich M., Visentin D. et al. Comparison of stationary and dynamic fractional CO2 laser modalities of large burns treatment: Experimental laboratory model. Burns. 2021; 49(1):162–8.
18. Issler-Fisher A.C. The importance of biomechanics and the kinetic chains of human movement in the development and treatment of burn scars — A narrative review with illustrative cases. Burns. 2022; 49(3): 707–15.
19. Keyloun J.W. Assessing Factor V Antigen and Degradation Products in Burn and Trauma Patients. J. Surg. Res. 2022; 274: 169–77.
20. Muthukumar V., Dash S., Danish A. F. et al. Fibrin sealant for split-thickness skin graft fixation in burn wounds — An ancillary postulated role in scar modulation. Wound Med. 2020; 31: 00197.
21. Ozturk S., Karagoz H. Experimental stem cell therapies on burn wound: Do source, dose, timing and method matter? Burns. 2015; 41(6): 1133–9.
22. Sun T.C., Yan B.Y., Ning X.C. et al. Cool and hot chitosan/platelet-derived growth factor nanofibers for outdoors burns. Int. J. Biol. Macromol. 2022; 218: 409–19.
23. Sun T.C. Icy core–shell composite nanofibers with cooling, antibacterial and healing properties for outdoor burns. J. Colloid Interface Sci. 2023; 629: 206–16.
24. Zinovyev E.V. Experience of stem cell use in treatment of skin burns. Pediatr. 2018; 9(4): 12–27.

ЛИТЕРАТУРА

1. Алексеев А.А. Комплексное лечение глубоких ожогов на основе применения хирургической некрэктомии и современных биотехнологических методов. Анналы хирургии. 2012; 6: 41–5.
2. Зиновьев Е.В., Цыган В.Н., Арцимович И.В. и др. Экспериментальная оценка эффективности местного лечения ожогов кожи гидрогелем легкодиспергируемого карбопола 2020 с пептидом человеческого лейкозного фактора дифференцировки-6. Вестник Российской военно-медицинской академии. 2020; 3(63): 48–152.
3. Копичев О.А., Николаев А.Е. Современные войны: анализ тенденций развития межгосударственного противоборства, классификация форм и способов борьбы, формирование признаков и критериев военного конфликта. Системы управления, связи и безопасности. 2021; 32(1): 1–32.
4. Лагвилава Т.О., Зиновьев Е.В., Ивахнюк Г.К. и др. Ранозаживляющие средства на основе карбополов. Известия Санкт-Петербургского государственного технологического института (Технического Университета). 2013; 18(44): 47–52.
5. Соснина А.В., Михайлова Е.С., Аутеншлюс А.И. и др. Классы и субклассы антител к фактору диф-ференцировки HLDF и пептидам гапонина, взаимосвязь их уровня с патогистологическими параметрами аденокарцином толстой кишки. Иммунология. 2012; 2: 92–3.
6. Сысоева Г.М., Даниленко Е.Д., Масычева В.И. и др. Влияние пептида HLDF-6 на пролиферативную активность спленоцитов в культуре клеток на фоне введения агонистов опиатных рецепторов. Сибирский медицинский журнал. 2009; 4: 55–9.
7. Усков В.М., Усков М.В. Основные задачи службы медицины катастроф в условиях чрезвычайных ситуаций мирного и военного времени. Вестник Воронежского государственного технического университета. 2010. Доступен по: https://cyberleninka.ru/article/n/osnovnye-zadachi-sluzhby-meditsiny-katastrof-v-usloviyah-chrezvychaynyh-situatsiy-mirnogo-i-voennogo-vremeni (дата обращения: 07.06.2023).
8. Ali Y., Ali T. Nandrolone decanoate safely combats catabolismin burned patients: A new potential indication after recall. Burns. 2022; 48(1): 59–68.
9. Bakadia B.M., Lamboni L., Abeer A.Q. Antibacterial silk sericin/poly (vinyl alcohol) hydrogel with antifungal property for potential infected large burn wound healing: Systemic evaluation. Smart Mater. Med. 2023; 4: 37–58.
10. Behshood P., Rezaei M. A glimpse into the use of silver-nanoparticles as a promising treatment for burn wounds Burns. 2023; 49(1): 241–3.
11. Cao Y.L., Liu Z.C., Chen X.L. Efficacy of hydrosurgical excision combined with skin grafting in the treatment of deep partial-thickness and full-thickness burns: A two-year retrospective study. Burns. 2022. Available at: https://www.researchgate.net/publication/362350344_Efficacy_of_hydrosurgical_excision_combined_with_skin_grafting_in_the_treatment_of_deep_partial-thickness_and_full-thickness_burns_a_two-year_retrospective_study (accessed 07.06.2023).
12. Cenkey A., Hargitai E., Pakai E. et al. Effectiveness of four topical treatment methods in a rat model of superficial partial-thickness burn injury: the advantages of combining zinc-hyaluronan gel with silver foam dressing. Injury. 2022; 53(12): 3912–9.
13. Dobrovolskaya I.P., Yudin V.E., Popryadukhin P.V., Lebedeva I.O. In vivo study of the nanofiber-based composite wound dressing intended for treatment of deep skin wounds. J. Appl. Cosmetol. 2016; 34(1): 1–8.
14. Evdokimov V.I., Kourov A.S. Genesis of research on burn injury (analysis of domestic articles in 2005–2017). Medico-Biological Socio-Psychological Issues Saf. Emerg. Situations. 2019; 6(4): 108–20.
15. Baassiri M., Dosh L., Haidar H. et al. Nerve growth factor and burn wound healing: Update of molecular interactions with skin cells. Burns. 2022. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0305417922002820?via%3Dihub (accessed 07.06.2023).
16. Gragnani A., Tonarelli E., Chomiski V. et al. Fibroblast growth factor in the treatment of burns: A systematic review. Burns. 2022; 48(1): 104–10.
17. Haik J., Segalivich M., Visentin D. et al. Comparison of stationary and dynamic fractional CO2 laser modalities of large burns treatment: Experimental laboratory model. Burns. 2021; 49(1):162–8.
18. Issler-Fisher A.C. The importance of biomechanics and the kinetic chains of human movement in the development and treatment of burn scars — A narrative review with illustrative cases. Burns. 2022; 49(3): 707–15.
19. Keyloun J.W. Assessing Factor V Antigen and Degradation Products in Burn and Trauma Patients. J. Surg. Res. 2022; 274: 169–77.
20. Muthukumar V., Dash S., Danish A. F. et al. Fibrin sealant for split-thickness skin graft fixation in burn wounds — An ancillary postulated role in scar modulation. Wound Med. 2020; 31: 00197.
21. Ozturk S., Karagoz H. Experimental stem cell therapies on burn wound: Do source, dose, timing and method matter? Burns. 2015; 41(6): 1133–9.
22. Sun T.C., Yan B.Y., Ning X.C. et al. Cool and hot chitosan/platelet-derived growth factor nanofibers for outdoors burns. Int. J. Biol. Macromol. 2022; 218: 409–19.
23. Sun T.C. Icy core–shell composite nanofibers with cooling, antibacterial and healing properties for outdoor burns. J. Colloid Interface Sci. 2023; 629: 206–16.
24. Zinovyev E.V. Experience of stem cell use in treatment of skin burns. Pediatr. 2018; 9(4): 12–27.

UDC 616.5-001.17-089+576.5+616-089.844+57.085.21+547.96+577.11
DOI: 10.56871/RBR.2023.66.21.002

COMPARISON OF THREE DIFFERENT METHODS FOR PROCESSING ACELLULAR DERMAL MATRIX

© Ilya A. Barsuk[1], Arina A. Kokorina[1, 2], Nikolai V. Belyi[1], Semyon S. Debenok[1], Nikolay S. Dedanishvili[2], Ruslan I. Glushakov[1, 2]

[1] Military Medical Academy named after S.M. Kirov. Akademician Lebedev str., 6, lit. G, Saint Petersburg, Russian Federation, 194044
[2] Saint Petersburg State Pediatric Medical University. Lithuania 2, Saint Petersburg, Russian Federation, 194100

Contact information: Ilya A. Barsuk — Associate of the Research Department (Biomedical Research) of the Research Center. E-mail: barsuk20220@gmail.com ORCID ID: 0000-0002-3728-9966

For citation: Barsuk IA, Kokorina AA, Belyi NV, Debenok SS, Dedanishvili NS, Glushakov RI. Comparison of three different methods for processing acellular dermal matrix // Russian biomedical research (St. Petersburg). 2023; 8(3): 12-17. DOI: https://doi.org/10.56871/RBR.2023.66.21.002

Received: 13.06.2023 **Revised: 04.07.2023** **Accepted: 21.09.2023**

Abstract. Tissue engineering is an inter-related and a multi-disciplinary field that blend of biology and engineering efforts that attempt to address clinical problem of skin damage by many reason including burn, trauma etc. Decellularization of allogeneic tissues witn subsequent combened of the decellularized tissue with autologous cells and/or the processed of hybrid structures plays a pivotal role in current tissue engineering approaches for temporary or constant closure of skin defects. The purpose of this study was to compare methods for processing a decellularized dermal matrix and to determine the optimal protocol for obtaining a decellularized dermal matrix scaffold. As a result of a comparative analysis, it was determined that all three skin decellularization protocols make it possible to obtain a product with desired properties by the absence of cellular and nuclear material. However, the use of various detergents for decellularization leads to some structural features of the resulting material. The significance of differences in the structural characteristics of the obtained matrices should be evaluated in future studies in terms of stimulation of cell migration and proliferation.

Key words: acellular dermal matrix; decellularization; burn injury; collagen; regenerative medicine.

СРАВНЕНИЕ МЕТОДИК ПОЛУЧЕНИЯ АЦЕЛЛЮЛЯРНОГО ДЕРМАЛЬНОГО МАТРИКСА

© Илья Александрович Барсук[1], Арина Александровна Кокорина[1, 2], Николай Викторович Белый[1], Семен Сергеевич Дебенок[1], Николай Сергоевич Деданишвили[2], Руслан Иванович Глушаков[1, 2]

[1] Военно-медицинская академия им. С.М. Кирова. 194044, г. Санкт-Петербург, ул. Академика Лебедева, 6, литера Ж
[2] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация: Илья Александрович Барсук — адъюнкт научно-исследовательского отдела (медико-биологических исследований) научно-исследовательского центра. E-mail: barsuk20220@gmail.com ORCID ID: 0000-0002-3728-9966

Для цитирования: Барсук И.А., Кокорина А.А., Белый Н.В., Дебенок С.С., Деданишвили Н.С., Глушаков Р.И. Сравнение методик получения ацеллюлярного дермального матрикса // Российские биомедицинские исследования. 2023. Т. 8. № 3. С. 12–17. DOI: https://doi.org/10.56871/RBR.2023.66.21.002

Поступила: 13.06.2023 **Одобрена: 04.07.2023** **Принята к печати: 21.09.2023**

Резюме. Развивающиеся технологии тканевой инженерии, несомненно, представляют интерес для разработки материала для закрытия дефектов кожных покровов. Одним из перспективных направлений является децеллюляризация аллогенных тканей для временного закрытия дефектов кожных покровов, насыщения децеллюляризированной ткани аутологичными клетками и/или создания гибридных конструкций. Цель данной работы состояла в сравнении методик получения децеллюляризированного дермального матрикса и определении оптимального протокола для последующей разработки тканеинженерной кожи. Для достижения цели была проведена оценка

трех различных методов получения ацеллюлярных дермальных матриксов путем децеллюляризации кожи. В результате сравнительного анализа было определено, что все три протокола децеллюляризации кожи позволяют получить продукт с заданными свойствами: отсутствие клеточного и ядерного материала. Однако использование для децеллюляризации различных детергентов приводит к некоторым структурным особенностям полученного материала. Значимость различий в структурных характеристиках полученных матриксов должна быть оценена в дальнейших работах с точки зрения стимуляции миграции и пролиферации клеток.

Ключевые слова: ацеллюлярный дермальный матрикс; децеллюляризация; ожоговая травма; коллаген; регенеративная медицина.

INTRODUCTION

Currently, the search for new optimal means of surgical treatment of skin lesions of various genesis is an extremely urgent task [5, 7]. It is necessary to achieve the maximum possible combination of therapeutic properties that improve the patient's condition and increase the quality of subsequent life, ease of use in routine clinical practice, facilitating the widespread implementation of the method. It is also important to create the possibility of relatively simple production of a large volume of medical devices, which will ensure the economic feasibility of their use in comparison with other possible options [2]. One of the areas of action to complete this task may be the development of medical products using biomedical technologies. A variant of such a multifunctional product may be a tissue processing product that preserves a number of properties necessary in the clinic: acellular dermal matrix (ADM) obtained by detergent-based decellularization. The application of this object seems to be promising in the treatment of deep skin lesions, including burns. The main advantages of this biological material are the composition and structural organization of the resulting product, corresponding to the patient's own dermis. This allows it to be used as a temporary biological coating that promotes the migration of the patient's cells and the regeneration of functionally competent skin, while effectively performing the functions of a wound dressing. After a full processing cycle, the ADM obtained from donor skin does not contain immunogenic factors that are caused by cellular structures and can lead to rejection of the donor material. At the same time, the native structure and composition of the extracellular matrix of the dermis are preserved [3]. This product can be considered both as an independent medical device and as a stage for further development of a tissue-engineered skin substitute. At present, a is a lot of practical experience has been accumulated in skin treatment for the purpose of decellularization. The wide range of reagent base for these tasks, as well as methods for assessing the obtained result, has been determined [4]. In addition, there is no perfect method approved in clinical recommendations and widely used. At the moment, the expansion of the range of methods and their technological development are especially relevant. This is due to the fact that in modern conditions logistical problems with the availability of various reagents are possible.

AIM

The aim of the study is to determine the optimal method of skin decellularization based on a comparative analysis of acellular dermal matrices obtained by different techniques.

MATERIALS AND METHODS

Skin area from the abdominal region was obtained during cosmetic surgery (tummy tuck or abdominoplasty) in a 37-year-old female patient and delivered to the Research Department of Medical and Biological Research of the Research Center of the Military Medical Academy named after S.M. Kirov of the Ministry of Defense of the Russian Federation for experimental work. Without breaking sterility, a fatty layer of subcutaneous tissue was mechanically removed using a surgical instrument. The resulting skin layer was divided into 9 equal parts, which were washed abundantly with sterile distilled water. 3 groups of samples were formed (3 in each group). The area of each sample was ≈7.78 cm^2. Then the skin layers were placed in a low temperature refrigerator for storage at a temperature of –80 °C for a period of one day (Angelantoni Life Science Platinum 340 V, Italy). In all cases, samples were thawed at room temperature for 4–6 hours.

Decellularization was then performed using three different protocols shown in Table 1.

Each sample was placed in a glass container with 200 ml of the corresponding detergent solution and subjected to shaking on an orbital shaker at 200 rpm at 37 °C for decellularization. The solutions were changed according to the protocols (Table 1). After each stage of detergent use, samples were thoroughly washed with sterile distilled water under the same conditions.

In accordance with the protocol No. 1, the samples were first placed in the Versen solution (Biolot, Russian Federation) after thawing, where they were kept for 16 hours. The next stage was to treat the samples with a 0.5% sodium dodecyl sulfate solution (SDS, LenReaktiv, Russian Federation) for 48 hours. The solution was changed to a fresh one every 12 hours.

Table 1

Stages of technologies for processing decellularized dermal matrix using three different methods

Processing stage number	Protocol No. 1	Protocol No. 2	Protocol No.3
1	Freezing–thawing	Freezing–thawing	Freezing–thawing
2	Versen solution (16 hours)	3% Tween 20 (16 hours)	1,8 M NaCl (3 hours)
3	Washing with sterile distilled water (15 minutes)	Washing with sterile distilled water (15 minutes)	Washing with sterile distilled water (15 minutes)
4	0.5% SDS (24 hours, 2 solution changes). ***Histological examination*** 0.5% SDS (24 hours, 2 solution changes)	0.5% SDS (48 hours, 4 solution changes)	3% Tween 20 (16 hours)
5	Washing solution ***Histological examination***	Washing solution ***Histological examination***	Washing with sterile distilled water (15 minutes)
6	–	–	0.5% SDS (48 hours, 4 solution changes)
7	–	–	Washing solution ***Histological examination***

Protocol No. 2 repeated method No. 1, except that the 3% Tween 20 solution (PanReac, Spain) was used instead of the Versen solution.

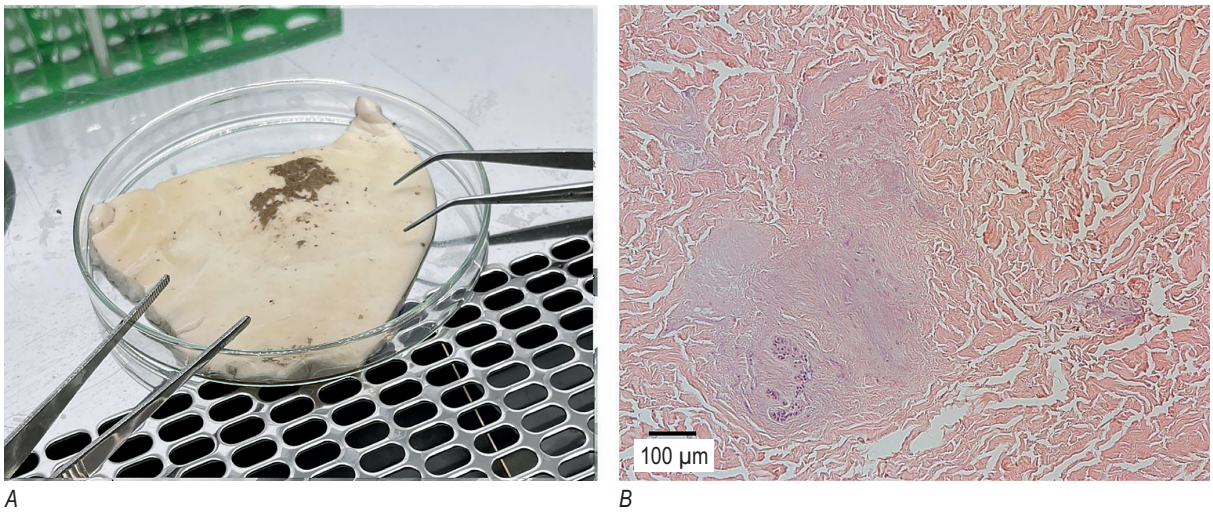
Protocol No. 3 differed from the previous one only by adding an additional stage after thawing the skin areas — a 3-hour treatment with 1.8 M NaCl (LenReaktiv, Russian Federation).

After all stages of detergent treatment, the samples were thoroughly washed with phosphate-buffered saline (Biolot, Russian Federation). The appearance of the samples was noted throughout the treatment. Then, upon completion of decellularization, a histological examination of the central and marginal areas of each sample carried out. When performing protocol No. 1, the histological examination was carried out twice (Table 1). The material was fixed in 10% formalin, dehydrated and embedded in paraffin blocks. 2–3 μm thick sections were stained with hematoxylin and eosin, according to Van Gieson (Biovitrum, Russian Federation), as well as with the nuclear-specific fluorescent dye DAPI (4',6-diamidino-2-phenylindole).

The study did not contradict the provisions of the Ethical principles for medical research involving human subjects of the World Medical Association of Helsinki. The postoperative material (skin flap) was transferred with the patient's approval after signing a written voluntary informed consent.

RESULTS

During protocol No. 1, the separation of the epidermal layer was detected only at the SDS processing stage and



A *B*

Fig. 1. Morphological study of acellular dermal matrix in incomplete decellularization of the skin: macroscopic (*A*) and microscopic (magnification 100×, hematoxylin and eosin staining) (*B*) images

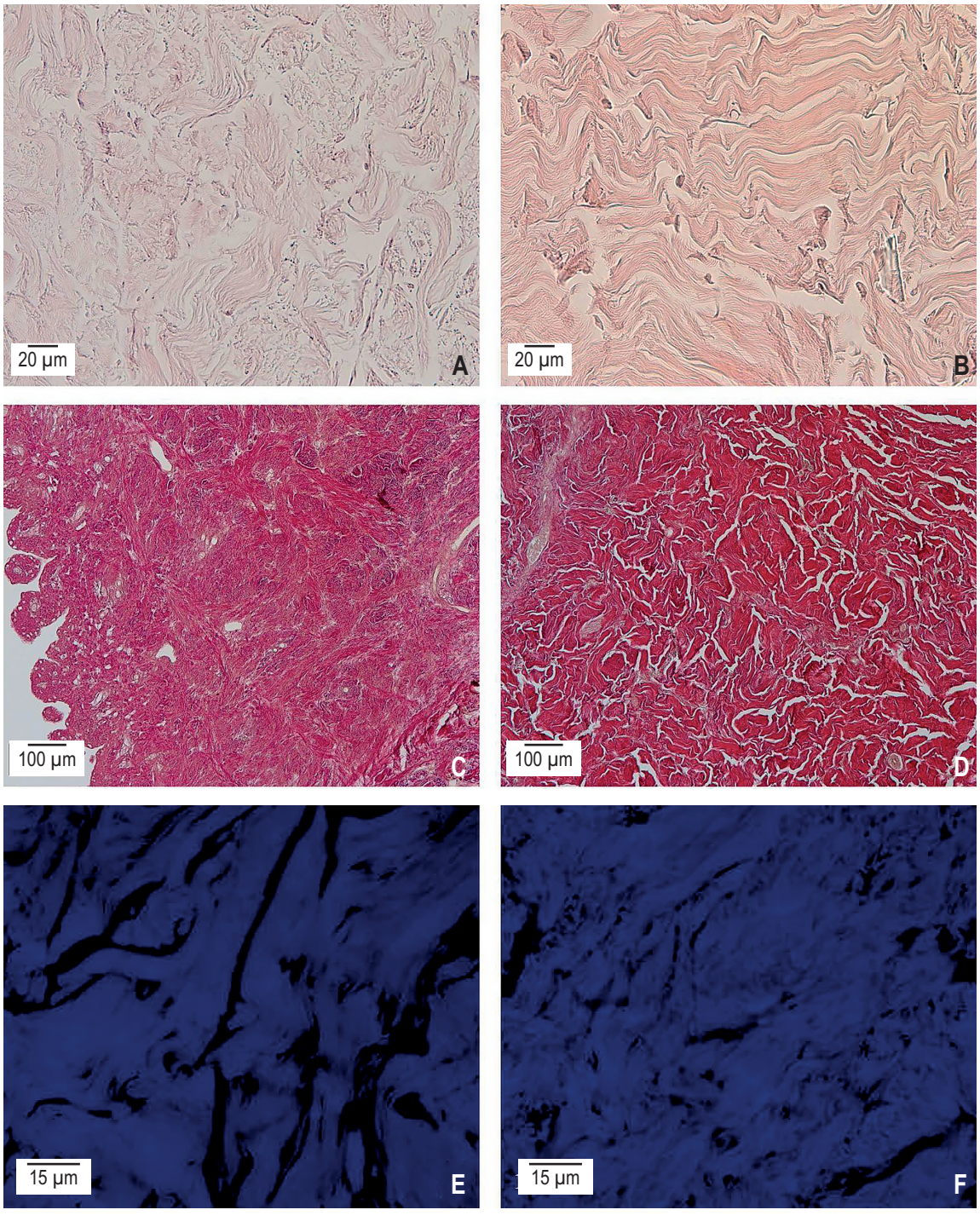


Fig. 2. **Acellular dermal matrix obtained according to protocol No. 1. A, C, F — marginal area; B, D, F — central area. Hematoxylin and eosin staining (*A*, *B*), van Gieson's staining (*C*, *D*), DAPI staining (*E*, *F*)**

was completed at the end of the protocol. The decellularized tissue was quite flexible and pliable, smooth on the epidermal side, but noticeably fibrous on the reverse side.

In the middle of the protocol (stage 4, Table 1), remnants of the epidermis were observed, mosaically located over the entire surface of the material. Histological examination also showed cellular structures in the central region of the samples (Fig. 1). No nuclei or other cellular elements were detected at the end of the protocol (Fig. 2).

Protocol No. 2 differed from Protocol No. 1 in that a softer detergent, Tween 20, was used for the initial treatment. In this case, the removal of epidermis from the dermis was slower, but the result (in terms of removing cellular elements and the epidermal layer) at the end of the protocol was similar.

However, there was a significant external difference in the resulting sample — there is no fiber unweaving on its reverse side, mechanically it was somewhat denser and more elastic.

The use of a hypertonic NaCl solution in Protocol No. 3 allowed for faster initiation of the process of separating the epidermal layer from the dermis. This process began almost immediately, but was completed closer to the end of the protocol. Thus, the additional stage did not provide any advantages, and at the end of the protocol, the result was similar to that obtained using Protocol No. 2, including in terms of appearance.

The study of ADM micropreparations obtained by all the methods researched showed complete removal of cellular elements. It was confirmed by staining with hematoxylin and eosin (Fig. 2, *A*, *B*) and the nuclear-specific dye DAPI — only autofluorescence of extracellular matrix proteins was visualized during microscopy (Fig. 2, *E*, *F*). Van Gieson's staining of sections made it possible to verify the integrity of collagen fibers (Fig. 2, *C*, *D*).

Morphological differences between the samples obtained by three different methods during microscopy of histological preparations were not detected. However, the use of Versen solution led to some fiber unweaving of the collagen matrix on one side, which may also have a positive effect on the migration of recipient cells.

DISCUSSION

Based on the obtained data on the quality assessment of the obtained cell-free material, it can be stated that all three protocols presented by us are quite effective in obtaining the final product with the required biological characteristics. The obtained ADM retains the structural organization necessary for the implementation of the therapeutic effect in clinical use. At the same time, there is no cellular component that creates an immunogenic potential that can cause rejection of the sample when placed on the wound surface. The physicochemical properties of the product ensure ease of handling and direct use in the treatment of skin lesions of various etiologies. At the same time, the production process is well-established, does not require complex technological solutions and expensive reagents, does not impose too high requirements on the qualifications of personnel. This makes it relatively easy to implement at the scientific and production base of the Military Medical Academy named after S.M. Kirov of the Ministry of Defense of the Russian Federation. The combination of these facts opens up great prospects for extensive production and clinical use of ADM in the treatment of skin defects of various geneses. Further definition of patient categories and the state of their wounds for the use of ADM seems quite logical.

Differences in the skin decellularization protocols had no significant effect on the final result. Protocol No. 3 took 3.5 hours longer than protocols No. 1 and 2, but no significant increase in the effect was found. Thus, there was acceleration of epidermal layer separation, which did not affect further processing. It can be assumed that to increase the efficiency of skin treatment with a hypertonic NaCl solution, a longer exposure with periodic change of the latter is necessary.

The same amount of reagents, time and labor is needed to execute protocols 1 No. 1 and 2. However, in the first case, the material was softer, with some fiber unweaving on one side. It is probably a consequence of the effect on the collagen matrix of ethylenediaminetetraacetic acid (EDTA), which is the basis of the Versen solution. A similar effect has been shown in the decellularization of corneal lenticular tissue with trypsin-EDTA solution [1]. In the case of skin, this effect may be useful, because there is no significant destruction of the extracellular matrix. But the increase in porosity and, accordingly, a decrease in the density of the material will facilitate the migration of the patient cells into the material [6].

CONCLUSION

1. All three protocols studied allow obtaining an acellular dermal matrix with the specified properties of absence of cellular and nuclear material.
2. Protocol No. 1 leads to fiber unweaving of the matrix, which may be a positive factor for the migration of recipient cells.
3. Acellular matrix obtained as a result of protocols No. 2 and 3, on the contrary, retained its density, while remaining elastic.
4. The features of the structural characteristics of the obtained matrices should be assessed in further studies in terms of their impact on the success of clinical application.

ADDITIONAL INFORMATION

Author 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.

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

Funding source. This study was not supported by any external sources of funding.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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.

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

REFERENCES

1. Borzenok S.A., Kostenev S.V., Doga A.V. i dr. Sravnitel'nyj analiz protokolov decelljuljarizacii lentikuljarnoj tkani rogovicy. [Comparative analysis of protocols for decellularization of lenticular corneal tissue]. Vestnik transplantologii i iskusstvennyh organov. 2021; 23(2): 137–46. (in Russian).
2. Dzhabrailova D.Sh., Zikirjahodzhaev A.D., Usov F.N. i dr. Ispol'zovanie alloimplantata na osnove tverdoj mozgovoj obolochki pri rekonstruktivno-plasticheskih operacijah u bol'nyh rakom molochnoj zhelezy. [The use of alloimplant based on the dura mater in reconstructive plastic surgery in patients with breast cancer]. Opuholi zhenskoj reproduktivnoj sistemy. 2021; 17(3): 44–50. (in Russian).
3. Sachkov A.V., Borovkova N.V., Zhirkova E.A. i dr. Ispol'zovanie trupnoj kozhi v lechenii ran. [Use of cadaveric skin in wound healing]. Transplantologija. 2018; 10(4): 327–35. (in Russian).
4. Sotnichenko A.S., Gilevich I.V., Melkonjan K.I. i dr. Razrabotka metodiki poluchenija dermal'nogo vnekletochnogo matriksa. [Development of a technique for obtaining a dermal extracellular matrix]. Vestnik transplantologii i iskusstvennyh organov. 2020; 21(4): 81–7.
5. Guo Z.Q., Qiu L., Gao Y. et al. Use of porcine acellular dermal matrix following early dermabrasion reduces length of stay in extensive deep dermal burns. Burns. 2016; 42(3): 598–604.
6. Nasiry D., Khalatbary A.R., Abdollahifar M.A. et al. Engraftment of bioengineered three-dimensional scaffold from human amniotic membrane-derived extracellular matrix accelerates ischemic diabetic wound healing. Arch Dermatol Res. 2021; 313(7): 567–82.
7. Stone R. 2nd, Saathoff E.C., Larson D.A. et al. Accelerated Wound Closure of Deep Partial Thickness Burns with Acellular Fish Skin Graft. Int J Mol Sci. 2021; 4, 22(4): 1590.

ЛИТЕРАТУРА

1. Борзенок С.А., Костенев С.В., Дога А.В. и др. Сравнительный анализ протоколов децеллюляризации лентикулярной ткани роговицы. Вестник трансплантологии и искусственных органов. 2021; 23(2): 137–46.
2. Джабраилова Д.Ш., Зикиряходжаев А.Д., Усов Ф.Н. и др. Использование аллоимплантата на основе твердой мозговой оболочки при реконструктивно-пластических операциях у больных раком молочной железы. Опухоли женской репродуктивной системы. 2021; 17(3): 44–50.
3. Сачков А.В., Боровкова Н.В., Жиркова Е.А. и др. Использование трупной кожи в лечении ран. Трансплантология. 2018; 10(4): 327–35.
4. Сотниченко А.С., Гилевич И.В., Мелконян К.И. и др. Разработка методики получения дермального внеклеточного матрикса. Вестник трансплантологии и искусственных органов. 2020; 21(4): 81–7.
5. Guo Z.Q., Qiu L., Gao Y. et al. Use of porcine acellular dermal matrix following early dermabrasion reduces length of stay in extensive deep dermal burns. Burns. 2016; 42(3): 598–604.
6. Nasiry D., Khalatbary A.R., Abdollahifar M.A. et al. Engraftment of bioengineered three-dimensional scaffold from human amniotic membrane-derived extracellular matrix accelerates ischemic diabetic wound healing. Arch Dermatol Res. 2021; 313(7): 567–82.
7. Stone R. 2nd, Saathoff E.C., Larson D.A. et al. Accelerated Wound Closure of Deep Partial Thickness Burns with Acellular Fish Skin Graft. Int J Mol Sci. 2021; 4, 22(4): 1590.

UDC 612.66:616.72-002
DOI: 10.56871/RBR.2023.80.61.003

POLYMORBID PATHOLOGY IN THE CITY OF MURMANSK IN PATIENTS WITH OSTEOARTHRITIS HAVING VARIOUS VITAMIN D LEVEL

© Maxim D. Kashpanov[1], Irina A. Novikova[2], Olga A. Har'kova[1, 2]

[1] Murmansk City Polyclinic No. 2. Kolsky Ave., 149a, Murmansk, Russain Federation, 183052
[2] Northern State Medical University. Trinity Ave., 5, Arkhangelsk, Russian Federation, 1163069

Contact information: Maxim D. Kashpanov — Head of the Center for the Rehabilitation of Patients with Diseases of the Heart and Cerebral Vessels, rheumatologist. E-mail: kashpanovm@mail.ru ORCID ID: 0000-0002-5826-9868

For citation: Kashpanov MD, Novikova IA, Har'kova OA. Polymorbid pathology in the city of Murmansk in patients with osteoarthritis having various vitamin D level // Russian biomedical research (St. Petersburg). 2023; 8(3): 18-25. DOI: https://doi.org/10.56871/RBR.2023.80.61.003

Received: 16.06.2023 **Revised: 07.07.2023** **Accepted: 21.09.2023**

Abstract. According to the Territorial Body of the Federal State Statistics Service for the Murmansk Region, the incidence of osteoarthritis among the adult population is 46.57 per 1000 people. In order to identify the features of comorbid pathology in patients over 60 years of age with osteoarthritis who have vitamin D deficiency and insufficiency, 100 patients over the age of 60 years (cf. age 69.03 ± 2.34 years). All patients live in Murmansk; 85% of patients were women and 15% men. Research methods were used: questionnaire, clinical examination, determination of the level of vitamin D. It was found that in patients with osteoarthritis over the age of 60 years, 1/3 have vitamin D deficiency and more than 1/2 — vitamin D deficiency. In patients with osteoarthritis with vitamin D deficiency and deficiency, such comorbid pathologies as arterial hypertension, coronary heart, rheumatoid arthritis. In patients with vitamin D deficiency, compared with the group with vitamin D deficiency, the following were more often noted: type 2 diabetes mellitus, cancer, chronic obstructive pulmonary disease, and a history of acute circulatory disorders. Subjects with lower levels of vitamin D have more often geriatric syndromes such as: hearing impairment, dysphagia, constipation, urinary incontinence and pathology of the oral cavity. Patients with vitamin D deficiency in comparison with its insufficiency have a more pronounced radiological stage of the disease and the degree of dysfunction of the joint, which, in turn, increases the percentage of disability among these patients. Thus, vitamin D deficiency is one of the risk factors for a number of comorbid pathologies in osteoarthritis. In this connection, it is expedient to include vitamin D in the complex therapy of osteoarthritis in patients over 60 years of age.

Key words: vitamin D; osteoarthritis; elderly and senile patients; comorbid pathology.

ОСОБЕННОСТИ ПОЛИМОРБИДНОЙ ПАТОЛОГИИ У ПАЦИЕНТОВ г. МУРМАНСКА С ОСТЕОАРТРИТОМ, ИМЕЮЩИХ РАЗЛИЧНЫЙ УРОВЕНЬ ВИТАМИНА D

© Максим Дауренбекович Кашпанов[1], Ирина Альбертовна Новикова[2], Ольга Александровна Харькова[1, 2]

[1] Мурманская городская поликлиника № 2. 183052, г. Мурманск, пр. Кольский, 149а
[2] Северный государственный медицинский университет. 163069, г. Архангельск, Троицкий пр., 51

Контактная информация: Максим Дауренбекович Кашпанов — заведующий центром реабилитации больных с заболеваниями сосудов сердца и головного мозга, врач-ревматолог. E-mail: kashpanovm@mail.ru ORCID ID: 0000-0002-5826-9868

Для цитирования: Кашпанов М.Д., Новикова И.А., Харькова О.А. Особенности полиморбидной патологии у пациентов г. Мурманска с остеоартритом, имеющих различный уровень витамина D // Российские биомедицинские исследования. 2023. Т. 8. № 3. С. 18–25. DOI: https://doi.org/10.56871/RBR.2023.80.61.003

Поступила: 16.06.2023 **Одобрена: 07.07.2023** **Принята к печати: 21.09.2023**

Резюме. По данным Территориального органа Федеральной службы государственной статистики по Мурманской области, заболеваемость остеоартритом среди взрослого населения составляет 46,57 на 1000 человек.

С целью выявления особенностей полиморбидной патологии и некоторых гериатрических синдромов у пациентов старше 60 лет с остеоартритом, имеющих дефицит и недостаточность витамина D, было обследовано 100 пациентов в возрасте старше 60 лет (средний возраст 69,03 ± 2,34 года). Все пациенты проживали в г. Мурманске; 85% пациентов составили женщины и 15% — мужчины. Использовались методы исследования: анкетирование, клиническое обследование, определение уровня витамина D. Было установлено, что у 1/3 пациентов, страдающих остеоартритом в возрасте старше 60 лет, имеется дефицит витамина D и недостаточность витамина D — у более половины исследуемых. У больных с остеоартритом с дефицитом и недостаточностью витамина D наиболее часто отмечались такие полиморбидные патологии, как гипертоническая болезнь, сердечно-сосудистая патология, ревматоидный артрит. У пациентов, имеющих дефицит витамина D, по сравнению с группой с недостаточностью витамина D чаще отмечались: сахарный диабет 2-го типа, онкологические заболевания, хроническая обструктивная болезнь легких, острое нарушение кровообращения в анамнезе. Обследуемые с низкими показателями содержания витамина D имеют более часто гериатрические синдромы, такие как нарушения слуха, дисфагия, запоры, недержание мочи и патология ротовой полости. Пациенты, страдающие дефицитом витамина D, в сравнении с пациентами, у которых он был на недостаточном уровне, имеют более прогрессивную рентгенологическую стадию заболевания и выраженность нарушений функций суставов, что, в свою очередь, увеличивает процент инвалидизации среди указанных пациентов. Таким образом, дефицит витамина D является одним из факторов риска целого ряда полиморбидной патологии при остеоартрите. В связи с вышеуказанным, целесообразно включить витамин D в комплексную терапию остеоартрита.

Ключевые слова: витамин D; остеоартрит; пациенты пожилого и старческого возраста; полиморбидная патология.

INTRODUCTION

Low vitamin D levels are a global problem for people of all ages. The current insufficient vitamin D supply of the Russian population is due to the low level of its synthesis and insufficient intake with food [1]. Vitamin D deficiency is characterized by extremely adverse health consequences [2].

Studies of vitamin D deficiency conducted in recent years show a high prevalence of deficiency in elderly patients. Thus, vitamin D deficiency among the elderly population in Europe was found in 47% of women and 36% of men. In Asian countries it was in 80% of the population [3]. In our country, the frequency of vitamin D deficiency among elderly and senile people is 86.4% [4].

In the elderly, low vitamin D levels increase the risk of fractures due to increased bone resorption and decreased bone mineral density [4]. Vitamin D deficiency in the elderly also affects muscle tissue, physical activity and general geriatric status. Vitamin D supplementation reduces the risk of falls, improves muscle tone, and also reduces the severity of cognitive impairment and improves overall health, and is therefore essential for vitamin D-deficient elderly people with senile asthenia [5].

In the development of vitamin D deficiency, the climatic and geographical features of the region of residence play a major role. Vitamin D deficiency is widespread in northern latitudes and especially in the Arctic region [6, 7].

Vitamin D deficiency is a leading factor in the development of osteoarthritis. It can be one of the etiologic factors of a number of other chronic non-infectious diseases, autoimmune and oncologic. The presence of vitamin D deficiency is also associated with a more severe course of various chronic diseases [8].

Osteoarthritis is the most common joint disease in the elderly and old age, which is accompanied by disability in the population [9].

According to the official data of the Territorial Department of the Federal State Statistics Service in the Murmansk region, the incidence of osteoarthritis among adults is 46.57 per 1000 people [11].

Currently, the problems of tactics of management of patients with concomitant pathology are of great relevance.

The literature contains data on polymorbidity of osteoarthritis with diseases of the cardiovascular system (arterial hypertension) and gastrointestinal tract [13]. At the same time, there are very few studies that describe the features of polymorbid pathology in patients depending on vitamin D deficiency, which is important in the selection of drugs with a favorable safety profile in osteoarthritis in combination with polymorbid pathology.

AIM

To identify the features of polymorbid pathology and some geriatric syndromes in patients over 60 years old

suffering from osteoarthritis with vitamin D deficiency and insufficiency.

MATERIALS AND METHODS

The study included 100 patients diagnosed osteoarthritis, who were under outpatient treatment and observed in outpatient clinics in Murmansk. The patients' age ranged from 60 to 80 years (mean age was 69.03±2.34 years), of which 85% were women and 15% were men.

The study was performed in accordance with the standards of good clinical practice and the principles of the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Northern State Medical University. Written informed consent was obtained from all participants before inclusion in the study. The study was conducted as the patients applied for it.

All patients had a confirmed diagnosis of osteoarthritis according to the clinical recommendations of the Association of Rheumatologists of Russia (2021).

Questionnaire data (socio-demographic indicators), clinical examination, determination of vitamin D levels, assessment of the radiologic stage of the disease and the degree of joint dysfunction were used. During clinical observation, the presence of chronic non-infectious diseases such as arterial hypertension (AH) [19], coronary heart disease (CHD), chronic cardiovascular insufficiency (CVI) [20], acute cerebral circulatory failure (ACF) — according to the neurologist's report, type 2 diabetes mellitus (DM) [21], rheumatoid arthritis (RA) [22], gastric or duodenal ulcer (DU) [23], cancer — according to the oncologist's report, chronic obstructive pulmonary disease (COPD) were assessed in patients [24].

We also determined the presence of age-associated conditions: pelvic organ disorders (urination, defecation), eye and hearing organs, swallowing problems (clinical recommendations of the Russian Association of Gerontologists and Geriatricians, 2020). In addition, the results of radiologic studies of joints (stage of osteoarthritis disease) and joint dysfunctions were assessed (clinical recommendations of the Russian Association of Rheumatologists, 2021).

Vitamin D levels were determined using HPLC-MS/MS (high-performance liquid chromatography with tandem mass spectrometry) method. The analyzed material was blood serum. Norms: less than 20 ng/mL — vitamin D deficiency, 20–30 ng/mL — vitamin D insufficiency, more than 30 ng/mL — normal vitamin D level. The study included patients who had not previously received vitamin D therapy (Russian Association of Endocrinologists, 2016).

The results were processed using statistical software SPSS Statistics (version 23.00, license Z125-5301-14). Data distribution was evaluated using the Kolmogorov–Smirnov test. To analyze the results, we used the parameters of descriptive statistics, Mann-Whitney U-criterion to compare the mean values of two independent samples, and the χ^2 test to evaluate differences in frequency of occurrence.

RESULTS

Vitamin D levels in patients with osteoarthritis older than 60 years of age (Figure 1) were found to be below target values in the majority of 92% (vitamin D deficiency or insufficient levels (20-30 ng/mL)). More than 1/3 of patients (33.0%) had vitamin D deficiency (< 20 ng/mL), and only 8% of patients had normal vitamin D levels (>30 ng/mL), which indicates the urgency of the problem of vitamin D insufficiency for patients in this group.

It was found that female patients with vitamin D insufficiency or deficiency accounted for 84.85%, while male patients accounted for 15.15% of cases.

Due to the fact that in our sample the number of individuals with normal vitamin D content was insufficient for statistical analysis, further analysis was performed in groups with vitamin D deficiency (severe vitamin D insufficiency) and mild vitamin D insufficiency. Thus, group 1 consisted of 33 patients (35.86%) with vitamin D deficiency (severe vitamin D insufficiency), group 2 consisted of 59 patients (64.14%) with mild vitamin D insufficiency.

Analysis of polymorbid diseases in two groups (patients with severe vitamin D deficiency (group 1) and mild vitamin D insufficiency (group 2)) (Fig. 2) showed that patients with osteoarthritis in both groups 1 and 2 most often had such concomitant pathologies as hypertension, CHD, RA, DM, oncological diseases, COPD, ACF in anamnesis.

In group 1, the frequency of concomitant polymorbid pathology in patients was distributed as follows: AH was present in all patients, DM was observed in more than 1/2 of subjects, CHD was present in almost 1/2 patients, and RA was present in less than 1/2 patients. A history of ACF was found in almost every second patient, 2/5 had a history of CVI, and oncologic diseases were present with the same frequency. COPD was observed in 2/5 of patients, every fourth patient had ulcer.

In the 2nd group of patients the incidence of chronic non-infectious diseases was distributed as follows: AH — in 9 out of 10 patients, more than 1/2 of patients had CHD, also more than 1/2 of patients had RA, every third patient had CVI and ulcer, every fourth patient had DM, oncological diseases were present in 1/6 patients, ACF in anamnesis was found in every tenth patient, COPD was noted less frequently — only in 3% of patients.

Analysis of differences between groups 1 and 2 showed that DM (χ^2=17.759, p=0.000), cancer (χ^2=14.612,

p=0.000), COPD (χ^2=36.125, p=0.000), and a history of ACF (χ^2=28.072, p=0.000) were more frequent in group 1 compared to group 2. At the same time, RA was significantly more frequent in group 2 compared to group 1 at the trend level (χ^2=2.001, p=0.101).

We analyzed the occurrence of age-associated conditions in patients with osteoarthritis (Fig. 3), which showed that hearing disorders, dysphagia, constipation, urinary incontinence, and oral pathology were significantly more common in group 1. Visual impairment, urinary incontinence and hearing impairment were common in 3/5 patients, constipation was common in almost 1/2 patients, dysphagia was common in 2/5 patients and 1/3 had oral pathology. In the 2nd group such disorders as visual disturbances were more frequently noted, typical for more than 1/2 patients, urinary incontinence was typical for 2/5 patients, hearing disturbances were noted for 1/3 patients, and every fifth patient had constipation.

Patients in group 1 compared to group 2 were more likely to have hearing impairment (χ^2=20.612, p=0.000), dysphagia (χ^2=35.526, p=0.000), constipation (χ^2=16.130, p=0.000), urinary incontinence (χ^2=12.511, p=0.000) and oral pathology (χ^2=10.528, p=0.002).

To analyze the radiological stage of osteoarthritis and joint dysfunction, 2 groups of patients were sampled (Table 1).

More progressive radiologic stage of the disease was noted in the 1st group of patients. Comparative analysis showed that 66.7% of patients in group 1 and 50.8% in group 2 had III and IV radiologic stage of osteoarthritis (χ^2=5.255, p=0.022). Stage II of the disease was present in 1/3 of patients in group 1 and 1/2 of subjects in group 2, i.e. stage II of the disease was more frequently observed in group 2 (χ^2=5.291, p=0.022).

In terms of severity of joint dysfunction, the groups differed at the trend level in that degree III was more frequent in group 1 compared to group 2 (χ^2=3.125, p=0.078).

Table 2 shows the functional impairment scores of patients with osteoarthritis over 60 years of age in different vitamin D content groups.

Patients in group 1 compared to group 2 had higher values for radiologic stage of disease (p=0.000) and degree of joint dysfunction (p=0.000).

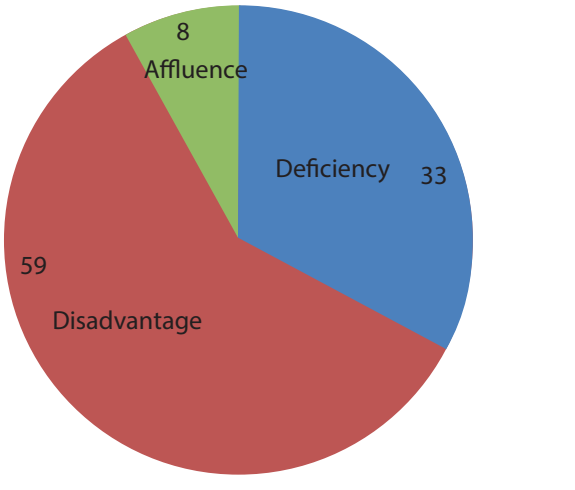


Fig. 1. Occurrence of different vitamin D levels in patients with osteoarthritis over the age of 60 (%)

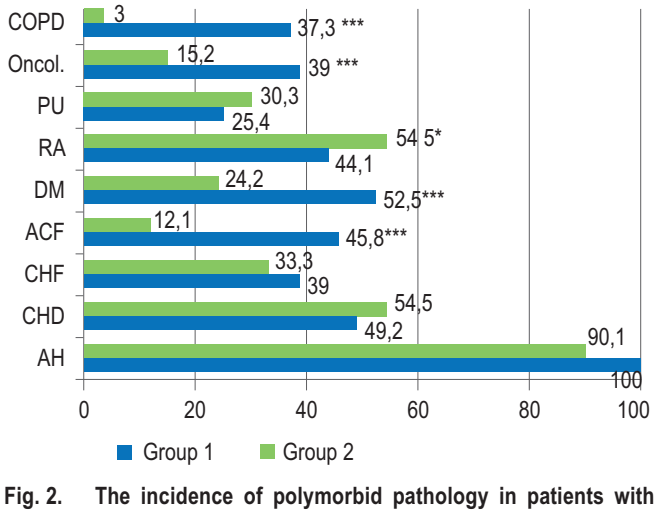


Fig. 2. The incidence of polymorbid pathology in patients with osteoarthritis over the age of 60 years with different levels of vitamin D (%). Group 1 — patients with vitamin D deficiency (severe vitamin D deficiency); Group 2 — patients with mild vitamin D deficiency. Note: the significance of the differences between the groups according to criterion χ^2 at ***p < 0.001, *p < 0.10

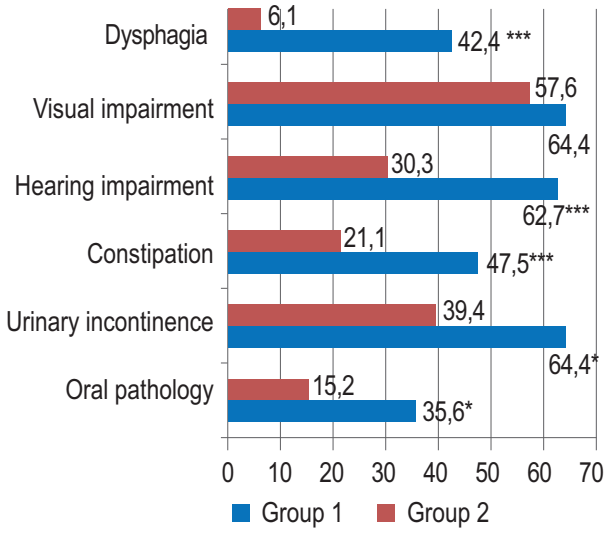


Fig. 3. The incidence of geriatric disorders in patients with osteoarthritis with different levels of vitamin D (%). *Note:* the significance of the differences between the 1st and the 2nd groups according to the criterion χ^2 at ***p < 0.001, *p < 0.05

Table 1

Incidence of functional disorders in patients with osteoarthritis over the age of 60 years in different vitamin D groups (abs. amount, %)

Indicators	Severity of violations	Group 1, N=33		Group 2, N = 59		Reliability of differences by the criterion χ^2
Radiological stage of the disease	Stage II	11	33,3	29	49,2	χ^2=5,291 (p=0,022)
	Stage III	18	54,5	27	45,7	
	Stage IV	4	12,2	3	5,1	
Degree of joint dysfunction	The 1st degree	3	9,1	8	13,6	
	The 2st degree	16	48,5	33	55,9	
	The 3st degree	14	42,4	18	30,5	χ^2=3,125 (p=0,078)

Note: reliability of differences between groups p=0.022, p=0.078.

DISCUSSION

Analysis of the results showed that 92% of patients with osteoarthritis over 60 years of age had deficiency or insufficient levels of vitamin D. It is worth noting that the study was conducted in the North of Russia in the Murmansk region. Most likely, the low level of vitamin D in patients is associated with a small number of sunny days per year in Murmansk and low average annual temperature, which do not allow to provide irradiation of sufficient skin surface for biosynthesis of the optimal amount of vitamin D.

We found that in elderly patients with osteo-arthritis with vitamin D deficiency and insufficiency such polymorbid pathology as AH, CHD, RA was most often observed. Our data are similar to the results of a study by other authors [13], who talk about the high frequency of polymorbidity of osteoarthritis and AH, but, unlike these authors, our study did not reveal a high frequency of gastrointestinal pathology in osteoarthritis.

At the same time, our results are somewhat different from those obtained earlier in another study on a sample of elderly and senile patients [14]. The similarity consists in the presence of AH in all patients over 60 years of age. In the previous study, it was found that the most frequent pathology in elderly patients was gastrointestinal (81.43%), muscular and skeletal (77.14%) and endocrine (77.14%) diseases. Probably, the revealed differences can be explained by the peculiarities of the sample and specificity of polymorbidity of osteoarthritis. Thus, CHD in osteoarthritis was noted more often than in the sample of patients without it (59% vs. 41%), a similar trend was observed in RA (49% vs. 8%).

According to I.B. Belyaeva et al. [15], a special role in the development and progression of osteoarthritis is attributed to systemic metabolic disorders, such as obesity and DM, which can modify the natural course of local inflammatory reactions in the joint [15]. It follows that the presence of DM in patients with osteoarthritis significantly worsens the course of the disease.

Table 2

Mean values of functional impairment indicators in patients with osteoarthritis over 60 years of age in different groups (points)

Indicators	The 1st group	The 2nd group	Mann–Whitney U-test
Radiologic stage of the disease	3,03 ± 0,11	2,27 ± 0,06	0,000
Degree of joint dysfunction	2,54 ± 0,08	2,01 ± 0,09	0,000

Note: the significance of the differences between the 1st and the 2nd groups is p=0.000.

Vitamin D deficiency is a risk factor for a number of polymorbid diseases. Analysis of our results showed that in group 1 compared to group 2 such diseases as DM, oncologic diseases, COPD, ACF in anamnesis were more frequently observed. The obtained results are generally consistent with the data of other authors. Thus, according to A.F. Verbovoy et al. [16], vitamin D deficiency is associated with the risk of cardiovascular diseases, obesity, diabetes, COPD.

In the elderly, low vitamin D levels are associated with osteoporosis, falls and fractures, DM, cancer, cerebrovascular disease, sarcopenia [17], and increased risk of cardiovascular mortality [18].

Our patients with lower vitamin D levels are more likely to have such geriatric syndromes as hearing impairment, dysphagia, constipation, urinary incontinence and oral pathology. The identified features suggest that patients over 60 years of age with osteoarthritis with lower vitamin D levels are more likely to have geriatric syndromes, which is consistent with the findings of a study by other authors [5].

Patients with vitamin D deficiency in comparison with its insufficiency in a greater percentage of cases have a

more severe radiological stage of the disease and more pronounced impairment of joint function, which, in turn, increases the percentage of disability among patients with vitamin D deficiency.

Thus, vitamin D deficiency is one of the risk factors for a number of polymorbid pathologies in osteoarthritis. Taking into account the identified features is important in the selection of highly effective drugs with a favorable safety profile in osteoarthritis in combination with polymorbid pathology. There is a need to include vitamin D in the complex therapy of osteoarthritis in elderly patients.

CONCLUSION

1. 1/3 of patients with osteoarthritis over 60 years of age have vitamin D deficiency and more than 1/2 of patients have vitamin D insufficiency. In patients with osteoarthritis with vitamin D deficiency and insufficiency, such comorbidities as hypertension, ischemic heart disease, and rheumatoid arthritis were most often noted. Type 2 diabetes mellitus, oncologic diseases, chronic obstructive pulmonary disease, acute circulatory failure in the history were more frequently observed in patients with vitamin D deficiency compared to the group with vitamin D insufficiency.

2. Patients with lower vitamin D levels were more likely to have geriatric syndromes such as hearing impairment, dysphagia, constipation, urinary incontinence, and oral pathology. Patients with vitamin D deficiency compared to those with vitamin D insufficiency have a more pronounced radiological stage of disease and degree of joint dysfunction, which in turn increases the rate of disability among these patients.

ADDITIONAL INFORMATION

Author 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.

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

Funding source. This study was not supported by any external sources of funding.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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.

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

REFERENCES

1. Petrushkina A.A., Pigarova Ye.A., Rozhinskaya L.Ya. Epidemiologiya defitsita vitamina D v Rossiyskoy Federatsii. [Epidemiology of vitamin D deficiency in the Russian Federation]. Osteoporoz i osteopatii. 2018; 21(3): 15–20. DOI: 10.14341/osteo10038. (in Russian).
2. Agranovich N.V., Pilipovich L.A., Albotova L.V., Klassova A.T. K voprosu o defitsite vitamina D pri khronicheskoy bolezni pochek. [To the question of vitamin D deficiency for chronic kidney disease]. Literaturnyy obzor. Nefrologiya. 2019; 23(3): 21–8. DOI: 10.24884/1561-6274-2019-23-3-21-28. (in Russian).
3. Cashman K.D., Dowling K.G., Škrabáková Z. et al. Vitamin D deficiency in Europe: pandemic? Am J Clin Nutr. 2016; 103(4): 1033–44. DOI: 10.3945/ajcn.115.120873.
4. Safonova Yu.A. Toroptsova N.V. Defitsit i nedostatochnost' vitamina D, faktory riska i yego korrektsiya u lyudey pozhilogo vozrasta. [Vitamin D deficiency and insufficiency, risk factors and its correction in elderly people]. Russkiy meditsinskiy zhurnal. 2021; 6: 96–100. (in Russian).
5. Machekhina L.V., Dudinskaya Ye.N., Tkacheva O.N. Defitsit vitamina D u pozhilykh lits s sindromom starcheskoy astenii. [Vitamin D deficiency in elderly faces with senile asthenia syndrome]. Profilakticheskaya meditsina. 2019; 22(5): 118–24. (in Russian).
6. Suplotova L.A., Avdeyeva V.A., Pigarova Ye.A. i dr. Defitsit vitamina D v Rossii: pervyye rezul'taty registrovogo neinterventsionnogo issledovaniya chastoty defitsita i nedostatochnosti vitamina D v razlichnykh geograficheskikh regionakh strany. [Vitamin D deficiency in Russia: the first results of register non -interventional study of the frequency of deficiency and deficiency of vitamin D in various geographical regions of the country]. Problemy endokrinologii. 2021; 67(2): 84–92. DOI: 10.14341/probl12736. (in Russian).
7. Malyavskaya S.I., Kostrova G.N., Lebedev A.V., Golysheva Ye.V. Obespechennost' vitaminom D razlichnykh vozrastnykh grupp naseleniya g. Arkhangel'ska. [Provision of vitamin D of various age groups of the population of Arkhangelsk]. Ekologiya cheloveka. 2016; 23(12): 37–42. DOI: 10.33396/1728-0869-2016-12-37-42. (in Russian).
8. Pigarova Ye.A., Petrushkina A.A. Neklassicheskiye effekty vitamina D. [Non -classical effects of vitamin D]. Osteoporoz i osteopatii. 2017; 20(3): 90–101. DOI: 10.14341/osteo20173. (in Russian).
9. Canizares M., Power J.D., Perrucio A.V., Badley E.M. Association of regional racial/cultural context and socioeconomics status with

arthritis in the population: A multilevel analysis. Arthritis Rheum. 2008; 59(3): 399–407. DOI: 10.1002/art.23316.
10. Drapkina O.M., Skripnikova I.A., Shepel' R.N., Kaburova A.N. Osteoartrit v praktike vracha-terapevta: algoritm diagnostiki i vybora terapii. [Osteoarthritis in the practice of a therapist: an algorithm for diagnosis and the selection of therapy]. Profilakticheskaya meditsina. 2018; 21(6): 12–22 DOI: 10.17116/profmed20182106112. (in Russian).
11. Murmanskaya oblast' v tsifrakh. [Murmansk region in numbers]. Federal'naya sluzhba gosudarstvennoy statistiki, Territorial'nyy organ Federal'noy sluzhby gosudarstvennoy statistiki po Murmanskoy oblasti. Murmansk; 2021. (in Russian).
12. Shostak N.A., Pravdyuk N.G., Klimenko A.A. i dr. Osteoartrit i assotsiirovannaya patologiya — kliniko-patogeneticheskiye vzaimosvyazi. [Osteoarthritis and associated pathology-clinical and pathogenetic relationships]. RMZH. Meditsinskoye obozreniye. 2019; 3(11(II)): 44–7. (in Russian).
13. Swain S., Sarmanova A., Coupland C. et al. Comorbidities in Osteoarthritis: A systematic review and meta-analysis of observational studies. Arthritis Care Res (Hoboken). 2019. DOI: 10.1002/acr.24008.
14. Popov V.V., Novikova I.A., Trokhova M.V. Osobennosti polimorbidnoy patologii u lits pozhilogo i starcheskogo vozrasta s arterial'noy gipertenziyey. [Features of polymorbid pathology in elderly and senile people with arterial hypertension]. Rossiyskiy kardiologicheskiy zhurnal. 2021; 26(4): 18–25. DOI: 10.15829/1560-4071-2021-3940. (in Russian).
15. Belyayeva I.B., Mazurov V.I., Sarantseva L.Ye. Ratsional'naya farmakoterapiya komorbidnykh patsiyentov s zabolevaniyami oporno-dvigatel'nogo apparata v usloviyakh pandemii COVID-19. [Rational pharmacotherapy of komorbid patients with diseases of the musculoskeletal system in the conditions of pandemia Covid-19]. Effektivnaya farmakoterapiya. 2021; 17(21): 40–6. DOI: 10.33978/2307-3586-2021-17-21-40-46. (in Russian).
16. Verbovoy A. F., Dolgikh Yu.A., Verbovaya N.I. Mnogolikiy vitamin D. [Manysided vitamin D]. Farmateka. 2020; 4: 12–21. DOI: https://dx.doi.org/10.18565/pharmateca. 2020.4.12–21. (in Russian).
17. Meehan M., Penckofer S. The role of vitamin D in the aging adult. J Aging Gerontol. 2014; 2: 60–71. DOI: 10.12974/2309-6128.2014.02.02.1.
18. Geriatriya: natsional'noye rukovodstvo. [Geriatrics: National leadership]. Pod red. O.N. Tkachevoy, Ye.V. Frolovoy, N.N. Yakhno. Moskva: GEOTAR-Media Publ. 2023. (in Russian).
19. Klinicheskiye rekomendatsii Rossiyskogo kardiologicheskogo obshchestva. [Clinical recommendations of the Russian Cardiological Society]. 2020. (in Russian).
20. Klinicheskiye rekomendatsii Rossiyskogo kardiologicheskogo obshchestva, pri uchastii natsional'nogo obshchestva po izucheniyu serdechnoy nedostatochnosti i zabolevaniy miokarda — obshchestvo spetsialistov po serdechnoy nedostatochnosti. [Clinical recommendations of the Russian Cardiological Society, with the participation of the National Society for the Study of heart failure and diseases of myocardium, the Society of Specialists in heart failure]. 2020. (in Russian).
21. Klinicheskiye rekomendatsii Rossiyskoy assotsiatsii endokrinologov. [Clinical recommendations of the Russian Association of Endocrinologists]. 2022. (in Russian).
22. Klinicheskiye rekomendatsii Assotsiatsii revmatologov Rossii ot 2021. [Clinical recommendations Association of Rheumatologists of Russia from 2021]. (in Russian).
23. Klinicheskiye rekomendatsii Rossiyskoy gastroenterologicheskoy assotsiatsii. [Clinical recommendations of the Russian Gastroenterological Association]. 2019. (in Russian).
24. Klinicheskiye rekomendatsii Rossiyskogo respiratornogo obshchestva ot 2021. [Clinical recommendations Russian respiratory society from 2021]. (in Russian).

ЛИТЕРАТУРА

1. Петрушкина А.А., Пигарова Е.А., Рожинская Л.Я. Эпидемиология дефицита витамина D в Российской Федерации. Остеопороз и остеопатии. 2018; 21(3): 15–20. DOI: 10.14341/osteo10038.
2. Агранович Н.В., Пилипович Л.А., Алботова Л.В., Классова А.Т. К вопросу о дефиците витамина D при хронической болезни почек. Литературный обзор. Нефрология. 2019; 23(3): 21–8. DOI: 10.24884/1561-6274-2019-23-3-21-28.
3. Cashman K.D., Dowling K.G., Škrabáková Z. et al. Vitamin D deficiency in Europe: pandemic? Am J Clin Nutr. 2016; 103(4): 1033–44. DOI: 10.3945/ajcn.115.120873.
4. Сафонова Ю.А. Торопцова Н.В. Дефицит и недостаточность витамина D, факторы риска и его коррекция у людей пожилого возраста. Русский медицинский журнал. 2021; 6: 96–100.
5. Мачехина Л.В., Дудинская Е.Н., Ткачева О.Н. Дефицит витамина D у пожилых лиц с синдромом старческой астении. Профилактическая медицина. 2019; 22(5): 118–24.
6. Суплотова Л.А., Авдеева В.А., Пигарова Е.А. и др. Дефицит витамина D в России: первые результаты регистрового неинтервенционного исследования частоты дефицита и недостаточности витамина D в различных географических регионах страны. Проблемы эндокринологии. 2021; 67(2): 84–92. DOI: 10.14341/probl12736.
7. Малявская С.И., Кострова Г.Н., Лебедев А.В., Голышева Е.В. Обеспеченность витамином D различных возрастных групп населения г. Архангельска. Экология человека. 2016; 23(12): 37–42. DOI: 10.33396/1728-0869-2016-12-37-42.
8. Пигарова Е.А., Петрушкина А.А. Неклассические эффекты витамина D. Остеопороз и остеопатии. 2017; 20(3): 90–101. DOI: 10.14341/osteo20173.
9. Canizares M., Power J.D., Perrucio A.V., Badley E.M. Association of regional racial/cultural context and socioeconomics status with arthritis in the population: A multilevel analysis. Arthritis Rheum. 2008; 59(3): 399–407. DOI: 10.1002/art.23316.
10. Драпкина О.М., Скрипникова И.А., Шепель Р.Н., Кабурова А.Н. Остеоартрит в практике врача-терапевта: алгоритм диагностики и выбора терапии. Профилактическая медицина. 2018; 21(6): 12–22 DOI: 10.17116/profmed20182106112.

11. Мурманская область в цифрах. Федеральная служба государственной статистики, Территориальный орган Федеральной службы государственной статистики по Мурманской области. Мурманск; 2021.
12. Шостак Н.А., Правдюк Н.Г., Клименко А.А. и др. Остеоартрит и ассоциированная патология — клинико-патогенетические взаимосвязи. РМЖ. Медицинское обозрение. 2019; 3(11(II)): 44–7.
13. Swain S., Sarmanova A., Coupland C. et al. Comorbidities in Osteoarthritis: A systematic review and meta-analysis of observational studies. Arthritis Care Res (Hoboken). 2019. DOI: 10.1002/acr.24008.
14. Попов В.В., Новикова И.А., Трохова М.В. Особенности полиморбидной патологии у лиц пожилого и старческого возраста с артериальной гипертензией. Российский кардиологический журнал. 2021; 26(4): 18–25. DOI: 10.15829/1560-4071-2021-3940.
15. Беляева И.Б., Мазуров В.И., Саранцева Л.Е. Рациональная фармакотерапия коморбидных пациентов с заболеваниями опорно-двигательного аппарата в условиях пандемии COVID-19. Эффективная фармакотерапия. 2021; 17(21): 40–6. DOI: 10.33978/2307-3586-2021-17-21-40-46.
16. Вербовой А.Ф., Долгих Ю.А., Вербовая Н.И. Многоликий витамин D. Фарматека. 2020; 4: 12–21. DOI: https://dx.doi.org/10.18565/pharmateca. 2020.4.12–21.
17. Meehan M., Penckofer S. The role of vitamin D in the aging adult. J Aging Gerontol. 2014; 2: 60–71. DOI: 10.12974/2309-6128.2014.02.02.1.
18. Гериатрия: национальное руководство. Под ред. О.Н. Ткачевой, Е.В. Фроловой, Н.Н. Яхно. М.: ГЭОТАР-Медиа. 2023.
19. Клинические рекомендации Российского кардиологического общества. 2020.
20. Клинические рекомендации Российского кардиологического общества, при участии национального общества по изучению сердечной недостаточности и заболеваний миокарда — общество специалистов по сердечной недостаточности. 2020.
21. Клинические рекомендации Российской ассоциации эндокринологов. 2022.
22. Клинические рекомендации Ассоциации ревматологов России от 2021.
23. Клинические рекомендации Российской гастроэнтерологической ассоциации. 2019.
24. Клинические рекомендации Российского респираторного общества от 2021.

UDC 616.2-007.1-084.81
DOI: 10.56871/RBR.2023.10.96.004

INCREASING FUNCTIONAL RESISTANCE OF TEETH TO CARIES BY MEANS OF HOME ROUTINES IN ADOLESCENTS OF ST. PETERSBURG

© Mikhail M. Shvetsov[1], Andrey K. Iordanishvili[2, 3], Anastasia N. Belogortseva[4]

[1] The International Academy of Sciences of Ecology, Human Safety and Nature (MANEB). Bolshoy Ave., Vasilievsky Island, 74, Saint Petersburg, Russian Federation, 199106
[2] North-Western State Medical University named after I.I. Mechnikov. Kirochnaya str., 41, Saint Petersburg, Russian Federation, 191014
[3] Military Medical Academy named after S.M. Kirov. Akademician Lebedeva st., 6, Saint Petersburg, Russian Federation, 194044
[4] Children's dental polyclinic No. 3. Bryusovskaya str., 2, lit. A, Saint Petersburg, Russian Federation, 195271

Contact information: Mikhail M. Shvetsov — dentist-surgeon, maxillofacial surgeon. E-mail: mishas140692@gmail.com ORCID ID: 0000-0003-3230-0334

For citation: Shvetsov MM, Iordanishvili AK, Belogortseva AN. Increasing functional resistance of teeth to caries by means of home routines in adolescents of St. Petersburg // Russian biomedical research (St. Petersburg). 2023; 8(3): 26-30. DOI: https://doi.org/10.56871/RBR.2023.10.96.004

Received: 13.06.2023 **Revised: 10.07.2023** **Accepted: 21.09.2023**

Abstract. To date, the prevention of caries in children and adolescents is an urgent medical and social problem of modern healthcare. The paper evaluates the dynamics of functional resistance of tooth enamel in adolescents living from birth in St. Petersburg and the possibility of its improvement at home. 38 adolescents aged 15 to 17 years were under observation for 9 months, who were periodically examined once a quarter to assess the functional resistance of tooth enamel, which was performed using a TER test. The 1st control group of the study included young men who carried out their usual 2-fold generally accepted individual oral hygiene per day. The 2nd main group of the study included young men who, after carrying out individual oral care, additionally used a remineralizing ASEPTA gel for teeth. At the beginning of the clinical study, the indicators of functional resistance of tooth enamel to acid were almost the same in patients of groups 1 and 2 and were, respectively, 2.47 ± 0.18 and 2.52 ± 0.17 cont. units. In the boys of group 1, during the study period, there was a tendency to improve the functional resistance of tooth enamel to 2.40 ± 0.19 units, while in the boys of group 2, the functional resistance of tooth enamel significantly increased to 1.10 ± 0.20 units, which indicates the effectiveness of the remineralizing ASEPT gel used by them. The daily use of remineralizing ASEPT gel for teeth by young men of the 2nd main group at home during a 9-month study made it possible to increase the digital indicators of tooth enamel resistance by 43.65%, which is an important factor in preventing the development of dental caries.

Key words: adolescents; teeth; enamel; functional resistance of enamel; tooth decay; oral hygiene; fluorides; dental care products and items; remineralizing agents.

ИССЛЕДОВАНИЕ ФУНКЦИОНАЛЬНОЙ РЕЗИСТЕНТНОСТИ ЭМАЛИ ЗУБОВ У ПОДРОСТКОВ САНКТ-ПЕТЕРБУРГА И ВОЗМОЖНОСТЕЙ ЕЕ ПОВЫШЕНИЯ В ДОМАШНИХ УСЛОВИЯХ

© Михаил Максимович Швецов[1], Андрей Константинович Иорданишвили[2, 3], Анастасия Николаевна Белогорцева[4]

[1] Международная академия наук экологии, безопасности человека и природы (МАНЭБ). 199106, г. Санкт-Петербург, Большой пр. Васильевского острова, 74
[2] Северо-Западный государственный медицинский университет им. И.И. Мечникова. 191014, г. Санкт-Петербург, ул. Кирочная, 41
[3] Военно-медицинская академия им. С.М. Кирова. 194044, г. Санкт-Петербург, ул. Академика Лебедева, 6
[4] Детская стоматологическая поликлиника № 3. 195271, г. Санкт-Петербург, ул. Брюсовская, 2, лит. А

Контактная информация: Михаил Максимович Швецов — врач стоматолог-хирург, челюстно-лицевой хирург. E-mail: mishas140692@gmail.com ORCID ID: 0000-0003-3230-0334

Для цитирования: Швецов М.М., Иорданишвили А.К., Белогорцева А.Н. Исследование функциональной резистентности эмали зубов у подростков Санкт-Петербурга и возможностей ее повышения в домашних условиях // Российские биомедицинские исследования. 2023. Т. 8. № 3. С. 26–30. DOI: https://doi.org/10.56871/RBR.2023.10.96.004

Поступила: 13.06.2023 **Одобрена: 10.07.2023** **Принята к печати: 21.09.2023**

Резюме. В настоящее время вопросы профилактики кариеса у детей и подростков представляют актуальную медико-социальную проблему современного здравоохранения. В работе проведена оценка динамики функциональной резистентности эмали зубов у подростков, проживающих с рождения в г. Санкт-Петербурге, и возможности ее повышения в домашних условиях. Под наблюдением в течение 9 месяцев находились 38 подростков в возрасте от 15 до 17 лет, которые 1 раз в квартал осматривались на предмет оценки функциональной резистентности эмали зубов, которая выполнялась с помощью ТЭР-теста. В 1-ю (контрольную) группу исследования вошли юноши, осуществлявшие обычную для них двукратную общепринятую индивидуальную гигиену полости рта в сутки. Во 2-ю (основную) группу исследования вошли юноши, которые после осуществления индивидуального ухода за полостью рта дополнительно использовали гель для зубов реминерализующий АСЕПТА. В начале клинического исследования показатели функциональной резистентности эмали зубов к кислоте были у пациентов 1-й и 2-й группы практически одинаковыми и составляли, соответственно, 2,47 ± 0,18 и 2,52 ± 0,17 усл. ед. У юношей 1-й группы за период исследования отмечалась тенденция к улучшению функциональной резистентности эмали зубов до 2,40 ± 0,19 усл. ед., то время как у юношей 2-й группы функциональная резистентность эмали зубов достоверно повышалась до 1,10 ± 0,20 усл. ед., что свидетельствует об эффективности используемого ими геля для зубов реминерализующего АСЕПТА. Ежедневное применение в домашних условиях юношами 2-й (основной) группы геля для зубов реминерализующего АСЕПТА в ходе 9-месячного исследования позволило обеспечить повышение цифровых показателей резистентности эмали зубов на 43,65%, что является важным фактором профилактики развития кариеса зубов.

Ключевые слова: подростки; зубы; эмаль; функциональная резистентность эмали; кариес зуба; гигиена полости рта; фториды; средства и предметы ухода за зубами; реминерализующие средства.

INTRODUCTION

Nowadays, conscripts are subjected to high requirements for their health, including dental health [1]. At the same time, the state of dental health among young recruits in the Armed Forces of the Russian Federation leaves much to be desired. This is due to their significant need for dental treatment due to dental caries and non-carious lesions, as well as treatment of periodontal diseases (gingivitis, localized periodontitis), which is mainly due to the need to maintain adequate oral hygiene [2, 3]. It is noted in the literature that even future doctors, i.e. students of dental faculties of medical universities of the country, are not always conscious of maintaining their dental health, which especially concerns the adequate use of dental and oral care items [4, 5]. Fluoride prophylaxis plays an important role in the prevention of the main dental pathology — dental caries [6, 7]. At the same time, a high prevalence of dental caries in children and adults in St. Petersburg is known [8, 9], which is promoted by insufficient fluoride ion content in drinking water [10, 11]. Therefore, any measures that can increase the resistance of teeth to dental caries in adolescents are an urgent task of practical medicine [12].

AIM

To evaluate the dynamics of functional resistance of tooth enamel in adolescents of St. Petersburg and the possibilities of its increase in home conditions.

MATERIALS AND METHODS

38 young men aged 15 to 17 years old, living since birth in St. Petersburg, were under observation for 9 months. They were examined once a quarter to assess the functional resistance of tooth enamel, using the enamel resistance test proposed by V.R. Okushko [13]. Young men were examined in depth on the first day of their visit to a dentist, and then every 3 months, that is, a total of 4 times for each patient examined. According to the methodology, in adolescents the enamel resistance study was conducted on one of the central incisors of the upper jaw, for which the crown of the tooth was cleaned from possible plaque, dried, and then 1 % HCl solution was applied, creating a drop of up to 2 mm in diameter on the surface of the crown. After 5 s the drop was washed off with distilled water, the crown of the tooth was dried with a cotton ball and a drop of 1% solution of methylene blue was applied to the place of etching, which was immediately removed with a cotton ball and the acid resistance of enamel was evaluated in points, i.e. its resistance, by the intensity of coloration formed on the crown part of the tooth. The result was recorded by comparing it with the standard 10-point scale of shades of blue color from 0 points (with complete absence of staining of the etched part of the tooth crown) to 10 points (with the most intense staining in the etched part of the tooth crown in blue color).

It was decided to increase the functional resistance of tooth enamel of young men living in St. Petersburg by means of their home use of ACEPTA remineralizing tooth gel (VERTEX,

St. Petersburg, Russia). To study the effectiveness of this remineralizing gel, all young men were divided into 2 groups. The 1st (control) group of the study consisted of 15 men who performed the usual twice daily individual oral hygiene, namely dental care with a manual toothbrush and toothpaste used by them. The 2nd (main) group of the study included 23 young men who performed individual oral care with the use of ACEPTA remineralizing dental gel, which, according to the abstract, contains biomimetic hydroxyapatite that promotes rapid and effective mineralization of tooth enamel [14, 15].

Using a toothbrush, the young men spread the gel over the surface of the teeth, allowed it to adhere to the hard tissues of the teeth for 1-2 minutes, and then spit out the excess gel without rinsing the mouth. Patients were warned that individual dental care should have been performed in the morning after breakfast and in the evening after dinner before going to bed. After application of the remineralizing gel, they were advised not to eat or drink for half an hour.

The study fully complied with the ethical standards of the Committee on Human Experiments of the Helsinki Declaration of 1975, its revised version of 2000, and was approved by the Ethical Committee of the International Academy of Sciences of Ecology, Safety of Man and Nature (Protocol No. 3 of 23.03.2023).

Reliability of differences between the mean values of independent samples was assessed using the parametric Student's criterion for normal distribution and nonparametric Mann-Whitney criterion for non-normal distribution. The test for normality of distribution was evaluated using the Shapiro–Wilk test. Pearson's c2 criterion with the Mantel–Haenszel likelihood correction was used for statistical comparison of fractions to assess the reliability of differences. In all statistical analysis procedures, the achieved level of significance (p) was considered, and the critical level of significance was 0.05.

RESULTS

The study of tooth enamel resistance in young men of the 1st and 2nd groups at the beginning showed that the indexes of functional resistance of tooth enamel to acid were practically the same and were 2.47±0.18 and 2.52±0.17 units, respectively ($p \geq 0.05$). After 3 months from the beginning of the clinical study and until the end of the study, a tendency toward a decrease in the functional resistance of tooth enamel was observed in the young men of group 1 (Fig. 1). After 9 months from the beginning of the study, the functional resistance of tooth enamel to acid was 2.40±0.19 ($p \geq 0.05$) in this group of young men. Although such a numerical index characterizes high structural and functional resistance of enamel [13], it should be said that, despite the regular oral hygiene performed by the patients of group 1, no positive dynamics of this index was observed, which may contribute to the development of dental caries in them.

In young men of the 2nd group throughout the clinical study a reliable tendency to increase the functional resistance of tooth enamel to acid was revealed (Fig. 1). Thus, after 3, 6 and 9 months of the study in the patients of the 2nd group the indices of functional resistance of tooth enamel were equal to 2.09±0.19; 1.76±0.18 and 1.10±0.20 units, respectively ($p \leq 0.01$). Figure 2 shows the dynamics of enamel resistance test parameters in young men from the control and main study groups during the clinical study.

DISCUSSION

Everyday life of the studied young men living in the city of St. Petersburg, due to the consumption of potable water used by them during the usual individual oral care, contributes to a decrease in tooth enamel resistance, which is shown in the example of patients from the 1st control group of the study. Lack of positive dynamics of functional enamel resistance may be a predisposing factor in the development of dental caries in young men, although the numerical index of the enamel resistance test after 9 months from the beginning of the clinical study showed the presence of high structural and functional resistance of enamel in them.

Daily application of ACEPTA remineralizing tooth gel by the young men of the 2nd group of the study during the clinical trial allowed to provide positive dynamics of the numerical indexes of tooth enamel resistance, which was significantly different from the similar ones in the 1st group of young men, although these indexes, according to the evaluation recommendations of the enamel resistance test [13, 16], also characterized high structural and functional resistance of enamel. But at the same time for the young men of the 2nd group of the study we can reliably speak about the favorable dynamics of the indicators of the test of enamel resistance, which indicates an increase in the functional resistance of enamel, which, obviously, will contribute to the prevention of dental caries development in them.

CONCLUSION

1. In young men living in St. Petersburg, with the generally accepted individual measures for oral care, there is insufficient positive dynamics of functional and functional resistance of tooth enamel, which may be a predisposing factor for the development of dental caries.

2. The use of modern domestic ACEPTA remineralizing tooth gel containing biomimetic hydroxyapatite allowed to increase the functional resistance of tooth enamel by

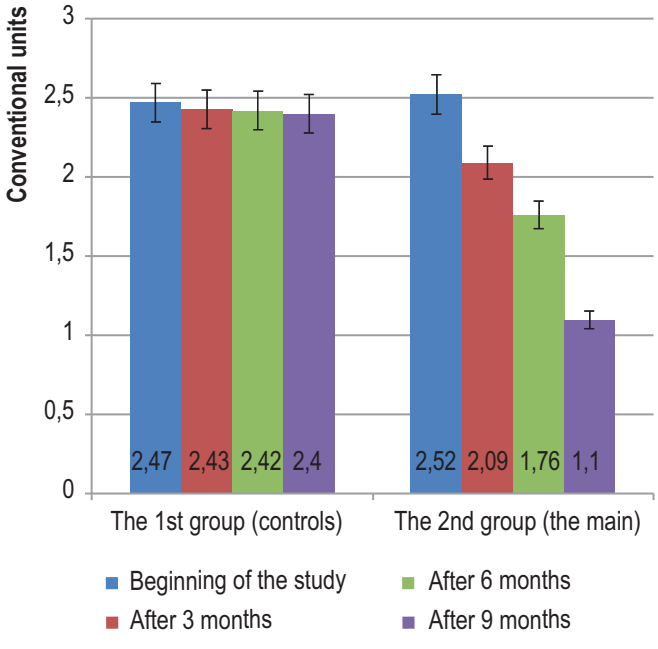


Fig. 1. Indicators of functional resistance of tooth enamel to acid in examined young men of the control and main study groups during the clinical trial

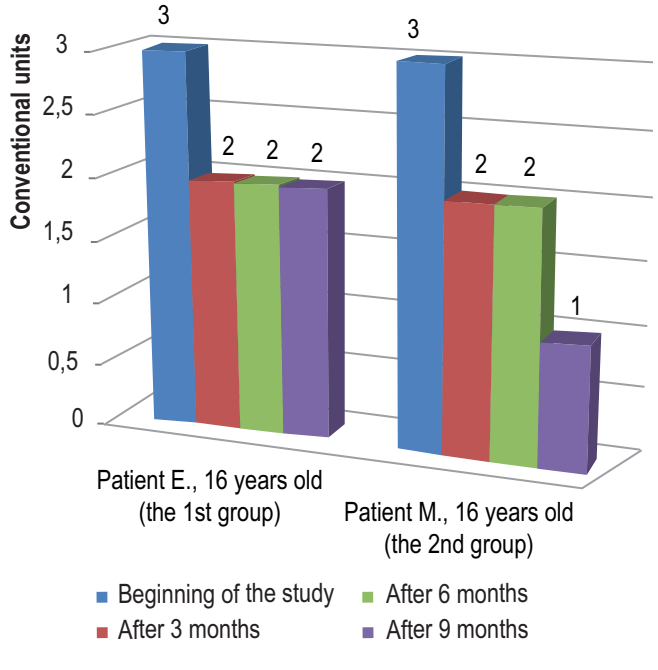


Fig. 2. Dynamics of indicators of functional resistance of tooth enamel to acid in two examined young men from the 1st and the 2nd study groups during the 9-month clinical trial

43.65% during a 9-month clinical study. It is an important factor in the prevention of dental caries development, so it can be recommended to adolescents living in St. Petersburg to include the use of ACEPTA remineralizing tooth gel in individual oral care measures.

ADDITIONAL INFORMATION

Author 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.

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

Funding source. This study was not supported by any external sources of funding.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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.

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

REFERENCES

1. Postanovleniye Pravitel'stva RF ot 04.07.2013 g. № 565 (red. ot 01.06.2020) «Ob utverzhdenii Polozheniya o voyenno-vrachebnoy ekspertize. [Decree of the Government of the Russian Federation dated 04.07.2013 No. 565 (as amended on 01.06.2020) "On approval of the Regulation on military medical examination"]. (in Russian).
2. Iordanishvili A.K., Soldatkina A.S. Zabolevaniya polosti rta u lits molodogo vozrasta. [Diseases of the oral cavity in young people]. Institut stomatologii. 2015; 3(68): 50–1. (in Russian).
3. Rogaleva L.V., Gorshkov L.K., Iordanishvili A.K. MANEB: Chetvert' veka sluzheniya ekologii i obshchestvu. [Maneb: A quarter of a century of ministry of ecology and society]. Ekologiya i razvitiye obshchestva. 2020; 2-3(33): 24–9. (in Russian).
4. Iordanishvili A.K., Idris A.Ya. Komplayens i zdorov'ye: sotsial'nyy aspekt problemy. [Compliance and health: the social aspect of the problem]. Ekologiya i razvitiye obshchestva. 2019; 3(30): 59–60. (in Russian).
5. Iordanishvili A.K., Soldatkina A.S. Zabolevaniya polosti rta u lits molodogo vozrasta. [Diseases of the oral cavity in young people]. Institut stomatologii.. 2015; 3(68): 50–1. (in Russian).
6. Leont'yev V.K., Ivanova G.G. Metody issledovaniya v stomatologii. Institut stomatologii. [Research methods in dentistry]. 2014; 2(63): 88–90. (in Russian).

7. Banks P. A prospective 20-year audit of a consultant workload. The British orthodontic society clinical effectiveness bulletin. 2010; 25: 15–8.
8. Iordanishvili A.K., Soldatova L.N., Pereverzev V.S., Tishkov D.S. Kariyes zubov u detey megapolisa i prigorodov. [Caries of teeth in children of a megalopolis and suburbs]. Stomatologiya detskogo vozrasta i profilaktika. 2016; 4(59): 73–6. (in Russian).
9. Sofronov G.A., Iordanishvili A.K. Rol' Mezhdunarodnoy akademii nauk ekologii bezopasnosti cheloveka i prirody v sokhranenii okruzhayushchey sredy i zdorov'ya cheloveka. [The role of the International Academy of Sciences of Man and Nature Ecology in the Preservation of Environment and Human Health]. Ekologiya i razvitiye obshchestva. 2019; 2(29): 16–7. (in Russian).
10. Iordanishvili A.K. Meditsina i sovremennaya ekologicheskaya doktrina. [Medicine and modern ecological doctrine]. Stomatologicheskiy nauchno-obrazovatel'nyy zhurnal. 2020; 1–2: 57–61. (in Russian).
11. Alferov Zh.I., Iordanishvili A.K. Rol' Mezhdunarodnoy akademii nauk ekologii, bezopasnosti cheloveka i prirody v razvitii fundamental'nykh issledovaniy. [The role of the International Academy of Sciences of Ecology, Human Security and Nature in the Development of Fundamental Research]. Materialy IV yezhegodnoy nauchno-prakticheskoy konferentsii s mezhdunarodnym uchastiyem «Dekabr'skiye chteniya po sudebnoy meditsine v RUDN: aktual'nyye voprosy sudebnoy meditsiny i obshchey patologii». Moskva: RUDN Publ.; 2020: 8–13. (in Russian).
12. Rogaleva L.V., Iordanishvili A.K. Mezhdunarodnaya akademiya nauk ekologii bezopasnosti cheloveka i prirody: nauchnyye i prikladnyye napravleniya deyatel'nosti. [International Academy of Sciences of Ecology of Human Safety and Nature: Scientific and Applied areas of activity]. Ekologiya i razvitiye obshchestva. 2019; 4(31): 7–11. (in Russian).
13. Okushko V.R. Fiziologiya emali i problema kariyesa zubov. [Physiology of enamel and the problem of tooth decay]. Kishinev: Shchtnitsa Publ.; 1989. (in Russian).
14. Leont'yev V.K. Emal' zubov kak biokiberneticheskaya sistema. [Emalus of teeth as a biokibernetic system]. Moskva: GEOTAR-Media Publ.; 2016. (in Russian).
15. Soldatov V.S., Soldatova L.N., Iordanishvili A.K. Funktsional'naya rezistentnost' emali u patsiyentov v period ortodonticheskogo lecheniya i puti yeye uluchsheniya. [The functional resistance of enamel in patients during orthodontic treatment and ways to improve it]. Institut stomatologii. 2022; 4: 50–1. (in Russian).
16. Khaytsev N.V., Vasil'yev A.G., Trashkov A.P., Kravtsova A.A., Balashov L.D. Vliyaniye vozrasta i pola na kharakter otvetnykh reaktsiy belykh krys pri deystvii khronicheskoy gipoksicheskoy gipoksii. [The influence of age and gender on the nature of the response of white rats under the action of chronic hypoxic hypoxia]. Pediatr. 2015; 6(2): 71–7. (in Russian).

ЛИТЕРАТУРА

1. Постановление Правительства РФ от 04.07.2013 г. № 565 (ред. от 01.06.2020) «Об утверждении Положения о военно-врачебной экспертизе».
2. Иорданишвили А.К., Солдаткина А.С. Заболевания полости рта у лиц молодого возраста. Институт стоматологии. 2015; 3(68): 50–1.
3. Рогалева Л.В., Горшков Л.К., Иорданишвили А.К. МАНЭБ: Четверть века служения экологии и обществу. Экология и развитие общества. 2020; 2-3(33): 24–9.
4. Иорданишвили А.К., Идрис А.Я. Комплаенс и здоровье: социальный аспект проблемы. Экология и развитие общества. 2019; 3(30): 59–60.
5. Иорданишвили А.К., Солдаткина А.С. Заболевания полости рта у лиц молодого возраста. Институт стоматологии. 2015; 3(68): 50–1.
6. Леонтьев В.К., Иванова Г.Г. Методы исследования в стоматологии. Институт стоматологии. 2014; 2(63): 88–90.
7. Banks P. A prospective 20-year audit of a consultant workload. The British orthodontic society clinical effectiveness bulletin. 2010; 25: 15–8.
8. Иорданишвили А.К., Солдатова Л.Н., Переверзев В.С., Тишков Д.С. Кариес зубов у детей мегаполиса и пригородов. Стоматология детского возраста и профилактика. 2016; 4(59): 73–6.
9. Софронов Г.А., Иорданишвили А.К. Роль Международной академии наук экологии безопасности человека и природы в сохранении окружающей среды и здоровья человека. Экология и развитие общества. 2019; 2(29): 16–7.
10. Иорданишвили А.К. Медицина и современная экологическая доктрина. Стоматологический научно-образовательный журнал. 2020; 1-2: 57–61.
11. Алферов Ж.И., Иорданишвили А.К. Роль Международной академии наук экологии, безопасности человека и природы в развитии фундаментальных исследований. Материалы IV ежегодной научно-практической конференции с международным участием «Декабрьские чтения по судебной медицине в РУДН: актуальные вопросы судебной медицины и общей патологии». М.: РУДН; 2020: 8–13.
12. Рогалева Л.В., Иорданишвили А.К. Международная академия наук экологии безопасности человека и природы: научные и прикладные направления деятельности. Экология и развитие общества. 2019; 4(31): 7–11.
13. Окушко В.Р. Физиология эмали и проблема кариеса зубов. Кишинев: Щтница; 1989.
14. Леонтьев В.К. Эмаль зубов как биокибернетическая система. М.: ГЭОТАР-Медиа; 2016.
15. Солдатов В.С., Солдатова Л.Н., Иорданишвили А.К. Функциональная резистентность эмали у пациентов в период ортодонтического лечения и пути ее улучшения. Институт стоматологии. 2022; 4: 50–1.
16. Хайцев Н.В., Васильев А.Г., Трашков А.П., Кравцова А.А., Балашов Л.Д. Влияние возраста и пола на характер ответных реакций белых крыс при действии хронической гипоксической гипоксии. Педиатр. 2015; 6(2): 71–7.

UDC 616.31: 681.3
DOI: 10.56871/RBR.2023.30.72.005

COMPARATIVE RATING OF ELECTROMYOGRAPHS USED IN CLINIC BY MEANS OF EXPERT EVALUATIONS METHOD

© Olga S. Chepuryaeva

Volgograd State Medical University. Fallen Fighters Square, 1, Volgograd, Russian Federation, 400131

Contact information: Olga S. Chepuryaeva — postgraduate student of the Department of Orthopedic Dentistry with a course in clinical Dentistry, candidate of the Department of Normal Physiology. E-mail: chepurjaeva@mail.ru ORCID ID: 0000-0003-1642-410X

For citation: Chepuryaeva OS. Comparative rating of electromyographs used in clinic by means of expert evaluations method // Russian biomedical research (St. Petersburg). 2023; 8(3): 31-35. DOI: https://doi.org/10.56871/RBR.2023.30.72.005

Received: 19.06.2023 **Revised: 10.07.2023** **Accepted: 21.09.2023**

Abstract. Electromyographic examination makes it possible to determine the lesion of muscle tissue, the prevalence, severity and nature of the pathological process, therefore, great importance is given to the choice of a high-quality apparatus used in clinical practice. In order to determine the optimal device for electromyography in clinical practice, a questionnaire of 50 questions was compiled to determine the most important parameters of the electromyograph. To confirm the differentiating ability of the questionnaire developed by us, a commission was recruited. In order to confirm the differentiating ability of the questionnaire, a commission was recruited. The expert commission consisted of: 10 specialists from among the teaching staff of the Department of Orthopedic Dentistry with a course in clinical dentistry and 10 other specialists this field from among the teaching staff of the department of Normal Physiology. By the method of expert assessments, the most significant parameters for doctors were selected and their weight was determined. The most significant parameters were: «informative value» and «accuracy», which gained 0.24 and 0.23 points, respectively. An expert assessment of popular electromyographs was carried out: adaptive electromyograph “Synapsis” (NMF “Neurotech” LLC, Russia), electroneuromyograph «Neuro-MVP-8» («Neurosoft», Russia), electroneuromyograph “Neuro-MVP-Micro” (“Neurosoft”, Russia). The sum of the points of all experts was multiplied by the weight of a certain parameter and entered into tables. After the calculation, the optimal electromyograph was determined. According to the results of the expert analysis of the devices, the highest points were scored by the electromyograph “Synapsis” (Neurotech, Russia): 85.85 points. We believe that in order to obtain the most accurate results in the clinic, this electromyograph can be recommended for medical use as having all important characteristics as being highly reliable.

Key words: electromyography; expert assessment; diagnostics; bioelectric activity of muscles.

СРАВНИТЕЛЬНАЯ ОЦЕНКА ЭЛЕКТРОМИОГРАФОВ, ПРИМЕНЯЕМЫХ В КЛИНИКЕ, МЕТОДОМ ЭКСПЕРТНЫХ ОЦЕНОК

© Ольга Сергеевна Чепуряева

Волгоградский государственный медицинский университет. 400131, г. Волгоград, площадь Павших Борцов, 1

Контактная информация: Ольга Сергеевна Чепуряева — аспирант кафедры ортопедической стоматологии с курсом клинической стоматологии, соискатель кафедры нормальной физиологии. E-mail: chepurjaeva@mail.ru ORCID ID: 0000-0003-1642-410X

Для цитирования: Чепуряева О.С. Сравнительная оценка электромиографов, применяемых в клинике, методом экспертных оценок // Российские биомедицинские исследования. 2023. Т. 8. № 3. С. 31–35. DOI: https://doi.org/10.56871/RBR.2023.30.72.005

Поступила: 19.06.2023 **Одобрена: 10.07.2023** **Принята к печати: 21.09.2023**

Резюме. Электромиографическое исследование позволяет определить очаг поражения мышечной ткани, распространенность, тяжесть и характер патологического процесса, поэтому выбору качественного аппарата, применяемого в клинической практике, уделяется большое значение. С целью определения оптимального аппарата для проведения электромиографии в клинической практике был составлен опросник из 50 вопросов

для определения наиболее важных параметров электромиографа. Для подтверждения дифференцирующей способности разработанного нами опросника была набрана комиссия. В состав экспертной комиссии вошли: 10 специалистов из числа профессорско-преподавательского состава кафедры ортопедической стоматологии с курсом клинической стоматологии и 10 специалистов из числа профессорско-преподавательского состава кафедры нормальной физиологии. Методом экспертных оценок были отобраны наиболее значимые для врачей параметры и определен их вес. Наиболее весомыми параметрами оказались «информативность» и «точность», набрав 0,24 и 0,23 балла соответственно. Далее проводили экспертную оценку популярных электромиографов: адаптивного электромиографа «Синапсис» (ООО НМФ «Нейротех», Россия), электронейромиографа «Нейро-МВП-8» («Нейрософт», Россия), электронейромиографа «Нейро-МВП-Микро» («Нейрософт», Россия). Сумму баллов всех экспертов умножали на вес определенного параметра и заносили в таблицы. После вычисления был определен оптимальный, по мнению экспертов, электромиограф. По результатам экспертного анализа аппаратов наибольшее количество баллов набрал электромиограф «Синапсис» («Нейротех», Россия) — 85,85 балла. Считаем, что для получения наиболее точного результата в клинике мы можем рекомендовать использовать данный электромиограф, так как он обладает необходимыми для качественной диагностики характеристиками.

Ключевые слова: электромиография; экспертная оценка; диагностика; биоэлектрическая активность мышц.

In the clinic, various apparatuses and devices are used to diagnose diseases, detect various pathological conditions and functional disorders. For example, to diagnose the functional state of skeletal muscles and peripheral nerve endings, electromyography data are used to assess the degree of bioelectric activity [2, 5].

Electromyographic study allows to determine the focus of muscle tissue lesions, prevalence, severity and nature of the pathological process. The speed, correctness of diagnosis and subsequent treatment, and sometimes even the life of the patient depends on timely diagnosis. And that is why the choice of diagnostic apparatuses and devices used in clinical practice is of great importance [7, 8]. We have analyzed the domestic and foreign sources available to us and found no studies on the evaluation of devices and apparatuses for electromyography. Both domestic and foreign authors give a description of electromyography data for assessing the state of muscles, but we did not find information on why this or that diagnostic device was chosen and whether it has all the parameters necessary for a doctor. According to the above-mentioned, we consider it reasonable to carry out an expert evaluation of electromyographs used in clinical practice.

AIM

To make a comparative assessment of electromyographs used in the clinic by the method of expert evaluations.

MATERIALS AND METHODS

In order to determine the optimal device for electromyography in clinical practice, we developed a questionnaire consisting of 50 questions divided into blocks according to certain parameters. To confirm the differentiating ability of the questionnaire developed by us, a commission was recruited. Age of expert specialists is from 45-65 years, the average age is 51.35 years. Scientific and medical experience in the specialty is from 20 to 40 years, the average is 35.5 years. All representatives of the commission are specialists of the highest qualification category and are experts in the field of diagnostics and work with electromyographs. All study participants signed consent to participate in the study, voluntary informed consent and consent to the processing of personal data.

Further, the commission gave an expert assessment of the statements with assignment of a weight coefficient ranging from 0 to 5 [1, 3, 4, 6]. The following evaluation criteria were selected: 1 — informativeness; 2 — accuracy; 3 — convenience; 4 — efficiency; 5 — portability; 6 — autonomy; 7 — cost; 8 — interface convenience; 9 — reliability; 10 — maintainability. Then we collected the opinions of experts by questionnaire survey. Experts assessed the degree of significance of the parameters by assigning them a rank number. The factor to which the expert gave the highest score was assigned rank 1. Then we performed calculations using standard formulas for calculating Pearson's concordance coefficient, summarized the obtained estimates to determine the consistency of experts and recorded them into tables [1, 3].

RESULTS AND DISCUSSION

The experts evaluated the statements proposed to them, and if the expert recognized several factors as equivalent, they were assigned the same rank number. On the basis of the questionnaire survey data, we compiled a summary

ranking matrix, and then we re-formed the associated ranks. If the sum of the matrix columns was equal to each other and to the control sum, the matrix was made correctly. The distribution of factors is presented in Table 1.

Next, we carried out the determination of the consistency of experts' opinions. For this purpose, we used the concordance coefficient, since the tables have related ranks (the same values of ranks in the assessments of one expert): S=25231.5, n=10, m=20. To estimate the average degree of consistency of opinions of all experts, we used Pearson's concordance coefficient W according to the standard formula. Since χ^2 calculated (151.04) ≥ to tabular (16.91898), W=0.84 indicates that this value is not random. Based on obtaining the sum of ranks, we calculated the weighting indices of the considered parameters. We transformed the survey matrix into a matrix of transformed ranks by the formula sij = x_{max} — xij, where x_{max} = 5. And then on the basis of the sum of the ranks of experts' opinions we calculated the value of the weighting of indicators [1, 3, 6] and recorded it in Table 2.

The opinions of 10 experts from the faculty of the Department of Orthopedic Dentistry with a course of clinical dentistry and 10 experts from the faculty of the Department of Normal Physiology were maximally coordinated. And after calculating the results, the most weighty parameters, judging by the number of points, were "informativeness" and "accuracy" for the experts, gaining 0.24 and 0.23 points, respectively. According to the experts, these are the parameters that an optimal electromyograph should possess. The least significant (weighty) parameters, with 0 points, were "interface convenience" and "maintainability".

Next, the experts evaluated the electromyographs offered to them: the adaptive electromyograph Synapsis ("Neurotech", Russia), the electroneuromyograph Neuro-MVP-8 ("Neurosoft", Russia), and the electroneuromyograph Neuro-MVP-Micro ("Neurosoft", Russia). The sum of scores of all experts was multiplied by the weight of a certain parameter and entered into tables. Here the experts' opinions were divided: specialists of the Department of Orthopedic Dentistry with a course of clinical dentistry gave more points to electromyograph "Synapsis" ("Neurotech", Russia), and their average score on the parameters amounted to 4.85 points for all parameters, while the expert specialists of the Department of Normal Physiology evaluated this electromyograph by 4.5 points. Electroneuromyograph "Neuro-MVP-Micro" ("Neurosoft", Russia) was given more points by the specialists of the Department of Normal Physiology, and their average score amounted to

Table 1

Distribution of evaluation criteria by importance for experts depending on the number of points scored

Factors	x_1	x_2	x_4	x_7	x_9	x_5	x_6	x_3	x_8	x_{10}
	informativeness	precision	efficiency	cost	reliability	portability	autonomy	convenience	user-friendly interface	maintainability
Sum of ranks	38	41,5	67	68,5	106,5	128,5	149,5	156	171	173,5

Table 2

Weighting of statements according to experts

Factors	x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	x_9	x_{10}	Total
	informativeness	precision	conconvenience	efficiency	portability	autonomy	cost	user-friendly interface	reliability	maintainability	
Sum of experts' scores	63	61	6	45	15	8	44	1	24	0	267
Weight, λ	0,24	0,23	0,02	0,17	0,06	0,03	0,16	0	0,09	0	1

4.79 points for all parameters, while the expert specialists of the Department of Orthopedic Dentistry with a course of clinical dentistry gave this electroneuromyograph only 4.47 points. As for the electroneuromyograph "Neuro-MVP-8" ("Neurosoft", Russia), the opinion of most of the experts was similar, and it scored an average of 3.7 points for all parameters.

We believe that this distribution of votes of expert specialists is justified by different approaches to diagnosis. Informativeness and accuracy are important to dentists, followed by convenience, cost and maintainability. These characteristics correspond to the electromyograph "Synapsis" ("Neurotech", Russia), which is popular in the clinic of dentistry, and provides an opportunity to obtain accurate information on four channels of signal perception.

It is important for physiologists to have all the necessary functions in a small-sized device, as well as informativeness and accuracy of diagnostics. All these parameters are presented in the electroneuromyograph Neuro-MVP-Micro ("Neurosoft", Russia). This device has a small size, provides sufficient diagnostic accuracy, transmits the signal through two channels of perception. It is enough for diagnostics of the majority of skeletal muscles, for conducting researches in the clinic, but it is not enough for analyzing the biopotential of masticatory muscles. Apparently, this is why dentists put this device on the second place.

Regarding the electroneuromyograph "Neuro-MVP-8" ("Neurosoft", Russia), we believe that it was evaluated in a similar way due to its insufficient accuracy, low informativeness and cumbersomeness.

Further, taking into account the weight of the most significant parameters for experts and the expression of these parameters in the devices presented for evaluation, the optimal apparatus was determined by carrying out calculations using the method of expert evaluations. 20 expert specialists answered 50 questions of the questionnaire, rated three devices in the range from 0 to 5, then the obtained results were multiplied by the weight of the statement and recorded in tables. Then we made calculations and it turned out that the experts evaluated the electromyograph Synapsis ("Neurotech", Russia) at 85.85 points, the electroneuromyograph Neuro-MVP-Micro ("Neurosoft", Russia) scored, according to the experts, 84.35 points, and the electroneuromyograph Neuro-MVP-8 ("Neurosoft", Russia) scored only 77.2 points.

Such estimates correspond to the actual state of affairs, as the most popular electromyograph in Russia is the electromyograph "Synapsis" ("Neurotech", Russia). It is the most popular because of its diagnostic accuracy, informativeness, convenience and successful advertising strategy.

To test this hypothesis and exclude unreasonable assumptions, we used the method of expert evaluations, as it allows us to translate subjective opinion into the language of numbers and give an objective, accurate assessment of various statements. In our case, the experts' opinion coincided with our assumptions about the most optimal device.

CONCLUSION

According to the results of the expert analysis of the devices, the electromyograph Synapsis ("Neurotech", Russia) received the highest scores with 85.85 points and took the first place among the proposed devices for electromyography. We believe that to obtain the most accurate result in the clinic we can recommend using electromyograph "Synapsis" ("Neurotech", Russia), as it has important characteristics for a doctor, namely, high diagnostic accuracy, informativeness, efficiency in operation and relatively low cost.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Автор прочитал и одобрил финальную версию перед публикацией.

Источник финансирования. Автор заявляет об отсутствии внешнего финансирования при проведении исследования.

REFERENCES

1. Bavrina A.P., Borisov I.B. Sovremennyye pravila primeneniya korrelyatsionnogo analiza. [Modern rules for applying correlation analysis]. Meditsinskiy al'manakh. 2021; 3(68). URL: https://cyberleninka.ru/article/n/sovremennye-pravila-primeneniya-korrelyatsionnogo-analiza (дата обращения: 10.06.2023). (in Russian).
2. Gus'kova A.A., Karpenko Yu.A., Arkharova O.N. i dr. Vozmozhnosti elektromiografii v diagnostike narusheniy zubochelyustnoy sistemy. [The possibilities of electromyography in the diagnosis of disorders of the dentition system]. Nauka molodykh — Eruditio Juvenium. 2019; 4. URL: https://cyberleninka.ru/article/n/vozmozhnosti-elektromiografii-v-diagnostike-narusheniy-zubochelyustnoy-sistemy (дата обращения: 20.04.2023). DOI: 10.23888/HMJ201974623-630. (in Russian).
3. Marapov D. Koeffitsiyent korrelyatsii Pirsona. [Pieron's correlation coefficient]. URL: http://biofeedback.com.ua/index.php/programmno-apparatnyj-kompleks-boslab-miografiya/ (02.05.2023). (in Russian).

4. Narkevich A.N., Vinogradov K.A. Vybor metoda dlya statisticheskogo analiza meditsinskikh dannykh i sposoba graficheskogo predstavleniya rezul'tatov. [The choice of a method for a statistical analysis of medical data and a method of graphic presentation of the results]. Sotsial'nyye aspekty zdorov'ya naseleniya. 2019; 4(68). URL: https://cyberleninka.ru/article/n/vybor-metoda-dlya-statisticheskogo-analiza-meditsinskih-dannyh-i-sposoba-graficheskogo-predstavleniya-rezultatov (data obrashcheniya: 20.04.2023). (in Russian).
5. Khudoroshkov Yu.G., Karagozyan Ya.S. Otsenka funktsional'nogo sostoyaniya zhevatel'nykh myshts u patsiyentov s postoyannym prikusom v norme i s narusheniyami okklyuzii. [Assessment of the functional state of the chewing muscles in patients with constant bite is normal and with disorders of occlusion]. Sovremennyye problemy nauki i obrazovaniya. 2016; 4. URL: https://science-education.ru/ru/article/view?id=25013 (data obrashcheniya: 10.06.2023). DOI: 10.17513/spno.25013. (in Russian).
6. Chepuryayeva O.S., Klauchek S.V., Shemonayev V.I., Zhivotov D.S. Ekspertnaya otsenka programmno-apparatnogo kompleksa BOSPUL'S, primenyayemogo v stomatologii. [Expert assessment of the software and hardware complex of the bospulse used in dentistry]. Rossiyskaya stomatologiya. 2019; 12(3): 68–9. (in Russian).
7. Shemonayev V.I., Mashkov A.V., Maloletkova A.A. i dr. Otsenka funktsional'nogo sostoyaniya zhevatel'nogo zvena zubochelyustnoy sistemy po dannym gnatodinamometrii i elektromiografii u lits 18–35 let s polnymi zubnymi ryadami pri ortognaticheskom prikuse. [Assessment of the functional state of the chewing link of the dentist system according to the data of the gnatodinamometry and electromyography in persons of 18–35 years with full dentitions with an orthogenic bite]. Vestnik Volgogradskogo gosudarstvennogo universiteta. Seriya 11: Yestestvennyye nauki. 2014; 4(10): 17–23. (in Russian).
8. Shishkin A.V., Mitin A.Ye., Filippova S.O. Problema primeneniya elektromiografii s tsel'yu povysheniya effektivnosti trenirovochnogo i sorevnovatel'nogo protsessov v adaptivnom sporte. [The problem of using electromyography in order to increase the efficiency of training and competitive processes in adaptive sports]. Sovremennyye problemy nauki i obrazovaniya. 2013; 6. URL: https://science-education.ru/ru/article/view?id=11055 (data obrashcheniya: 01.07.2023). (in Russian).

ЛИТЕРАТУРА

1. Баврина А.П., Борисов И.Б. Современные правила применения корреляционного анализа. Медицинский альманах. 2021; 3(68). URL: https://cyberleninka.ru/article/n/sovremennye-pravila-primeneniya-korrelyatsionnogo-analiza (дата обращения: 10.06.2023).
2. Гуськова А.А., Карпенко Ю.А., Архарова О.Н. и др. Возможности электромиографии в диагностике нарушений зубочелюстной системы. Наука молодых — Eruditio Juvenium. 2019; 4. URL: https://cyberleninka.ru/article/n/vozmozhnosti-elektromiografii-v-diagnostike-narusheniy-zubochelyustnoy-sistemy (дата обращения: 20.04.2023). DOI: 10.23888/HMJ201974623-630.
3. Марапов Д. Коэффициент корреляции Пирсона. URL: http://biofeedback.com.ua/index.php/programmno-apparatnyj-kompleks-boslab-miografiya/ (02.05.2023).
4. Наркевич А.Н., Виноградов К.А. Выбор метода для статистического анализа медицинских данных и способа графического представления результатов. Социальные аспекты здоровья населения. 2019; 4(68). URL: https://cyberleninka.ru/article/n/vybor-metoda-dlya-statisticheskogo-analiza-meditsinskih-dannyh-i-sposoba-graficheskogo-predstavleniya-rezultatov (дата обращения: 20.04.2023).
5. Худорошков Ю.Г., Карагозян Я.С. Оценка функционального состояния жевательных мышц у пациентов с постоянным прикусом в норме и с нарушениями окклюзии. Современные проблемы науки и образования. 2016; 4. URL: https://science-education.ru/ru/article/view?id=25013 (дата обращения: 10.06.2023). DOI: 10.17513/spno.25013.
6. Чепуряева О.С., Клаучек С.В., Шемонаев В.И., Животов Д.С. Экспертная оценка программно-аппаратного комплекса БОСПУЛЬС, применяемого в стоматологии. Российская стоматология. 2019; 12(3): 68–9.
7. Шемонаев В.И., Машков А.В., Малолеткова А.А. и др. Оценка функционального состояния жевательного звена зубочелюстной системы по данным гнатодинамометрии и электромиографии у лиц 18–35 лет с полными зубными рядами при ортогнатическом прикусе. Вестник Волгоградского государственного университета. Серия 11: Естественные науки. 2014; 4(10): 17–23.
8. Шишкин А.В., Митин А.Е., Филиппова С.О. Проблема применения электромиографии с целью повышения эффективности тренировочного и соревновательного процессов в адаптивном спорте. Современные проблемы науки и образования. 2013; 6. URL: https://science-education.ru/ru/article/view?id=11055 (дата обращения: 01.07.2023).

UDC 612.66
DOI: 10.56871/RBR.2023.19.40.006

FUNCTIONAL FEATURES OF THE CARDIORESPIRATORY SYSTEM OF THE ALIEN POPULATION LIVING IN THE REGIONS OF THE FAR NORTH AND AREAS EQUATED TO THEM (LITERATURE REVIEW)

© Olga G. Litovchenko, Narmin G. kizi Gadzhibekova

Surgut State University. Lenin ave., 1, Surgut, Russian Federation, 628412

Contact information: Narmin G. kizi Gadzhibekova — Doctor of functional diagnostics. E-mail: narmina567@mail.ru ORCID ID: 0000-0003-3772-569X

For citation: Litovchenko OG, Gadzhibekova N kizi G. Functional features of the cardiorespiratory system of the alien population living in the regions of the Far North and areas equated to them (literature review) // Russian biomedical research (St. Petersburg). 2023; 8(3): 36-49. DOI: https://doi.org/10.56871/RBR.2023.19.40.006v

Received: 02.06.2023 **Revised: 11.07.2023** **Accepted: 21.09.2023**

Abstract. The development of oil and gas resources of the Far North and equivalent areas of Russia is accompanied by the construction of strategically important facilities and territorial production complexes, which lead to the migration of a large number of people from various regions of Russia. Specific climatogeographic and ecological conditions of the North determine the unique course of all biological processes, affecting all functional systems of the body, including cardiorespiratory. The study of functional capabilities and adaptation mechanisms to environmental conditions remains an urgent task of human physiology in connection with the active development of natural resources at the expense of productive forces coming from other regions. The article presents a brief overview of research papers that reflect the functional features of the cardiorespiratory system of the alien population living in various regions of the Far North and equivalent areas of Russia. The presented literature data indicate the presence of specific adaptation processes of the cardiorespiratory system in representatives of the alien population in the harsh climatic and geographical conditions of the northern regions, manifested in hyperfunction of external respiration, hemodynamic reactions, special compensatory changes in the respiratory and circulatory systems. The development of the northern regions increases the relevance of the development and implementation of measures to assess the endurance of the respiratory and circulatory systems of representatives of the alien population, as well as the prediction of possible risks to their health.

Key words: cardiorespiratory system; adaption; alien population; northern region.

ФУНКЦИОНАЛЬНЫЕ ОСОБЕННОСТИ КАРДИОРЕСПИРАТОРНОЙ СИСТЕМЫ ПРИШЛОГО НАСЕЛЕНИЯ, ПРОЖИВАЮЩЕГО В РАЙОНАХ КРАЙНЕГО СЕВЕРА И ПРИРАВНЕННЫХ К НИМ МЕСТНОСТЯХ (ОБЗОР ЛИТЕРАТУРЫ)

© Ольга Геннадьевна Литовченко, Нармин Гаджибала кызы Гаджибекова

Сургутский государственный университет, 628412, г. Сургут, пр. Ленина, 1

Контактная информация: Нармин Гаджибала кызы Гаджибекова — врач функциональной диагностики. E-mail: narmina567@mail.ru ORCID ID: 0000-0003-3772-569X

Для цитирования: Литовченко О.Г., Гаджибекова Н.Г. Функциональные особенности кардиореспираторной системы пришлого населения, проживающего в районах Крайнего Севера и приравненных к ним местностях (обзор литературы) // Российские биомедицинские исследования. 2023. Т. 8. № 3. С. 36–49. DOI: https://doi.org/10.56871/RBR.2023.19.40.006

Поступила: 02.06.2023 **Одобрена: 11.07.2023** **Принята к печати: 21.09.2023**

Резюме. Освоение нефтяных и газовых ресурсов Крайнего Севера и приравненных к ним местностей России сопровождается строительством стратегически важных объектов и территориально-производственных комплексов, которые приводят к миграции большого количества людей из различных регионов России. Специфичные климатогеографические и экологические условия Севера определяют уникальное протекание всех биологических процессов, влияя на все функциональные системы организма, в том числе и кардиореспираторную. Исследование функциональных возможностей и адаптационных механизмов к условиям окружающей среды остается актуальной задачей физиологии человека в связи с активным освоением природных ресурсов за счет производительных сил, приезжающих из других регионов. В статье представлен краткий обзор исследовательских работ, в которых отражены функциональные особенности кардиореспираторной системы пришлого населения, проживающего в различных регионах Крайнего Севера и приравненных к ним местностях России. Представленные литературные данные свидетельствуют о наличии специфичных адаптационных процессов кардиореспираторной системы у представителей пришлого населения в суровых климатогеографических условиях северных регионов, проявляющихся в гиперфункции внешнего дыхания, реакциях гемодинамики, особых компенсаторных изменениях систем дыхания и кровообращения. Освоение северных регионов повышает актуальность разработки и внедрения мероприятий по оценке выносливости систем дыхания и кровообращения у представителей пришлого населения, а также прогнозированию возможных рисков для их здоровья.

Ключевые слова: кардиореспираторная система; адаптация; пришлое население; северный регион.

INTRODUCTION

The evolutionary formation of an organism as a biological species is directly connected with the external environment and is determined by the influence of various climatic, geophysical and geochemical conditions. In the process of evolution, corresponding natural rhythms were formed in the activity of the cardiovascular and respiratory systems of the body [27]. In the process of adaptation to environmental conditions, an organism forms characteristics and properties that prove to be the most beneficial and thanks to which the organism acquires the ability to exist normally in a specific habitat [5].

Adaptation of an organism to new natural and production conditions necessary for the sustainable existence of the organism in a specific ecological environment occurs at the cellular, organ, systemic and organismic levels [7, 61]. The cardiovascular and respiratory systems together are a marker of the organism's adaptation to new environmental conditions, which is reflected in the morphological and functional changes of these systems [64, 75]. The cardiorespiratory system (CRS) as the main link in the life activity of the human body is aimed at continuously supplying it with oxygen [12]. The CRS is interconnected with external environment, so the system also is influenced by a complex of negative environmental factors [13]. The cardiovascular and respiratory systems serve as the most important link in the complex of visceral systems that ensure metabolism and maintain the constant internal environment of the body [34, 55].

The life activities of the immigrant and indigenous population living in regions of the Far North and equivalent localities are sharply limited due to harsh natural conditions. A number of researchers have proven the negative impact of the climatic features of the northern region on health of residents [41, 52]. Thus, a third of the residents of the surveyed territories describe the northern climate as "very severe" and "rather severe" (no differences in assessments were found between groups formed on the basis of age and gender criteria and degree of sedentarism) [41]. Moreover, immigrant population more often talk about the influence of certain climatic characteristics (for example, the polar night) on their physical and mental state [41]. Indigenous people, unlike the migrant population, have a natural adaptation to external environmental factors, as a result of which they are less susceptible to stress and premature pathologies [31]. The immigrant population is influenced by various factors of the changed habitat, as it finds itself in new social and cultural, physical and geographical conditions [66]. A study of technogenic impact on biological systems in the conditions of the Far North demonstrated the disastrous ecological state of the landscape in the territory of oil producing enterprises [37]. Increased physical and mental stress against the background of existing natural pressure can provoke high tension in the body's adaptation systems and the development of a special condition of the complex od symptoms [39].

Adaptation of the body of an immigrant population allows it to endure significant changes in the external environment and actively restructure organism's physiological functions in accordance with these changes, sometimes even ahead of them [1]. The immigrant population turned out to be more vulnerable to associated effects of northern risk

factors, which contributed to the development of the "polar tension" syndrome with its inherent initiation of free-radical oxidation and a decrease in overall antioxidant activity [37].

The health status of the immigrant population is under the continuous influence of specific risk factors, which leads to the formation of typical northern pathology. Since northern conditions require increased energy consumption and increased oxygen consumption, the cardiovascular and respiratory systems require a constant increase in oxygen supply. The appropriate utilization of oxygen is ensured by the respiratory and hemodynamic systems, which in different combinations lead to a change in the type of functional relationship between the parameters of the heart and lungs at certain age periods of a person [23]. For example, the same level of oxygen consumption can be achieved by different strategies: either increased ventilation or increased oxygen utilization [55]. To effectively assess the functional state of the body of the immigrant population, informative criteria of the cardiorespiratory system are considered in a complex, since each individual physiological parameter of respiration and heart is not as reliable and objective as a complex approach consisting of recording numerous indicators. In this regard, it is necessary to carry out a systemic quantitative analysis of the organism, which are the part of the general functional system of adaptation of the organism [27]. In this regard, it is necessary to carry out a systemic-quantitative analysis of the organism, which are part of the general functional system of adaptation of the organism [27].

The adaptation of the immigrants' body in northern latitudes has specific features. Some migrants adapt quickly, their organism is rebuilt to the so-called polar metabolic type, while others have a long adaptation period [30]. The adaptation of the immigrants' body in northern latitudes has specific features. Some migrants adapt quickly, their organism is rebuilt to the so-called polar metabolic type, while others have a long adaptation period [30]. With the increase in number of generations of people living in conditions of the northern region, optimization of the cardiorespiratory system indicators is observed with a decrease in the degree of reactivity in a series from zero to the second generation in response to the activation of the orthostatic test. This occurs against the background of an increase in the degree of influence of the autonomic nervous system in a state of rest and with a greater expression of the decrease in response to orthostatic test [2]. With an increase in the time of residence in the North-East of Russia, there is a gradual decrease in the level of stress in the work of the cardiorespiratory system, a decrease in the incidence of basal metabolic parameters exceeding the normative values [1]. At the same time, an increase in the specific weight of deviations in microcirculation indicators is observed in a series from zero to the third generation (a decrease in the diameter of arterial and venous sections, an increase in the coefficient of deformation of capillaries).

The study of the patterns and physiological mechanisms of adaptation of the aborigines of the North is of great importance for the preservation and development of health not only of small ethnic groups, but also of immigrants, since the indigenous population represents the adaptive standard that is most adequate to its habitat [73]. In order to minimize the incidence of heart and lung pathologies in the immigrant population living in the northern region, it is necessary to pay special attention to the cardiorespiratory system. The relevance of the topic is related to the need to generalize and analyze existing approaches to the study of adaptive capabilities on the health status of the migrant population under the influence of harsh climatic conditions.

GENERAL PATTERNS OF ADAPTATION IN THE NORTH

The development of new deposits, which have great political and economic potential, is closely linked with the study of the adaptation of the organism [70]. In this regard, the basis of modern medicine should be adaptive physiology [5]. The indigenous population is adapted to environmental factors both at the phenotypic and genetic levels. The best effect of the adaptation process is achieved with greater similarity of morphological and physiological characteristics in the indigenous and immigrant populations, and acclimatization in harsh living conditions requires the greatest stress on the adaptation processes [1]. Expeditions conducted in various extreme conditions of the Far North have shown that the body always pays with stress and expenditure of vital resources for adaptation to new environmental conditions [4]. This is why the leading aspect of the formation of the current morphological and functional state of human organs and its reserve capabilities is the type of adaptation of important body systems to climatic, geographical and seasonal conditions [33].

The difference between the functional characteristics of immigrants and native population is that even after the completion of the process of successful acclimatization, the organism of immigrants will work with maximum use of resources [72]. In immigrants, many physiological processes shift in the direction of characteristics typical for the natives of a given region [64, 82]. A transitional process of adaptation is established and characterized by the totality of the existing capabilities of the organism. The influence of climatological and territorial conditions of the North on the body's state was identified by researchers in the seventies and eighties of the last century. Scientists have proven that the hereditary capabilities of adaptation processes in more than 70% of the migrant population in the North can-

not ensure long-term health maintenance in harsh climatic conditions [30].

The entire adaptation process can be divided into stages. The first stage is the stage of anxiety, when the body rapidly rebuilds itself and the mechanism of adaptation to new living conditions begins. The second stage (resistance) is the level of significant resistance of the body's systems to the effects of the northern region. By the end of this stage, the body's condition stabilizes, functional indicators are normalized, and a completely new state of balanced, stable equilibrium is realized [5]. Thus, the respiratory and cardiac organs manage to successfully adapt to the climatic conditions of the northern region thanks to the restructuring of the most important systems of the body [56].

Exposure to the harsh conditions of the Far North and similar areas, such as pronounced ultraviolet deficiency due to low solstice, long and cold winters, and low air temperatures inevitably lead to the process of "light starvation" at night and "light excess" during the day. The complex of these mechanisms represents a difficult multi-stage social and physiological process, which is combined with pronounced stress on the body's adaptive systems [48]. As a result of the research, it was clearly demonstrated that at the first stage of adaptation to harsh environmental conditions, an urgent set of compensatory, protective reactions is acquired that support the normal functioning of the body's systems by straining functional reserves [1, 38].

The immigrant population is characterized by a specific form of continuous stress on the cardiovascular and respiratory systems, which is caused by the weakening of the body's stable resistance to extreme conditions [13]. Common features of the adaptation process are an increase in the size of the adrenal cortex and an increase in their secretory activity, a decrease in the lymph nodes, thymus, spleen, and a reorganization of blood composition indicators, a change in the ratio of metabolic processes in the body, the prevalence of decay processes that lead to a decrease in blood pressure and weight loss [66]. It has been proven that in the harsh conditions of the North, sympathicotonia is reduced in winter and increased in summer [56]. So, at low air temperatures the tone of the vagus nerve predominates. On the part of the immune system, there is a weakening of immunity and a tendency towards a protracted, chronic course of diseases in northerners [44]. Ineffective functioning of the immune system of immigrants of the north often leads to the spread of acute infectious pathology, which creates a threat of failure of protective adaptive mechanisms and determines the tendency for acute inflammation to become chronic [68].

A survey of the cardiorespiratory system indicators of the Salekhard population revealed a stress in the functional characteristics of the lungs and heart of immigrants, which is characterized by increased functional activity of the external respiration parameters, an increase in systolic and diastolic blood pressure, minute blood volume, and total peripheral vascular resistance [67]. Such a characteristic adaptive change in the functioning of the cardiovascular and respiratory systems is necessary to ensure the normal functioning of the body of the immigrant population in the conditions of the North [31].

When the body adapts to changing factors in the North, profound shifts in the internal environment of the body occur (hypoxia, hypercapnia, hypocapnia, acidemia), which, according to the principle of feedback, activate the physiological processes of regulation and the function of gas exchange of the respiratory system. Some northerners experience an increase in pulmonary ventilation, while others experience an increase in heart rate, which becomes one of the leading factors in providing the body with oxygen. It is necessary to coordinate work to ensure the supply and consumption of oxygen, which affects the contractility of the myocardium and the frequency of respiratory movements, which depend on the body's reserves [53].

FEATURES OF RESPIRATORY SYSTEM ADAPTATION

A pronounced feature of the adaptation process to the extreme conditions of the Far North are morphogical, physiological and functional changes in the respiratory system, which are often characterized by dyspnea [61], which is called polar. As compensation for hyperventilation of immigrants' lungs, metabolic acidosis develops in the conditions of the Middle Ob region [81]. The increase in the minute volume of respiration, typical for the northern region in plain conditions, is explained not only by metabolic acidosis, but also by a decrease in the aeroionisation of air [4]. When studying the mechanism of dyspnea as a phenomenon that occurs in depressive and anxious states, 4 clinical variants of hyperventilation syndrome not accompanied by hypoxia were identified [30].

CRS is susceptible to somatic, biological and psychological influences. The functional state of CRS depends on environmental factors. At the beginning of the adaptation process to cold, the functional depot accumulates due to additional opening of the alveoli at the level of the medium and large bronchi [3]. However, the long-term presence of immigrants in northern conditions leads to an increase in the area of gas exchange, which occurs due to morphological changes: diameter, quantity and volume due to morphological changes, quantity and volume of capillaries that bulge into the lumen of the alveoli. Against the background of these processes, the blood pressure in the pulmonary circulation significantly exceeds the normal values [56]. Changes in the respiratory system of a person living in the

North for several years correspond to adaptation to hypoxia [3, 5, 27].

Almost the entire immigrant population experiences difficulty breathing and shortness of breath at low air temperatures in the uncomfortable conditions of the northern region [48]. A study conducted in Surgut notes the highest and progressive incidence of diseases of the respiratory system and pathologies that make up metabolic syndrome — diabetes mellitus and obesity [15]. Blood oxygenation is controlled by important functions of the cardiorespiratory system: inhalation, exhalation, depth of breathing and respiratory rate, as well as the condition and functional characteristics of red blood [35]. In residents of the European North, the levels of red blood cells circulating in the peripheral blood and hemoglobin are within the physiological norm for the immigrant population [3]. The peculiarities of morphological and physiological data of erythrocytes in the blood test of the population of the northern territories are associated with an increased intensification of erythropoiesis [74]. These processes are directly dependent on the severity of the climatic conditions of the regions of the European North and worsen as one moves north [74]. An increase in the volume of pulmonary ventilation in northerners at rest and a decrease in the vital capacity of the lungs (VC) in residents of the North were also revealed [22, 46, 65]. It has been established that in population of the Magadan region, living in uncomfortable conditions for more than 5 years, the value of VC is reduced by 3% compared to the control parameters of Moscow [42]. Features of lungs of the Middle Ob region immigrants were identified, which consisted of a more developed bronchial system, which ensured more efficient gas exchange [9].

In different seasons of light aperiodicity, depending on the polar night and polar day, changes in external respiration were revealed according to spirometric examinations of natives of the Far North, residents of Murmansk [20]. It has been proven that the indicators and structure of vital capacity in girls and boys, the respiratory volume and the nature of the relationships between the indicators that comprise them decrease. The magnitude of the respiratory volume is one of the most demonstrative criteria of the external respiratory system, characterizing its pattern. As a result of the conducted studies, it was established that during the polar day, the residents of the Far North have a lower respiratory volume than during the polar night [69].

The adverse effect of hypoxia on the body is that during the transition to the cold period of the year, the load on the respiratory system increases [51]. A decrease in the oxygen utilization function in immigrants living in the conditions of the northern region has been established [70].

Chronic hypoxia in the North is the main cause of increased activity of the respiratory system, manifested by tissue hypoxia, the action of a complex of geophysical factors of high latitudes, which in the future may lead to high incidence of respiratory diseases [25]. During the compensation phase, reactions that are characteristic of hypoxia are formed in the body of northerners: the utilization of oxygen from the inhaled air and the delivery of oxygen by blood increases, and then the coefficient of oxygen utilization by tissues increases [14]. The adaptation mechanism in immigrants of the Far North is accompanied by a complex of symptoms that includes chronic hypoxia with corresponding changes in the cardiovascular and respiratory systems, forced to “fight” for oxygen. In northerners, oxygen saturation in arterial blood does not differ from the corresponding indicators in mid-latitudes [27], while carbon dioxide tension in both arterial [36] and venous blood [3] is increased. The arteriovenous difference in oxygen significantly exceeds the norms of mid-latitudes [10], which reflects the metabolic restructuring of energy processes [8].

It has been found that high hemoglobin level in blood of immigrants contribute to better oxygen exchange [43]. The ability of the body of northerners to tolerate hypoxia depends on the individual genetic characteristics of their body, as well as on the time of year and environmental conditions. The observed low levels of red blood cells and hemoglobin negatively affect a person’s mental activity [54].

In conditions of the northern region, the greatest impact on the functional state of the body is exerted by cold and a specific heliogeomagnetic environment [72]. With continuous exposure to cold, there is a decrease in respiratory heat loss and protection of the respiratory tract from the effects of cold, leading to morphological and functional restructuring of the respiratory system and the oxygen transport system of the blood [56]. In the cold season, heat emission through the respiratory system is also saved by reducing ventilation, the minute respiratory volume and respiratory rate are reduced [47].

The extreme impact of the oscillatory dynamics of heliogeomagnetic activity on the human body occurs against the background of meteorological factors or through them [31]. The activation of cold receptors leads to the activation and excitation of thermoregulation centers, which in the future, as a rule, leads to increased intensification of energy exchange processes in the central nervous system [18].

A number of studies have demonstrated a decrease in the vital capacity of the immigrant population of the northern region [46, 65, 76]. It has been shown that with more than 10 years of experience in the north, the vital capacity value is significantly lower by 8.2%, which indicates a morphological restructuring of the lung parenchyma [1].

During spirometry examination of the external respiration parameters in immigrants of the North-East of Russia, it was revealed that in healthy men, the residual volume of the lungs (RVL) and the functional residual capacity of the

lungs (FRC) are most often significantly increased in winter. An increase in functional dead space has been proven in immigrants of the Magadan Region, which is 90–110 ml higher than its value in men living in Western Siberia [19]. A close study of the mechanisms of the FRC clearly showed that the parameters of the FRC depend on the influence of external environmental factors. There is an increase in FRC parameters due to the opening of reserve acini involved in gas exchange and ventilation of the lungs. The identified adaptive changes in the respiratory system contribute to the protection of bronchial tree from cold exposure and damage, as well as the economical expenditure of energy under cooling conditions [72]. In the conditions of the North, a change in the vital capacity may be a cause of the formation of signs of obstructive pulmonary disorders [50]. This is evidenced by a violation of bronchial patency, identified by the Tiffeneau index.

In the majority of both the immigrants and indigenous populations of the northern region, in combination with the effective adaptive restructuring of the respiratory system, destruction and atrophy of the mucociliary, elastic and muscular apparatuses of the respiratory tract may be observed, followed by the formation of a violation of the bronchial drainage function, an increase in bronchial resistance and dynamic compression of the small bronchi. These lead to a decrease in the efficiency of gas exchange and an increase in the unevenness of alveolar ventilation [46]. The nature of the morphological and functional changes in the respiratory system of immigrant population allows us to consider such changes as a manifestation of compensatory and protective reactions aimed at reducing heat loss and minimizing the impact of cold air on the respiratory tract [57].

Most studies show that the incidence of pulmonary pathology in the North is very high and reaches more than 55% of all diseases [64]. The peculiarities of the development of pathological processes of the respiratory system in the North include: hyperventilation of the lungs in combination with obstructive changes in respiratory volumes; shortness of breath with little physical exertion; hypertrophy of the right ventricle of the heart; decreased respiratory reserves; pulmonary hypertension; dilation of the pulmonary artery and increased pulmonary pattern [51]. When studying the functional state of the aerohematic barrier in humans in the conditions of the Far North, a reliable increase in surfactant was revealed in histologically normal lungs of individuals who had lived in the North for more than 5 years [3]. Chronic respiratory diseases in the migrant population living in the North are characterized by rapid progression and the manifestation of severe intoxication, unlike similar diseases in the middle latitudes. Despite adequate drug therapy, the diseases become protracted and are manifested by long periods of exacerbation and short remissions [51].

FEATURES OF CARDIOVASCULAR SYSTEM ADAPTATION IN NORTH CONDITIONS

For population of the North, the most important limiting factor in the formation of health is adaptation to climatic conditions. At the initial stage of adaptation in immigrant population in the North, hypertension often develop [51]. The right heart side is a subject to the greatest stress, which subsequently manifests itself as adaptive pulmonary hypertension. As the migrant population adapts and stays for a long time, living and working in the conditions of the North, there is a decrease and subsequent depletion of the adaptation reserves of the left heart side, which in some migrants leads to an increase in pressure in the vessels of the systemic circulation [1]. High pressure in the pulmonary circulation and pronounced changes in pulmonary ventilation are not only interconnected, but also interdependent [46]. A moderate increase of systolic pressure to 40 mm Hg in pulmonary artery is aimed at ensuring optimal blood flow to the lungs and optimizing oxygen transport delivery under conditions of increased energy exchange [60].

During the adaptation process of the migrant's body to cold, the sensitivity of tissues to norepinephrine also increases, which indicates the transition of the cardiorespiratory system to a more economical regulation path [13]. A study conducted in Arkhangelsk confirms that local exposure to low temperatures activates the sympathetic nervous system, causing a reflex increase in the concentration of norepinephrine, adenosine triphosphate, a decrease in the intensity of peripheral blood flow, and an increase in heart rate [74].

In people living in the Middle Ob region, there is a "rejuvenation" of arterial hypertension [3, 32], which, being a multifactorial disease, develops as a violation of the processes of human adaptation to environmental conditions in presence of genetically predetermined violations of regulatory mechanisms and against the background of emerging pathophysiological and involutional processes in the body [21]. Blood pressure in men and women in the European North is higher than in residents of comfortable climate zones, and its age-related increase over decades of life is more significant than in those living in warm climates [13]. The risk of developing hypertension increases threefold in the working population after 10 years of work in the North. Hypertension was detected in 13.2% of northerners aged 30–39 years [71]. In Chukotka, a higher incidence of hypertension is observed among the population aged 30 to 60 years. An unfavorable outcome of cardiovascular system's adaptation is vascular dystonia, which represents a phenomenon of maladaptation.

Reduced humidity in the air of the external environment in northern conditions leads to stress on the right side of

heart, accelerates energy and water metabolism, reduces diuresis by 19% [55], leading to hyperventilation syndrome [80]. The immigrant population has a larger heart compared to the indigenous inhabitants, since the cardiovascular system of migrants is forced to adapt to harsh environmental conditions, which required more intensive work in uncomfortable conditions. This made it possible to improve blood circulation and provide the body tissues with oxygen [26].

Heart rate (HR) is one of the main integral characteristics of the cardiovascular system state [29]. At rest, HR fluctuates in the range from 60 to 90 beats per minute [79]. Conducted studies prove that northerners have higher systolic and diastolic blood pressure and heart rate than average age norms [24].

The prevalence of high functional values of minute blood volume, pressure, and heart rate in the conditions of the Middle Ob region has been confirmed by studies on the cardiorespiratory system in residents of northern regions [28, 62]. It can be argued that an increase in heart rate in immigrant population living in the Northern conditions indicates intense cardiac activity even at rest [63]. These indicators increase progressively with increasing duration of residence in harsh conditions and ultimately lead to a decrease in the reserve capacity of the cardiovascular system and the chronotropic reserve of heart [12].

There is data that allows us to reliably say that heart rate depends on the type of blood circulation [49]. The lowest heart rate values are observed with the hypokinetic type of circulation in all subjects. The highest heart rate values are observed in eukinetic and hyperkinetic types of circulation. Along with an increase in heart rate, when adapting the cardiac system and cardiac activity to muscle loads, the main role is played by stroke volume (SV), an increase of which is an important condition for ensuring muscle activity [69].

Changes in blood pressure in immigrant population of the Middle Ob region are one of the controversial issues. A tendency towards a decrease in blood pressure is noted [11]. When studying the parameters of the cardiovascular system in immigrant population of Surgut, it was noted that systolic blood pressure (SBP) slightly exceeded the level of 130 mm Hg in men and was consistently higher than in women [17]. The functional health of the immigrant population is characterized by a more pronounced tension of the body's adaptive capabilities compared to the native population. A study conducted in the Yamalo-Nenets Autonomous Okrug clearly showed that the immigrant population is characterized by a significantly smaller number of people with vagotonia and a high percentage of people with sympathicotonia, which should be attributed to signs of tension of the adaptive mechanisms [73]. It should be noted that for the indigenous peoples of the North, the shift in vegetative regulation towards vagotonia is a genetically fixed adaptation mechanism, which is also confirmed by a number of studies [45].

Seasonal fluctuations in blood pressure have been identified in both healthy individuals and individuals suffering from arterial hypertension, with higher levels in winter compared to summer. This is associated with an increase in the level of catecholamines in blood and total peripheral vascular resistance [12]. Determining the chronotype of the human body leaves its mark on the daily fluctuations of the heart rate variability indices. Thus, individuals with the morning chronotype are characterized by a tendency to sympathicotonia in the morning, weakening at the end of the day. Individuals with the evening chronotype are characterized by the manifestation of signs of sympathetic cardiointervalogram in the evening [24].

Morphofunctional changes in cardiac activity, which manifest themselves in the form of neurocirculatory dystonia in young people and increased blood pressure in older age groups, were identified in 55% of the examined people living in the North [13]. Every third of the examined northerners suffers from hypertension at the age of 20–59 years, with 60% of all cases of arterial hypertension occurring before the age of 40 years [51].

The fact that hypertension is malignant in the North is confirmed by the greater severity and high frequency of hypertensive crises [70]. Residents of the North-West region of Russia have higher blood pressure and lipid metabolism disorders, which may be associated with unfavorable climatic conditions and lifestyle. Arterial hypertension was detected in 35.4% of cases among visiting residents of the Tyumen North [6]. Among working-age residents of Novy Urengoy, borderline arterial hypertension was detected in 16.2% of those examined, essential hypertension in 30.5%, and symptomatic hypertension in 4.1% [71]. The highest incidence of coronary heart disease (CHD) among residents of this region was observed in the winter months [12]. A study by Litovchenko et al. (2021) showed that at the age of 26 years and older, there is a risk of developing cardiovascular changes in male students working in the oil industry. Changes in indicators such as the endurance coefficient, the circulatory efficiency coefficient and the Ruffier test indicate a deviation from the age norm and a disruption of the cardiovascular system [40].

Heart rate variability (HRV) reflects the ability of the cardiovascular system (CVS) to adapt. HRV decreases with increasing age [77, 78]. Deviation from the norm of HRV indicators is an unfavorable prognostic factor [58]. Against the background of a general decrease in both time and frequency indices of HRV, the subjects show an increase in parasympathetic influences with lower indices of differentiated assessment of the condition in those living for no more than 6 months and a predominance of sympathetic tone

with a high level of personal anxiety in those living for more than six months. This is expressed in a hyperadaptive state of mobilization of energy and metabolic reserves [59]. In 62 healthy young people aged 20 to 30 years, using the Holter monitoring, episodes of sinus arrhythmia were detected in 90% of subjects, in contrast to healthy older people, and a night-time decrease in blood pressure in healthy subjects within 10–20% compared to the daytime level [16].

Analyzing the frequency of detection of variations in the electrical axis of the heart in the population living in Surgut, Nifontova O.L. and co-authors concluded that with age, regardless of gender, the frequency of deviations of the cardiac axis from its normal position increased and the appearance of a fairly large percentage of people of both sexes with a horizontal position of the heart and a deviation to the right or left was determined [49]. Thus, the central hemodynamics, heart rate, and electrocardiogram data served as the basis for the conclusions about the presence of a tendency for hypertrophic changes in the myocardium with age in northerners. Most often, hypertrophic changes were determined in the left atrium, less often in the right atrium [49].

CONCLUSION

The territories of the Far North and equivalent areas remain the main source of fuel and energy resources for Russia. The extensive development of northern regions attracts new human resources. The immigrant population of the North is forced to adapt to severe climatic and geographical conditions, and the cardiorespiratory system determines the adaptive capabilities of the entire organism. Literary data indicate a significant strain on the functional capabilities of the oxygen-transport system in northerners, which leads to a decrease in the efficiency of gas exchange and an increase in the unevenness of alveolar ventilation.

The immigrant population exhibits significant seasonal variability in the parameters of the cardiorespiratory system, hemodynamic characteristics and external respiration parameters undergo changes, and an increase in heart rate, blood pressure, pulmonary ventilation, minute respiratory volume, vital capacity of the lungs, and bronchial resistance are observed.

REFERENCES

1. Aver'yanova I.V., Vdovenko S.I. Otsenka stepeni napryazheniya funktsional'nogo sostoyaniya organizma cheloveka pri razlichnykh srokakh adaptatsii k usloviyam Severa. [Assessment of the degree of stress of the functional state of the human body at various times of adaptation to the conditions of the North]. Ekologiya cheloveka. 2021; 7: 12–7. (in Russian).
2. Aver'yanova I.V., Maksimov A.L. Osobennosti perestroek kardiogemodinamiki i variabel'nosti serdechnogo ritma u evropeoidov — migrantov i urozhentsev Severa pervogo i vtorogo pokoleniy pri aktivnoy ortostaticheskoy probe. [Features of alterations of cardiohemodynamics and heart rate variability in Caucasians — migrants and natives of the North of the first and second generations with an active orthostatic test]. Sibirskiy nauchnyy meditsinskiy zhurnal. 2021; 41(3): 45–52. (in Russian).
3. Avtsyn A.P., Maracheev A.G., Matveev L.N. Vestnik AMN SSSR. [Sciences of the USSR]. 1979; 6: 32–9. (in Russian).
4. Agadzhanyan N.A. Ekologicheskaya fiziologiya cheloveka. [Environmental physiology of man]. Kruk Publ.; 1998. (in Russian).
5. Agadzhanyan N.A., Baevskiy R.M., Berseneva A.P. Problemy adaptatsii i uchenie o zdorov'e: RUDN. [Adaptation problems and health doctrine: RUDN]. 2006. (in Russian).
6. Akimov A.M. Zdorov'e sberezhenie uchastnikov osvoeniya arkticheskogo neftegazovogo regiona: monografiya. [Health savings of participants in the development of the Arctic oil and gas region: monograph]. Tyumen'; 2019. (in Russian).
7. Andronova T.I. Otsenka meteotropnykh reaktsiy organizma cheloveka k faktoram vneshney sredy: metod.razrabotki. [Assessment of meteorotropic reactions of the human body to environmental factors: methods of developmen]. Institut klinicheskoy i eksperimental'noy meditsiny. Novosibirsk; 1979. (in Russian).
8. Boyko E.R. Fiziologo-biokhimicheskie osnovy zhiznedeyatel'nosti cheloveka na Severe. [Assessment of meteorotropic reactions of the human body to environmental factors: methods of developmen]. Ekaterinburg: UrO RAN; 2005. (in Russian).
9. Borisenko I.V., Kosykh E.V., Kharlamov A.N. Osobennosti funktsional'nogo sostoyaniya legkikh zhiteley Srednego Priob'ya. [Features of the functional state of the lungs of residents of the Middle Priobye]. Vestnik Tomskogo gosudarstvennogo universiteta. 2017; 2: 94–102. (in Russian).
10. Bichkaeva F.A. Rezervnye vozmozhnosti endokrinnoy regulyatsii metabolicheskikh protsessov u cheloveka na Severe. [Reserve capabilities of endocrine regulation of metabolic processes in humans in the North]. Institut fiziologii prirodnykh adaptatsiy Ural'skogo otdeleniya Rossiyskoy akademii nauk. 2006. (in Russian).
11. Bobrov N.I., Lomov O.P., Tikhomirov V.P. Fiziologo-gigienicheskie aspekty akklimatizatsii cheloveka na Severe. [Physical and hygienic aspects of human acclimatization in the North]. Gigiena i sanitariya. 1979; 3: 75–8. (in Russian).
12. Vanyushin Yu.S., Khayrullin R.R., Elistratov D.E., Fedorov N.A. Adaptatsiya kardiorespiratornoy sistemy k dvigatel'noy deyatel'nosti. [Adaptation of the cardiorespiratory system to motor activity]. Fiziologiya sporta. Kazan'. 2020; 2: 31–2. (in Russian).
13. Varlamova N.G., Boyko E.R. Ob»emnye kharakteristiki funktsii vneshnego dykhaniya v godovom tsikle. [Volumetric characteristics of the external respiration function in the annual cycle]. Vestnik Tomskogo gosudarstvennogo universiteta. 2021; 55: 77–96. (in Russian).
14. Vasil'eva A., Konkieva N.A. Adaptatsiya cheloveka k usloviyam Kraynego Severa. [Adaptation of man to the conditions of the Far North]. Materialy VII Mezhdunarodnoy studencheskoy elektronnoy

nauchnoy konferentsii «Studencheskiy nauchnyy forum»; 2015. (in Russian).
15. Verizhnikova L.N., Aryamkina O.L., Terent'eva N.N. Somaticheskaya patologiya u zhiteley Khanty-Mansiyskogo avtonomnogo okruga — Yugry. [Somatic pathology in residents of the Khanty-Mansiysk Autonomous Okrug — Ugra]. Byulleten' sibirskoy meditsiny. 2020; 2: 13–9. (in Russian).
16. Voronin I.M., Bazhenova E.A. Variabel'nost' arterial'nogo davleniya v norme i pri patologii. [Variability in blood pressure is normal and in pathology]. Vestnik Tambovskogo universiteta. Seriya: estestvennye i tekhnicheskie nauki. 2007; 1(12). (in Russian).
17. Grigoruk S.D. Faktor meteochuvstvitel'nosti v razvitii serdechnoy nedostatochnosti u bol'nykh serdechno-sosudistogo kontinuuma. [Variability in blood pressure is normal and in pathology]. Materialy VI ezhegodnoy konferentsii Obshcherossiyskoy obshchestvennoy organizatsii: tezisy dokl. nauch. konf. Moskva: Institut biokhimii i genetiki; 2005: 37–9. (in Russian).
18. Gribanov A.V., Anikina N.Yu., Kottsova O.N. Raspredelenie tserebral'nykh energeticheskikh protsessov u molodykh lyudey, postoyanno prozhivayushchikh v Arkticheskom regione. [Kottsova Distribution of cerebral energy processes in young people permanently residing in the Arctic region]. Zhurn. med.-biol. issledovaniy. 2019; 1 (7): 118–23. (in Russian).
19. Gudkov A.B., Degteva G.N., Shepeleva O.A. Ekologo-gigienicheskie problemy na Arkticheskikh territoriyakh intensivnoy promyshlennoy deyatel'nosti (obzor). [Ecological and hygienic problems in the Arctic territories of intensive industrial activity (review)]. Obshchestvennoe zdorov'e. 2021; 1(4): 49–55. (in Russian).
20. Gudkov A.B., Popova O.N., Shcherbina Yu.F. Izmenenie prokhodimosti dykhatel'nykh putey u zhiteley kraynego Severa v kontrastnye sezony goda. [Change in airway patency among residents of the Far North in the contrasting seasons of the year]. Arkhangel'sk. 2013; 33–40. (in Russian).
21. Dzhanashiya P.Kh., Poteshkina N.G., Selivanova G.B. Arterial'naya gipertenziya. [Arterial hypertension]. Miklosh Publ., 2007. (in Russian).
22. Evdokimov V.G. Vozmozhnye puti normalizatsii sostoyaniya organizma cheloveka v usloviyakh Severa. [Possible ways to normalize the state of the human body in the conditions of the North]. Tez. dokl. II simpoziuma s mezhdunar. Uchastiem. Syktyvkar. 2004. (in Russian).
23. Es'kov V.M., Gudkov A.B., Filatov M.A. Printsipy gomeostaticheskogo regulirovaniya funktsiy organizma v ekologii cheloveka. [Principles of homeostatic regulation of body functions in human ecology]. Ekologiya cheloveka. 2019; 10: 41–9. (in Russian).
24. Zenina O.Yu., Makarova I.I., Ignatova Yu.P., Aksenova A.V. Khronofiziologiya i khronopatologiya serdechno-sosudistoy sistemy (obzor literatury). [Chronophysiology and chronopathology of the cardiovascular system (literature review)]. Ekologiya cheloveka. 2017; 1: 25–33. (in Russian).
25. Zyryanov B.N., Sokolova T.F. Adaptatsionnye reaktsii i immunitet u prishlogo naseleniya kraynego severa. [Adaptation reactions and immunity in the alien population of the far north]. Nauchnyy vestnik Yamalo-Nenetskogo avtonomnogo okruga. 2021; 2(111): 48–58. (in Russian).
26. Irzhak L.I., Dudnikova E.A., Parshukova A.N. i dr. Vliyanie fizicheskoy nagruzki na bioelektricheskuyu aktivnost' serdtsa zhiteley Evropeyskogo Severa Rossii. [Effect of physical activity on the bioelectric activity of the heart of residents of the European North of Russia]. Ekologiya cheloveka. 2021; 7: 35–42. (in Russian).
27. Kaznacheev V.P. Sovremennye aspekty adaptatsii. [Modern aspects of adaptation]. Novosibirsk: Nauka Publ. 1980. (in Russian).
28. Kandror I.S. Ocherki po fiziologii i gigiene cheloveka na Kraynem Severe. [Essays on human physiology and hygiene in the Far North]. Moskva: Meditsina Publ. 1968. (in Russian).
29. Kapel'ko V.I. Fiziologiya serdtsa i sosudistoy sistemy [Physiology of the heart and vascular system]. Vestnik Rossiyskogo fonda fundamental'nykh issledovaniy. 2017; 1: 78–86. (in Russian).
30. Karpin V.A. Meditsinskaya ekologiya Severa: aktual'nost', dostizheniya i perspektivy (obzor literatury). [Medical Ecology of the North: Relevance, Achievements and Perspectives (literature review)]. Ekologiya cheloveka. 2021; 8: 4–11. (in Russian).
31. Karpin V.A., Gudkov A.B., Shuvalova O.I. Analiz vozdeystviya klimatotekhnogennogo pressinga na zhiteley severnoy urbanizirovannoy territorii. [Analysis of the impact of climatotechnogenic pressure on residents of the northern urbanized territory]. Ekologiya cheloveka. 2018; 10: 9–14. (in Russian).
32. Katyukhin V.N. Arterial'naya gipertenziya na Severe. [Arterial hypertension in the North]. Monografiya. Surgutskiy gosudarstvennyy univer. Surgut; 2000. (in Russian).
33. Kim L.B. Transport kisloroda pri adaptatsii cheloveka k usloviyam Arktiki i kardiorespiratornoy patologii. [Oxygen transport in human adaptation to Arctic conditions and cardiorespiratory pathology]. Novosibirsk. 2015. (in Russian).
34. Koynosov P.G., Chiryat'eva T.V., Orlov S.A. i dr. Anatomo-antropologicheskie osobennosti fizicheskogo razvitiya zhiteley Srednego Priob'ya. [Anatomical and anthropological features of the physical development of residents of the Middle Priobye]. Meditsinskaya nauka i obrazovanie Urala. 2016; 17. (in Russian).
35. Koval'kova N.A., Travnikova N.Yu., Ragino Yu.I., Voevoda M.I. Rasprostranennost' disfunktsii vneshnego dykhaniya u molodykh lyudey. [Prevalence of respiratory dysfunction in young people]. Terapevticheskiy arkhiv. 2017; 3: 38–42. (in Russian).
36. Kozyreva T.V. Vliyanie Sa (2+) na termoregulyatornye reaktsii, sostav oipoproteidov krovi i immunnyy otvet pri deystvii kholoda na organizm v norme i pri arterial'noy gipertenzii. [Influence of Sa (2+) on thermoregulatory reactions, composition of blood oipoproteins and immune response under cold action on the body in normal and arterial hypertension]. Byulleten' SO RAMN. Novosibirsk. 2000; 4(126): 138–44. (in Russian).
37. Korchin V.I., Korchina T.Ya., Ternikova E.M. i dr. Vliyanie klimatogeograficheskikh faktorov Yamalo-Nenetskogo avtonomnogo okruga na zdorov'e naseleniya. [Effect of climatogeographic factors of

the Yamalo-Nenets Autonomous Okrug on population health. Journal of Biomedical Research]. Zhurnal mediko-biologicheskikh issledovaniy. 2021; 1(1): 77–88. (in Russian).
38. Krivoshchekov S.G., Okhotnikov S.V. Proizvodstvennye migratsii i zdorov'e cheloveka na Severe. [Industrial migrations and human health in the North]. Moskva–Novosibirsk: Izd-vo SO RAMN; 2000. (in Russian).
39. Litovchenko O.G., Bagnetova E.A., Tostanovskiy A.V. Ekologo-fiziologicheskie aspekty zdorov'e sberezheniya molodogo naseleniya Yugry. [Ecological and physiological aspects of the health of the savings of the young population of Ugra]. Sovremennye voprosy biomeditsiny. 2022; 1(6). (in Russian).
40. Litovchenko O.G., Ivanova N.L., Nishetenko E.Yu. Pokazateli molodykh rabotnikov neftyanoy otrasli Khanty-Mansiyskogo avtonomnogo okruga — Yugry. [Indicators of young workers in the oil industry of the Khanty-Mansiysk Autonomous Okrug–Ugra]. Chelovek. Sport. Meditsina. 2021; 1(21): 80–5. (in Russian).
41. Lebedeva-Nesevrya N.A., Barg A.O., Chechkin V.M. Prirodno-klimaticheskie i antropogennye faktory riska dlya zdorov'ya v sub»ektivnykh otsenkakh zhiteley gorodov kraynego severa. [Natural-climatic and anthropogenic health risk factors in subjective assessments of residents of cities of the far north]. Zdorov'e naseleniya i sreda obitaniya. 2020; 7(328): 8–13. (in Russian).
42. Lugovaya E.A., Aver'yanova I.V. Otsenka koeffitsienta napryazheniya adaptatsionnykh perestroek organizma pri khronicheskom vozdeystvii Severa. [Assessment of the stress coefficient of adaptation rearrangements of the body under chronic exposure to the North]. Analiz riska zdorov'yu. 2020; 2: 84–2. (in Russian).
43. Mayorova E.L., Kalacheva A.G., Voronkova I.A. Funktsional'noe sostoyanie kardiorespiratornoy sistemy u naseleniya Srednego Priob'ya. [Functional state of the cardiorespiratory system in the population of the Middle Priobye]. Sibirskiy meditsinskiy zhurnal. 2015; 5(30): 5–9. (in Russian).
44. Marasanov A.V., Stekhin A.A., Yakovleva G.V. Podkhod k obespecheniyu zdorov'esberezheniya naseleniya Arkticheskoy zony Rossiyskoy Federatsii (obzor). [Approach to ensuring the health of the population of the Arctic zone of the Russian Federation (review)]. Zhurnal mediko-biologicheskikh issledovaniy. 2021; 2(9): 201–12. (in Russian).
45. Markin V.V., Silin A.N., Vershinin I.S. Zdorov'e lyudey v Arktike: sotsial'no-prostranstvennyy diskurs (na primere Yamalo-Nenetskogo avtonomnogo okruga). [Health of people in the Arctic: socio-spatial discourse (using the example of the Yamalo-Nenets Autonomous Okrug)]. Ekonomicheskie i sotsial'nye peremeny: fakty, tendentsii, prognoz. 2020; 5(13): 182–99. (in Russian).
46. Marachev A.G. Patologiya cheloveka na Severe. [Human pathology in the North]. Moskva: Meditsina Publ.; 1985. (in Russian).
47. Matyukhin V.A., Razumov A.N. Ekologicheskaya fiziologiya cheloveka i vosstanovitel'naya meditsina [Environmental physiology of man and restorative medicine]. Moskva: Meditsina; 2009. (in Russian).
48. Naymushina A.G., Bakieva E.M., Solov'eva S.V. i dr. Psikhofiziologicheskie markery adaptatsii u muzhchin aktivnogo trudosposobnogo vozrasta, prozhivayushchikh na yuge i severe Tyumenskoy oblasti. [Psychophysiological adaptation markers in men of active working age living in the south and north of the Tyumen region]. Meditsinskaya nauka i obrazovanie Urala. 2020; 4(104): 35–40. (in Russian).
49. Nifontova O.L. Vozrastnaya izmenchivost' elektricheskoy aktivnosti serdtsa zhiteley Yugry. [Age variability of the electrical activity of the heart of residents of Ugra]. Vestnik Surgutskogo gosudarstvennogo pedagogicheskogo universiteta. Surgut; 2014: 11–7. (in Russian).
50. Nifontova O.L., Kon'kova K.S. Osobennosti parametrov vneshnego dykhaniya korennykh zhiteley Khanty-Mansiyskogo avtonomnogo okruga — Yugry v vozraste 11–14 let. [Features of external breathing parameters of the indigenous inhabitants of the Khanty-Mansiysk Autonomous Okrug — Ugra at the age of 11–14 years]. Ekologiya cheloveka. 2019; 8: 18–24. (in Russian).
51. Ovechkina E.S., Ovechkin F.Yu. Patofiziologiya cheloveka v usloviyakh severa Rossii. [Human pathophysiology in the north of Russia]. Byulleten' nauki i praktiki. 2021; 8(7): 185–91. (in Russian).
52. Pak A.V., Trufanova K.G. Vliyanie polyarnogo dnya i polyarnoy nochi na organizm cheloveka [Effects of polar day and polar night on the human body]. Byulleten' Severnogo gosudarstvennogo meditsinskogo universiteta. 2018; 1(40): 300–1. (in Russian).
53. Parshukova O.I., Varlamova N.G., Boyko E.R. Funktsional'naya rol' metabolitov oksida azota u vysokokvalifitsirovannykh lyzhnikov-gonshchikov s gipertonicheskoy reaktsiey na fizicheskuyu nagruzku. [Functional role of nitric oxide metabolites in highly qualified skier riders with hypertensive response to physical activity]. Chelovek. Sport. Meditsina. 2022; 2(22): 55–60. (in Russian).
54. Petrova N.B., Goncharov N.I., Nakhimova M.A. Kolichestvennye parametry i funktsional'nye svoystva eritrotsitov cheloveka na Severe. [Quantitative parameters and functional properties of human red blood cells in the North]. Vestnik Syktyvkarskogo universiteta. 2022; 3: 80–8. (in Russian).
55. Pogonysheva I.A., Pogonyshev D.A. Osobennosti morfofunktsional'nykh parametrov organizma molodykh lyudey, prozhivayushchikh v raznykh klimatogeofizicheskikh usloviyakh okruzhayushchey sredy. [Features of morphofunctional parameters of the body of young people living in different climatogeophysical environmental conditions]. Vestnik Nizhnevartovskogo gosudarstvennogo universiteta. 2017; 1: 68–74. (in Russian).
56. Pogonysheva I.A., Pogonyshev D.A., Postnikova V.V. Dinamika osnovnykh pokazateley fizicheskogo razvitiya studentov severnogo vuza. [Dynamics of the main indicators of the physical development of students of the northern university]. Teoriya i praktika fizicheskoy kul'tury. 2019; 8: 33–5. (in Russian).
57. Pushkina V.N., Gernet I.N., Olyashev N.V., Lubyshev E.A. Sostoyanie sistemy vneshnego dykhaniya u yunoshey, prozhivayushchikh v raznykh regionakh Rossii. [The state of the respiratory system in young men living in different regions of Russia]. Teoriya i praktika fizicheskoy kul'tury. 2020; 4: 17–9. (in Russian).
58. Prekina V.I., Chernova I.Yu., Efremova O.N., Esina M.V. Variabel'nost' serdechnogo ritma u zdorovykh lyudey. [Variability of heart rate in healthy people]. RKZh. 2020; 2. (in Russian).

59. Pryanichnikov S.V. Psikhofiziologicheskoe sostoyanie organizma v zavisimosti ot dlitel'nosti prebyvaniya v vysokikh shirotakh Arktiki. [Psychophysiological state of the body depending on the duration of stay in the high latitudes of the Arctic]. Ekologiya cheloveka. 2020; 12: 4–10. (in Russian).
60. Rusak S.N., Filatova O.E., Bikmukhametova L.M. Meteochuvstvitel'nye zabolevaniya naseleniya Yugry v usloviyakh pogodnoy izmenchivosti. [Meteorological-sensitive diseases of the population of Ugra in conditions of weather variability]. Vestnik novykh meditsinskikh tekhnologiy. 2017; 1: 30–7. (in Russian).
61. Saltykova M.M., Bobrovnitskiy I.P., Yakovlev M.Yu. i dr. Novyy podkhod k analizu vliyaniya pogodnykh usloviy na organizm cheloveka. [A new approach to analyzing the impact of weather conditions on the human body]. Gigiena i sanitariya. 2018; 11(97); 1038–42. (in Russian).
62. Serdyukovskaya G.N., red. Vnutrennie bolezni i funktsional'nye rasstroystva v podrostkovom vozraste. Okhrana zdorov'ya podrostkov. [Internal diseases and functional disorders in adolescence. Adolescent Health Care]. Moskva: Promedek Publ.; 1993. (in Russian).
63. Sokolov S.F. Klinicheskoe znachenie otsenki variabel'nosti serdechnogo ritma. [Clinical significance of estimating heart rate variability]. Serdtse. 2002; 2: 72–5. (in Russian).
64. Solov'ev V.S., Litovchenko O.G., Solov'eva S.V. i dr. Opyt kompleksnykh issledovaniy v izuchenii adaptatsii na Severe. [Experience in comprehensive studies in the study of adaptation in the North]. Vestnik Surgutskogo gosudarstvennogo universitetata. 2016; 3(13): 54–6. (in Russian).
65. Solonin Yu.G. Issledovaniya po shirotnoy fiziologii (obzor). [Studies in latitudinal physiology (review)]. Zhurnal mediko-biologicheskikh issledovaniy. 2019; 2(7): 228–39. (in Russian).
66. Staroded A.S., Maydan V.A., Tsvetkov S.V. Vliyanie medikogeograficheskikh osobennostey kraynego severa na protsessy adaptatsii. [Influence of medicogeographic features of the far north on adaptation processes]. Izvestiya Rossiyskoy Voennomeditsinskoy akademii. 2020; 3–5(39): 160–3. (in Russian).
67. Ustyushin B.V., Dedenko I.I. Osobennosti obespecheniya gomeostaza organizma cheloveka na Kraynem Severe. [Features of ensuring homeostasis of the human body in the Far North]. Vestnik AMN. 1992; 1: 6–10. (in Russian).
68. Utenkova E.O., Kaluzhskikh T.I. Estestvennoe proepidemichivanie u lits, prozhivayushchikh v endemichnykh rayonakh. [Natural epidemic in people living in endemic areas]. Zhurnal infektologii. 2020; 4(12): 112–3. (in Russian).
69. Filatova O.E., Gudkov A.B., Es'kov V.V., Chempalova L.S. Ponyatie odnorodnosti gruppy v ekologii cheloveka. [The concept of group homogeneity in human ecology]. Ekologiya cheloveka. 2020; 2: 40–4. (in Russian).
70. Frolkov V.K., Nagornev S.N., Bobrovnitskiy I.P. Patofiziologicheskie mekhanizmy neblagopriyatnogo vliyaniya klimatogeograficheskikh faktorov Arktiki na zdorov'e cheloveka i tekhnologii vosstanovitel'noy meditsiny. [Pathophysiological mechanisms of the adverse effect of climatogeographic factors of the Arctic on human health and technologies of restorative medicine]. Fizioterapevt. 2020; 1: 57–63. (in Russian).
71. Hajcev N.V., Vasil'ev A.G., Trashkov A.P. i dr. Vliyanie vozrasta i pola na harakter otvetnyh reakcij belyh krys pri dejstvii hronicheskoj gipoksicheskoj gipoksii. [The Influence of age and sex on the character of responce reactions of white rats to chronical hypoxic hypoxia]. Pediatr. 2015; 6(2): 71–7. (in Russian).
72. Khasnulin V.I., Voevoda M.I., Khasnulin P.V., Artamonova O.G. Sovremennyy vzglyad na problemu arterial'noy gipertenzii v pripolyarnykh i arkticheskikh regionakh. Obzor literatury. [A modern look at the problem of arterial hypertension in the circumpolar and Arctic regions. Literature review]. Ekologiya cheloveka. 2016; 3: 43–51. (in Russian).
73. Chashchin V.P., Gudkov A.B., Chashchin M.V., Popova O.N. Prediktivnaya otsenka individual'noy vospriimchivosti organizma cheloveka k opasnomu vozdeystviyu kholoda. [Predictive assessment of the individual susceptibility of the human body to the dangerous effects of cold]. Ekologiya cheloveka. 2017; 5: 3–13. (in Russian).
74. Shaymardanov A.R. Otsenka funktsional'nogo sostoyaniya organizma korennogo i prishlogo naseleniya v usloviyakh kraynego severa. [Assessment of the functional state of the body of the indigenous and alien population in the conditions of the far north]. Sovremennye voprosy biomeditsiny. 2022; 2(2). (in Russian).
75. Shan'gina A.A., Popova O.N., Tikhonova E.V. i dr. Osobennosti reaktsii legochnogo gazoobmena na lokal'noe kholodovoe vozdeystvie u molodykh lits trudosposobnogo vozrasta. [Features of the reaction of pulmonary gas exchange to local cold exposure in young people of working age]. Ekologiya cheloveka. 2018; 5: 33–8. (in Russian).
76. Abdurakhmonov S. K. The Importance Of A Healthy Lifestyle In Achieving Physical Perfection. The American Journal of Applied sciences. 2021; 3(03): 42–7.
77. Bassett Jr., Howley E.T. Limiting factors for maximum oxygen and determinants of endurance performance. Medicine and Science in Sports and Exercise. 2000; 32(1): 70–84.
78. Brewer H., Jalongo M.R. Physical Activity and Health Promotion in the Early Years: Effective. Springer. 2018; 14.
79. Brown S.J., Barnes M.J., Mündel T. Effects of hypoxia and hypercapnia on human HRV and respiratory sinus arrhythmia. Acta Physiol. Hung. 2014; 101: 263–72.
80. Garcia-Retortillo S., Javierre C., Hristovski R. et al. Cardiorespiratory coordination reveals training-specific physiological adaptations. Eur. J. Appl. Physiol. 2019; 119: 1701–9.
81. Goldberg S., Ollila H.M., Lin L. et al. Analysis of hypoxic and hypercapnic ventilatory response in healthy volunteers. 2017.
82. Lindsey B.G., Nuding S.C., Segers L.S., Morris K.F. Carotid bodies and the integrated cardiorespiratory response to hypoxia. Physiology. 2018; 33: 281–97.

ЛИТЕРАТУРА

1. Аверьянова И.В., Вдовенко С.И. Оценка степени напряжения функционального состояния организма человека при различ-

ных сроках адаптации к условиям Севера. Экология человека. 2021; 7: 12–7.
2. Аверьянова И.В., Максимов А.Л. Особенности перестроек кардиогемодинамики и вариабельности сердечного ритма у европеоидов — мигрантов и уроженцев Севера первого и второго поколений при активной ортостатической пробе. Сибирский научный медицинский журнал. 2021; 41(3): 45–52.
3. Авцын А.П., Марачеев А.Г., Матвеев Л.Н. Вестник АМН СССР. 1979; 6: 32–9.
4. Агаджанян Н.А. Экологическая физиология человека. Крук» 1998.
5. Агаджанян Н.А., Баевский Р.М., Берсенева А.П. Проблемы адаптации и учение о здоровье: РУДН; 2006.
6. Акимов А.М. Здоровье сбережение участников освоения арктического нефтегазового региона: монография. Тюмень; 2019.
7. Андронова Т.И. Оценка метеотропных реакций организма человека к факторам внешней среды: метод. разработки. Институт клинической и экспериментальной медицины. Новосибирск; 1979.
8. Бойко Е.Р. Физиолого-биохимические основы жизнедеятельности человека на Севере. Екатеринбург: УрО РАН; 2005.
9. Борисенко И.В., Косых Е.В., Харламов А.Н. Особенности функционального состояния легких жителей Среднего Приобья. Вестник Томского государственного университета. 2017; 2: 94–102.
10. Бичкаева Ф.А. Резервные возможности эндокринной регуляции метаболических процессов у человека на Севере. Институт физиологии природных адаптаций Уральского отделения Российской академии наук. 2006.
11. Бобров Н.И., Ломов О.П., Тихомиров В.П. Физиолого-гигиенические аспекты акклиматизации человека на Севере. Гигиена и санитария. 1979; 3: 75–8.
12. Ванюшин Ю.С., Хайруллин Р.Р., Елистратов Д.Е., Федоров Н.А. Адаптация кардиореспираторной системы к двигательной деятельности. Физиология спорта. Казань. 2020; 2: 31–2.
13. Варламова Н.Г., Бойко Е.Р. Объемные характеристики функции внешнего дыхания в годовом цикле. Вестник Томского государственного университета. 2021; 55: 77–96.
14. Васильева А., Конкиева Н.А. Адаптация человека к условиям Крайнего Севера. Материалы VII Международной студенческой электронной научной конференции «Студенческий научный форум»; 2015.
15. Верижникова Л.Н., Арямкина О.Л., Терентьева Н.Н. Соматическая патология у жителей Ханты-Мансийского автономного округа — Югры. Бюллетень сибирской медицины. 2020; 2: 13–9.
16. Воронин И.М., Баженова Е.А. Вариабельность артериального давления в норме и при патологии. Вестник Тамбовского университета. Серия: естественные и технические науки. 2007; 1(12).
17. Григорук С.Д. Фактор метеочувствительности в развитии сердечной недостаточности у больных сердечно-сосудистого континуума. Материалы VI ежегодной конференции Общероссийской общественной организации: тезисы докл. науч. конф. М.: Институт биохимии и генетики; 2005: 37–9.
18. Грибанов А.В., Аникина Н.Ю., Котцова О.Н. Распределение церебральных энергетических процессов у молодых людей, постоянно проживающих в Арктическом регионе. Журн. мед.-биол. исследований. 2019; 1(7): 118–23.
19. Гудков А.Б., Дегтева Г.Н., Шепелева О.А. Эколого-гигиенические проблемы на Арктических территориях интенсивной промышленной деятельности (обзор). Общественное здоровье. 2021; 1(4): 49–55.
20. Гудков А.Б., Попова О.Н., Щербина Ю.Ф. Изменение проходимости дыхательных путей у жителей крайнего Севера в контрастные сезоны года. Архангельск. 2013; 33–40.
21. Джанашия П.Х., Потешкина Н.Г., Селиванова Г.Б. Артериальная гипертензия. Миклош; 2007.
22. Евдокимов В.Г. Возможные пути нормализации состояния организма человека в условиях Севера. Тез. докл. II симпозиума с междунар. участием. Сыктывкар; 2004: 38.
23. Еськов В.М., Гудков А.Б., Филатов М.А. Принципы гомеостатического регулирования функций организма в экологии человека. Экология человека. 2019; 10: 41–9.
24. Зенина О.Ю., Макарова И.И., Игнатова Ю.П., Аксенова А.В. Хронофизиология и хронопатология сердечно-сосудистой системы (обзор литературы). Экология человека. 2017; 1: 25–33.
25. Зырянов Б.Н., Соколова Т.Ф. Адаптационные реакции и иммунитет у пришлого населения крайнего севера. Научный вестник Ямало-Ненецкого автономного округа. 2021; 2(111): 48–58.
26. Иржак Л.И., Дудникова Е.А., Паршукова А.Н. и др. Влияние физической нагрузки на биоэлектрическую активность сердца жителей Европейского Севера России. Экология человека. 2021; 7: 35–42.
27. Казначеев В.П. Современные аспекты адаптации. Новосибирск: Наука; 1980: 191.
28. Кандрор И.С. Очерки по физиологии и гигиене человека на Крайнем Севере. М.: Медицина; 1968.
29. Капелько В.И. Физиология сердца и сосудистой системы. Вестник Российского фонда фундаментальных исследований. 2017; 1: 78–86.
30. Карпин В.А. Медицинская экология Севера: актуальность, достижения и перспективы (обзор литературы). Экология человека. 2021; 8: 4–11.
31. Карпин В.А., Гудков А.Б., Шувалова О.И. Анализ воздействия климатотехногенного прессинга на жителей северной урбанизированной территории. Экология человека. 2018; 10: 9–14.
32. Катюхин В.Н. Артериальная гипертензия на Севере. Монография. Сургутский государственный универ. Сургут; 2000.
33. Ким Л.Б. Транспорт кислорода при адаптации человека к условиям Арктики и кардиореспираторной патологии. Новосибирск; 2015.
34. Койносов П.Г., Чирятьева Т.В., Орлов С.А. и др. Анатомо-антропологические особенности физического развития жителей Среднего Приобья. Медицинская наука и образование Урала. 2016; 17.

35. Ковалькова Н.А., Травникова Н.Ю., Рагино Ю.И., Воевода М.И. Распространенность дисфункции внешнего дыхания у молодых людей. Терапевтический архив. 2017; 3: 38–42.
36. Козырева Т.В. Влияние Са (2+) на терморегуляторные реакции, состав оипопротеидов крови и иммунный ответ при действии холода на организм в норме и при артериальной гипертензии. Бюллетень СО РАМН. Новосибирск. 2000; 4(126): 138–44.
37. Корчин В.И., Корчина Т.Я., Терникова Е.М. и др. Влияние климатогеографических факторов Ямало-Ненецкого автономного округа на здоровье населения. Журнал медико-биологических исследований. 2021; 1(1): 77–88.
38. Кривощеков С.Г., Охотников С.В. Производственные миграции и здоровье человека на Севере. Москва–Новосибирск: Изд-во СО РАМН; 2000.
39. Литовченко О.Г., Багнетова Е.А., Тостановский А.В. Эколого-физиологические аспекты здоровье сбережения молодого населения Югры. Современные вопросы биомедицины. 2022; 1(6).
40. Литовченко О.Г., Иванова Н.Л., Нишетенко Е.Ю. Показатели молодых работников нефтяной отрасли Ханты-Мансийского автономного округа — Югры. Человек. Спорт. Медицина. 2021; 1(21): 80–5.
41. Лебедева-Несевря Н.А., Барг А.О., Чечкин В. М. Природно-климатические и антропогенные факторы риска для здоровья в субъективных оценках жителей городов крайнего севера. Здоровье населения и среда обитания. 2020; 7(328): 8–13.
42. Луговая Е.А., Аверьянова И.В. Оценка коэффициента напряжения адаптационных перестроек организма при хроническом воздействии Севера. Анализ риска здоровью. 2020; 2: 84–2.
43. Майорова Е.Л., Калачева А.Г., Воронкова И.А. Функциональное состояние кардиореспираторной системы у населения Среднего Приобья. Сибирский медицинский журнал. 2015; 5(30): 5–9.
44. Марасанов А.В., Стехин А.А., Яковлева Г.В. Подход к обеспечению здоровьесбережения населения Арктической зоны Российской Федерации (обзор). Журнал медико-биологических исследований. 2021; 2(9): 201–12.
45. Маркин В.В., Силин А.Н., Вершинин И.С. Здоровье людей в Арктике: социально-пространственный дискурс (на примере Ямало-Ненецкого автономного округа). Экономические и социальные перемены: факты, тенденции, прогноз. 2020; 5(13): 182–99.
46. Марачев А.Г. Патология человека на Севере. М.: Медицина; 1985.
47. Матюхин В.А., Разумов А.Н. Экологическая физиология человека и восстановительная медицина. М.: Медицина; 2009.
48. Наймушина А.Г., Бакиева Э.М., Соловьева С.В. и др. Психофизиологические маркеры адаптации у мужчин активного трудоспособного возраста, проживающих на юге и севере Тюменской области. Медицинская наука и образование Урала. 2020; 4(104): 35–40.
49. Нифонтова О.Л. Возрастная изменчивость электрической активности сердца жителей Югры. Вестник Сургутского государственного педагогического университета. Сургут; 2014: 11–7.
50. Нифонтова О.Л., Конькова К.С. Особенности параметров внешнего дыхания коренных жителей Ханты-Мансийского автономного округа — Югры в возрасте 11–14 лет. Экология человека. 2019; 8: 18–24.
51. Овечкина Е.С., Овечкин Ф.Ю. Патофизиология человека в условиях севера России. Бюллетень науки и практики. 2021; 8(7): 185–91.
52. Пак А.В., Труфанова К.Г. Влияние полярного дня и полярной ночи на организм человека. Бюллетень Северного государственного медицинского университета. 2018; 1(40): 300–1.
53. Паршукова О.И., Варламова Н.Г., Бойко Е.Р. Функциональная роль метаболитов оксида азота у высококвалифицированных лыжников-гонщиков с гипертонической реакцией на физическую нагрузку. Человек. Спорт. Медицина. 2022; 2(22): 55–60.
54. Петрова Н.Б., Гончаров Н.И., Нахимова М.А. Количественные параметры и функциональные свойства эритроцитов человека на Севере. Вестник Сыктывкарского университета. 2022; 3: 80–8.
55. Погонышева И.А., Погонышев Д.А. Особенности морфофункциональных параметров организма молодых людей, проживающих в разных климатогеофизических условиях окружающей среды. Вестник Нижневартовского государственного университета. 2017; 1: 68–74.
56. Погонышева И.А., Погонышев Д.А., Постникова В.В. Динамика основных показателей физического развития студентов северного вуза. Теория и практика физической культуры. 2019; 8: 33–5.
57. Пушкина В.Н., Гернет И.Н., Оляшев Н.В., Лубышев Е.А. Состояние системы внешнего дыхания у юношей, проживающих в разных регионах России. Теория и практика физической культуры. 2020; 4: 17–9.
58. Прекина В.И., Чернова И.Ю., Ефремова О.Н., Есина М.В. Вариабельность сердечного ритма у здоровых людей. РКЖ. 2020; 2.
59. Пряничников С.В. Психофизиологическое состояние организма в зависимости от длительности пребывания в высоких широтах Арктики. Экология человека. 2020; 12: 4–10.
60. Русак С.Н., Филатова О.Е., Бикмухаметова Л.М. Метеочувствительные заболевания населения Югры в условиях погодной изменчивости. Вестник новых медицинских технологий. 2017; 1: 30–7.
61. Салтыкова М.М., Бобровницкий И.П., Яковлев М.Ю. и др. Новый подход к анализу влияния погодных условий на организм человека. Гигиена и санитария. 2018; 11(97); 1038–42.
62. Сердюковская Г.Н., ред. Внутренние болезни и функциональные расстройства в подростковом возрасте. Охрана здоровья подростков. М.: Промедэк; 1993.
63. Соколов С.Ф. Клиническое значение оценки вариабельности сердечного ритма. Сердце. 2002; 2: 72–5.
64. Соловьев В.С., Литовченко О.Г., Соловьева С.В. и др. Опыт комплексных исследований в изучении адаптации на Севере. Вестник Сургутского государственного университета. 2016; 3(13): 54–6.
65. Солонин Ю.Г. Исследования по широтной физиологии (обзор). Журнал медико-биологических исследований. 2019; 2(7): 228–39.
66. Стародед А.С., Майдан В.А., Цветков С.В. Влияние медико-географических особенностей крайнего севера на процессы адап-

тации. Известия Российской Военно-медицинской академии. 2020; 3–5(39): 160–3.
67. Устюшин Б.В., Деденко И.И. Особенности обеспечения гомеостаза организма человека на Крайнем Севере. Вестник АМН. 1992; 1: 6–10.
68. Утенкова Е.О., Калужских Т.И. Естественное проэпидемичивание у лиц, проживающих в эндемичных районах. Журнал инфектологии. 2020; 4(12): 112–3.
69. Филатова О.Е., Гудков А.Б., Еськов В.В., Чемпалова Л.С. Понятие однородности группы в экологии человека. Экология человека. 2020; 2: 40–4.
70. Фролков В.К., Нагорнев С.Н., Бобровницкий И.П. Патофизиологические механизмы неблагоприятного влияния климатогеографических факторов Арктики на здоровье человека и технологии восстановительной медицины. Физиотерапевт. 2020; 1: 57–63.
71. Хайцев Н.В., Васильев А.Г., Трашков А.П. и др. Влияние возраста и пола на характер ответных реакций белых крыс при действии хронической гипоксической гипоксии. Педиатр. 2015; 6(2): 71–7.
72. Хаснулин В.И., Воевода М.И., Хаснулин П.В., Артамонова О.Г. Современный взгляд на проблему артериальной гипертензии в приполярных и арктических регионах. Обзор литературы. Экология человека. 2016; 3: 43–51.
73. Чащин В.П., Гудков А.Б., Чащин М.В., Попова О.Н. Предиктивная оценка индивидуальной восприимчивости организма человека к опасному воздействию холода. Экология человека. 2017; 5: 3–13.
74. Шаймарданов А.Р. Оценка функционального состояния организма коренного и пришлого населения в условиях крайнего севера. Современные вопросы биомедицины. 2022; 2(2).
75. Шаньгина А.А., Попова О.Н., Тихонова Е.В. и др. Особенности реакции легочного газообмена на локальное холодовое воздействие у молодых лиц трудоспособного возраста. Экология человека. 2018; 5: 33–8.
76. Abdurakhmonov S. K. The Importance Of A Healthy Lifestyle In Achieving Physical Perfection. The American Journal of Applied sciences. 2021; 3(03): 42–7.
77. Bassett Jr., Howley E.T. Limiting factors for maximum oxygen and determinants of endurance performance. Medicine and Science in Sports and Exercise. 2000; 32(1): 70–84.
78. Brewer H., Jalongo M.R. Physical Activity and Health Promotion in the Early Years: Effective. Springer. 2018; 14.
79. Brown S.J., Barnes M.J., Mündel T. Effects of hypoxia and hypercapnia on human HRV and respiratory sinus arrhythmia. Acta Physiol. Hung. 2014; 101: 263–72.
80. Garcia-Retortillo S., Javierre C., Hristovski R. et al. Cardiorespiratory coordination reveals training-specific physiological adaptations. Eur. J. Appl. Physiol. 2019; 119: 1701–9.
81. Goldberg S., Ollila H.M., Lin L. et al. Analysis of hypoxic and hypercapnic ventilatory response in healthy volunteers. 2017.
82. Lindsey B.G., Nuding S.C., Segers L.S., Morris K.F. Carotid bodies and the integrated cardiorespiratory response to hypoxia. Physiology. 2018; 33: 281–97.

UDC 615.35+616.12-008.331.1-085+577.125+616-008.3/.5+612.018+615.214.32
DOI: 10.56871/RBR.2023.32.88.007

A NEW LOOK AT THE PROTECTIVE ROLE OF MELATONIN IN CASE OF POLYMORBID CARDIOVASCULAR PATHOLOGY

© Vasiliy N. Tsygan, Maksim A. Antyukhin, Aleksandr S. Parcernyak

Military Medical Academy named after S.M. Kirov. Akademician Lebedev st., 6, Saint Petersburg, Russian Federation, 194044

Contact information: Aleksandr S. Parcernyak — Candidate of Medical Sciences, Lecturer at the Department of Military Field Therapy.
E-mail: partsernyak@mail.ru ORCID ID: 0000-0002-9721-1319

For citation: Tsygan VN, Antyukhin MA, Parcernyak AS. A new look at the protective role of melatonin in case of polymorbid cardiovascular pathology // Russian biomedical research (St. Petersburg). 2023; 8(3): 50-60. DOI: https://doi.org/10.56871/RBR.2023.32.88.007

Received: 22.05.2023 **Revised: 17.07.2023** **Accepted: 21.09.2023**

Abstract. Over the past years, close attention of the world scientific community has been directed to the main hormone of the pineal gland — melatonin. In the course of many studies, the protective properties of this hormone were found in various pathological conditions. Thus, in a chronic inflammatory process, melatonin stimulates the production of anti-inflammatory and suppresses the activity of pro-inflammatory cytokines and neuronal NO-synthases and cyclooxygenase-2, participates in the removal of reactive oxygen species from the cell, and also optimizes mitochondrial function through mitofusin-2. Melatonin performs its antihypertensive function by regulating the renin-angiotensin system, suppressing endothelin expression, enhancing the production of nitrosyl radical and endothelial nitric oxide synthase, and also by interacting with the central nervous system by modulating melatonin activity due to GABAergic signaling in neurons from the suprachiasmatic nucleus to various parts of the central nervous system, including the ventrolateral part of the medulla oblongata. In addition, it modulates the SIRT1/mitofusin 2 pathway by reducing the production of reactive oxygen species, deactivates LDL-induced pyroptosis in endothelial cells via the MEG3/miR-223/NLRP3 axis, and inhibits serum cholesterol absorption and biosynthesis, thereby achieving a lipid-lowering effect. Another significant function of melatonin is participation in the regulation of glycemia and control of insulinemia. It reduces insulin secretion through the melatonin 1 receptor by inhibiting the adenylate cyclase — cyclic adenosine monophosphate pathway, and through the melatonin 2 receptor it inhibits the guanylate cyclase — cyclic guanosine monophosphate pathway. On the other hand, melatonin can also stimulate insulin secretion by releasing inositol triphosphate through interaction with the melatonin 2 receptor. It should be noted that the antidepressant effect of melatonin is achieved by modulating neuroplastic reactions in the hippocampus and stimulating neurogenesis, axogenesis, and dendritogenesis. Thus, melatonin is an important protective factor in polymorbid cardiovascular pathology due to its positive effect on lipid metabolism, obesity and insulin resistance, correction of arterial hypertension level of glucose, as well as antidepressant action.

Key words: melatonin; polymorbid cardiovascular pathology; lipid metabolism; obesity; insulin resistance; correction of arterial hypertension, level of glucose; antidepressant effect.

НОВЫЙ ВЗГЛЯД НА ПРОТЕКТИВНУЮ РОЛЬ МЕЛАТОНИНА ПРИ ПОЛИМОРБИДНОЙ СЕРДЕЧНО-СОСУДИСТОЙ ПАТОЛОГИИ

© Василий Николаевич Цыган, Максим Александрович Антюхин, Александр Сергеевич Парцерняк

Военно-медицинская академия им. С.М. Кирова. 194044, г. Санкт-Петербург, ул. Академика Лебедева, 6

Контактная информация: Александр Сергеевич Парцерняк — к.м.н., преподаватель кафедры военно-полевой терапии.
E-mail: partsernyak@mail.ru ORCID ID: 0000-0002-9721-1319

Для цитирования: Цыган В.Н., Антюхин М.А., Парцерняк А.С. Новый взгляд на протективную роль мелатонина при полиморбидной сердечно-сосудистой патологии // Российские биомедицинские исследования. 2023. Т. 8. № 3. С. 50–60. DOI: https://doi.org/10.56871/RBR.2023.32.88.007

Поступила: 22.05.2023 **Одобрена: 17.07.2023** **Принята к печати: 21.09.2023**

Резюме. В прошедшие годы пристальное внимание мирового научного сообщества было направлено на основной гормон шишковидной железы — мелатонин. В ходе множества проведенных исследований были обнаружены протективные свойства данного гормона при различных патологических состояниях. Так, при хроническом воспалительном процессе мелатонин стимулирует продукцию противовоспалительных и подавляет активность провоспалительных цитокинов, нейрональных NO-синтаз и циклооксигеназы-2, участвует в удалении активных форм кислорода из клетки, а также оптимизирует митохондриальную функцию посредством митофузина-2. Антигипертензивную функцию мелатонин осуществляет за счет регуляции ренин-ангиотензиновой системы, подавления экспрессии эндотелина, усиления продукции нитрозил-радикала и эндотелиальной синтазы оксида азота и, кроме этого, благодаря взаимодействию с центральной нервной системой посредством модулирования активности мелатонина за счет ГАМК-эргической передачи сигналов в нейронах от супрахиазматического ядра к различным частям центральной нервной системы, в том числе и к вентролатеральной части продолговатого мозга. Кроме того, он моделирует путь SIRT1/митофузина-2 путем снижения продукции активных форм кислорода, деактивирует индуцированный липопротеинами низкой плотности (ЛПНП) пироптоз в эндотелиальных клетках через ось MEG3/miR-223/NLRP3 и ингибирует абсорбцию и биосинтез холестерина в сыворотке, благодаря чему достигается гиполипидемический эффект. Еще одной значимой функцией мелатонина является участие в регуляции уровня гликемии и контроль инсулинемии. Он снижает секрецию инсулина через рецептор мелатонина-1, ингибируя путь аденилатциклазы — циклического аденозинмонофосфата, а через рецептор мелатонина-2 подавляет путь гуанилатциклазы — циклического гуанозинмонофосфата. В то же время мелатонин может также стимулировать секрецию инсулина за счет высвобождения инозитолтрифосфата — через взаимодействие с рецептором мелатонина-2. Нельзя не отметить антидепрессивное действие мелатонина, которое достигается путем модулирования нейропластических реакций в гиппокампе и стимуляции нейрогенеза, аксогенеза и дендритогенеза. Таким образом, мелатонин является важным защитным фактором при полиморбидной сердечно-сосудистой патологии за счет положительного влияния на липидный обмен, ожирение и инсулинорезистентность, коррекции артериальной гипертензии, гликемии, а также антидепрессивного действия.

Ключевые слова: мелатонин; полиморбидная сердечно-сосудистая патология; липидный обмен; ожирение; инсулинорезистентность; коррекция артериальной гипертензии, гликемии; антидепрессивное действие.

Over the last decade, the scientific community has paid special attention to a wide range of biological activity of melatonin (MT) and its role in intra- and intercellular regulation, intersystem interactions, maintenance of homeostasis and protection of the organism in interaction with constantly changing environmental factors [23]. An important feature of MT is regulating circadian rhythms . It is a high-level function of the brain that includes physiological, endocrine and behavioural changes arising in connection with the change of a daily cycle.

MT, or N-acetyl-5-methoxytryptamine, is a highly conserved indolamine molecule (Fig. 1) that is found in all plants, animals [45] and microorganisms [44]. MT is mainly synthesised in the epiphysis [12, 17], but it can also be produced in the retina, thymus, spleen, heart, muscle, liver, stomach, pancreas, intestine, placenta, bone marrow, skin, hair follicles, cerebral cortex and many other parts of the body [4, 42, 49].

The substrate for MT synthesis is tryptophan amino acid, which is converted into serotonin by hydroxylation and decarboxylation, from which MT is formed with the help of N-acetyltransferase and hydroxyindole-O-methyltransferase enzymes (Fig. 2) [23]. Information on light from retinal ganglion cells passes through the retinohypothalamic tract to the suprachiasmatic nucleus (SCN), then to the upper cervical ganglia, and then through the sympathetic noradrenergic nerves reaches the pineal gland and activates pinealocytes, suppressing the production and secretion of MT. In this regard, the maximum level of MT in human

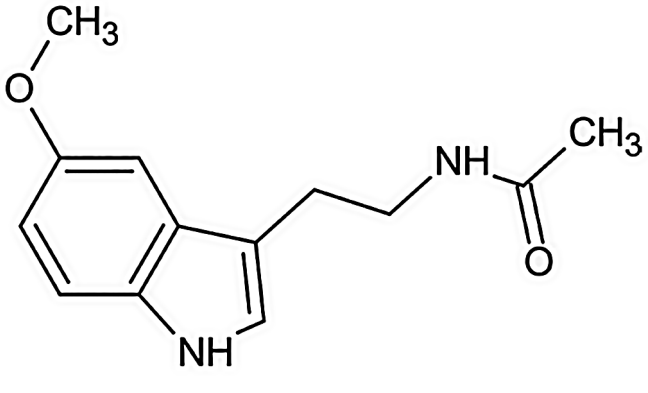


Fig. 1. Structural formula of melatonin molecule

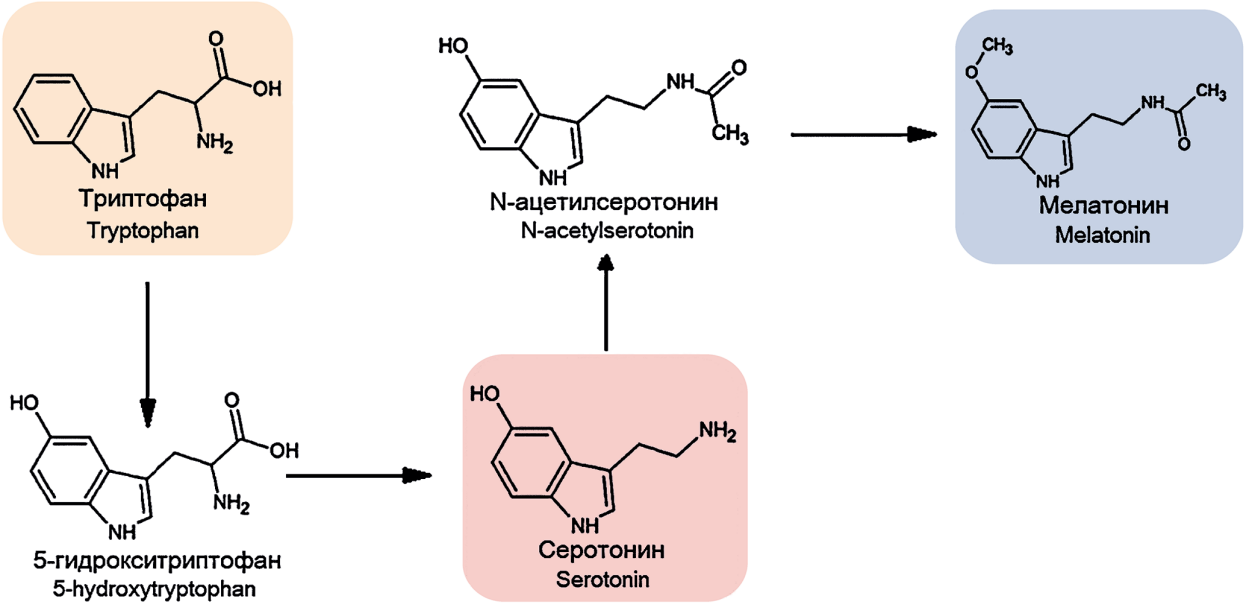


Fig. 2. Classical pathway of melatonin synthesis in humans

epiphysis and blood is observed at midnight, and the minimum — in the daytime [30]. In turn, the daytime plasma MT fraction is of peripheral origin [11]. MT plays a key role in regulating seasonal, circadian rhythms, as well as metabolism, immune response, reproductive function and other vital physiological processes [9].

The development of technology does not always lead to positive consequences. Thus, the widespread use of mobile gadgets, personal computers and other computing equipment in the dark time of day has a negative impact on the body, causing cartilage destruction due to a decrease in MT synthesis. This can further lead to negative consequences, such as the formation of various types of oncopathology (breast, prostate, endometrial, ovarian, colon, skin, etc.); as well as cardiovascular diseases; digestive disorders; diabetes mellitus; obesity; depression; sleep deprivation; cognitive impairment and premature aging [8, 10, 36].

Besides regulating biological rhythms, MT has many different functions [33]. It is known to affect gastrointestinal (GI) motility through membrane receptors that include MT receptors (melatonin receptor type 1 (MT 1) and type 2 (MT 2)) and serotonin (5-HT). At physiological levels, MT acts as a serotonin antagonist in the regulation of intestinal motility [46]. The immunomodulatory effect of MT is based on the endocrine response of circulating immunological cells and progenitor cells in the bone marrow that express its receptors. Rhythmic synthesis of MT has been found to be essential for modulating both circadian and seasonal fluctuations in immune functions, as well as for the efficient functioning of the immune-pineal axis [25]. MT influences growth processes and thyroid hormone synthesis [38]. Its antioxidant function is also important to note [23]. It has the ability to scavenge free radicals and also induces the expression of antioxidant enzymes (superoxide dismutase and glutathione peroxidase) with the formation of indirect antioxidant effects [3]. Next, we are going to discuss the role of MT in various somatic pathologies.

MELATONIN AND INFLAMMATION

The main anti-inflammatory action of MT is enhancing the activity of anti-inflammatory cytokines and suppressing the production of leptin and pro-inflammatory cytokines such as interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1) and tumor necrosis factor-α (TNF-α) [16]. In addition, MT suppression of pro-inflammatory cytokines can lead to multiple antioxidant effects, removal of reactive oxygen species (ROS), inhibition of neuronal NO synthases and cyclooxygenase-2 (COX-2), and inhibition of Nod-like receptor containing pyrin domain 3 (NLRP3) inflammasome formation [24]. Nuclear factor kappa-B (NF-κB) and NLRP3 are inhibited through activation of the MT-dependent gene for the NAD-dependent sirtuin deacetylase-1 (SIRT1) protein (Fig. 3) [18].

Importantly, the anti-inflammatory effect of MT is also related to its ability to optimize mitochondrial function. It exerts a beneficial effect on mitochondria via mitofusin-2 (Fig. 4), which modulates the neuronal activity of orexigenic agouti-related protein (AgRP) and diet-induced obesity, as well as the intrinsic regulation of the apoptotic cascade [41].

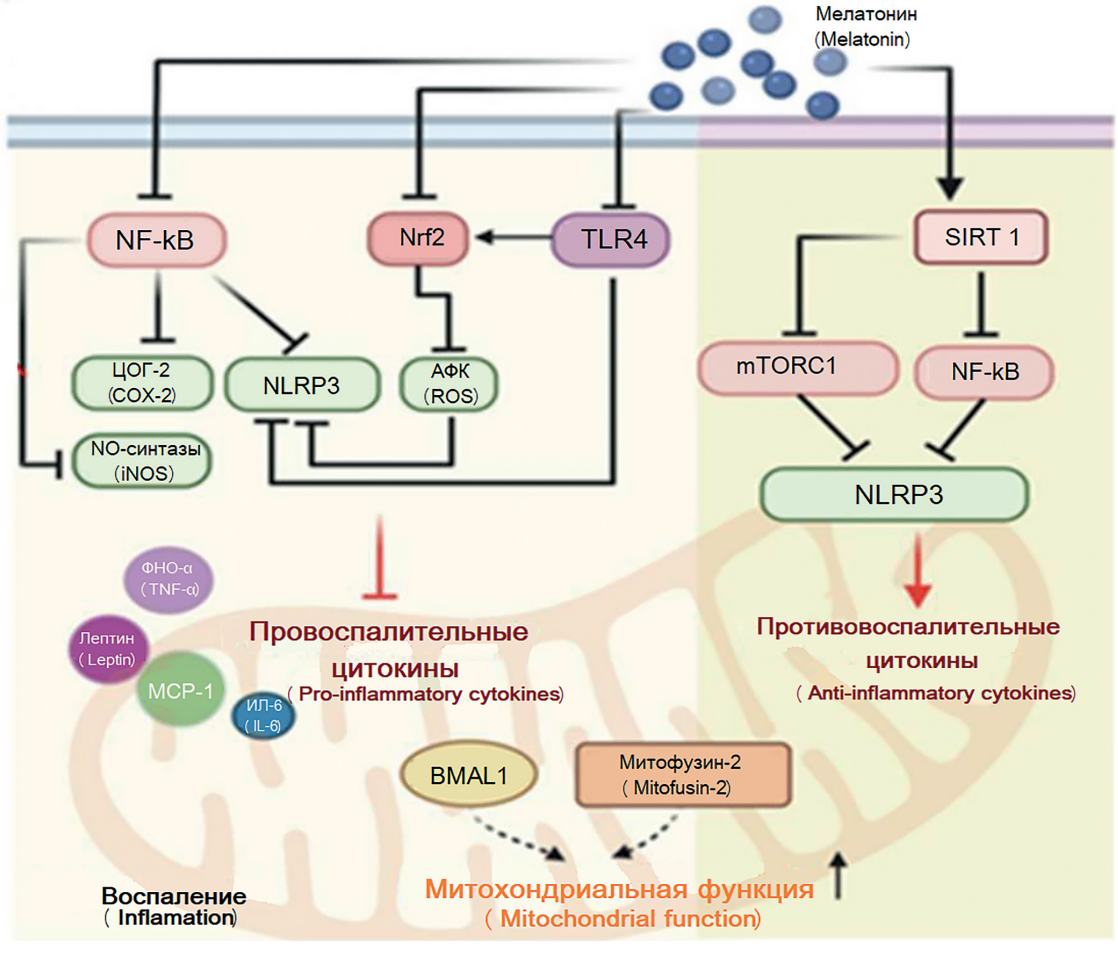


Fig. 3. **Reduction of inflammation activity by melatonin through inhibition of NF-κB, NRF2, TLR4, and SIRT1 signaling pathways, resulting in suppression of proinflammatory and enhancement of anti-inflammatory cytokines. AFC, reactive oxygen species; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; COX-2, cyclooxygenase-2; BMAL1, aromatic hydrocarbon nuclear translocator-like protein-1; MCP-1, monocyte chemotactic protein-1; mTORC1, mammalian target of rapamycin signaling complex; NF-κB, nuclear factor kappa-bi; NLRP3, Nod-like receptor containing pyrin domain 3; Nrf2, erythroid 2-dependent nuclear factor; SIRT1, sirtuin NAD-dependent deacetylase-1 protein; TLR4, toll-like receptor 4**

A number of experiments have confirmed anti-inflammatory properties of MT. Thus, the results of a clinical study conducted at the Second Hospital of Jilin University of the People's Republic of China (PRC) demonstrated that MT prevents inflammation-induced hepatocyte damage in laboratory mice. It reduces mitochondrial oxidative stress through activation of the Akt-SIRT3 pathway involved in antioxidant synthesis, and at the same time regulates reactive oxygen species (ROS) formation [34].

MELATONIN AND HYPERTENSION

Hypertension (HT) is one of the most common causes of mortality in the adult population [2]. Persistent hypertension leads to chronic tension of arterial walls, which in turn is associated with their stiffness, inflammatory process in the intima and atherogenesis.

The positive effect of MT in terms of HT has been known for a long time. Thus, in the study of 1976, conducted by the Department of Medicines of the county of Herdfordshire (UK), it was found that pinealectomy in rats led to a pronounced HT. The findings suggest a positive effect of endogenous MT on blood pressure regulation [19].

It was also found that patients with cardiovascular diseases associated with HT have decreased serum MT levels [51]. MT may reduce hypertension through regulation of vasoconstriction and vasodilation and interaction with the renin-angiotensin system [7]. A study conducted at Suzhou University Medical College (PRC) demonstrated that endothelial cells cultured under high blood pressure conditions expressed significantly more vasoactive substances including endothelin and angiotensin II [37]. Co-incubation of MT with these cells resulted in suppression of endothelin and angiotensin II and increased nitrosyl radical production and endothelial nitric oxide synthase expression [51].

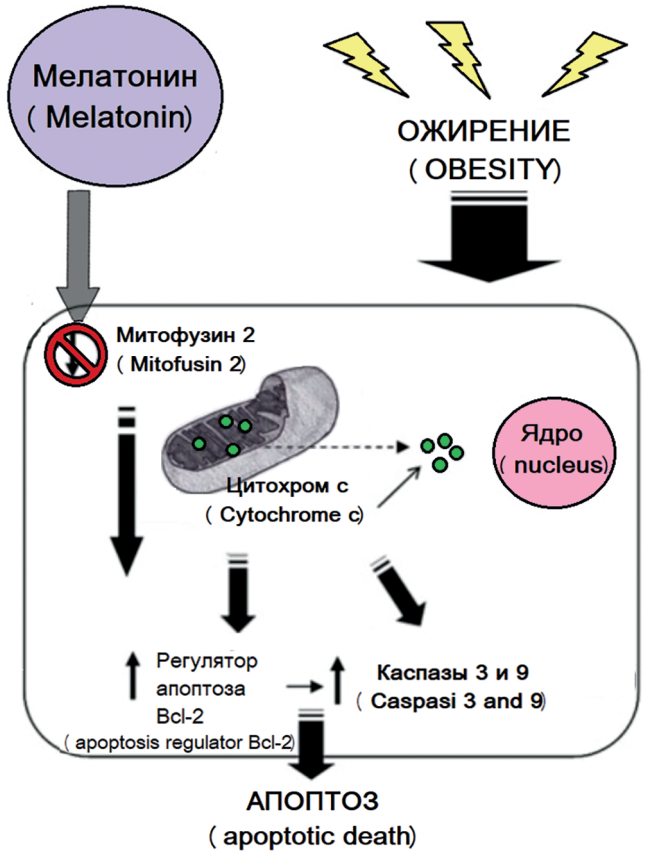


Fig. 4. Schematic representation of the inhibitory effect of melatonin on the intrinsic, mitochondria-driven apoptotic cascade and apoptosis pathways induced by mitofusin-2-mediated changes in the kidney on the background of obesity

The anti-remodeling effect of MT should be emphasized as well. A study conducted at Comenius University in Bratislava (Slovakia) demonstrated that MT reduced fibrosis activity in rats with spontaneous hypertension [40], hypertension induced by N-ω-nitro-L-arginine methyl ester (L-NAME), and hypertension induced by constant exposure to light (Fig. 5) [39].

In addition to its effects on the vascular system, MT may also exert antihypertensive effects through interaction with the central nervous system (CNS). On the one hand, MT release is controlled by sympathetic afferentation to the pineal gland, involving the interaction of light with the retina, suprachiasmatic nucleus, paraventricular nucleus and stimulation of β1- and α1-adrenoreceptors of the pineal gland [39]. On the other hand, transmission of signals by GABA from the suprachiasmatic nucleus to various parts of the CNS, including the ventrolateral part of the medulla oblongata, may be modulated by MT activity, providing a protective mechanism against excessive sympathetic excitation [31].

MELATONIN AND HYPERLIPIDAEMIA

Hyperlipidemia is a consequence of an aberrant process of increasing levels of low-density lipoprotein (LDL), total cholesterol (TC), triglycerides and decreasing levels of high-density lipoprotein (HDL). According to the University Hospital of the Canary Islands (Spain), an inverse correlation between serum levels of endogenous MT and LDL was found in patients with atherosclerosis [13]. In vitro studies have also demonstrated the beneficial effects of MT in the metabolic function of hepatocytes through modelling the SIRT1/mitofusin-2 pathway, by reducing ROS production. Pretreatment of HepG2 cell line with MT showed improved lipid consumption and activation of PPARα and carnitine palmitoyl-CoA transferase 1, which are lipolytic genes essential for metabolism [51].

According to Harbin Medical University (PRC), MT appeared to deactivate LDL-induced pyroptosis in endothelial cells via the MEG3/miR-223/NLRP3 axis [52]. It should be added that LDLs trigger inflammation activation and pro-inflammatory factor secretion, whereas MT significantly reduces NLRP3-inflammatory production by NLRP3-inflammasomes and IL-1 secretion in macrophages [51]. In another study conducted by the State University of São Paulo (Brazil), healthy laboratory rats were compared with rats which undergone pineal gland resection. Thus, the animals had a significant decrease in serum HDL level after surgery, but normalization of the level of this lipoprotein was observed when MT was administered [14].

Researchers from the University of Granada (Spain) reported MT positively influenced on overweight and lipid profile in obese and diabetic rats [5]. Prolonged stimulation of MT synthesis is able to reduce weight gain [47], inhibit the absorption and biosynthesis and serum levels of OX [21], and enhance its catabolism [32]. MT reduces cholesterol by enhancing the mechanisms of endogenous cholesterol clearance through bilirubin acid synthesis and inhibition of LDL receptor activity. The hypolipidemic effect of MT is also determined by an increase in the level of circulating irisin, which enhances the excretion of total cholesterol by its clearance into bile [16].

MELATONIN AND DIABETES MELLITUS

The results of a number of foreign studies prove that circadian rhythm disturbance may contribute to the development of both diabetes and cardiovascular diseases [29]. A correlation between MT secretion and insulin at night has been described in young patients with metabolic syndrome [1]. The large-scale Nurses' Health Study found an association between MT secretion, assessed by urinary 6-sulfatoxymelatonin levels, and the subsequent development of

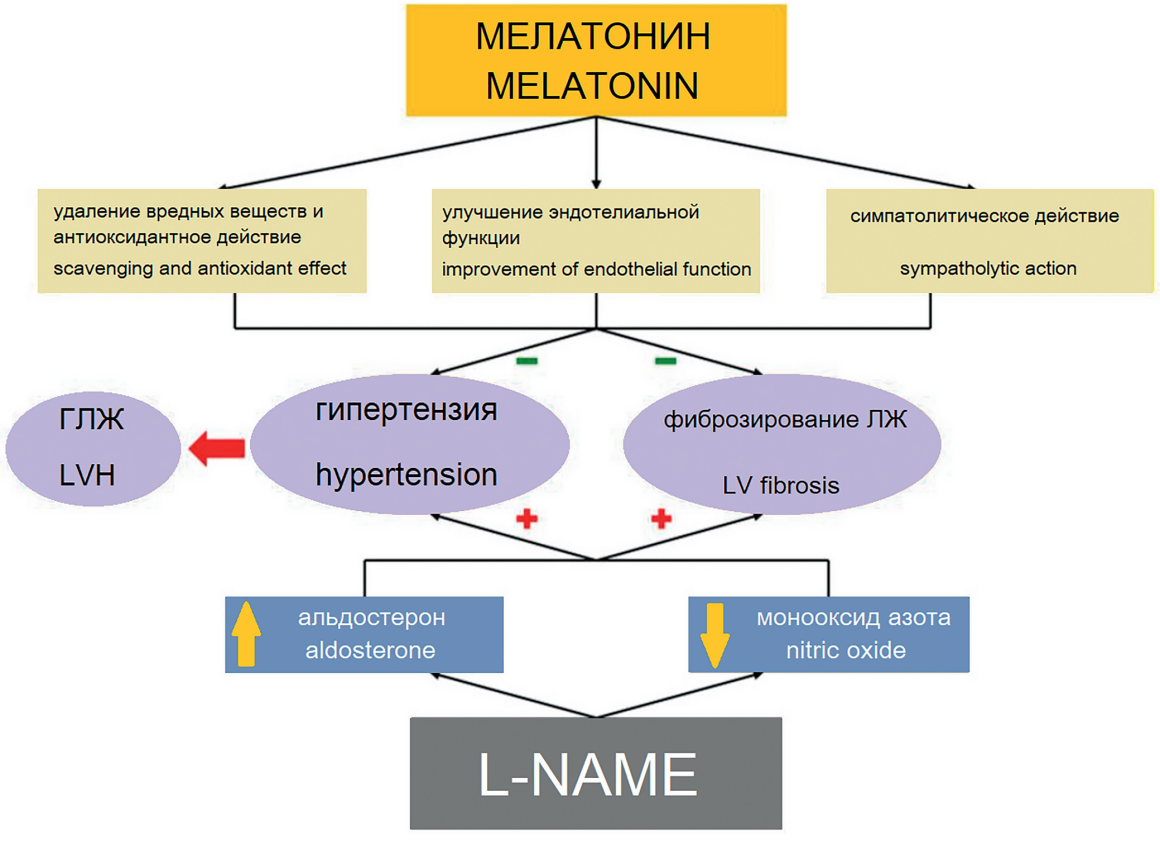


Fig. 5. Mechanisms of the protective effect of melatonin in hypertension induced by N-ω-nitro-L-arginine methyl ester. Chronic administration of L-NAME provokes the development of arterial hypertension, left ventricular (LV) fibrosis, and as a consequence of increased hemodynamic load, left ventricular hypertrophy develops. Melatonin reduces free radicals through its antioxidant action, improves endothelial function and has a central sympatholytic effect. These actions of melatonin lead to normalization of blood pressure, prevention of further myocardial remodeling in the left ventricle

type 2 diabetes mellitus (DM 2). Individuals with the lowest levels of MT secretion had a twofold risk of developing DM 2 compared to subjects with normal or high levels of its secretion [26].

In addition, MT regulates blood glucose levels. Several hypotheses are proposed to explain this process. Thus, the “Equilibrium Hypothesis” suggests that both increased and decreased MT signaling can cause carbohydrate disorders [27]. Another hypothesis suggests a functional antagonism between MT secretion and food intake. Low MT levels during the day potentiate normal glycemic tolerance after a food load, while high MT levels during overnight fasting ensure pancreatic beta-cell recovery. Elevated MT concentrations during meal periods result in pathological changes in glucose metabolism in both nighttime eaters and those awake during dark periods [15]. Despite conflicting data and hypotheses, it is clear that the pineal hormone performs fine-tuning of carbohydrate metabolism through its receptors in the pancreas, liver and adipose tissue [28].

Experimental studies have revealed that MT receptors in pancreas are associated with several parallel signaling pathways affecting insulin secretion. Thus, MT decreases insulin secretion via the MT 1 receptor by inhibiting the adenylate cyclase-cyclic adenosine monophosphate pathway, and inhibits the guanylate cyclase-cyclic guanosine monophosphate pathway via the MT 2 receptor. In addition, MT can also stimulate insulin secretion by releasing inositol triphosphate — through interaction with the MT 2 receptor [28].

It has also been found that patients with DM have a decreased number of MT1 and MT2 receptors in beta cells. According to a study by King’s College London, MT stimulates glucagon secretion by alpha cells followed by a paracrine-mediated indirect increase in insulin levels by β cells. MT also modulates somatostatin secretion by delta cells in both healthy individuals and DM 2 patients [35].

MTNR1B is an important diabetic gene encoding the MT2 receptor protein. A decade ago It was associated with pancreatic beta-cell dysfunction which gave a huge impetus to research the correlation between pineal hormone

signaling, receptor polymorphism and impaired carbohydrate metabolism. *MTNR1B* rs10830963 C > G was associated with elevated fasting glucose levels in a large cohort of individuals of European origin. Moreover, the presence of a minor G allele of the same polymorphism was associated with an increased risk of DM 2 in a meta-analysis of 18,236 cases from a cohort of 64,453 patients. The rs10830963G allele determines both elevated fasting glucose levels and a low early insulin response to glucose loading [28].

In addition, several meta-analyses have shown an association between the *MTNR1B* rs10830963 and the development of gestational diabetes mellitus (GDM). Carriers of GG genotype have a 78% higher risk of developing GDM compared to SS carriers, regardless of ethnicity [6, 20, 22].

A number of other common polymorphisms of the *MTNR1B* gene also modulate fasting glucose levels and early insulin secretion by beta cells, thereby influencing the risk of developing DM2 and GDM in different ethnic groups. Moreover, the same polymorphisms may determine different effects of lifestyle modification and/or drug treatment in metabolic disorders [28].

Taking into account the expression of MT receptors in many tissues, studies have revealed the influence of MT signaling on glucose metabolic processes in peripheral tissues such as liver, skeletal muscle and pancreas. MT is required for insulin-stimulated activity of phosphatidylinositol-3-kinase and protein kinase B. MT mediated glycogen synthesis in hepatocyte cells through insulin receptor substrate 1 via Gi protein. Notably, MT promotes SIRT 1 expression and phosphorylation of signal transducer and activator of transcription 3 in rat liver to regulate gluconeogenesis. MT also activates the IRS1-PI3K-PKCζ pathway to promote glucose uptake in skeletal muscle [16].

MELATONIN AND DEPRESSIVE SPECTRUM DISORDERS

An observational study conducted at Uppsala University (Sweden) found a negative correlation between evening MT levels and quantitative measures of depressive symptoms in young patients seeking psychiatric care. Similarly, patients with low MT levels demonstrated worsening of symptoms on the MADRS-S scale in a prospective study [43].

A possible mechanism for the antidepressant action of MT is its ability to modulate neuroplastic responses in the hippocampus. A wide range of meta-analyses points to structural and functional abnormalities of the hippocampus in depression. In addition, inflammatory processes significantly contribute to structural changes in the hippocampus in depressive disorders [50]. Preclinical data have shown that the hippocampus is one of the main targets for MT action in the brain, with MT promoting branching of distal dendrites in layers II/III of cortical pyramidal cells [48]. It was also found that MT stimulates neurogenesis, axogenesis and dendritogenesis of neurons in the limbic region of the brain. Disruption of MT expression, which further promotes meta-inflammation and decreases the cytoprotective and neuroprotective effects of hippocampal cells, may be one of the major mechanisms underlying the pathophysiology of depression [50].

CONCLUSION

Melatonin has a wide range of protective properties in various pathological processes, it has a positive effect on lipid metabolism, promotes weight loss in obesity and, as a consequence, the degree of severity of insulin resistance. Melatonin normalizes blood pressure and elevated glycemic levels and has antidepressant functions, which are attributed to their role in regulating circadian rhythms, the renin-angiotensin system, insulin levels, as well as lipid metabolism and deactivation of chronic inflammation. Although melatonin is a neurohormone, it plays a pivotal role in modulating oxidative stress through both direct antioxidant action and induction by inflammation. Thus, regulation of circulating melatonin levels may serve as a potential target for reducing the intensity of oxidative stress leading, among other things, to meta-inflammation.

So far, there is still no consensus on the possible role of melatonin as an adjuvant drug for the treatment of metabolic diseases, although it shows great potential in many aspects. The wide range of positive properties of melatonin leads us to the conclusion that it is necessary to study the use of MT exogenous form as an adjunct to the main therapy in various diseases, primarily metabolic and anxiety-depressive spectrum disorders. Exogenous melatonin, as well as endogenous one, reduces the level of pro- inflammatory cytokines and suppresses the activity of oxidative stress, which can be used for prevention and adjuvant treatment of polymorbid pathology. Melatonin is relatively safe and has few mild side effects such as dizziness, headache, nausea, morning drowsiness, which makes it an excellent agent for preventing many pathological conditions.

ADDITIONAL INFORMATION

Author 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.

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

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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.

REFERENCES

1. Antyukhin M.A., Partsernyak A.S. Izucheniye roli melatonina i khronicheskogo vospaleniya v razvitii i progressirovanii metabolicheskogo sindroma u lits molodogo vozrasta. [Study of the role of melatonin and chronic inflammation in the development and progression of the metabolic syndrome in young adults]. Izvestiya Rossiyskoy Voyenno-Meditsinskoy Akademii. 2020; 39(1-1): 9–12. (in Russian).
2. Kryukov Ye.V., Potekhin N.P., Fursov A.N. i dr. Gipertonicheskiy kriz: sovremennyy vzglyad na problemu i optimizatsiya lechebno-diagnosticheskikh podkhodov. [Hypertensive crisis: a modern view on the problem and optimization of treatment and diagnostic approaches]. Klinicheskaya Meditsina. 2016; 94(1): 52–6. (in Russian).
3. Partsernyak A.S., Kryukov Ye.V., Tsygan V.N. i dr. Metabolicheskiy sindrom i ateroskleroz u molodykh muzhchin. Metabolic syndrome and atherosclerosis in young men. Lecheniye i profilaktika. 2021; 4: 5–11. (in Russian).
4. Acuna-Castroviejo D., Noguiera-Navarro M.T., Reiter R.J. Melatonin actions in the heart: more than a hormone. Melatonin Res. 2018; 1(1): 21–6.
5. Agil A., Navarro-Alarcon M., Ruiz R. et al. Beneficial effects of melatonin on obesity and lipid profile in young Zucker diabetic fatty rats. J Pineal Res. 2011; 50(2): 207–12.
6. Bai Y., Tang L., Li L. et al. The roles of ADIPOQ rs266729 and MTNR1B rs10830963 polymorphisms in patients with gestational diabetes mellitus: A meta-analysis. Gene. 2020.
7. Baltatu O.C., Amaral F.G., Campos L.A. et al. Melatonin, mitochondria and hypertension. Cell Mol Life Sci. 2017; 74(21): 395–64.
8. Bass J., Lazar M.A. Circadian time signatures of fitness and disease. Science. 2016; 354(6315): 994–9.
9. Boden M.J., Varcoe T.J., Kennaway D.J. Circadian regulation of reproduction: From gamete to offspring. Progress in Biophysics and Molecular Biology. 2013; 113(3): 387–97.
10. Bonmati-Carrion M.A., Arguelles-Prieto R., Martinez-Madrid M.J. et al. Protecting the melatonin rhythm through circadian healthy light exposure. International Journal of Molecular Sciences. 2014; 15(12): 23448–500.
11. Chen C., Fichna J., Bashashati M. et al. Distribution, function and physiological role of melatonin in the lower gut. World Journal of Gastroenterology. 2011; 17(34): 3888–98.
12. Claustrat B., Leston J. Melatonin: Physiological effects in humans. Neurochirurgie. 2015; 61(2–3): 77–84.
13. Dominguez-Rodriguez A., Abreu-Gonzalez P., Garcia-Gonzalez M. et al. Elevated levels of oxidized low-density lipoprotein and impaired nocturnal synthesis of melatonin in patients with myocardial infarction. Atherosclerosis. 2005; 180 (1): 101–5.
14. Dos Santos R.M., Marani F., Chiba F.Y. et al. Melatonin promotes reduction in TNF levels and improves the lipid profile and insulin sensitivity in pinealectomized rats with periodontal disease. Life Sciences. 2018; 213: 32–9.
15. Garaulet M., Qian J., Florez J.C. et al. Melatonin Effects on Glucose Metabolism: Time To Unlock the Controversy. Trends Endocrinol Metab. 2020; 31 (3): 192–204.
16. Guan Q., Wang Z., Cao J. et al. Mechanisms of Melatonin in Obesity: A Review. nternational Journal of Molecular Sciences. 2022; 23 (1): 218.
17. Hardeland R., Pandi-Perumal S.R., Cardinali Melatonin D.P. The International Journal of Biochemistry & Cell Biology. 2006; 38(3): 313–6.
18. Hardeland R. Melatonin and inflammation-story of a double-edged blade. J Pineal Res. 2018; 65 (4).
19. Holmes S.W., Sugden D. Proceedings: The effect of melatonin on pinealectomy-induced hypertension in the rat. British Journal of Pharmacology. 1976; 56 (3): 360–1.
20. Huang B., Wang Y., Qin L. et al. A functional polymorphism rs10830963 in melatonin receptor 1B associated with the risk of gestational diabetes mellitus. Bioscience Reports. 2019; 39(12).
21. Hussain S. Effect of melatonin on cholesterol absorption in rats. J Pineal Res. 2007; 42 (3): 267–71.
22. Jia G., Gao Y., Li C. et al. Effects of MTNR1B Genetic Variants on Individual Susceptibility to Gestational Diabetes Mellitus: A Meta-Analysis. American Journal of Perinatology. 2020; 37(6): 607–12.
23. Kvetnoy I., Ivanov D., Mironova E. et al. Melatonin as the Cornerstone of Neuroimmunoendocrinology. International Journal of Molecular Sciences. 2022; 23(3): 1835.
24. Liu Z., Gan L., Xu Y. et al. Melatonin alleviates inflammasome-induced pyroptosis through inhibiting NF-κB/GSDMD signal in mice adipose tissue. J. Pineal Res. 2017; 63 (1).
25. Markus R.P., Fernandes P.A., Kinker G.S. et al. Immune-pineal axis — acute inflammatory responses coordinate melatonin synthesis by pinealocytes and phagocytes. British Journal of Pharmacology. 2018; 175 (16): 3239–50.
26. McMullan C.J., Schernhammer E.S., Rimm E.B. et al. Melatonin secretion and the incidence of type 2 diabetes. Journal of the American Medical Association. 2013; 309(13): 1388–96.
27. Mulder H. Melatonin signalling and type 2 diabetes risk: too little, too much or just right? Diabetologia. 2017; 60 (5): 826–9.

28. Nikolaev G., Robeva R., Konakchieva R. Membrane Melatonin Receptors Activated Cell Signaling in Physiology and Disease. International Journal of Molecular Sciences. 2022; 23 (1): 471.
29. Otamas A., Grant P.J., Ajjan R.A. Diabetes and atherothrombosis: The circadian rhythm and role of melatonin in vascular protection. Diab Vasc Dis Res. 2020; 13(3).
30. Pandi-Peruumal S.R., Cardinali D.P. Melatonin: Biological Basis of its Function in Health and Disease. CRC Press. 2005.
31. Pechanova O., Paulis L., Simko F. Peripheral and central effects of melatonin on blood pressure regulation. Int J Mol Sci. 2014; 15(10): 17920–37.
32. Pita M.L., Hoyos M., Martin-Lacave I. et al. Long-term melatonin administration increases polyunsaturated fatty acid percentage in plasma lipids of hypercholesterolemic rats. J Pineal Res. 2002; 32 (3): 179–86.
33. Posadzki P.P., Bajpai R., Kyaw B.M. et al. Melatonin and health: an umbrella review of health outcomes and biological mechanisms of action. BMC Medicine. 2018; 16 (1).
34. Qiu J., Liu D., Li P. et al. NADPH Oxidase Mediates Oxidative Stress and Ventricular Remodeling through SIRT3/FOXO3a Pathway in Diabetic Mice. Antioxidants. 2022; 11 (9): 1745.
35. Ramracheya R.D., Muller D.S., Squires P.E. et al. Function and expression of melatonin receptors on human pancreatic islets. J Pineal Res. 2008; 44 (3): 273–9.
36. Schlafer O., Wenzel V., Hogl B. Sleep disorders among physicians on shift work. Anaesthetist. 2014; 63 (11): 844–51.
37. Shao G., Zhang S., Nie J. et al. Effects of melatonin on mechanisms involved in hypertension using human umbilical vein endothelial cells. Journal of Toxicology and Environmental Health. 2017; 80 (23–24): 1342–8.
38. Shavali S.S., Haldar C. Effects of continuous light, continuous darkness and pinealectomy on pineal-thyroid-gonadal axis of the female Indian palm squirrel, Funambulus pennant. Journal of Neural Transmission. 1998; 105 (4–5): 407–13.
39. Simko F., Baka T., Krajcirovicova K. et al. Effect of Melatonin on the Renin-Angiotensin-Aldosterone System in l-NAME-Induced Hypertension. Molecules. 2018; 23 (2): 265.
40. Simko F., Pechanova O., Pelouch V. et al. Effect of melatonin, captopril, spironolactone and simvastatin on blood pressure and left ventricular remodelling in spontaneously hypertensive rats. J Hypertens Suppl. 2009; 27(6): 5–10.
41. Stacchiotti A., Favero G., Giugno L. et al. Mitochondrial and metabolic dysfunction in renal convoluted tubules of obese mice: protective role of melatonin. PLOS One. 2014; 9 (10).
42. Stefulj J., Hortner M., Ghosh M. et al. Gene expression of the key enzymes of melatonin synthesis in extrapineal tissues of the rat. Journal of Pineal Research. 2001; 30(4): 243–7.
43. Sundberg I., Ramklint M., Stridsberg M. et al. Salivary Melatonin in Relation to Depressive Symptom Severity in Young Adults. PLOS One. 2016; 11(4).
44. Tan D., Zheng X., Kong J. et al. Fundamental issues related to the origin of melatonin and melatonin isomers during evolution: relation to their biological functions. International Journal of Molecular Sciences. 2014; 15(9): 15858–90.
45. Tan D.X., Hardeland R., Manchester L.C. et al. Functional roles of melatonin in plants, and perspectives in nutritional and agricultural science. Journal of Experimental Botany. 2012; 63(2): 577–97.
46. Thor P.J., Krolczyk G., Gil K. et al. Melatonin and serotonin effects on gastrointestinal motility. Journal of Physiology and Pharmacology. 2007; 58: 97–103.
47. Tung Y., Chiang P., Chen Y. et al. Effects of Melatonin on Lipid Metabolism and Circulating Irisin in Sprague-Dawley Rats with Diet-Induced Obesity. Molecules. 2020; 25(15): 3329.
48. Valdes-Tovar M., Estrada-Reyes R., Solis-Chagoyan H. et al. Circadian modulation of neuroplasticity by melatonin: a target in the treatment of depression. British Journal of Pharmacology. 2018; 175 (16): 3200–8.
49. Venegas C., Garcia J.A., Escames G. et al. Extrapineal melatonin: analysis of its subcellular distribution and daily fluctuations. Journal of Pineal Research. 2012; 52(2): 217–27.
50. Won E., Na K., Kim Y. Associations between Melatonin, Neuroinflammation, and Brain Alterations in Depression. International Journal of Molecular Sciences. 2022; 23 (1): 305.
51. Zhang R., Ni L., Di X. et al. Potential Role of Melatonin as an Adjuvant for Atherosclerotic Carotid Arterial Stenosis. Molecules. 2021; 26 (4).
52. Zhang Y., Liu X., Bai X. et al. Melatonin prevents endothelial cell pyroptosis via regulation of long noncoding RNA MEG3/miR-223/NLRP3 axis. J Pineal Res. 2018; 64 (2).

ЛИТЕРАТУРА

1. Антюхин М.А., Парцерняк А.С. Изучение роли мелатонина и хронического воспаления в развитии и прогрессировании метаболического синдрома у лиц молодого возраста. Известия Российской Военно-медицинской академии. 2020; 39(1-1): 9–12.
2. Крюков Е.В., Потехин Н.П., Фурсов А.Н. и др. Гипертонический криз: современный взгляд на проблему и оптимизация лечебно-диагностических подходов. Клиническая медицина. 2016; 94(1): 52–6.
3. Парцерняк А.С., Крюков Е.В., Цыган В.Н. и др. Метаболический синдром и атеросклероз у молодых мужчин. Лечение и профилактика. 2021; 4: 5–11.
4. Acuna-Castroviejo D., Noguiera-Navarro M.T., Reiter R.J. Melatonin actions in the heart: more than a hormone. Melatonin Res. 2018; 1(1): 21–6.
5. Agil A., Navarro-Alarcon M., Ruiz R. et al. Beneficial effects of melatonin on obesity and lipid profile in young Zucker diabetic fatty rats. J Pineal Res. 2011; 50(2): 207–12.
6. Bai Y., Tang L., Li L. et al. The roles of ADIPOQ rs266729 and MTNR1B rs10830963 polymorphisms in patients with gestational diabetes mellitus: A meta-analysis. Gene. 2020.
7. Baltatu O.C., Amaral F.G., Campos L.A. et al. Melatonin, mitochondria and hypertension. Cell Mol Life Sci. 2017; 74(21): 395–64.

8. Bass J., Lazar M.A. Circadian time signatures of fitness and disease. Science. 2016; 354(6315): 994–9.
9. Boden M.J., Varcoe T.J., Kennaway D.J. Circadian regulation of reproduction: From gamete to offspring. Progress in Biophysics and Molecular Biology. 2013; 113(3): 387–97.
10. Bonmati-Carrion M.A., Arguelles-Prieto R., Martinez-Madrid M.J. et al. Protecting the melatonin rhythm through circadian healthy light exposure. International Journal of Molecular Sciences. 2014; 15(12): 23448–500.
11. Chen C., Fichna J., Bashashati M. et al. Distribution, function and physiological role of melatonin in the lower gut. World Journal of Gastroenterology. 2011; 17(34): 3888–98.
12. Claustrat B., Leston J. Melatonin: Physiological effects in humans. Neurochirurgie. 2015; 61(2-3): 77–84.
13. Dominguez-Rodriguez A., Abreu-Gonzalez P., Garcia-Gonzalez M. et al. Elevated levels of oxidized low-density lipoprotein and impaired nocturnal synthesis of melatonin in patients with myocardial infarction. Atherosclerosis. 2005; 180 (1): 101–5.
14. Dos Santos R.M., Marani F., Chiba F.Y. et al. Melatonin promotes reduction in TNF levels and improves the lipid profile and insulin sensitivity in pinealectomized rats with periodontal disease. Life Sciences. 2018; 213: 32–9.
15. Garaulet M., Qian J., Florez J.C. et al. Melatonin Effects on Glucose Metabolism: Time To Unlock the Controversy. Trends Endocrinol Metab. 2020; 31 (3): 192–204.
16. Guan Q., Wang Z., Cao J. et al. Mechanisms of Melatonin in Obesity: A Review. nternational Journal of Molecular Sciences. 2022; 23 (1): 218.
17. Hardeland R., Pandi-Perumal S.R., Cardinali Melatonin D.P. The International Journal of Biochemistry & Cell Biology. 2006; 38(3): 313–6.
18. Hardeland R. Melatonin and inflammation-story of a double-edged blade. J Pineal Res. 2018; 65 (4).
19. Holmes S.W., Sugden D. Proceedings: The effect of melatonin on pinealectomy-induced hypertension in the rat. British Journal of Pharmacology. 1976; 56 (3): 360–1.
20. Huang B., Wang Y., Qin L. et al. A functional polymorphism rs10830963 in melatonin receptor 1B associated with the risk of gestational diabetes mellitus. Bioscience Reports. 2019; 39(12).
21. Hussain S. Effect of melatonin on cholesterol absorption in rats. J Pineal Res. 2007; 42 (3): 267–71.
22. Jia G., Gao Y., Li C. et al. Effects of MTNR1B Genetic Variants on Individual Susceptibility to Gestational Diabetes Mellitus: A Meta-Analysis. American Journal of Perinatology. 2020; 37(6): 607–12.
23. Kvetnoy I., Ivanov D., Mironova E. et al. Melatonin as the Cornerstone of Neuroimmunoendocrinology. International Journal of Molecular Sciences. 2022; 23(3): 1835.
24. Liu Z., Gan L., Xu Y. et al. Melatonin alleviates inflammasome-induced pyroptosis through inhibiting NF-κB/GSDMD signal in mice adipose tissue. J. Pineal Res. 2017; 63 (1).
25. Markus R.P., Fernandes P.A., Kinker G.S. et al. Immune-pineal axis — acute inflammatory responses coordinate melatonin synthesis by pinealocytes and phagocytes. British Journal of Pharmacology. 2018; 175 (16): 3239–50.
26. McMullan C.J., Schernhammer E.S., Rimm E.B. et al. Melatonin secretion and the incidence of type 2 diabetes. Journal of the American Medical Association. 2013; 309(13): 1388–96.
27. Mulder H. Melatonin signalling and type 2 diabetes risk: too little, too much or just right? Diabetologia. 2017; 60 (5): 826–9.
28. Nikolaev G., Robeva R., Konakchieva R. Membrane Melatonin Receptors Activated Cell Signaling in Physiology and Disease. International Journal of Molecular Sciences. 2022; 23 (1): 471.
29. Otamas A., Grant P.J., Ajjan R.A. Diabetes and atherothrombosis: The circadian rhythm and role of melatonin in vascular protection. Diab Vasc Dis Res. 2020; 13(3).
30. Pandi-Peruumal S.R., Cardinali D.P. Melatonin: Biological Basis of its Function in Health and Disease. CRC Press. 2005.
31. Pechanova O., Paulis L., Simko F. Peripheral and central effects of melatonin on blood pressure regulation. Int J Mol Sci. 2014; 15(10): 17920–37.
32. Pita M.L., Hoyos M., Martin-Lacave I. et al. Long-term melatonin administration increases polyunsaturated fatty acid percentage in plasma lipids of hypercholesterolemic rats. J Pineal Res. 2002; 32 (3): 179–86.
33. Posadzki P.P., Bajpai R., Kyaw B.M. et al. Melatonin and health: an umbrella review of health outcomes and biological mechanisms of action. BMC Medicine. 2018; 16 (1).
34. Qiu J., Liu D., Li P. et al. NADPH Oxidase Mediates Oxidative Stress and Ventricular Remodeling through SIRT3/FOXO3a Pathway in Diabetic Mice. Antioxidants. 2022; 11 (9): 1745.
35. Ramracheya R.D., Muller D.S., Squires P.E. et al. Function and expression of melatonin receptors on human pancreatic islets. J Pineal Res. 2008; 44 (3): 273–9.
36. Schlafer O., Wenzel V., Hogl B. Sleep disorders among physicians on shift work. Anaesthetist. 2014; 63 (11): 844–51.
37. Shao G., Zhang S., Nie J. et al. Effects of melatonin on mechanisms involved in hypertension using human umbilical vein endothelial cells. Journal of Toxicology and Environmental Health. 2017; 80 (23–24): 1342–8.
38. Shavali S.S., Haldar C. Effects of continuous light, continuous darkness and pinealectomy on pineal-thyroid-gonadal axis of the female Indian palm squirrel, Funambulus pennant. Journal of Neural Transmission. 1998; 105 (4–5): 407–13.
39. Simko F., Baka T., Krajcirovicova K. et al. Effect of Melatonin on the Renin-Angiotensin-Aldosterone System in l-NAME-Induced Hypertension. Molecules. 2018; 23 (2): 265.
40. Simko F., Pechanova O., Pelouch V. et al. Effect of melatonin, captopril, spironolactone and simvastatin on blood pressure and left ventricular remodelling in spontaneously hypertensive rats. J Hypertens Suppl. 2009; 27(6): 5–10.
41. Stacchiotti A., Favero G., Giugno L. et al. Mitochondrial and metabolic dysfunction in renal convoluted tubules of obese mice: protective role of melatonin. PLOS One. 2014; 9 (10).
42. Stefulj J., Hortner M., Ghosh M. et al. Gene expression of the key enzymes of melatonin synthesis in extrapineal tissues of the rat. Journal of Pineal Research. 2001; 30(4): 243–7.

43. Sundberg I., Ramklint M., Stridsberg M. et al. Salivary Melatonin in Relation to Depressive Symptom Severity in Young Adults. PLOS One. 2016; 11(4).
44. Tan D., Zheng X., Kong J. et al. Fundamental issues related to the origin of melatonin and melatonin isomers during evolution: relation to their biological functions. International Journal of Molecular Sciences. 2014; 15(9): 15858–90.
45. Tan D.X., Hardeland R., Manchester L.C. et al. Functional roles of melatonin in plants, and perspectives in nutritional and agricultural science. Journal of Experimental Botany. 2012; 63(2): 577–97.
46. Thor P.J., Krolczyk G., Gil K. et al. Melatonin and serotonin effects on gastrointestinal motility. Journal of Physiology and Pharmacology. 2007; 58: 97–103.
47. Tung Y., Chiang P., Chen Y. et al. Effects of Melatonin on Lipid Metabolism and Circulating Irisin in Sprague-Dawley Rats with Diet-Induced Obesity. Molecules. 2020; 25(15): 3329.
48. Valdes-Tovar M., Estrada-Reyes R., Solis-Chagoyan H. et al. Circadian modulation of neuroplasticity by melatonin: a target in the treatment of depression. British Journal of Pharmacology. 2018; 175 (16): 3200–8.
49. Venegas C., Garcia J.A., Escames G. et al. Extrapineal melatonin: analysis of its subcellular distribution and daily fluctuations. Journal of Pineal Research. 2012; 52(2): 217–27.
50. Won E., Na K., Kim Y. Associations between Melatonin, Neuroinflammation, and Brain Alterations in Depression. International Journal of Molecular Sciences. 2022; 23 (1): 305.
51. Zhang R., Ni L., Di X. et al. Potential Role of Melatonin as an Adjuvant for Atherosclerotic Carotid Arterial Stenosis. Molecules. 2021; 26 (4).
52. Zhang Y., Liu X., Bai X. et al. Melatonin prevents endothelial cell pyroptosis via regulation of long noncoding RNA MEG3/miR-223/NLRP3 axis. J Pineal Res. 2018; 64 (2).

UDC 616.151.5-072.7+612.115+616.13/.14-005.6-092-084-085+578.834.1
DOI: 10.56871/RBR.2023.85.16.008

CONTEMPORARY CONCEPT OF ARTERIAL THROMBOSIS MECHANISMS. ARTERIAL THROMBOSIS IN CASE OF COVID INFECTION

© Iskander Albertovich Latypov[1], Sarng Sanalovich Purveev[1, 2], Mikhail S. Nekrasov[1], Nikolay S. Dedanishvili[1], Nair Sabirovich Tagirov[1]

[1] Saint Petersburg State Pediatric Medical University. Lithuania 2, Saint Petersburg, Russian Federation, 194100
[2] Institute of Experimental Medicine. Academician Pavlova st., 12, Saint Petersburg, Russian Federation, 19702

Contact information: Sarng S. Pyurveev — Senior Assistant Department of pathological physiology with immunopathology course. E-mail: dr.purveev@gmail.com ORCID ID: 0000-0002-4467-2269 SPIN: 5915-9767

For citation: Latypov IA, Purveev SS, Nekrasov MS, Dedanishvili NS, Tagirov NS. Contemporary concept of arterial thrombosis mechanisms. Arterial thrombosis in case of COVID infection // Russian biomedical research (St. Petersburg). 2023; 8(3): 61-68. DOI: https://doi.org/10.56871/RBR.2023.85.16.008

Received: 22.05.2023 **Revised: 17.07.2023** **Accepted: 21.09.2023**

Abstract. Complex mechanisms of thrombosis are traditionally regarded within the so called Virchov's pathogenic thriade consisting of blood vessel injury + hypercoagulation + blood-flow slowing down. On spite of multiple additions and attempts at sophistications its essence remaiтs unchanged. However this threenominal scheme which is more or less applicable for explaining the pathogeny of venous thrombosis can be used in case of arterial ones only to a limited degree. Of late a different concept is under discussion namely that of arterial thriade consisting of different components: 1. Arterial stenosis and acceleration of bloodflow; 2. Platelets activation and their interaction with Von Willebrand factor (VWF); 3. Blood vessel wall injury. This composition of arterial thriade is more successfully explaining thrombosis mechanisms in case of arterial stenosis especially in case of atherosclerosis. Of late the attention is focused also at the association between new COVID-infection and increased risk of thrombosis. The new "arterial thriade" concept in addition to classical "Virchov's thriade" or even that of "tetrade" will help pathophysiologists to better discriminate pathogenetical features of arterial thromboses vs the venous ones and for the clinical doctors to improve prophylaxis and treatment of these separate conditions.

Key words: venous thrombosis; arterial thrombosis; Virchow triad; COVID-19.

СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ О МЕХАНИЗМАХ АРТЕРИАЛЬНОГО ТРОМБОЗА. АРТЕРИАЛЬНЫЙ ТРОМБОЗ ПРИ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ

© Искандер Альбертович Латыпов[1], Сарнг Саналович Пюрвеев[1, 2], Михаил Сергеевич Некрасов[1], Николай Сергоевич Деданишвили[1], Наир Сабирович Тагиров[1]

[1] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2
[2] Институт экспериментальной медицины. 197022, г. Санкт-Петербург, ул. Академика Павлова, 12

Контактная информация: Сарнг Саналович Пюрвеев — старший лаборант кафедры патологической физиологии с курсом иммунопатологии. E-mail: dr.purveev@gmail.com ORCID ID: 0000-0002-4467-2269 SPIN: 5915-9767

Для цитирования: Латыпов И.А., Пюрвеев С.С., Некрасов М.С., Деданишвили Н.С., Тагиров Н.С. Современные представления о механизмах артериального тромбоза. Артериальный тромбоз при новой коронавирусной инфекции // Российские биомедицинские исследования. 2023. Т. 8. № 3. С. 61–68. DOI: https://doi.org/10.56871/RBR.2023.85.16.008

Поступила: 22.05.2023 **Одобрена: 17.07.2023** **Принята к печати: 21.09.2023**

Резюме. Сложные механизмы тромбообразования традиционно принято рассматривать в рамках так называемой патогенетической триады Вирхова: повреждение сосуда + гиперкоагуляция + замедление кровотока. Несмотря на многократные дополнения и усовершенствования данной концепции, ее суть оставалась прежней. Однако

эта трехчленная схема, более или менее применимая для объяснения патогенеза тромбообразования в венах, в классическом ее виде для артериальных тромбозов имеет ограниченное значение. В последнее время начали обсуждать несколько иную концепцию артериальной триады, включающую другие компоненты: 1 — стеноз артерии и ускорение кровотока, 2 — активация тромбоцитов и их взаимодействие с фактором фон Виллебранда (VWF), 3 — повреждение сосудистой стенки. Эта компоновка артериальной триады успешнее объясняет механизмы тромбообразования при стенозах артерий, в первую очередь, при атеросклерозе. С недавних пор также повысилось внимание к связи между заболеваемостью новой коронавирусной инфекцией (COVID-19) и повышением риска тромбообразования. Введение понятия «артериальная триада» в дополнение к «триаде Вирхова» или «тетраде» позволит патофизиологам лучше разделить патогенетические особенности артериальных и венозных тромбозов, а для клиницистов — профилактику и терапию этих состояний в отдельности.

Ключевые слова: венозный тромбоз; артериальный тромбоз; триада Вирхова; COVID-19.

The complex mechanisms of thrombosis have been commonly considered as part of the so-called classical Virchow triad, including: 1) vascular injury; 2) hypercoagulability and 3) slowing of blood flow. Despite repeated additions and improvements of this concept, its essence remained the same. Besides damage to the vascular wall, hypercoagulation is still considered to be one of the main elements of thrombosis. Activation of the coagulation link of hemostasis leads to fibrin filaments formation on vessel endothelial lining. In addition, platelet aggregates are more often found on the outer side of the clot and additionally contribute to its growth. Moreover, there are factors that increase blood clotting, they are congenital and acquired ones. Congenital factors include deficiencies of antithrombin III, protein C, protein S, as well as mutations of factors V (Leiden) and prothrombin 20210A. Acquired factors include surgery, trauma, cancer, medications (hormonal contraceptives), autoimmune diseases (lupus anticoagulant), prolonged bed rest, and so on. Processes which are close to neoplasia are also a typical example of acquired hypercoagulability [16, 26].

The relationship between slower blood flow and thrombosis has not yet been definitively elucidated. There are various hypotheses explaining how this factor may increase thrombosis. There is evidence that decreased blood flow velocity favors the accumulation of procoagulant proteins [4, 8]. Venous hyperemia and hypoxia induce inflammatory changes in the endothelium, release of reactive oxygen species and expression of cell adhesion molecules. In addition, hypoxia induces a complex of changes leading to a decrease in nitric oxide (NO) synthesis. However, it is worth noting that activation of thrombosis is largely driven by the release of tissue factor as a result of gross damage to the vascular endothelium. However, it is difficult to fully explain the mechanism of fibrin formation in the absence of endothelial damage. There is evidence that tissue factor expression is increased upon exposure to bacterial toxins as well as on the vascular endothelium of malignant tumors [5]. Nevertheless, no tissue factor expression has been found in microcirculation disorders only [5, 36].

An important factor affecting the hemostasis system is pregnancy. The balance of hemostasis is shifted towards physiological hypercoagulation to prevent major blood loss during delivery [1, 2, 25]. Pregnant women have increased activity of coagulation factors, decreased levels of protein S. Moreover, resistance of factor V to protein C is formed [20]. The fibrinolysis system is suppressed due to an increase in plasminogen activator inhibitor-1 (IAP-1), as well as the appearance of placental plasminogen activator inhibitor (IAP-2) [8, 25]. Decrease in the number of platelets is compensated by their increased activity. Similar effects are observed when taking outdated drugs of exogenous sex steroids in order to contracept, to obtain non-contraceptive effects or as perimenopausal therapy. The concentration of clotting factors increases, anticoagulants decrease, and acquired (or congenital) resistance of factor V to protein C occurs [3, 6].

Recently, the attention of researchers to von Willebrand factor (VWF) has increased [4, 14, 22] (Fig. 1), which enhances platelet fixation on fibrin filaments during blood flow disorders.

Anyway, Virchow's pathogenetic triad describes the mechanisms of venous clot formation quite well. These clots are predominantly composed of fibrin and erythrocytes. At the same time, when describing the pathogenesis of arterial thrombi,

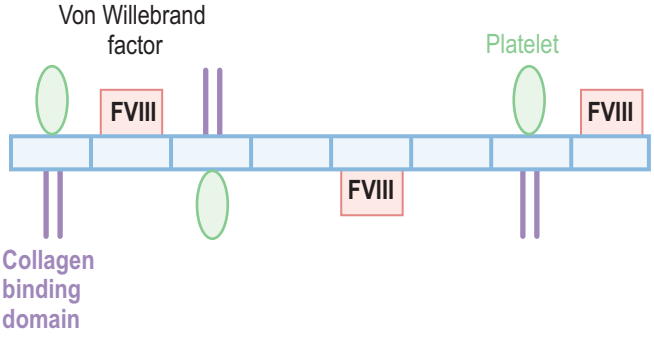


Fig. 1. Von Willebrand factor enhances platelet fixation on fibrin filaments

Virchow's triad is often not mentioned in its original form, or its interpretation differs from the original version. Thus, instead of the term "blood flow slowdown" or "stasis", the broader concept of "blood flow disturbance" is more often used [13].

It should be kept in mind that ideas resembling the arterial triad existed long before its modern description: "For some time scientists hoped to explain the interesting connection between kidney disease on the one hand and increased blood pressure and arteriolosclerosis on the other hand by the newly discovered properties of adrenaline" [5, 27]. More than 100 years ago, experts already noted the relationship between changes in blood flow as a result of vasospasm and thrombosis and the development of atherosclerosis, which often leads to the formation of large wall clots [27]. Accordingly, the doctrine of the arterial triad of thrombosis should not be considered unique and something completely new.

It may seem strange that hypercoagulability is less significant within arterial clotting: for example, the *20210A* gene mutation does not affect the risk of arterial thrombosis. However, it is associated with the risk of acute myocardial infarction and pregnancy complications [9, 14]. In any case, hypercoagulability, as interpreted by the classical Virchow triad, has much less influence on arterial clot formation.

In contrast to the two factors mentioned above, blood flow velocity occupies central role in the pathophysiology of arterial thrombosis. The effect of blood flow velocity is assessed by two parameters: *shear rate* and *shear stress*.

Shear rate is the rate at which neighboring fluid layers move in relation to each other. It is directly proportional to the blood flow velocity and inversely proportional to the vessel diameter. Accordingly, the higher the blood flow velocity and smaller the vessel diameter, the greater the value of shear rate [5].

Shear stress is the frictional force generated by the blood current along the endothelium of the vessel and directed along the blood flow.

In case of arterial vasoconstriction and corresponding increase in blood flow velocity, platelet hemostasis is activated, which, in turn, promotes the formation of "white" clot. VWF normally circulates in the blood in globular form as huge proteins (more than 20 000 kDa) and has a unique property to change its geometry when blood flow velocity increases. The factor spreads from its globular form and becomes filamentous, opening up hundreds of additional sites for binding to platelet receptors and their subsequent activation and aggregation. At high shear rates, VWF is capable of so-called *self-association* — the protein multimers begin to bind to each other as a result of A2 domain opening [3, 5]. Self-association leads to the formation of grid-like structures, which is an excellent place for platelet attachment and further clot growth.

It is worth mentioning that VWF is cut by the enzyme called ADAMTS-13 in the A2 domain to inhibit excessive platelet activity. When the enzyme is not active enough, less VWF is exposed to it, which, again, leads to an increased risk of thrombosis. In some cases, a condition called thrombotic thrombocytopenic purpura (TTP) occurs. TTP is a rare, acute, and life-threatening condition resulting from thrombocytopenia consumption in diffuse thrombosis processes in microvessels. As a consequence of mechanical intravascular hemolysis, non-immune hemolytic anemia occurs, as well as multi-organ failure. A key link in the pathogenesis of TTP is congenital or acquired ADAMTS-13 enzyme deficiency [13, 19, 28].

The conditions of clot formation in arterial vessels do not have an absolute correspondence to Virchow's triad in its classical interpretation. Several different components have been proposed to describe the pathogenesis of arterial thrombosis: 1) vessel stenosis, 2) endothelial damage, 3) prothrombotic processes (VWF and platelet activation, decreased ADAMTS-13 activity) [6, 21, 28]. We can say that this concept has a connection with Virchow's classical triad in terms of endothelial damage. The platelet response is undoubtedly one of the elements of arterial thrombogenesis and is to some extent equivalent to the presence of hypercoagulability in Virchow's triad (Fig. 2). In contrast to venous thrombosis, the presence of initially high platelet activity is not necessary for arterial clot formation.

Considering specifically arterial clotting, platelet activation with increased blood flow velocity in stenosed vessels should be assumed. Various types of erythrocyte pathology should also be taken into account. The new coronavirus infection COVID-19 [30] may cause the possible complications, as well as preventive vaccination against it [31] (Table 1). There are pathologic reactions that occur after administration of recombinant adenovirus vector [32, 39] and mRNA vaccines [33, 34]. These reactions include thrombocytopenia, thrombosis, and hemorrhage, and are associated with sex and age, life history, the vaccine administered, and concomitant use of other drugs. Thrombi are most often localized in the cerebral venous system. Women are most commonly affected [37]. The main risk factors are anticoagulant therapy, pregnancy, brain infections, head trauma, and use of medication contraceptives. Therefore, the use of Astrazeneca vaccine has been temporarily restricted in European countries [38, 39].

Understanding the pathogenesis of arterial and venous thrombosis has become particularly important in clinical practice after the COVID-19 pandemic, which, according to WHO, lasted from January 30, 2020, to May 5, 2023. According to various reports, the incidence of acute thrombosis as a complication of coronavirus infection ranged from 0.39% to 11.1% [7, 18, 24, 35].

The discovery of SARS-CoV-2 virus tropism to vascular endothelium [11, 12, 20] radically changed the approach to therapy of this infection. In general, when analyzing the literature data for 2020-2021, the association of the incidence of thrombosis as a complication of COVID-19 with gender

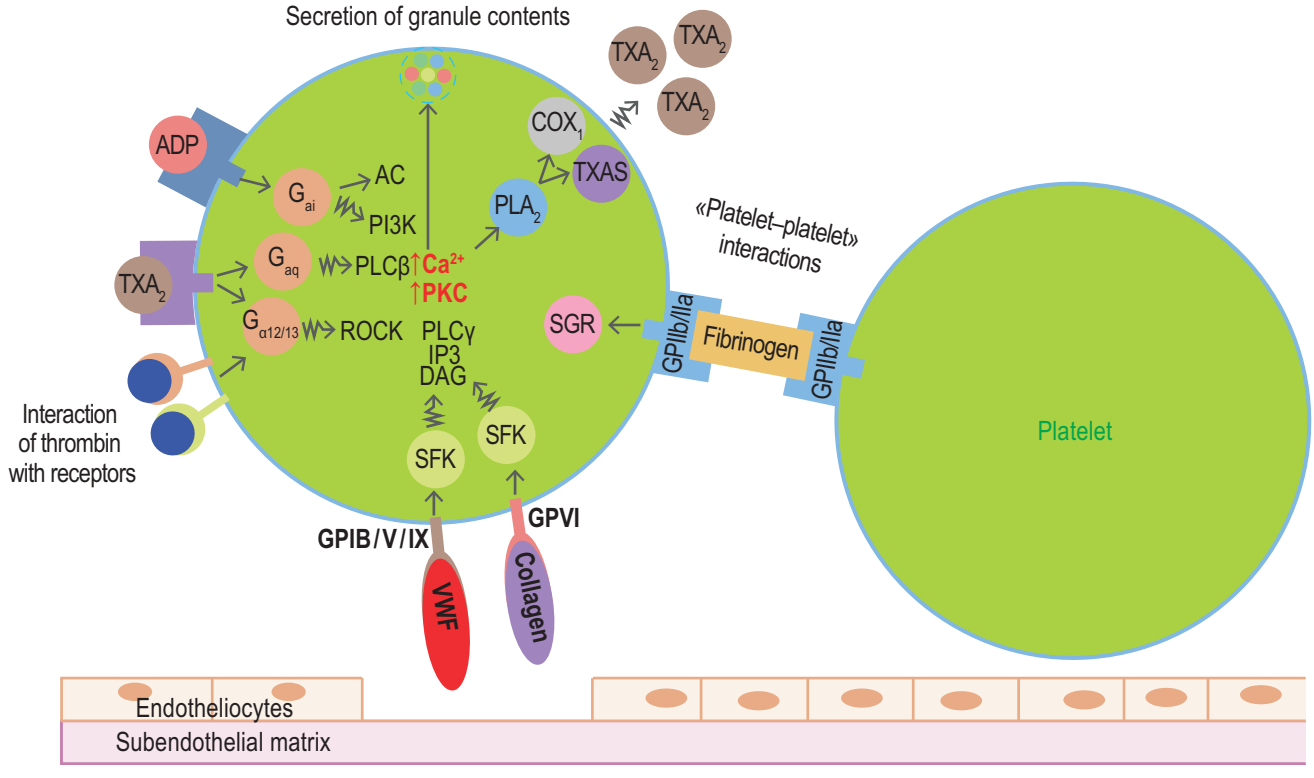


Fig. 2. **Schematic of platelet activation. ADP, adenosine diphosphate; TXA2, thromboxane A2; Gai, α subunit of G-protein; Gaq, αq subunit of G-protein; Gα12/13, α12/13 subunits of G-protein; AC, adenylate cyclase; PI3K, phosphoinositide-3-kinase; PLCβ, phospholipase C β; PLCγ, phospholipase C γ; PLA2, phospholipase A2; ROCK, Rho-associated protein kinase; IP3, inositol-3-phosphate; DAG, diacylglycerol; SFK, Src-family kinase; GP (IB, IIa, IIb V, VI, IX), glycoproteins; VWF, von Willebrand factor; SGR, small regulatory G-protein; COX1, cytochrome oxidase subunit 1; TXAS, thromboxane A synthase**

Table 1

Association of thrombosis with COVID-19 vaccination

Vaccine	Number of patients	Type of vaccine	Age	Women, %	Venous sinus thrombosis, %	Mortality, %
Astrazeneca [32]	11	Vector	22–49	18%	82%	55%
Moderna [33]	23	mRNA	21–77	61%	57%	30%
Pfizer [34]	19	mRNA	20–89	63%	58%	5%

and age is revealed. Men over 50 y.o. are significantly more prone to thrombosis. However, the mortality rate due to acute thrombosis is many times and sometimes 10 times higher in women [7, 17, 23, 29, 37].

The correlation between risks of thrombosis and severity of the disease remains a matter of debate. According to numerous data [18, 25, 29], thrombosis is more likely to develop in moderate and severe course of infection. However, some sources report that thrombosis also occurs in the mild course of COVID-19 [28]. Criteria for assessing severity may vary not only between countries but also between physicians themselves. It is quite possible that thrombosis in the mild course of infection was an isolated incident and not reliably associated with the severity of the disease course. In addition, there are no reliably identified cases of thrombosis in outpatients. This could be attributed to various factors: death of patients from other causes, development of acute thrombosis as iatrogenic complications (which are more likely to occur in inpatient care rather than outpatient care), and asymptomatic course and spontaneous resolution of thrombosis during recovery. In general, the development of coagulopathies at any severity of coronavirus infection is associated with a significant increase in D-dimer levels [15, 18, 24]. Meanwhile, studies of platelet levels, activated partial thromboplastin time (APTT) and

prothrombin time (PTT) did not reveal statistically significant changes, which suggests a different mechanism of COVID-associated coagulopathies.

There is evidence that SARS-CoV-2 particles are capable to adhere to erythropoiesis precursor cells [7, 28, 35]. Erythroid cells showed significant expression of arginases and reactive oxygen species exerting a damaging effect on the endothelium. The virus is able to penetrate erythrocytes, leaving S1 spike proteins, CD147 receptors and band 3 transmembrane proteins on their surface. In general, these changes lead to a decrease in erythrocyte ATP activity, impaired erythrocyte deformability and consequently tissue hypoxia, which can lead to hypercoagulability. Shear stress increases, VWF activity rises, which, as described above, enhances thrombosis even more. As a result, erythrocyte adhesion to the endothelium increases, and huge VWF multimers attach, which initiates blood stasis [10, 14].

Analyzing the data on venous and arterial thromboses, it is possible to distinguish them as complications of the new coronavirus infection. Taking into account the above mentioned, it is possible to put forward the question whether thromboses in COVID-19 are a new form of pathologic processes that unite both components of Virchow's triad and arterial triad. Perhaps it even makes sense to identify a new pathogenetic chain of thrombosis in form of a tetrad rather than a triad, including hypercoagulability, decreased or increased blood flow velocity, endothelial damage, and platelet activation, which we would suggest labeling as the "Virchow tetrad" (Fig. 3).

CONCLUSION

Presumably, a new interpretation of the pathophysiologic patterns of thrombosis will allow clinicians to take a closer look at the tactics of treatment of arterial thrombosis, including those associated with COVID-19. In any case, the introduction of the concept of "arterial triad" in addition to the "Virchow triad" or "tetrad" instead of it will allow pathophysiologists to separate pathogenetic features of arterial and venous thrombosis better. As for clinicians, it will help to prevent and treat these conditions separately.

ADDITIONAL INFORMATION

Author 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.

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

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования

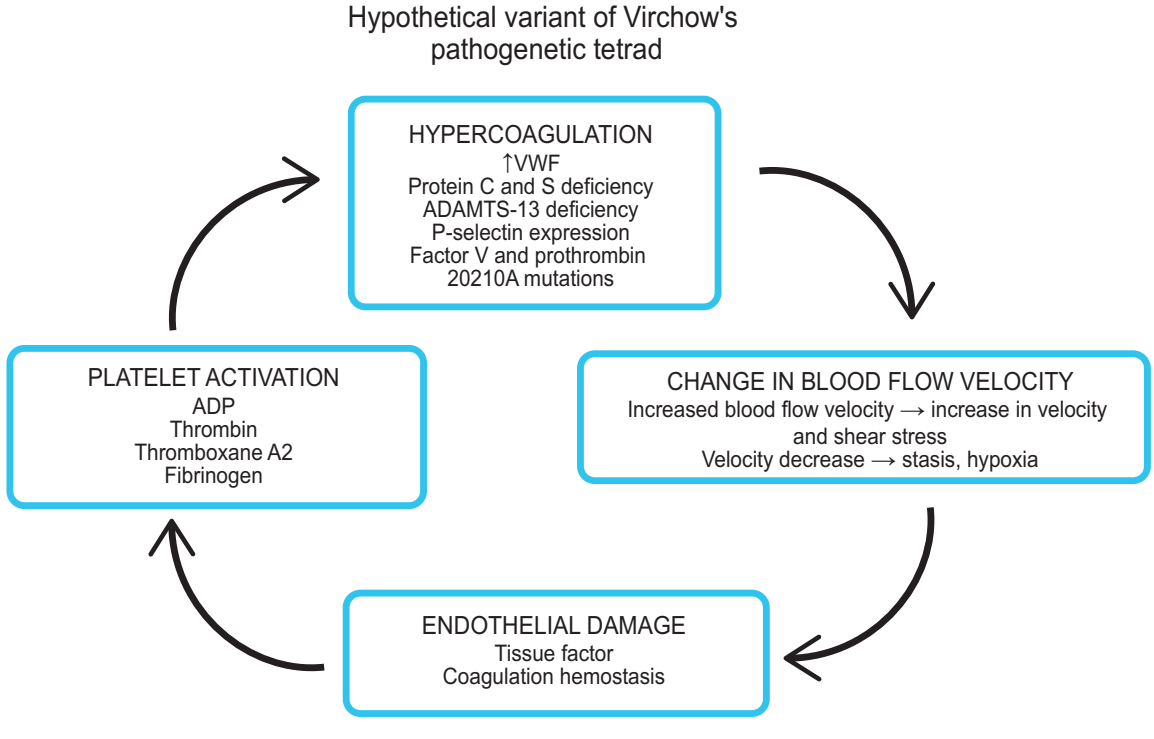


Fig. 3. Hypothetical variant of the scheme of thrombosis formation within the framework of pathogenetic "tetrad"

и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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.

REFERENCES

1. Vasil`ev A.G., Komyakov B.K., Tagirov N.S., Musaev S.A. Chreskozhnaya nefrolitotripsiya v lechenii korallovidnogo nefrolitiaza. [Percutaneous nephrolithotripsy in the treatment of staghorn nephrolithiasis] Vestnik Sankt-Peterburgskoj gosudarstvennoj meditsinskoj akademii im. I.I. Mechnikova. 2009; 4(33): 183–186. (in Russian).
2. Vasina L.V., Vlasov T.D., Petrishhev N.N. Funktsional`naya geterogennost` e`ndoteliya (obzor) [Functional heterogeneity of the endothelium (review)]. Arterial`naya gipertenziya. 2017; 23(2): 88–102. (in Russian).
3. Vlasov T.D., Petrischev N.N., Lazovskaya O.A. Disfunktsiya endoteliya. Pravil`no li my` ponimaem e`tot termin? Vestnik anesteziologii i reanimatologii. 2020; 17(2): 76–84.
4. Vlasov T.D., Yashin S.M. Arterial'nye i venoznye trombozy. Vsegda li primenima triada Virhova? [Arterial and venous thromboses. Is Virchow's triad always applicable?]. Regionarnoe krovoobrashchenie i mikrocirkuljacija. 2022; 21(1): 78–86. (in Russian).
5. Gagun V.E., Luk'janov N.G., Osmanov Z.A. Retrospektivnyj analiz chastoty arterial'nyh trombozov, associirovannyh s virusom SARS-CoV-2. [Retrospective analysis of the frequency of arterial thrombosis associated with the SARS-CoV-2 virus]. Izvestija Rossijskoj voenno-medicinskoj akademii. 2022; 41(2): 103–107. (in Russian).
6. Dutova T.I., Banin I.N., Sazonov I.E. i dr. Geneticheski determinirovannaja predraspolozhennost' k razvitiju sosudistoj katastrofy: est' li svjaz' s tjazhelym techeniem novoj koronavirusnoj infekcii COVID-19? [Genetically determined predisposition to the development of vascular catastrophe: is there a connection with the severe course of the new coronavirus infection COVID-19?]. Tromboz, gemostaz i reologija. 2023; 1: 12–22. (in Russian).
7. Kruchinina M.V., Gromov A.A., Logvinenko I.I., Kruchinina E.V. Izmenenija kletok krasnoj krovi, svjazannye s razvitiem serdechno-sosudistyh oslozhnenij, u pacientov s koronavirusnoj infekciej COVID-19. [Changes in red blood cells associated with the development of cardiovascular complications in patients with coronavirus infection COVID-19]. Ateroskleroz. 2023; 19(1): 35–46. (in Russian).
8. Magamedov I.D., Pivovarova L.P., Noxrin S.P. i dr. Klinicheskij sluchaj ostroj ishemii nizhnih konechnostej, associirovannoj s novoj koronavirusnoj infektsiej COVID-19. [A clinical case of acute ischemia of the lower extremities associated with a new coronavirus infection COVID-19]. Dzhanelidzevskie chteniya — 2023: Sbornik nauchny`kh trudov nauchno-prakticheskoj konferentsii, Sankt-Peterburg, 01–03 marta 2023 goda. Sankt-Peterburg: Gosudarstvennoe byudzhetnoe uchrezhdenie "Sankt-Peterburgskij nauchno-issledovatel`skij institut skoroj pomoschi im. I.I. Dzhanelidze", 2023; 103–105. (in Russian).
9. Mukanova A.D., Mukanova A.D., Erekesh A. A.i dr. D-dimer — potencial'nyj biomarker tiazhesti COVID-19. [D-dimer is a potential biomarker for COVID-19 severity]. Farmacija Kazahstana. 2021; 5: 17–21. (in Russian).
10. Tagirov N.S., Nazarov T.X., Vasil`ev A.G., Lichtschanghof A.Z., Lazarenko I.B., Madzhidov S.A., Ahmedov M.A. Opy`t primeneniya chreskozhnoj nefrolitotripsii i kontaktnoj ureterolitotripsii v kompleksnom lechenii mochekamennoj bolezni. [Experience in the use of percutaneous nephrolithotripsy and contact ureterolithotripsy in the complex treatment of urolithiasis]. Profilakticheskaya i klinicheskaya medicina. 2012; 4(45): 30–33. (in Russian).
11. Trashkov A.P., Brus T.V., Vasil`ev A.G., Artemenko M.R., Pechatnikova V.A., Gumennaya M.A. Bioximicheskij profil` kry`s s nealkogol`noj zhirovoj bolezn`yu pecheni razlichnoj stepeni tyazhesti i ego korrekciya preparatom Remaksol. [Biochemical profile of rats with non-alcoholic fatty liver disease of varying severity and its correction with Remaxol]. Pediatr. 2017; 8(4): 78–85. (in Russian).
12. Hajcev N.V., Vasil`ev A.G., Trashkov A.P., Kravtsova A.A., Balashov L.D. Vliyanie vozrasta i pola na harakter otvetny`h reakcij bely`h kry`s pri dejstvii hronicheskoj gipoksicheskoj gipoksii [Influence of age and sex on the nature of response reactions of white rats under the action of chronic hypoxic hypoxia]. Pediatr. 2015; 6(2): 71–77. (in Russian).
13. Abou-Ismail M.Y., Citla Sridhar D., Nayak L. Estrogen and thrombosis: A bench to bedside review. Thromb Res. 2020; 192: 40–51.
14. Alam W. COVID-19 vaccine-induced immune thrombotic thrombocytopenia: A review of the potential mechanisms and proposed management. Sci Prog. 2021; 104(2): DOI: 10.1177/00368504211025927.
15. Al-Ali D., Elshafeey A., Mushannen M. et al. Cardiovascular and haematological events post COVID-19 vaccination: A systematic review. J Cell Mol Med. 2022; 26(3): 636–653.
16. Ali MAM, Spinler S.A. COVID-19 and thrombosis: From bench to bedside. Trends Cardiovasc Med. 2021; 31(3): 143–160.
17. Bank I., Libourel E.J., Middeldorp S. et al. Prothrombin 20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Archives of Internal Medicine. 2004; 164(17): 1932–1937. DOI: 10.1001/archinte.164.17.
18. Bank I., Libourel E.J., Middeldorp S. et al. Elevated levels of FVIII:C within families are associated with an increased risk for venous and arterial thrombosis. Journal of Thrombosis and Haemostasis. 2003; (3): 79–84.
19. Bennett P.C., Silverman S.H., Gill P.S. et al. Peripheral arterial disease and Virchow's triad. Thrombosis and Haemostasis. 2009; 101(6): 1032–1040. DOI: 10.1160/TH08-08-0518.
20. Brill A. Multiple Facets of Venous Thrombosis. Int J Mol Sci. 2021; 22(8): 3853.
21. Bilotta C., Perrone G., Adelfio V. et al. COVID-19 Vaccine-Related Thrombosis: A Systematic Review and Exploratory Analysis. Front Immunol. 2021; 12:729251. DOI: 10.3389/fimmu.2021.729251.

22. Bjarne Osterud, Eirik Bjorklid. Tissue factor in blood cells and endothelial cells. Frontiers in Bioscience (Elite Edition). 2012; 4(1): 289–299. DOI: 10.2741/e376.
23. Dr. Adolf Strumpell, Lehrbuch der speciel'en Pathologie und Therapie der inneren Krankheiten. Neunzehnte vielvach cerbesserte und vermehrte Auflage. Erster Band. Leipzig. 1914.
24. Furie K.L., Cushman M., Elkind M.S.V. et al. American Heart Association/American Stroke Association Stroke Council Leadership. Diagnosis and Management of Cerebral Venous Sinus Thrombosis With Vaccine-Induced Immune Thrombotic Thrombocytopenia. Stroke. 2021; 52(7): 2478–2482. DOI: 10.1161/STROKEAHA.121.035564.
25. Gonzalez-Fajardo J.A., Ansuategui M., Romero C. et al. Mortality of COVID-19 patients with vascular thrombotic complications. Med Clin (Engl Ed). 2021; 156(3): 112–117.
26. Greinacher A., Thiele T., Warkentin T.E. et al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med. 2021; 384(22): 2092–2101.
27. Malik B., Kalantary A., Rikabi K. et al. Pulmonary embolism, transient ischaemic attack and thrombocytopenia after the Johnson & Johnson COVID-19 vaccine. BMJ Case Reports. 2021; 14(7): e243975. Published 2021 Jul 14. DOI: 10.1136/bcr-2021-243975.
28. Iba T., Levy J.H. Thrombosis and thrombocytopenia in COVID-19 and after COVID-19 vaccination. Trends Cardiovasc Med. 2022; 32(5): 249–256.
29. Pyurveev S.S., Sizov V.V., Lebedev A.A. et al. Registration of Changes in the Level of Extracellular Dopamine in the Nucleus Accumbens by Fast-Scan Cyclic Voltammetry during Stimulation of the Zone of the Ventral Tegmental Area, Which Also Caused a Self-Stimulation. Journal of Evolutionary Biochemistry and Physiology. 2022; 58(5): 1613–1622.
30. Sadler J.E. Pathophysiology of thrombotic thrombocytopenic purpura. Blood. 2017; 130(10): 1181–1188.
31. Sastry S., Cuomo F., Muthusamy J. COVID-19 and thrombosis: The role of hemodynamics. Thromb Res. 2022; (212): 51–57.
32. Sahu K.K., Borogovac A., Cerny J. COVID-19 related immune hemolysis and thrombocytopenia. J Med Virol. 2021; 93(2): 1164–1170.
33. Scully M., Singh D., Lown R. et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021; 384(23): 2202–2211. DOI: 10.1056/NEJMoa2105385.
34. Shankaran H., Alexandridis P., Neelamegham S. Aspects of hydrodynamic shear regulating shear-induced platelet activation and self-association of von Willebrand factor in suspension. Blood. 2003; 101(7): 2637–45.
35. Silvis S.M., de Sousa D.A., Ferro J.M. et al. Cerebral venous thrombosis. Nature Reviews. Neurology. 2017; 13(9): 555–565. DOI: 10.1038/nrneurol.2017.104.
36. Tsygan N.V., Trashkov A.P., Litvinenko I.V. et al. Autoimmunity in acute ischemic stroke and the role of blood-brain barrier: the dark side or the light one? Frontiers of Medicine. 2019. 13(4): 420–426.
37. Veyre F., Poulain-Veyre C., Esparcieux A. et al. Femoral Arterial Thrombosis in a Young Adult after Nonsevere COVID-19. Ann Vasc Surg. 2020; 69: 85–88. DOI: 10.1016/j.avsg.2020.07.013.
38. Wells P.S., Anderson D.R., Rodger M. et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003; 349(13): 1227–1235. DOI: 10.1056/NEJMoa023153.
39. Wool G.D., Miller J.L. The Impact of COVID-19 Disease on Platelets and Coagulation. Pathobiology. 2021; 88(1): 15–27.

ЛИТЕРАТУРА

1. Васильев А.Г., Комяков Б.К., Тагиров Н.С., Мусаев С.А. Чрескожная нефролитотрипсия в лечении коралловидного нефролитиаза. Вестник Санкт-Петербургской государственной медицинской академии им. И.И. Мечникова. 2009. 4(33): 183–186.
2. Васина Л.В., Власов Т.Д., Петрищев Н.Н. Функциональная гетерогенность эндотелия (обзор). Артериальная гипертензия. 2017; 23(2): 88–102.
3. Власов Т.Д., Петрищев Н.Н., Лазовская О.А. Дисфункция эндотелия. Правильно ли мы понимаем этот термин? Вестник анестезиологии и реаниматологии. 2020; 17(2): 76–84.
4. Власов Т.Д., Яшин С.М. Артериальные и венозные тромбозы. Всегда ли применима триада Вирхова? Регионарное кровообращение и микроциркуляция. 2022; 21(1): 78–86.
5. Гагун В.Э., Лукьянов Н.Г., Османов З.А. Ретроспективный анализ частоты артериальных тромбозов, ассоциированных с вирусом SARS-CoV-2. Известия Российской военно-медицинской академии. 2022; 41(S2): 103–107.
6. Дутова Т.И., Банин И.Н., Сазонов И.Э. и др. Генетически детерминированная предрасположенность к развитию сосудистой катастрофы: есть ли связь с тяжелым течением новой коронавирусной инфекции COVID-19? Тромбоз, гемостаз и реология. 2023; 1: 12–22.
7. Кручинина М.В., Громов А.А., Логвиненко И.И., Кручинина Э.В. Изменения клеток красной крови, связанные с развитием сердечно-сосудистых осложнений, у пациентов с коронавирусной инфекцией COVID-19. Атеросклероз. 2023; 19(1): 35–46.
8. Магамедов И.Д., Пивоварова Л.П., Нохрин С.П. и др. Клинический случай острой ишемии нижних конечностей, ассоциированной с новой коронавирусной инфекцией COVID-19. Джанелидзевские чтения — 2023: Сборник научных трудов научно-практической конференции, Санкт-Петербург, 01–03 марта 2023 года. Санкт-Петербург: Государственное бюджетное учреждение «Санкт-Петербургский научно-исследовательский институт скорой помощи им. И.И. Джанелидзе», 2023. 103–105.
9. Муканова А.Д., Муканова А.Д., Ерекеш А.А. и др. D-димер — потенциальный биомаркер тяжести COVID-19. Фармация Казахстана. 2021; 5: 17–21.
10. Тагиров Н.С., Назаров Т.Х., Васильев А.Г., Лихтшангоф А.З., Лазаренко И.Б., Маджидов С.А., Ахмедов М.А. Опыт применения чрескожной нефролитотрипсии и контактной уретеролитотрипсии в комплексном лечении мочекаменной болезни. Профилактическая и клиническая медицина. 2012. 4(45): 30–33.
11. Трашков А.П., Брус Т.В., Васильев А.Г., Артеменко М.Р., Печатникова В.А., Гуменная М.А. Биохимический профиль крыс с неалкогольной жировой болезнью печени различной степени

тяжести и его коррекция препаратом Ремаксол. Педиатр. 2017. 8(4): 78–85.
12. Хайцев Н.В., Васильев А.Г., Трашков А.П., Кравцова А.А., Балашов Л.Д. Влияние возраста и пола на характер ответных реакций белых крыс при действии хронической гипоксической гипоксии. Педиатр. 2015. 6(2): 71–77.
13. Abou-Ismail M.Y., Citla Sridhar D., Nayak L. Estrogen and thrombosis: A bench to bedside review. Thromb Res. 2020; 192: 40–51.
14. Alam W. COVID-19 vaccine-induced immune thrombotic thrombocytopenia: A review of the potential mechanisms and proposed management. Sci Prog. 2021; 104(2): DOI: 10.1177/00368504211025927.
15. Al-Ali D., Elshafeey A., Mushannen M. et al. Cardiovascular and haematological events post COVID-19 vaccination: A systematic review. J Cell Mol Med. 2022; 26(3): 636–653.
16. Ali MAM, Spinler S.A. COVID-19 and thrombosis: From bench to bedside. Trends Cardiovasc Med. 2021; 31(3): 143–160.
17. Bank I., Libourel E.J., Middeldorp S. et al. Prothrombin 20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Archives of Internal Medicine. 2004; 164(17): 1932–1937. DOI: 10.1001/archinte.164.17.
18. Bank I., Libourel E.J., Middeldorp S. et al. Elevated levels of FVIII:C within families are associated with an increased risk for venous and arterial thrombosis. Journal of Thrombosis and Haemostasis. 2003; (3): 79–84.
19. Bennett P.C., Silverman S.H., Gill P.S. et al. Peripheral arterial disease and Virchow's triad. Thrombosis and Haemostasis. 2009; 101(6): 1032–1040. doi: 10.1160/TH08-08-0518
20. Brill A. Multiple Facets of Venous Thrombosis. Int J Mol Sci. 2021; 22(8): 3853
21. Bilotta C., Perrone G., Adelfio V. et al. COVID-19 Vaccine-Related Thrombosis: A Systematic Review and Exploratory Analysis. Front Immunol. 2021; 12:729251. DOI: 10.3389/fimmu.2021.729251.
22. Bjarne Osterud, Eirik Bjorklid. Tissue factor in blood cells and endothelial cells. Frontiers in Bioscience (Elite Edition). 2012; 4(1): 289–299. DOI: 10.2741/e376.
23. Dr. Adolf Strumpell, Lehrbuch der speciel'en Pathologie und Therapie der inneren Krankheiten. Neunzehnte vielvach cerbesserte und vermehrte Auflage. Erster Band. Leipzig. 1914.
24. Furie K.L., Cushman M., Elkind M.S.V. et al. American Heart Association/American Stroke Association Stroke Council Leadership. Diagnosis and Management of Cerebral Venous Sinus Thrombosis With Vaccine-Induced Immune Thrombotic Thrombocytopenia. Stroke. 2021; 52(7): 2478–2482. DOI: 10.1161/STROKEAHA.121.035564.
25. Gonzalez-Fajardo J.A., Ansuategui M., Romero C. et al. Mortality of COVID-19 patients with vascular thrombotic complications. Med Clin (Engl Ed). 2021; 156(3): 112–117.
26. Greinacher A., Thiele T., Warkentin T.E. et al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med. 2021; 384(22): 2092–2101.
27. Malik B., Kalantary A., Rikabi K. et al. Pulmonary embolism, transient ischaemic attack and thrombocytopenia after the Johnson & Johnson COVID-19 vaccine. BMJ Case Reports. 2021; 14(7): e243975. Published 2021 Jul 14. DOI: 10.1136/bcr-2021-243975.
28. Iba T., Levy J.H. Thrombosis and thrombocytopenia in COVID-19 and after COVID-19 vaccination. Trends Cardiovasc Med. 2022; 32(5): 249–256.
29. Pyurveev S.S., Sizov V.V., Lebedev A.A. et al. Registration of Changes in the Level of Extracellular Dopamine in the Nucleus Accumbens by Fast-Scan Cyclic Voltammetry during Stimulation of the Zone of the Ventral Tegmental Area, Which Also Caused a Self-Stimulation. Journal of Evolutionary Biochemistry and Physiology. 2022; 58(5): 1613–1622.
30. Sadler J.E. Pathophysiology of thrombotic thrombocytopenic purpura. Blood. 2017; 130(10): 1181–1188.
31. Sastry S., Cuomo F., Muthusamy J. COVID-19 and thrombosis: The role of hemodynamics. Thromb Res. 2022; (212): 51–57.
32. Sahu K.K., Borogovac A., Cerny J. COVID-19 related immune hemolysis and thrombocytopenia. J Med Virol. 2021; 93(2): 1164–1170.
33. Scully M., Singh D., Lown R. et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021; 384(23): 2202–2211.
34. Shankaran H., Alexandridis P., Neelamegham S. Aspects of hydrodynamic shear regulating shear-induced platelet activation and self-association of von Willebrand factor in suspension. Blood. 2003; 101(7): 2637–45.
35. Silvis S.M., de Sousa D.A., Ferro J.M. et al. Cerebral venous thrombosis. Nature Reviews. Neurology. 2017; 13(9): 555–565. DOI: 10.1038/nrneurol.2017.104.
36. Tsygan N.V., Trashkov A.P., Litvinenko I.V. et al. Autoimmunity in acute ischemic stroke and the role of blood-brain barrier: the dark side or the light one? Frontiers of Medicine. 2019; 13(4): 420–426.
37. Veyre F., Poulain-Veyre C., Esparcieux A. et al. Femoral Arterial Thrombosis in a Young Adult after Nonsevere COVID-19. Ann Vasc Surg. 2020; 69: 85–88.
38. Wells P.S., Anderson D.R., Rodger M. et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003; 349(13): 1227–1235. DOI: 10.1056/NEJMoa023153.
39. Wool G.D., Miller J.L. The Impact of COVID-19 Disease on Platelets and Coagulation. Pathobiology. 2021; 88(1): 15–27.

UDC 617.58-005.4-036.11-089.844+616.98+616.13-008.64+615.273.53+578.834.1
DOI: 10.56871/RBR.2023.44.71.009

COVID-19 IN PATIENTS WITH ACUTE LIMB ISCHEMIA

© Arshed A. Kuchay[1, 2], Alexander N. Lipin[2, 3], Natalia R. Karelina[1], Nikita N. Gruzdev[2], Kirill A. Atmatzas[2], Linard Yu. Artyukh[1], Olga Yu. Smirnowa[1], Anna V. Zaicheva[1]

[1] Saint Petersburg State Pediatric Medical University. Lithuania 2, Saint Petersburg, Russian Federation, 194100

[2] Limb Salvage Center, City Hospital № 14. Kosinova str., 19/9, Saint Petersburg, Russian Federation, 198099

[3] Military Medical Academy named after S.M. Kirov. Akademician Lebedeva st., 6, Saint Petersburg, Russian Federation, 194044

Contact information: Arshed A. Kuchay — cardiovascular surgeon, clinical researcher of the City Limb Salvage Center, Senior lecturer at the department of human anatomy SPbSPMU. E-mail: drarshedcvs@gmail.com ORCID ID: 0000-0002-7974-9369

For citation: Kuchay AA, Lipin AN, Karelina NR, Gruzdev NN, Atmatzas KA, Artyukh LYu., Smirnowa OYu, Zaicheva AV. COVID-19 in patients with acute limb ischemia // Russian biomedical research (St. Petersburg). 2023; 8(3): 69-75. DOI: https://doi.org/0000000000000

Received: 19.05.2023 **Revised: 06.07.2023** **Accepted: 21.09.2023**

Abstract. ***Introduction.*** Acute limb ischemia (ALI) is defined as an abrupt decrease in arterial perfusion of a limb with a threat to viability of the limb. Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2, and has been declared as a global pandemic by the World Health Organization. Infection with SARS-CoV-2 has been shown to have a wide range of clinical presentations from asymptomatic in a large percentage of patients to devastating pulmonary failure, sepsis, and death. Patients with COVID-19 have deranged blood coagulation parameters and are prone to thrombo-embolic events. This hypercoagulable state caused by COVID-19 mainly manifests as venous thromboembolism. Peripheral arterial involvement is less frequent. We present 3 cases of a spontaneous ALI in a COVID-19 patient. ***Case.*** A 62-year-old man with an insignificant past medical history presented with ALI 12 days after an initial diagnosis of COVID-19. He was on therapeutic doses of low molecular weight heparin when ischemic symptoms developed. A surgical thrombectomy was unsuccessful. He partially benefited from intravenous unfractionated heparin and iloprost infusions. He was discharged home on postoperative day 14, and is scheduled to have an amputation of the 1st toe. ***Conclusions.*** COVID-19 infection is associated with an increased incidence of thromboembolic events, including ALI. Even young and otherwise healthy patients may develop ALI despite the use of prophylactic anticoagulation. Management of ALI in COVID-19 patients might be harder than expected, due to the hypercoagulable state. Patients may benefit from prolonged post-operative unfractionated heparin administration.

Key words: acute limb ischemia: coronavirus disease 2019; low molecular weight heparin; severe acute respiratory syndrome coronavirus-2; thrombectomy; unfractionated heparin.

COVID-19 У ПАЦИЕНТОВ С ОСТРОЙ ИШЕМИЕЙ КОНЕЧНОСТЕЙ

© Аршед Ахмад Кучай[1, 2], Александр Николаевич Липин[2, 3], Наталья Рафаиловна Карелина[1], Никита Николаевич Груздев[2], Кирилл Александрович Атмадзас[2], Линард Юрьевич Артюх[1], Ольга Юрьевна Смирнова[1], Анна Валерьевна Зайцева[1]

[1] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

[2] Городская больница № 14. 198099, г. Санкт-Петербург, ул. Косинова, 19/9

[3] Военно-медицинская академия им. С.М. Кирова. 194044, г. Санкт-Петербург, ул. Академика Лебедева, 6

Контактная информация: Аршед Ахмад Кучай — врач сердечно-сосудистый хирург, клинический исследователь Городского центра спасения конечностей, старший преподаватель кафедры анатомии человека СПбГПМУ. E-mail: drarshedcvs@gmail.com
ORCID ID: 0000-0002-7974-9369

Для цитирования: Кучай А.А., Липин А.Н., Карелина Н.Р., Груздев Н.Н., Атмадзас К.А., Артюх Л.Ю., Смирнова О.Ю., Зайцева А.В. COVID-19 у пациентов с острой ишемией конечностей // Российские биомедицинские исследования. 2023. Т. 8. № 3. С. 69–75. DOI: https://doi.org/10.56871/RBR.2023.44.71.009

Поступила: 19.05.2023 **Одобрена: 06.07.2023** **Принята к печати: 21.09.2023**

Резюме. Острую ишемию конечностей можно определить как резкое снижение артериальной перфузии конечности с угрозой ее жизнеспособности. Коронавирусная инфекция 2019 года (COVID-19) вызвана тяжелым острым респираторным синдромом коронавируса 2. Она объявлена Всемирной организацией здравоохранения глобальной пандемией. Было показано, что инфекция SARS-CoV-2 имеет широкий спектр клинических проявлений: от бессимптомного течения у большого процента пациентов до легочной недостаточности, сепсиса и смерти. Пациенты с COVID-19 имеют нарушения показателей свертываемости крови и склонны к тромбоэмболическим осложнениям. Это состояние гиперкоагуляции, вызванное COVID-19, в основном проявляется как венозная тромбоэмболия. Поражение периферических артерий встречается реже. Представляем три случая спонтанной острой ишемии конечностей у пациента с COVID-19.

Ключевые слова: острая ишемия конечностей; коронавирусная болезнь 2019; низкомолекулярный гепарин; коронавирус-2 с тяжелым острым респираторным синдромом; тромбэктомия; нефракционированный гепарин.

INTRODUCTION

Acute limb ischemia (ALI) is defined as an abrupt decrease in arterial perfusion of a limb with a threat to viability of the limb [1]. The clinical presentation is considered to be acute if symptom duration is less than 2 weeks [1]. The most common causes include embolism from cardiac chambers mainly associated with atrial fibrillation or acute myocardial infarction, embolism from arterial aneurysms, thrombosis of native limb arteries or vascular grafts, iatrogenic thromboembolism during vascular interventions, aortic dissection, and traumatic vascular injuries [1].

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and has been declared as a global pandemic by the World Health Organization [2]. Several reports revealed that patients with COVID-19 have deranged blood coagulation parameters and are prone to thromboembolic events [2–5]. This hypercoagulable state caused by COVID-19 is associated with poor overall prognosis, and mainly manifests as venous thromboembolism (VTE) [4, 5]. Peripheral arterial involvement is less frequent [2, 5].

Herein we present 3 cases of a spontaneous ALI in a COVID-19 patient.

CLINICAL CASE 1

A 62-year-old man presented to the emergency room with complaints of fever, nausea, fatigue and muscle aches. His past medical history was insignificant. Body temperature was 36.7 °C, pulse rate 82 beats per minute, respiratory rate 24 breathes per minute, blood pressure 125/72 mmHg, and oxygen saturation 95%. There were bilateral diffuse fine crackles on auscultation. Laboratory findings were normal except for a D-dimer level of 670 ng/ml (normal range < 500 ng/ml) (Table 1). A computed tomography (CT) scan of the chest revealed bilateral ground-glass opacities (Fig. 1). A swab test result came back positive for COVID-19, and the patient was discharged home on favipiravir, hydroxychloroquine and low-dose subcutaneous enoxaparin.

Table 1

Laboratory findings at initial diagnosis (day 0), hospitalization (day 5), discharge (day 10), re-hospitalization for acute limb ischemia (day 12)

Таблица 1

Результаты лабораторных исследований при первоначальном диагнозе (0-й день), госпитализации (5-й день), выписке (10-й день), повторной госпитализации при острой ишемии конечностей (12-й день)

Parameters	Day 0	Day 5	Day 10	Day 12	Normal range
White blood cell, 10^3/μL	12.4	16	19.6	20.5	4–11
Neutrophil count, 10^3/μL	10.2	12.6	15.2	16.4	2–7
Lymphocyte count, 10^3/μL	1.2	1.4	1.6	2.5	1–3
Platelet count, 10^3/μL	269	306	422	374	100–450
Hemoglobin, g/dL	13.7	14	13.3	11	14–18
Prothrombin time, seconds	15.5	15.1	12.5	12.6	11.5–15.5
Partial thromboplastin time, seconds	23.1	26.2	23.2	22.8	23.5–35
C-reactive protein, mg/dl	0.78	15.4	7.34	13.38	< 0.5
D-dimer, ng/mL	670	950	590	–	< 500
Fibrinogen, mg/dL	280	315	172	–	200–400
Lactate dehydrogenase, IU/L	109	1276	1045	–	0–250
Creatine kinase, IU/L	22	386	103	398	30–200
Serum creatinine, mg/dL	1.14	1.39	1.34	3.54	0.67–1.17

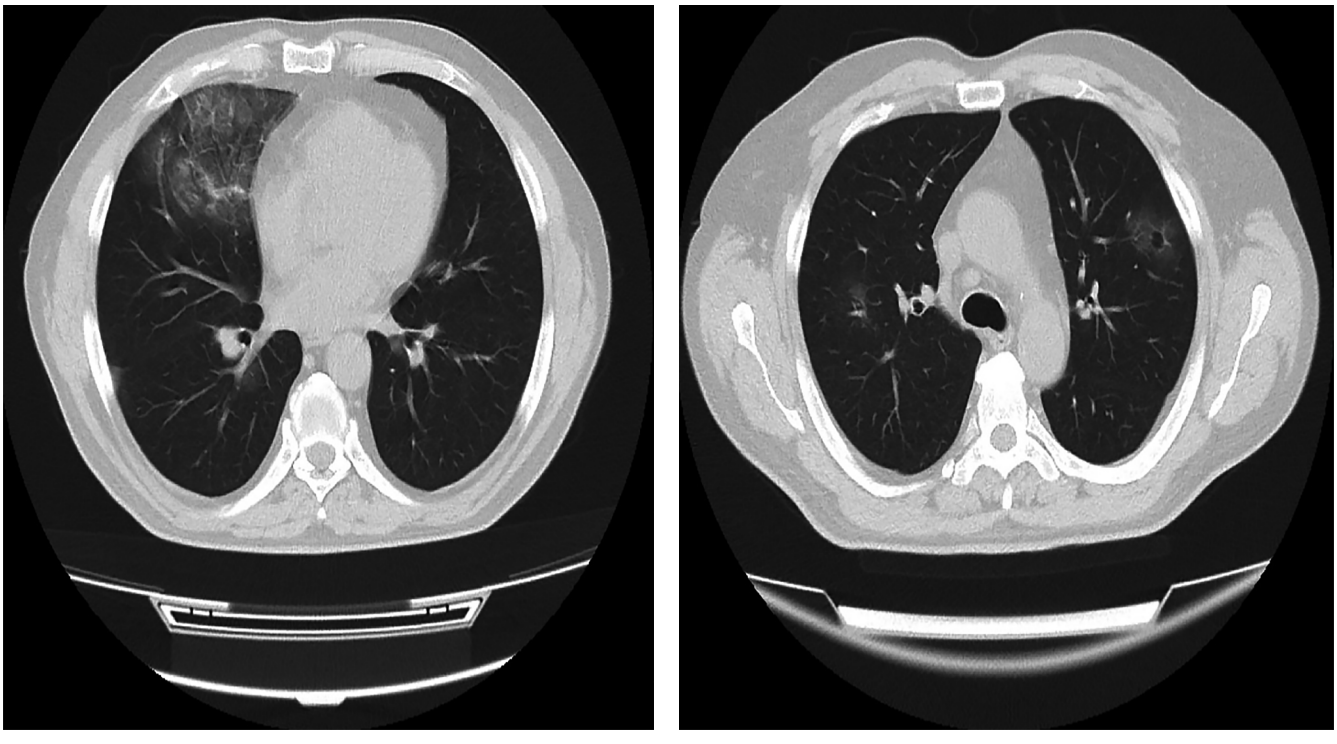


Fig. 1. Computed tomography scan of the chest demonstrating bilateral ground-glass opacities

Рис. 1. Компьютерная томография грудной клетки, демонстрирующая двустороннее просвечивание

Five days later, he was hospitalized for worsening of respiratory symptoms. He appeared severely tachypneic with a respiratory rate of 40 breathes per minute, and dyspneic with an oxygen saturation of 82% on ambient air. D-dimer level was elevated to 950 ng/ml. Low molecular weight heparin dosage was increased to therapeutic doses (enoxaparin 8000 IU twice daily). The patient was discharged home 5 days after his hospitalization with complete resolution of symptoms.

However, 2 days later, he presented to emergency room with a cold, cyanotic and painful left foot. Left pedal pulses were absent with minimal sensory loss and normal motor function. A CT angiography of the lower extremities revealed occlusion of left tibial arteries (Fig. 2). The arterial tree was free of atherosclerotic plaques, and there were no collateral vessels, suggesting an acute occlusion. Transthoracic echocardiography and thoraco-abdominal aortic imaging were negative for proximal sources of thromboembolism. 5000 IU unfractionated heparin (UFH) bolus was administered intravenously. Patient was transferred to the operating theatre for surgical intervention. Popliteal trifurcation was explored through medial infragenicular approach under local anesthesia. Popliteal artery and all of its branches appeared healthy without any atherosclerotic plaques. A longitudinal arteriotomy revealed excellent antegrade blood flow with absent retrograde flow. An attempt was made to remove the thrombus using 2 and 3F Fogarty catheters. However, the thrombus was densely organized and catheters could not be passed across the occluded segment.

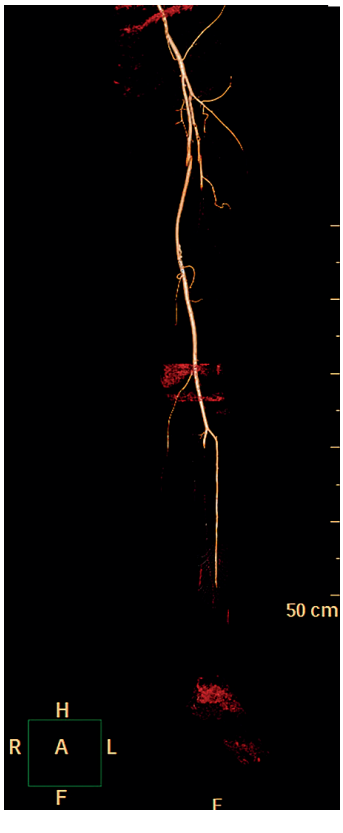


Fig. 2. Computed tomography angiography of the left lower extremity demonstrating occlusion of left tibial arteries, 3-dimensional reconstruction

Рис. 2. Компьютерная томография ангиографии левой нижней конечности, демонстрирующая окклюзию левой большеберцовой артерии, трехмерная реконструкция

We did not perform thrombolysis due to organized nature of the thrombus. The arteriotomy was closed with patch plasty. Patient was transferred toward. Intravenous UFH and iloprost infusions were started. Heparin dose was adjusted to maintain an activated clotting time (ACT) of 200–250 seconds. Continuous iloprost infusion was maintained until discharge. The ischemic foot improved significantly with systemic anticoagulation, and posterior tibial and dorsalis pedis arterial Doppler signals became audible on postoperative 2nd day. However, 1st and 2nd toes and medial aspect of the foot became cyanotic again on postoperative day 5, while the ACT was within the target range (Fig. 3). Posterior tibial artery pulse was once again absent. A more than two fold increase of serum creatinine was observed following the initial CT angiography therefore a repeat angiography was not performed (Table 1). A duplex ultrasound of the lower leg performed prior to discharge revealed biphasic flow pattern in anterior tibial artery, and no flow in peroneal and posterior tibial arteries. The patient was discharged home with dry gangrene of the 1st toe on postoperative day 14 on enoxaparin 8000 IU twice daily and dual anti-platelet therapy with aspirin and clopidogrel. His condition remains stable 1 month after discharge, and a digital amputation is scheduled.

Fig. 3. **Recurrent ischemia of the left foot**
Рис. 3. **Рецидивирующая ишемия левой ноги**

Fig. 4. **Initial (before operation)**
Рис. 4. **Исходная картина**

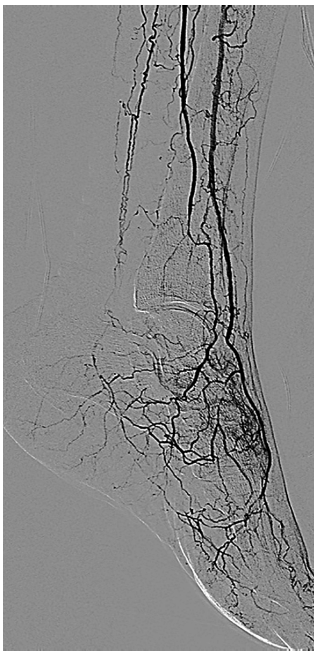


Fig. 5. **Control angiography after TBA**
Рис. 5. **Контрольная ангиография после ТЛБА**

CLINICAL CASE 2

Patient G., 79 years old. Admitted with pain at rest in the left lower limb, with the presence of necrotic ulcer of the 1st finger of the left foot.

Anamnesis: Considers herself ill from more than a year, when pain first appeared in the left lower limb, an ulcer formed in the area of the first finger of the left foot. The patient received conservative treatment, no effect. Worsening in late March 2023, increasing pain syndrome, progressing necrosis of the 1st finger of the left foot.

Date of admission in the hospital: 29.03.2023. The patient was investigated. CT-angiography reports shows: occlusion of tibial arteries of the left lower limb (Fig. 4).

18.04.2023 — Balloon angioplasty of the tibial arteries of the left lower limb (Fig.5).

CLINICAL CASE 3

Patient S., 90 years old. Admitted with pain at rest in the right lower limb, with the presence of black necrosis on the fingers of the right foot.

Anamnesis: The patient has been ill from the last two months, when these complaints came in. She approached to clinic affiliated with her residence, she got treatment by conservative therapy. The conservative therapy was without effect.

Date of admission in the hospital: 20.03.2023. The patient was investigated. CT-angiography report shows: occlusion of SFA from proximal/3, Pop artery stenosis 75%, the distal/3 part of Pop artery is occlusive, anterior tibial artery is occlusive, peroneal artery, posterior tibial artery with CTO stenoses up to 90% in right lower limb (Fig. 6).

04.04.2023 — Balloon angioplasty of arteries in right lower limb (Fig. 7).

DISCUSSION

Present report describes a case of ALI in a patient with confirmed COVID-19 infection. The patient was otherwise

Fig. 6. Initial (before operation)
Рис. 6. Исходная картина

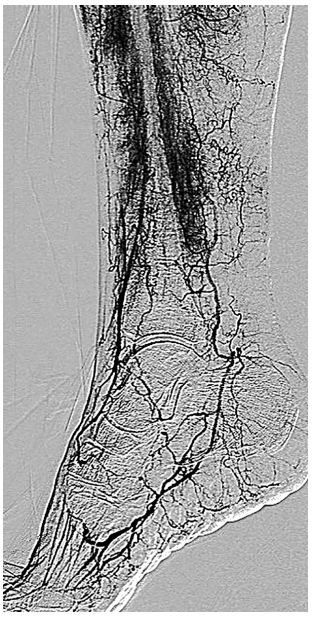


Fig. 7. Control angiography after TBA
Рис. 7. Контрольная ангиография после ТЛБА

healthy and did not have any conventional risk factors for ALI. However, his condition was resistant to treatment, and tended to recur. This finding is in correlation with reports by others [2, 6–8]. Bellosta and colleagues [6] described 20 patients (18 men) with COVID-19-associated ALI over a period of 3 months. Seventeen patients underwent surgical treatment with a successful revascularization in only 12 (70.6%). Authors argued that this lower-than-expected success rate was due to a COVID-19-related hypercoagulable state [6]. They also reported that prolonged use of systemic heparin was associated with better outcomes in this subset of patients [6]. Perini and colleagues [7] reported 4 patients presenting with ALI caused by COVID-19. Two of their patients did not have any comorbidities, were relatively young, and receiving prophylactic doses of LMWH at presentation. One of them, a 53-year-old man, died on postoperative day 2 due to a recurrent aortoiliac occlusion. The other patient, a man aged 37 years with upper extremity thrombosis was successfully managed with UFH administration [7]. Baccellieri and colleagues [8] reported a patient who developed COVID-19-associated ALI while under prophylactic LMWH. The 67-year-old man with no relevant medical history was successfully treated with surgical intervention for simultaneous lower and upper limb ischemia [8].

Thromboembolic events associated with COVID-19 mainly manifest as VTE [5]. This is reasonable since COVID-19 exposes patients to all 3 components of Virchow's triad: (1) there is direct viral infection of endothelial cells [9]; (2) patients are frequently hospitalized and immobilized; (3) blood coagulation parameters are deranged representing a hypercoagulable state [3, 4]. Bilaloglu and colleagues [5] reported less than 1% incidence of ALI in their analysis of 3334 patients hospitalized with COVID-19. Of note, although not as frequent as VTE, incidence of ALI is increased during the COVID-19 pandemic [6].

Evidence from early experience suggests that pathogenesis of arterial thrombosis in COVID-19 patients differs from that of classical arterial thrombosis [10–16]. In-situ arterial thrombosis mainly occurs due to plaque breakdown or reduced perfusion through an atherosclerotic lesion, or stent or graft [14, 17, 18]. However, such as in the present case and others, COVID-19 patients may exhibit acute thrombosis of non-atherosclerotic native arteries [2]. Various mechanisms have been proposed to explain this phenomenon. A dysregulated hyperinflammatory response is thought to be responsible for arterial and venous thromboembolic events seen in patients with COVID-19 [11, 12, 19, 20]. Increased levels of D-dimer, fibrinogen, coagulation factors, acquired antiphospholipid antibodies, and decreased levels of protein C, protein S, antithrombin, and hyperactivation of platelets and neutrophils are observed [10]. A consumption coagulopathy similar to sepsis-associated disseminated intravascular coagulopathy (DIC) is seen in COVID-19 patients. However, thrombotic component is more predominant than hemorrhagic component when compared with DIC [11, 12, 21]. It has been also speculated that direct viral infection of endothelial cells through the angiotensin-converting enzyme 2 receptor may be the cause of arterial thrombosis in patients with COVID-19 [9–11]. It is possible that a combination of these mechanisms, but not one, is responsible for increased rate of arterial thromboembolic events in COVID-19 patients.

CONCLUSION

COVID-19 infection is associated with an increased incidence of thromboembolic events, including ALI. Even young and otherwise healthy patients may develop ALI despite the use of prophylactic anticoagulation. SARS-CoV-2 infection is associated with a high thrombotic risk probably by promoting a systematic inflammatory response and a hypercoagulable state. COVID-associated ALI usually presents in patients with low number of comorbidities, and it is associated with a high mortality and amputation risk. Mortality risk seems to be greater with conservative treatment compared with any intervention, although the amputation risk is similar. Management of ALI in COVID-19 patients might be harder than expected, due to the hypercoagulable state. Patients may benefit from prolonged postoperative UFH administration.

Future studies should focus on identifying optimal medical treatment for these patients as well as potential prognostic factors for mortality and amputation risks.

ADDITIONAL INFORMATION

Author 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.

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

Funding source. This study was not supported by any external sources of funding.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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.

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

REFERENCES

1. Bjorck M., Earnshaw J.J., Acosta S. et al. J.C. Van Den Berg, Editor's choice-European society for vascular surgery (ESVS) 2020 clinical practice guidelines on the management of acute limb ischaemia, Eur. J. Vasc. Endovasc. Surg. 2020; 59(2): 173–218.
2. Gomez-Arbelaez D., Ibarra-Sanchez G., Garcia-Gutierrez A. et al. COVID-19-related aortic thrombosis: a report of four cases, Ann. Vasc. Surg. 2020; 67: 10–3.
3. Han H., Yang L., Liu R. et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection, Clin. Chem. Lab. Med. 2020; 58(7): 1116–20.
4. Tang N., Li D., Wang X., Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J. Thromb. Haemostasis. 2020;18(4): 844–7.
5. Bilaloglu S., Aphinyanaphongs Y., Jones S. et al. Thrombosis in hospitalized patients with COVID-19 in a New York city Health system, JAMA. 2020; 324(8): 799–801.
6. Bellosta R., Luzzani L., Natalini G. et al. Acute limb ischemia in patients with COVID-19 pneumonia, J. Vasc. Surg. 2020. (article in press).
7. Perini P., Nabulsi B., Massoni C.B. et al. Acute limb ischaemia in two young, non-atherosclerotic patients with COVID-19, Lancet. 2020; 395(10236): 1546.
8. Baccellieri D., Bilman V., Apruzzi L. et al. A case of COVID-19 patient with acute limb ischemia and heparin resistance, Ann. Vasc. Surg. 2020; 68: 88–92.
9. Varga Z., Flammer A.J., Steiger P., Haberecker M. et al. Endothelial cell infection and endotheliitis in COVID-19, Lancet. 2020; 395(10234): 1417–8.
10. Piazza G., Morrow D.A. Diagnosis, management, and pathophysiology of arterial and venous thrombosis in COVID-19, JAMA. 2020; 324 (24): 2548–9.
11. Imdes J.E., Koleilat I., Hatch A.N. et al. Early experience with arterial thromboembolic complications in patients with COVID-19, J. Vasc. Surg. 2020. (article in press).
12. Shalbub S. The mystery of COVID-19-associated arterial thrombosis, J. Vasc. Surg. 2020. (article in press).
13. Obara H., Matsubara K., Kitagawa Y. Acute limb ischemia, Ann. Vasc. Dis. 2018; 11 (4): 443–7.
14. Kuchay A.A., Lipin A.N., Antropov A.V. et al. Treatment of multilevel lesions of arteries in lower extremities in cases of CLTI. Medical Alliance. 2022; 10(S3): 187–9. EDN IWSMIP.
15. Kuchay A.A., Lipin A.N., Karelina N.R., Artyukh L.Yu. Revascularization of lower limb based on the angiosome concept with early local flap reconstruction (A CASE REPORT). Forcipe. 2022; 5(4): 29–35.
16. Kuchay A.A., Lipin A.N., Karelina N.R. et al. Revascularization in extended occlusions of the superficial part of the femoral artery and multi-storey lesions of the arteries of the lower extremity. Forcipe. 2022; 5(3): 4–14.
17. Kuchay A.A., Lipin A. N., Antropov A.V. et al. Hybrid approach in treatment of extended occlusive arteries of the lower extremities in CLTI. Angiology and vascular surgery; 2019; 25(S2): 260–4.
18. Kuchay A.A., Lipin A. N., Antropov A.V. et al. Treatment for multistory lesions of lower extremities in CLTI. Angiology and vascular surgery; 2021; 27(S2): 410–2.
19. Kuchay A.A., Lipin A. N., Antropov A.V. et al. Concept of a "DISTAL HYBRID" for long occlusions of the superficial femoral artery with severe damage to the outflow pathways at critical ischemia of the lower extremity. Angiology and vascular surgery. 2022; 28(S1): 157–61.
20. Kuchay A.A., Lipin A. N., Antropov A.V. et al. Hybrid approach to long occlusion of SFA with CLTI. Angiology and vascular surgery. 2022; 28(S1): 161–3.
21. Kurianov P., Lipin A., Antropov A. et al. Popliteal artery angioplasty for chronic total occlusions with versus without the distal landing zone. Annals of vascular surgery; 2020; 62(68): 417–25.

ЛИТЕРАТУРА

1. Bjorck M., Earnshaw J.J., Acosta S. et al. J.C. Van Den Berg, Editor's choice-European society for vascular surgery (ESVS) 2020 clinical practice guidelines on the management of acute limb ischaemia, Eur. J. Vasc. Endovasc. Surg. 2020; 59(2): 173–218.
2. Gomez-Arbelaez D., Ibarra-Sanchez G., Garcia-Gutierrez A. et al. COVID-19-related aortic thrombosis: a report of four cases, Ann. Vasc. Surg. 2020; 67: 10–3.
3. Han H., Yang L., Liu R. et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection, Clin. Chem. Lab. Med. 2020; 58(7): 1116–20.
4. Tang N., Li D., Wang X., Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J. Thromb. Haemostasis. 2020;18(4): 844–7.
5. Bilaloglu S., Aphinyanaphongs Y., Jones S. et al. Thrombosis in hospitalized patients with COVID-19 in a New York city Health system, JAMA. 2020; 324(8): 799–801.
6. Bellosta R., Luzzani L., Natalini G. et al. Acute limb ischemia in patients with COVID-19 pneumonia, J. Vasc. Surg. 2020. (article in press).
7. Perini P., Nabulsi B., Massoni C.B. et al. Acute limb ischaemia in two young, non-atherosclerotic patients with COVID-19, Lancet. 2020; 395(10236): 1546.
8. Baccellieri D., Bilman V., Apruzzi L. et al. A case of COVID-19 patient with acute limb ischemia and heparin resistance, Ann. Vasc. Surg. 2020; 68: 88–92.
9. Varga Z., Flammer A.J., Steiger P., Haberecker M. et al. Endothelial cell infection and endotheliitis in COVID-19, Lancet. 2020; 395(10234): 1417–8.
10. Piazza G., Morrow D.A. Diagnosis, management, and pathophysiology of arterial and venous thrombosis in COVID-19, JAMA. 2020; 324 (24): 2548–9.
11. Imdes J.E., Koleilat I., Hatch A.N. et al. Early experience with arterial thromboembolic complications in patients with COVID-19, J. Vasc. Surg. 2020. (article in press).
12. Shalbub S. The mystery of COVID-19-associated arterial thrombosis, J. Vasc. Surg. 2020. (article in press).
13. Obara H., Matsubara K., Kitagawa Y. Acute limb ischemia, Ann. Vasc. Dis. 2018; 11 (4): 443–7.
14. Kuchay A.A., Lipin A.N., Antropov A.V. et al. Treatment of multilevel lesions of arteries in lower extremities in cases of CLTI. Medical Alliance. 2022; 10(S3): 187–9. EDN IWSMIP.
15. Кучай А.А., Липин А.Н., Карелина Н.Р., Артюх Л.Ю. Реваскуляризация нижней конечности на основе концепции ангиосомы с ранней локальной реконструкцией лоскута (клинический случай). Forcipe. 2022; 5(4): 29–35.
16. Кучай А.А., Липин А.Н., Карелина Н.Р. и др. Реваскуляризация при протяженных окклюзиях поверхностной части бедренной артерии и многоэтажных поражениях артерий нижней конечности. Forcipe. 2022; 5(3): 4–14.
17. Кучай А.А., Липин А.Н., Антропов А.В. и др. Гибридный подход в лечении протяженных окклюзий артерий нижних конечностей при КИНК. Ангиология и сосудистая хирургия. 2019; 25(2): 260–264.
18. Кучай А.А., Липин А.Н., Антропов А.В. и др. Лечение многоэтажных поражений артерий нижних конечностей при КИНК. Ангиология и сосудистая хирургия. 2021; 27(2): 410–412.
19. Кучай А.А., Липин А.Н., Антропов А.В. и др. Концепция «ДИСТАЛЬНОГО ГИБРИДА» при протяженных окклюзиях поверхностной бедренной артерии с тяжелым поражением путей оттока при критической ишемии нижних конечности. Ангиология и сосудистая хирургия. 2022; 28(S1): 157–161.
20. Кучай А.А., Липин А.Н., Антропов А.В. и др. Гибридный подход к протяженным окклюзиям ПБА при КИНК. Ангиология и сосудистая хирургия. 2022; 28 (S1): 161–163.
21. Курьянов П., Липин А., Антропов А. и др. Ангиопластика подколенной артерии при хронических тотальных окклюзиях с дистальной посадочной зоной и без нее. Annals of vascular surgery; 2020; 62 (68): 417–425.

ПРАВИЛА ДЛЯ АВТОРОВ

Утв. приказом и.о. ректора
ФГБОУ ВО СПбГПМУ Минздрава России от 23.06.16

НАСТОЯЩИЕ ПРАВИЛА ДЛЯ АВТОРОВ ЯВЛЯЮТСЯ ИЗДАТЕЛЬСКИМ ДОГОВОРОМ

Условия настоящего Договора (далее «Договор») являются публичной офертой в соответствии с п. 2 ст. 437 Гражданского кодекса Российской Федерации. Данный Договор определяет взаимоотношения между редакцией журнала «**Russian Biomedical Research»** (далее по тексту «Журнал»), зарегистрированного Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (РОСКОМНАДЗОР), свидетельство: ПИ № ФС77-74228 от 02 ноября 2018 г. (ранее ПИ № ТУ78-01869 от 17 мая 2016 г.), именуемой в дальнейшем «Редакция» и являющейся структурным подразделением ФГБОУ ВО СПбГПМУ Минздрава России, и автором и/или авторским коллективом (или иным правообладателем), именуемым в дальнейшем «Автор», принявшим публичное предложение (оферту) о заключении Договора.

Автор передает Редакции для издания авторский оригинал или рукопись. Указанный авторский оригинал должен соответствовать требованиям, указанным в разделах «Представление рукописи в журнал», «Оформление рукописи». При рассмотрении полученных авторских материалов Журнал руководствуется «Едиными требованиями к рукописям, представляемым в биомедицинские журналы» (Intern. committee of medical journal editors. Uniform requirements for manuscripts submitted to biomedical journals // Ann. Intern. Med. 1997; 126: 36–47).

В Журнале печатаются ранее не опубликованные работы по профилю Журнала.

Журнал не рассматривает работы, результаты которых по большей части уже были опубликованы или описаны в статьях, представленных или принятых для публикации в другие печатные или электронные средства массовой информации. Представляя статью, автор всегда должен ставить редакцию в известность обо всех направлениях этой статьи в печать и о предыдущих публикациях, которые могут рассматриваться как множественные или дублирующие публикации той же самой или очень близкой работы. Автор должен уведомить редакцию о том, содержит ли статья уже опубликованные материалы, и предоставить ссылки на предыдущую, чтобы дать редакции возможность принять решение, как поступить в данной ситуации. Не принимаются к печати статьи, представляющие собой отдельные этапы незавершенных исследований, а также статьи с нарушением «Правил и норм гуманного обращения с биообъектами исследований».

Размещение публикаций возможно только после получения положительной рецензии.

Все статьи, в том числе статьи аспирантов и докторантов, публикуются бесплатно.

Подача статей в журнал «Russian Biomedical Research» осуществляется по адресу электронной почты avas7@mail.ru с пометкой «для Russian Biomedical Research».

Требования к отправке статей

Перед заполнением анкеты авторам рекомендуется подготовить все необходимые для ввода данные, а также выбрать автора (в случае коллектива авторов статьи), ОТВЕТСТВЕННОГО ЗА ПЕРЕПИСКУ. Для успешного заполнения анкеты необходимо иметь всю указанную информацию и на русском, и на английском языках!!!

Все названия на английском языке, включая названия статьи, названия учреждений, их подразделений должны приводиться с заглавных букв (например: Sex Differences In Aging, Life Span And Spontaneous Tumorigenesis; Bulletin of Experimental Biology and Medicine; Saint Petersburg State Pediatric Medical University) и непременно в соответствии с официальными наименованиями без самодеятельности.

Анкетные данные всех авторов — ФИО (полностью), ученая степень, звание, должность, место работы (кафедра, отделение), название учреждения, адрес учреждения, e-mail, телефон, ФИО автора, ответственного за переписку, и т.д. — заполняются в соответствующих полях формы заявки.

Резюме, ключевые слова и название статьи — также заполняются онлайн.

Статья предоставляется в электронной форме (файл MS Word версии не старше 2003, т.е. с расширением doc, заархивированный в формат .zip, .rar).

Файл статьи называется Фамилией первого автора, например, Иванов.doc или Petrov.doc.

Статья должна соответствовать правилам оформления статей к публикации (см. ниже).

К каждой статье прилагается файл Экспертного Заключения (ЭЗ). Для авторов СПбГПМУ ЭЗ может только подписываться авторами статьи, печать необязательна. Для авторов других учреждений — ЭЗ оформляется обязательно полностью, с печатями (круглая печать учреждения) и подписями руководителей и комиссий данного учреждения. Заполненный, подписанный и «опечатанный» ЭЗ для отправки онлайн предварительно сканируется или фотографируется. Образец ЭЗ можно запросить по адресу: scrcenter@mail.ru

Отправленные анкетные данные авторов, статья, ЭЗ поступают на E-mail автору-отправителю (для подтверждения и проверки отправки) и на E-mail редакции scrcenter@mail.ru техническому редактору журнала «Russian Biomedical

Research», с которым осуществляется вся дальнейшая работа по подготовке статьи в печать. Все вопросы по отправке статей можно адресовать на электронный адрес scrcenter@mail.ru техническому редактору журнала «Russian Biomedical Research» Марии Александровне Пахомовой.

Рукопись считается поступившей в Редакцию, если она представлена комплектно и оформлена в соответствии с описанными требованиями. Предварительное рассмотрение рукописи, не заказанной Редакцией, не является фактом заключения между сторонами издательского Договора.

При представлении рукописи в Журнал Авторы несут ответственность за раскрытие своих финансовых и других конфликтных интересов, способных оказать влияние на их работу. В рукописи должны быть упомянуты все лица и организации, оказавшие финансовую поддержку (в виде грантов, оборудования, лекарств или всего этого вместе), а также другое финансовое или личное участие.

В конце каждой статьи обязательно указываются вклад авторов в написание статьи, источники финансирования (если имеются), отсутствие конфликта интересов, наличие согласия на публикацию со стороны пациентов.

Правила оформления статей к публикации

Статья предоставляется в электронной форме (файл MS Word версии не старше 2003, т.е. с расширением doc, заархивированный в формат .zip, .rar), шрифт — 14, интервал — полуторный.

Файл статьи называется по Фамилии первого автора, например, Иванов.doc или Petrov.doc. Никаких других слов в названии не должно быть!

Ориентировочные размеры статьи, включая указатель литературы, таблицы и резюме, — 10–12 страниц текста через полтора интервала или 20–25 тысяч знаков с пробелами. Рекомендуемый размер обзора — 18–20 страниц «машинописного» текста или 35–40 тысяч знаков с пробелами. Примерное число литературных ссылок для экспериментальной статьи — 20, для обзоров и проблемных статей — 50.

Файл статьи должен содержать
НА РУССКОМ И АНГЛИЙСКОМ ЯЗЫКАХ:

- Заглавие (Title) должно быть кратким (не более 120 знаков), точно отражающим содержание статьи.
- Сведения об авторах (публикуются). Для каждого автора указываются: фамилия, имя и отчество, место работы, почтовый адрес места работы, e-mail, ORCID. Фамилии авторов рекомендуется транслитерировать так же, как в предыдущих публикациях, или по системе BGN (Board of Geographic Names), см. сайт http://www.translit.ru.
- Резюме (Summary) (1500–2000 знаков, или 200–250 слов) помещают перед текстом статьи. Резюме не требуется при публикации рецензий, отчетов о конференциях, информационных писем.

  Авторское резюме к статье является основным источником информации в отечественных и зарубежных информационных системах и базах данных, индексирующих журнал. Резюме доступно на сайте журнала «Russian Biomedical Research» и индексируется сетевыми поисковыми системами. Из аннотации должна быть понятна суть исследования, нужно ли обращаться к полному тексту статьи для получения более подробной, интересующей его информации. Резюме должно излагать только существенные факты работы. Рекомендуемая структура как аннотации, так и самой статьи IMRAD (для оригинальных исследований структура обязательна): введение (Introduction), материалы и методы (Materials and methods), результаты (Results), обсуждение (Biscussion), выводы (Conclusion). Предмет, тему, цель работы нужно указывать, если они не ясны из заглавия статьи; метод или методологию проведения работы целесообразно описывать, если они отличаются новизной или представляют интерес с точки зрения данной работы. **Объем текста авторского резюме** определяется содержанием публикации (объемом сведений, их научной ценностью и/или практическим значением) и должен быть в пределах **200–250 слов (1500–2000 знаков)**.
- Ключевые слова (Key words) от 3 до 10 ключевых слов или словосочетаний, которые будут способствовать правильному перекрестному индексированию статьи, помещаются под резюме с подзаголовком «ключевые слова». Используйте термины из списка медицинских предметных заголовков (Medical Subject Headings), приведенного в Index Medicus (если в этом списке еще отсутствуют подходящие обозначения для недавно введенных терминов, подберите наиболее близкие из имеющихся). Ключевые слова разделяются точкой с запятой.
- Текст статьи может быть написан либо на русском, либо на английском языке, также возможна публикация статьи с полным переводом. На русском и английском языках необходимо предоставить все рисунки и таблицы (заголовки и все надписи должны иметь перевод).

  Структура основного текста статьи: введение, изложение основного материала, заключение, литература. Для оригинальных исследований — введение, методика, результаты исследования, обсуждение результатов, литература (IMRAD).

  В разделе «методика» обязательно указываются сведения о статистической обработке экспериментального или клинического материала. Единицы измерения даются в соответствии с Международной системой единиц — СИ. Фамилии иностранных авторов, цитируемые в тексте рукописи, приводятся в оригинальной транскрипции.

  Таблицы и рисунки приводятся непосредственно в теле статьи, каждый из которых имеет номер и название с обязательными ссылками на них в тексте статьи — в контексте предложения (например: «…как показано на рисунке 1…») или в конце предложения в круглых скобках (например: «...выявлена положительная корреляционная связь умеренной степени (r=0,41) между уровнем ТТГ матери и новорожденного (рис. 2)»; просьба учитывать, что в печатной версии журнала рисунки будут воспроизводиться в черно-белом варианте.

- Список литературы обязательно в алфавитном порядке: сначала все отечественные, затем иностранные авторы с дополнительным транслитерированным списком (методика транслитерации описана подробно ниже).

Текст статьи должен быть подготовлен в строгом соответствии с настоящими правилами и тщательно выверен автором. В случае обнаружения значительного количества опечаток, небрежностей, пунктуационных и орфографических ошибок, нерасшифрованных сокращений, отсутствия основных компонентов и других технических дефектов оформления статей редакция возвращает статью автору для доработки. Небольшие погрешности редакция может исправить сама без согласования с автором. Кроме того, редакция оставляет за собой право осуществления литературного редактирования статей.

Сокращений, кроме общеупотребляемых, следует избегать. Сокращения в названии статьи, названиях таблиц и рисунков, в выводах недопустимы. Если аббревиатуры используются, то все они должны быть непременно расшифрованы полностью при первом их упоминании в тексте (например: «Наряду с данными о РОН (резидуально-органической недостаточности), обусловливающей развитие ГКС (гиперкинетического синдрома), расширен диапазон исследований по эндогенной природе данного синдрома».

Все цитирования производятся следующим образом:

ФИО автора, год издания и прочая информация не упоминаются в тексте. Вместо этого указывается ссылка на источник литературы в виде номера в квадратных скобках (пример: «Ряд исследователей отмечает различные нарушения речевых функций при эпилепсии в детском возрасте [17, 21, 22].»), который включен в расставленный в алфавитном порядке список источников в конце статьи.

Все ссылки должны иметь соответствующий источник в списке, а каждый источник в списке — ссылку в тексте.

В виде исключения в тексте могут приводиться ФИО конкретных авторов в формате И. О. Фамилия, год и даже название источника, но при этом все равно обязательна ссылка (в квадратных скобках в конце предложения) на источник, включенный в список литературы.

(Например: «В 1892 году великий Эраст Гамильтонский описал в своем бессмертном труде «Об открытии третьего уха у человека» третье (непарное) ухо» [34].)

Литература (References)

Учитывая требования международных систем цитирования, список литературы приводится не только в обычном виде, но также и дополнительно в транслитерированном (см. Транслитерация).

В статье приводятся ссылки на все упоминаемые в тексте источники.

Фамилии и инициалы авторов в пристатейном списке приводятся в алфавитном порядке, сначала русского, затем латинского алфавита.

В описании указываются все авторы публикации.

Библиографические ссылки в тексте статьи даются в квадратных скобках.

Ссылки на неопубликованные работы не допускаются.

Список литературы комплектуется в следующем порядке:

Нормативные акты

Приказы, нормативные акты, методические письма и прочие законные акты, патенты, полезные модели не вносятся в список литературы, оформляются в виде сносок. Сноска — примечание, помещаемое внизу страницы (постраничная сноска). Знак сноски ставят цифрой после фрагмента основного текста, где есть упоминание об этих источниках. Рекомендуется сквозная нумерация сносок по тексту.

Интернет-ресурс

1. Интернет-ресурс, где есть название источника, автор — вносится в список литературы (в порядке алфавита) с указанием даты обращения (см. ниже пример оформления).

2. Если есть только ссылка на сайт — вносится в список литературы в конце, с указанием даты обращения.

Щеглов И. Насколько велика роль микрофлоры в биологии вида-хозяина? Живые системы: научный электронный журнал. Доступен по: http://www.biorf.ru/catalog.aspx?cat_id=396&d_no=3576 (дата обращения 02.07.2012).

Kealy M. A., Small R. E., Liamputtong P. Recovery after caesarean birth: a qualitative study of women's accounts in Victoria, Australia. BMC Pregnancy and Childbirth. 2010. Available at: http://www.biomedcentral. com/1471–2393/10/47/ (Accessed 11.09.2013).

Книга

Автор(ы) название книги (знак точка) место издания (двоеточие) название издательства (знак точка с запятой) год издания. Если в качестве автора книги выступает редактор, то после фамилии следует ред.

Айламазян Э.К., Новиков Б.Н., Зайнулина М.С., Палинка Г.К., Рябцева И.Т., Тарасова М.А. Акушерство: учебник. 6-е изд. СПб.; 2007.

Преображенский Б.С., Темкин Я.С., Лихачев А.Г. Болезни уха, горла и носа. М.: Медицина; 1968.

Радзинский В.Е., ред. Перинеология: учебное пособие. М.: РУДН; 2008.

Brandenburg J.H., Ponti G.S., Worring A.F. eds. Vocal cord injection with autogenous fat. 3 rd ed. NY:Mosby; 1998.

Domeika M. Diagnosis of genital chlamydial infection in humans as well as in cattle. Uppsala; 1994.

Глава из книги

Автор(ы) название главы (знак точка) В кн.: или In: далее описание книги [Автор(ы) название книги (знак точка) место издания (двоеточие) название издательства (знак точка с запятой) год издания] (двоеточие) стр. от и до.

Коробков Г.А. Темп речи. В кн.: Современные проблемы физиологии и патологии речи: сб. тр. Т. 23. М.; 1989: 107–11.

Статья из журнала:

Автор(ы) название статьи (знак точка) название журнала (знак точка) год издания (знак точка с запятой) том (если есть в круглых скобках номер журнала) затем знак (двоеточие) страницы от и до.

Кирющенков А.П., Совчи М.Г., Иванова П.С. Поликистозные яичники. Акушерство и гинекология. 1994; N 1: 11–4.

Brandenburg J.H., Ponti G.S., Worring A.F. Vocal cord injection with autogenous fat: a long-term magnetic resona. Laryngoscope. 1996; l06(2,pt l): 174–80.

Simpson J. et al. Association between adverse perinatal outcomes and serially obtained second and third trimester MS AFP measurements. Am. J. Obstet. Gynecol. 1995; 173: 1742.

Deb S., Campbell B.K., Pincott-Allen C. et al. Quantifying effect of combined oral contraceptive pill on functional ovarian reserve as measured by serum anti-Müllerian hormone and small antral follicle count using three-dimensional ultrasound. Ultrasound. Obstet. Gynecol. 2012; 39 (5): 574–80.

Тезисы докладов, материалы научных конференций

Бабий А.И., Левашов М.М. Новый алгоритм нахождения кульминации экспериментального нистагма (миниметрия). III съезд оториноларинг. Беларуси: тез. докл. Минск; 1992: 68–70.

Салов И.А., Маринушкин Д.Н. Акушерская тактика при внутриутробной гибели плода. В кн.: Материалы IV Российского форума «Мать и дитя». М.; 2000; ч. 1: 516–9.

Авторефераты

Петров С.М. Время реакции и слуховая адаптация в норме и при периферических поражениях слуха. Автореф. дис. … канд. мед. наук. СПб.; 1993.

Прочее

World Health Organization. Prevalence and incidence of selected sexually transmitted infections, 2005 global estimates. Geneva: World Health Organization; 2011.

Транслитерация

Список литературы подается в двух вариантах: первый на языке оригинала (русскоязычные источники кириллицей, англоязычные латиницей), второй — (References) в романском алфавите (для Scopus и других международных баз данных, повторяя в нем все источники литературы, независимо от того, имеются ли среди них иностранные). Если в списке есть ссылки на иностранные публикации, они полностью повторяются в списке, готовящемся в романском алфавите.

В романском алфавите для русскоязычных источников требуется следующая структура библиографической ссылки: автор(ы) (транслитерация), [перевод названия книги или статьи на английский язык], название источника (транслитерация), выходные данные в цифровом формате, указание на язык статьи в скобках (in Russian).

Пример:

Preobrazhenskiy B.S., Temkin Ya.S., Likhachev A.G. Bolezni ukha, gorla i nosa [Diseases of the ear, nose and throat]. M.: Meditsina; 1968. (in Russian).

Технология подготовки ссылок с использованием системы автоматической транслитерации и переводчика:

На сайте http://www.translit.ru можно бесплатно воспользоваться программой транслитерации русского текста в латиницу. Программа очень простая.

Входим в программу Translit.ru. В окошке «варианты» выбираем систему транслитерации BGN (Board of Geographic Names). Вставляем в специальное поле весь текст библиографии на русском языке и нажимаем кнопку «в транслит».

Копируем транслитерированный текст в готовящийся список References. Переводим на английский язык название книги, статьи, постановления и т.д., переносим его в готовящийся список. **Внимание!** Необходим авторский корректный перевод названия. Автоматический перевод, предполагающий возможное искажение сути названия статьи, недопустим.

Объединяем описания в соответствии с принятыми правилами и редактируем список. В конце ссылки в круглых скобках указывается (in Russian). Ссылка готова.

Примеры транслитерации русскоязычных источников литературы для англоязычного блока статьи.

Книга: Avtor (y) Nazvanie knigi (znak tochka) [The title of the book in english]. mesto izdaniya (dvoetochie) nazvanie izdatel'stva (znak tochka s zapyatoy) god izdaniya.

Preobrazhenskiy B. S., Temkin Ya. S., Likhachev A. G. Bolezni ukha, gorla i nosa [Diseases of the ear, nose and throat]. M.: Meditsina; 1968. (in Russian).

Radzinskiy V. E., ed. Perioneologiya: uchebnoe posobie [Perineology tutorial]. M.: RUDN; 2008. (in Russian).

Глава из книги: Avtor (y) nazvanie glavy (znak tochka) [The title of the article in english]. In: Avtor (y) nazvanie knigi (znak tochka) mesto izdaniya (dvoetochie) nazvanie izdatel'stva (znak tochka s zapyatoy) god izdaniya]. (dvoetochie) str. ot i do.

Korobkov G. A. Temp rechi [Rate of speech]. V kn.: Sovremennye problemy fiziologii i patologii rechi: sb. tr. T. 23. M.;1989:107–11. (in Russian).

Статья из журнала: Avtor (y) nazvanie stat'i [The title of the article in english] (znak tochka) nazvanie zhurnala (znak tochka) god izdaniya (znak tochka s zapyatoy) tom (esli est' v kruglykh skobkakh nomer zhurnala) zatem znak (dvoetochie) stranitsy ot i do.

Kiryushchenkov A. P., Sovchi M. G., Ivanova P. S. Polikistoznye yaichniki [Polycystic ovary]. Akusherstvo i ginekologiya. 1994; N 1: 11–4. (in Russian).

Тезисы докладов, материалы научных конференций

Babiy A. I., Levashov M. M. Novyy algoritm nakhozhdeniya kul'minatsii eksperimental'nogo nistagma (minimetriya) [New algorithm of finding of the culmination experimental nystagmus (minimetriya)]. III s»ezd otorinolaringologov Resp. Belarus': tez. dokl. Minsk; 1992: 68–70. (in Russian).

Salov I. A., Marinushkin D. N. Akusherskaya taktika pri vnutriutrobnoy gibeli ploda [Obstetric tactics in intrauterine fetal death]. V kn.: Materialy IV Rossiyskogo foruma «Mat' i ditya». M.; 2000; ch.1:516–9. (in Russian).

Авторефераты

Petrov S. M. Vremya reaktsii i slukhovaya adaptatsiya v norme i pri perifericheskikh porazheniyakh slukha [Time of reaction and acoustical adaptation in norm and at peripheral defeats of hearing]. PhD thesis. SPb.; 1993. (in Russian).

Описание Интернет-ресурса

Shcheglov I. Naskol'ko velika rol' mikroflory v biologii vida-khozyaina? [How great is the microflora role in type-owner

biology?]. Zhivye sistemy: nauchnyy elektronnyy zhurnal. Available at: http://www.biorf.ru/catalog.aspx?cat_id=396&d_no=3576 (accessed 02.07.2012). (in Russian).

Пример списка литературы, включающего транслитерированный вариант:

ЛИТЕРАТУРА

1. Кофиади И.А. Генетическая устойчивость к заражению ВИЧ и развитию СПИД в популяциях России и сопредельных государств. Автореф. дис. ... канд. биол. наук. М.; 2008. Доступен по: http://www.dnatechnology.ru/ files/images/d/0b136b567d25d4be1dfa26a8b39ec2b9.pdf (дата обращения 18.09.2014).
2. Flynn E., Eyre S., Packham J. Childhood Arthritis Prospective Study (CAPS), UKRAG Consortium, BSPAR Study Group, Barton A., Worthington J., Thomson W. Association of the CCR5 gene with juvenile idiopathic arthritis. Genes Immun. 2010; 11 (7): 584–89.

и т.д.

REFERENCES

1. Kofiadi I.A. Geneticheskaya stoychivost' k zarazheniyu VICh i razvitiyu SPID v populyatsiyakh Rossii i sopredel'nykh gosudarstv [Genetic resistance to HIV infection and development of AIDS in populations of Russia and neighboring countries]. PhD-thesis. M.; 2008. Available from: http://www.dna-technology.ru/files/images/d/0b136b567d25d-4be1dfa26a8b39ec2b9.pdf (accessed 18.09.2014) (in Russian).
2. Flynn E., Eyre S., Packham J. Childhood Arthritis Prospective Study (CAPS), UKRAG Consortium, BSPAR Study Group, Barton A., Worthington J., Thomson W. Association of the CCR5 gene with juvenile idiopathic arthritis. Genes Immun. 2010; 11 (7): 584–89.

Etc.

Для всех статей, имеющих DOI, индекс необходимо указывать в конце библиографического описания.

ОТВЕТСТВЕННОСТЬ ЗА ПРАВИЛЬНОСТЬ БИБЛИОГРАФИЧЕСКИХ ДАННЫХ НЕСЕТ АВТОР.

АВТОРСКОЕ ПРАВО

Редакция отбирает, готовит к публикации и публикует переданные Авторами материалы. Авторское право на конкретную статью принадлежит авторам статьи. Авторский гонорар за публикации статей в Журнале не выплачивается. Автор передает, а Редакция принимает авторские материалы на следующих условиях:

1) Редакции передается право на оформление, издание, передачу Журнала с опубликованным материалом Автора для целей реферирования статей из него в Реферативном журнале ВИНИТИ, РНИЦ и базах данных, распространение Журнала/авторских материалов в печатных и электронных изданиях, включая размещение на выбранных либо созданных Редакцией сайтах в сети Интернет в целях доступа к публикации в интерактивном режиме любого заинтересованного лица из любого места и в любое время, а также на распространение Журнала с опубликованным материалом Автора по подписке;
2) территория, на которой разрешается использовать авторский материал, — Российская Федерация и сеть Интернет;
3) срок действия Договора — 5 лет. По истечении указанного срока Редакция оставляет за собой, а Автор подтверждает бессрочное право Редакции на продолжение размещения авторского материала в сети Интернет;
4) Редакция вправе по своему усмотрению без каких-либо согласований с Автором заключать договоры и соглашения с третьими лицами, направленные на дополнительные меры по защите авторских и издательских прав;
5) Автор гарантирует, что использование Редакцией предоставленного им по настоящему Договору авторского материала не нарушит прав третьих лиц;
6) Автор оставляет за собой право использовать предоставленный по настоящему Договору авторский материал самостоятельно, передавать права на него по договору третьим лицам, если это не противоречит настоящему Договору;
7) Редакция предоставляет Автору возможность безвозмездного получения справки с электронными адресами его официальной публикации в сети Интернет;
8) при перепечатке статьи или ее части ссылка на первую публикацию в Журнале обязательна.

ПОРЯДОК ЗАКЛЮЧЕНИЯ ДОГОВОРА

Заключением Договора со стороны Редакции является опубликование рукописи данного Автора в журнале «Russian Biomedical Research» и размещение его текста в сети Интернет. Заключением Договора со стороны Автора, т.е. полным и безоговорочным принятием Автором условий Договора, является передача Автором рукописи и экспертного заключения.

РЕЦЕНЗИРОВАНИЕ

Статьи, поступившие в редакцию, обязательно рецензируются. Если у рецензента возникают вопросы, то статья с комментариями рецензента возвращается Автору. Датой поступления статьи считается дата получения Редакцией окончательного варианта статьи. Редакция оставляет за собой право внесения редакторских изменений в текст, не искажающих смысла статьи (литературная и технологическая правка).

АВТОРСКИЕ ЭКЗЕМПЛЯРЫ ЖУРНАЛА

Редакция обязуется выдать Автору 1 экземпляр Журнала на каждую опубликованную статью вне зависимости от числа авторов. Авторы, проживающие в Санкт-Петербурге, получают авторский экземпляр Журнала непосредственно в Редакции. Иногородним Авторам авторский экземпляр Журнала высылается на адрес автора по запросу от автора. Экземпляры спецвыпусков не отправляются авторам.

АДРЕС РЕДАКЦИИ

194100, Санкт-Петербург, Литовская ул., 2
e-mail: scrcenter@mail.ru. Сайт журнала: http://www.gpmu.org/science/pediatrics-magazine/Russian_Biomedical_Research.