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EDITOR-IN-CHIEF'S PREFACE

EDITOR-IN-CHIEF'S PREFACE TO ISSUE 5, 2025

Sergey I. Kolesnikov

Member of the RAS

From the articles published in this issue, I would single out the work of T.A. Belogorova and others (Irkutsk) under the guidance of corresponding member of the RAS L.V. Rychkova, which successfully tested a new medical simulator "Glove" for correcting hands spasticity in treatment of common spastic syndrome in children.

A number of studies continue **to focus on COVID-19 and post-COVID-19 syndrome**. N.A. Ishutina and I.A. Andrievskaya (Blagoveshchensk) found that COVID-19 in second trimester of pregnancy leads to changes in the content of phospholipids, arachidonic acid and oxylipins in the blood serum, which makes it necessary to optimize therapy. E.V. Zhdanova, E.V. Rubtsova (Tyumen, Kurgan) revealed an immunocomplex mechanism in the pathogenesis of arthralgia, arthritis, and the onset of osteoarthropathy in post-COVID syndrome with active participation of IgE. Attention should be paid to I.A. Cherevikova and co-authors (Irkutsk) study, which showed depressive symptoms, increased anxiety, and reduced activity in girls with post-COVID syndrome for 6–12 months after COVID-19. Elevated TSH and cortisol levels were noted.

The topic of infections has been developed in several clinical and experimental studies. The work of O.M. Gordeeva, A.M. Tikhonov and N.L. Karpina (Moscow) provides optimistic data on kidney transplantation and the appointment of immunosuppressive therapy **without reactivation of tuberculosis** within a year in 6 out of 7 patients with tuberculosis. N.A. Smetannikova et al. (Novosibirsk, Khabarovsk) based on the study of a fatal case, two hypotheses were put forward for the formation of a third urban focus of Orthohantavirus Seoul in Khabarovsk, and T.A. Bayanova (Irkutsk) conducted a retrospective analysis of the incidence of whooping cough, measles, chickenpox, and meningococcal infection in the Irkutsk region in 1955–2023.

The work of A.B. Pyatidesyatnikova et al. (Irkutsk) demonstrated the ability of a new selenium-containing drug to increase the immunogenicity of the vaccine strain *Y. pestis* EV regardless of the dose. In another experimental work by N.A. Lyapunova et al. (Irkutsk) about the culture of *M. sibiricus* kidney cells, where only background expression of *IFN*-β is observed, refuted the hypothesis about the constantly "switched on" activity of interferon pathway proteins in bats.

A series of works is devoted to practical **issues of ophthalmology:** pterygopalatine blockade after donor corneal transplantation (I.G. Oleshchenko and T.N. Yuryeva, Irkutsk); improving the effectiveness of combined treatment of Coates retinitis with anti-VEGF drugs as neoadjuvant therapy (V.V. Bukina et al., Irkutsk); description of a clinical case of corneal ulcer as the first of HIV infection (T.Yu. Matnenko et al., Omsk); expansion of diagnostic capabilities using computer accommodation (R.N. Zelentsov et al., Arkhangelsk).

Clinical and biochemical work. I.E. Esimova and others (Tomsk), it was found that adolescents with grades 1–3 obesity have elevated levels of insulin and C-peptide in their blood, a decrease in the concentration of GLP-2 and a fatty acid imbalance (a decrease in the proportion of GLA, DGLA, DPA, DHA, AA and an increase in the content of ALA, OA, POA, BA, MA, PA, MAA), as well as low-intensity sub-optimal inflammatory response. I.A. Yatskov et al. (Crimea) demonstrated a significant effect of lipopolysaccharide-binding protein (LSD), bactericidal permeability – enhancing protein (BPI), and sCD14, as well as a marker of systemic inflammation (CRP) on the risk of macrovascular and microvascular complications in type 1 diabetes mellitus.

In the study of O.V. Smirnova and others (Krasnoyarsk) was found that different polymorphisms of the *PNPLA3*, *HFE*, and *UCP2* genes are associated with an imbalance in the LPO-AOD system, which can be caused by a violation of iron levels and a change in the antioxidant activity of the UCP2 proteinUCP2.

As a morphologist, I was very interested in the article by the authors of both Italy and Russia O.K. Zenin, E.S. Kafarov, I Miltiadis (Penza, Grozny, Palermo-Italy) who, based on the results of morphometry of corrosion preparations of the coronary arteries of the human heart, established a discrepancy between their real data and the traditionally used equations proposed by Mette S. Olufsen and G. Finet, this calls into question the validity of their use of AI for numerical modeling of realistic riverbed geometry.

Two works are devoted **to psychology.** Yu.A Marakshina and others (Yekaterinburg), proved the validity of using the "Hospital Scale of Anxiety and Depression" (HADS) for screening emotional distress in Russian-speaking students. A.A. Martynova et al. (Apatite) assessing the life quality of pregnant women, it was shown that, first of all, the psychoemotional state of a pregnant woman is influenced by physical functioning, the relationship exist between psychoemotional state and family status, the number of children and average per capita income.

Another **experimental work** of V.Ya. Kolesnik, R.A. Pakhomova and A.A. Kolesnik (Moscow), showed that the solution with the membrane protector dimethyloxobutylphosphonyl dimethylate was the most effective for preserving adipose tissue graft.

Readers will undoubtedly be interested in several review articles, including those devoted to pregnancy: A.M. Ziganshin et al (Ufa, St. Petersburg) on the use of mass spectrometry to study the role of posttranslational protein modifications in miscarriage, which provides new opportunities for diagnosis and prognosis, and review by E.S. Taskina et al. (Chita) on blood-brain barrier dysfunction in preeclampsia.

A joint review by O.A. Makarova et al. **(**Irkutsk, St. Petersburg) reveals the potential for predicting a number of diseases based on blood group analysis, and a study by R.-L. Zaranaina et al. (Moscow, Dolgoprudny) describes the characteristics of *Piper betle* of the peppercorn family *Piperaceae* as a promising object for further research in the field of phytopharmacology.

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ПРЕДИСЛОВИЕ ГЛАВНОГО РЕДАКТОРА К № 5 (2025)

Колесников Сергей Иванович

Академик РАН

Из опубликованных в этом номере работ я бы выделил работу Белоголовой Т.А. и др. (Иркутск) под руководством члена-корреспондента РАН Рычковой Л.В., в которой проведена успешная апробация нового медицинского тренажера для коррекции спастичности рук «Перчатка» для лечения распространенного спастического синдрома у детей.

Ряд работ посвящен **COVID-19 и постковидному синдрому.** Ишутина Н.А. и Андриевская И.А. (Благовещенск) выявили, что COVID-19 у беременных во втором триместре приводит к изменениям содержания фосфолипидов, арахидоновой кислоты и оксилипинов в сыворотке крови, что делает необходимым оптимизацию терапии. Жданова Е.В., Рубцова Е.В. (Тюмень, Курган) выявили иммунокомплексный механизм в патогенезе артралгии, артрита и дебюта остеоартропатии при постковидном синдроме с активным участием IgE. Следует обратить внимание на исследование Черевиковой И.А. с соавторами (Иркутск), показавших у девочек с постковидным синдромом наличие постковидной депрессивной симптоматики на протяжении 6-12 месяцев: повышенную тревожность, сниженную активность. Отмечен повышенный уровень ТТГ и кортизола 19.

Тема инфекций получила развитие в нескольких клинических и экспериментальных работах. В работе Гордеевой О.М., Тихоновой А.М. и Карпиной Н.Л. (Москва) приводятся оптимистичные данные по пересадке почки и назначении иммуносупрессивной терапии **без реактивации туберкулеза** в течение года у 6 из 7 больных туберкулезом. Сметанникова Н.А. и др. (Новосибирск, Хабаровск) на основе исследования летального случая выдвинули две гипотезы формирования третьего городского очага Ортохантавируса Сеул в Хабаровске, а Баянова Т.А. (Иркутск) провела ретроспективный анализ заболеваемости коклюшем, корью, ветряной оспой, менингококковой инфекцией в Иркутской области в период 1955–2023 гг.

В работе Пятидесятниковой А.Б. и др. (Иркутск) продемонстрирована способность нового селенсодержащего препарата повышать иммуногенность вакцинного штамма *Y. pestis* EV независимо от дозы. В еще одной экспериментальной работе Ляпуновой Н.А. и др. (Иркутск) при исследовании культуры клеток почки *M. sibiricus*, где наблюдается только фоновая экспрессия *IFN*-β, опровергнута гипотеза о постоянно «включенной» активности белков интерферонового пути у рукокрылых.

Серия работ посвящена практическим **вопросам офтальмологии**: крылонебной блокаде после трансплантации донорской роговицы (Олещенко И.Г. и Юрьева Т.Н., Иркутск); повышению эффективности комбинированного лечения ретинита Коатса с применением анти-VEGF препаратов в качестве неоадъювантной терапии (Букина В.В. и др., Иркутск); описанию клинического случая язвы роговицы как первому проявлению ВИЧ-инфекции (Матненко Т.Ю. и др., Омск); расширению диагностических возможностей с использованием компьютерной аккомодографии (Зеленцов Р.Н. и др., Архангельск).

Клинико-биохимические работы. Есимовой И.Е. и др (Томск) установлено, что у подростков с ожирением 1–3 степеней в крови регистрируются повышенные уровни инсулина и С-пептида, снижение концентрации GLP-2 и жирнокислотный дисбаланс (снижение доли GLA, DGLA, DPA, DHA, AA и повышение содержания ALA, OA, POA, BA, MA, PA, MAA), а также низкоинтенсивная субинтимальная воспалительная реакция. Яцков И.А. и др. (Крым)

доказали значимое влияние липополисахарид-связывающего белка (ЛСБ), бактерицидного белка, повышающего проницаемость (BPI) и sCD14, а также маркера системного воспаления – СРБ на риск развития макро- и микрососудистых осложнений при сахарном диабете 1 типа.

Смирнова О.В. и др. (Красноярск) выявили связь разных полиморфизмов генов *PNPLA3*, *HFE* и *UCP2* с дисбалансом в системе «ПОЛ-АОЗ», что может быть вызвано нарушением уровня железа и изменением антиоксидантной активности белка UCP2.

Как морфолога меня очень заинтересовала статья авторов из Италии и России Зенина О.К., Кафарова Э.С, Милтиадиса И. (Пенза, Грозный, Палермо-Италия), которые по результатам морфометрии коррозионных препаратов венечных артерий сердца человека установили расхождение их реальных данных с традиционно используемыми уравнениями, предложенными ранее Mette S. Olufsen и G. Finet, что ставит под сомнение правомерность их применения и численного моделирования реалистичной геометрии русла.

Две работы посвящены **психологии**. Маракшина Ю.А и др. (Екатеринбург) доказали правомерность применения «Госпитальной шкалы тревоги и депрессии» (HADS) для скрининга эмоционального дистресса у русскоязычных студентов. Мартынова А.А. и др. (Апатиты) при оценке качества жизни и психоэмоционального состояния беременных женщин показали, что в первую очередь на психоэмоциональное состояние беременной оказывает влияние физическое функционирование, взаимосвязь между психоэмоциональным состоянием и семейным статусом, количеством детей и среднедушевой доход.

В номер также вошла **экспериментальная работа** – Колесник В.Я., Пахомовой Р.А. и Колесник А.А. (Москва), – в которой показано, что наиболее эффективным для сохранения трансплантата жировой ткани оказался раствор с мембранопротектором диметилоксобутилфосфонилдиметилатом.

Читателей, несомненно, заинтересуют обзорные статьи, посвященные беременности: Зиганшин А.М. и др. (Уфа, Санкт-Петербург) по использованию масс-спектрометрии для исследования роли посттрансляционных модификаций белков при невынашивании беременности, что дает новые возможности для диагностики и прогноза, а также обзор Таскиной Е.С., и др. (Чита) по дисфункции гематоэнцефалического барьера при преэклампсии.

Совместный обзор Макаровой О.А. и др. (Иркутск, Санкт-Петербург) раскрывает потенциальные возможности прогнозирования ряда заболеваний по анализу групп крови, а работа Заранайна Р.-Л. и др. (Москва, Долгопрудный) описывает характеристики *Piper betle* семейства перечных *Piperaceae* как перспективного объекта для дальнейших исследований в области фитофармакологии.

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ПЕДИАТРИЯ

EXPERIENCE OF USING A NEW MEDICAL SIMULATOR FOR CORRECTING SPASTICITY OF THE UPPER LIMB IN COMPLEX REHABILITATION OF CHILDREN WITH HEMIPLEGIC CEREBRAL PALSY

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RESUME

Background. *The hemiplegic form of cerebral palsy (CP) is the most prognostically promising in terms of the possibilities of correction and social adaptation of disabled children. However, the main limitation of successful rehabilitation is severe limb muscle spasticity, because so reducing muscle hypertonicity is a priority task in this disease.*
The aim. *To evaluate the effectiveness of improved method for correcting of upper limb spasticity in children with the hemiplegic form of CP.*
Materials and methods. *An open, non-randomized, prospective, comparative study was conducted involving two groups of patients with spastic hemiplegia with predominant damage to the upper limb, compared to the case-control type. The control group of children (n = 20) was treated using standard methods – drug therapy, exercise therapy, massage, physiotherapy; the main group (n = 20) was additionally prescribed exercises on the new medical simulator "Glove". The study participants in the groups were compared by gender, age and severity of motor impairment. The course in comprehensive rehabilitation lasted 10 days. The effectiveness of the improved method for correcting upper limb spasticity was assessed by studying the dynamics of motor function indices using scales for assessing muscle tone (modified Ashworth scale) and manual skills (Frenchai and ARAT tests, V.G. Bosykh and N.T. Pavlovskaya method).*
Results. *The additional inclusion of training using the new medical simulator for correcting upper limb spasticity "Glove" in the rehabilitation program for children with hemiplegic CP allowed achieving a significantly better treatment result with a significant decrease in muscle tonus, an increase in the volume and accuracy of movements, including in the section of small differentiated acts, with the elimination of the phenomenon of the «learned non-use» phenomenon.*
Conclusions. *The use of a new medical simulator in the complex therapy of children with spastic hemiplegia allows increasing its effectiveness relative to standard rehabilitation methods. However, the question of the long-term effect remains open and requires an assessment of longer-term use of the simulator in the interhospital period.*

Keywords: *cerebral palsy, hemiplegia, upper limb, spasticity, rehabilitation, medical simulators, functional electrical stimulation, children*

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ОПЫТ ПРИМЕНЕНИЯ НОВОГО МЕДИЦИНСКОГО ТРЕНАЖЕРА ДЛЯ КОРРЕКЦИИ СПАСТИЧНОСТИ ВЕРХНЕЙ КОНЕЧНОСТИ В КОМПЛЕКСНОЙ РЕАБИЛИТАЦИИ ДЕТЕЙ С ГЕМИПЛЕГИЧЕСКОЙ ФОРМОЙ ЦЕРЕБРАЛЬНОГО ПАРАЛИЧА

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РЕЗЮМЕ

Обоснование. *Гемиплегическая форма детского церебрального паралича (ДЦП) является наиболее прогностически перспективной в отношении возможностей коррекции и социальной адаптации детей-инвалидов. Однако основным ограничением успешности реабилитации является выраженная спастичность мышц пораженной конечности, поэтому снижение мышечного гипертонуса является первоочередной задачей при данном заболевании.*

Цель исследования. *Оценить эффективность применения усовершенствованного способа коррекции спастичности верхних конечностей у детей с гемиплегической формой ДЦП.*

Методы. *Проведено открытое нерандомизированное проспективное сравнительное исследование с участием двух групп пациентов со спастической гемиплегией с преимущественным поражением рук, сопоставленных по типу случай-контроль. Контрольная группа детей (n = 20) была пролечена по стандартным методикам: медикаментозная терапия, лечебная физкультура, массаж, физиолечение; основной группе (n = 20) дополнительно были прописаны занятия на новом медицинском тренажере «Перчатка». Участники исследования в группах были сопоставлены по полу, возрасту и степени тяжести двигательных нарушений. Курс комплексной реабилитации составил 10 дней. Оценка эффективности усовершенствованного способа коррекции спастичности верхних конечностей проводилась за счет изучения динамики показателей двигательных функций по шкалам для оценки мышечного тонуса (модифицированная шкала Ашфорта) и мануальных навыков (тесты Френчай и ARAT, методика В.Г. Босых и Н.Т. Павловской).*

Результаты. *Дополнительное включение в программу реабилитации детей с гемиплегической формой ДЦП тренировок с помощью нового медицинского тренажера для коррекции спастичности рук «Перчатка» позволило достичь достоверно лучшего результата лечения со значимым снижением гипертонуса мышц, увеличением объема и точности движений, в том числе в разделе мелких дифференцированных актов, с устранением феномена «игнорирования» паретичной руки.*

Заключение. *Применение нового медицинского тренажера в комплексной терапии детей со спастической гемиплегией позволяет повысить ее эффективность относительно стандартных методик реабилитации. Однако вопрос о долгосрочности эффекта до сих пор остается открытым и требует более длительного применения тренажера в межстационарный период.*

Ключевые слова: *церебральный паралич, гемиплегия, верхняя конечность, спастичность, реабилитация, медицинские тренажеры, функциональная электростимуляция, дети*

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INTRODUCTION

Cerebral palsy (CP) is a complex of non-hereditary, non-progressive disorders of the motor functions of maintaining posture and balance that arise as a result of damage to the central nervous system (CNS) in the ante-, intra-, or neonatal period, causing persistent limitation of activity, often combined with intellectual-mnestic, speech, visual, and paroxysmal disorders [1]. The prevalence of this pathology as a whole, according to various sources, is 2.5-3 people per 1000 children per year. In the Russian Federation, this figure exceeds the prevalence in other countries and amounts to 4–5 cases per 1000 newborns [2]. The CP consequences significantly contribute to the increase in childhood disability rates due to neurological diseases. Moreover, the leading clinical CP manifestation, causing limitation of life activities and the need for outside assistance to perform everyday activities, is a syndrome of movement disorders [3, 4]. A common form of cerebral palsy, which ranks second in terms of incidence among the child population after classical diplegia (Little's paralysis), is spastic hemiplegia, which is clinically manifested by impaired movement function of the right or left limbs due to increased tone and decreased muscle strength when the opposite hemisphere of the brain is affected [5]. The leading symptom of this cerebral palsy form is spasticity, which develops as a result of damage to the central motor neurons and impairs the patients' quality of life. Such children require constant care and assistance from loved ones, long-term courses of expensive complex therapy, both in-patient and out-patient settings. Despite the fact that hemiplegic cerebral palsy has the most promising prognosis in terms of rehabilitation and social integration for children with disabilities, the main challenge to successful rehabilitation efforts is the pronounced muscle spasticity in the affected limb; therefore, reducing muscle tone is a priority for this condition [6, 7]. The most challenging aspect of rehabilitation for children with spastic hemiplegia is restoring motor function in the upper limb due to the paretic position of the hand and fingers, as well as the frequently occurring phenomenon of "ignoring" the paretic hand, also known as "learned non-use" [8, 9]. It should be noted that the hand is the most important part of the upper limb due to its ability to perform complex and varied motor acts, precisely coordinated by the central nervous system [10]. Restoring movement in a paired organ such as the upper limb is not enough; it is also necessary to identify and overcome the "learned non-use" phenomenon. Despite the high relevance of this problem in modern neurology and pediatrics, as well as the development of science and technology, there is currently no consensus on the rehabilitation of children with movement disorders, including spastic hemiplegia and upper limb dysfunction. This necessitates the priority and potential of additional scientific research in this area.

THE AIM OF THE STUDY

To evaluate the effectiveness of improved method for correcting upper limb spasticity in children with hemiplegic cerebral palsy.

MATERIALS AND METHODS

Study design: open, non-randomized, prospective, comparative study in parallel groups.

Following the initial examination of children, including an assessment of clinical and anamnestic data and neurological status, a clinical and rehabilitation diagnosis was made, short-term and long-term rehabilitation goals were determined, two groups of patients with hemiplegic cerebral palsy with predominant damage to the upper limbs were formed, compared according to the case-control type, and a rehabilitation plan was developed.

The study included 40 children aged 4 to 16 years: 20 (8 girls and 12 boys) formed the main group (MG) and 20 (7 girls and 13 boys) formed the control group (CG). Patients were matched by sex, age, clinical symptoms, and severity of motor impairments. Overall motor development was assessed and motor impairments were identified using the Gross Motor Function Classification System (GMFCS). Upper limb motor function was assessed using the Manual Ability Classification System (MACS) for children with cerebral palsy.

Eligibility criteria

Inclusion criteria:

- patients aged 4 to 16 years;
- hemiplegic cerebral palsy;
- moderate motor impairment (GMFCS II-III and MACS II-IV);
- preserved cognitive status;
- signed informed consent to participate in the study.

Exclusion criteria:

- consequences of severe traumatic brain injury and neuroinfections;
- congenital brain malformations with severe neurological deficits;
- low rehabilitation potential due to severe comorbidities;
- patients/legal representatives who are not familiar with the aims and objectives of the study.

Exclusion criteria:

- development or exacerbation of comorbidities, acute infectious diseases;
- patient/legal representative's refusal to participate in the study at any stage.

Study design

Patients were recruited for the study groups and rehabilitation programs at the Department of Neurology and Department of Physiotherapy, Exercise Therapy, and Massage at the Clinic of the Scientific Center for Family Health and Human Reproduction problems

(Irkutsk) from January 2024 to July 2025, from patients hospitalized with a diagnosis of cerebral palsy, according to the inclusion/exclusion criteria.

Study duration

The study duration was limited to the time of patients' hospitalization in the neurology department for rehabilitation and was 10 days (with a weekend break). Motor performance was assessed on the day of hospitalization and discharge, taking into account the patient's baseline motor status and its dynamics after completing the comprehensive rehabilitation program.

Description of the medical intervention

In accordance with clinical guidelines and the study protocol, all patients in the MG and CG received ultrasound-guided injections of botulinum toxin (BTA) on the day of hospitalization [11-14].

From the second day of hospitalization, all patients underwent intensive comprehensive rehabilitation, including standard drug therapy and a range of physiotherapeutic procedures (exercise therapy, physiotherapy, massage, and reflexology). All training and procedures under the rehabilitation program began 1 hour after breakfast. Exercise therapy sessions, including those using a medical simulator, were conducted by a qualified physician-instructor and included a set of special exercises to prevent the development of contractures, hypotonia, and/or muscle atrophy, as well as the formation of correct motor patterns and stimulation of object-manipulative activity. In order to reduce the hypertonicity of the upper limb muscles, patients in both groups were provided with a set of relaxation exercises at the start and throughout each exercise therapy session (including the use of the "Glove" simulator), in the form of free swinging and shaking of the hand, clapping on a flat surface using a relaxed hand, and massaging the hand and fingers [15]. Physiotherapy was performed using segmental electropulse stimulation of the cervical spine with the Lymphavizine device (No. 10). Patients in the MG and CG received standard nootropic and metabolic medications at age-appropriate doses.

Patients in the MG were additionally underwent daily training using a new medical simulator "Glove" to further correct upper limb spasticity (the training course lasted 10 days and included five sessions per week, lasting 30–40 minutes each, depending on the patient's age and ability to tolerate the physical activity) (Fig. 1).

The "Glove" rehabilitation simulator (developed in collaboration with Prototype LLC (Samara, Russia)) is a device for kinesiotherapy for upper limb spasticity. It improves the effectiveness of physical rehabilitation methods (specifically, kinesiotherapy) for patients with cerebral palsy, both in out-patient settings (at clinics, rehabilitation departments, sanatoriums, etc.) and at home, where patients often find the most comfort between hospitalizations. This portable medical device allows children to develop and strengthen skills in using their paretic hand, particularly the wrist and fingers, in a playful manner, and to reduce the severity of the common phenomenon known as "learned non-use" creating a positive emotional environment and additional motivation for the rehabilitation process. Built-in median nerve electrical stimulation, which activates damaged nerve pathways and improves muscle impulse transmission, helps restore control over paralyzed limbs by enhancing the activity of surviving neural connections and helps prevent muscle atrophy and secondary biomechanical complications [16].

Study outcomes

The primary outcome of the study was to determine whether there were differences between the MG and CG in terms of motor skills, muscle tone, and upper limb muscle strength at the time of hospital admission and after completion of an intensive short-term rehabilitation program.

Secondary outcome: not included.

Subgroup analysis: not performed.

Methods of recording outcomes

The effectiveness of the improved method for correcting upper limb spasticity was assessed based on the dynamics of muscle tone indicators, as well as the level of motor activity and motor skills of the upper limb, using the following methods and scales:

1) Modified Ashworth Scale. This scale was validated in the Russian Federation in 2020 [17]. The test results are scored as follows:

0 points – no increase in muscle tone;

1 point – slight increase in muscle tone and minimal muscle tension at the end of the movement pattern when flexing or extending the affected limb;

2 points – mild increase in muscle tone during grasping, accompanied by minimal resistance;

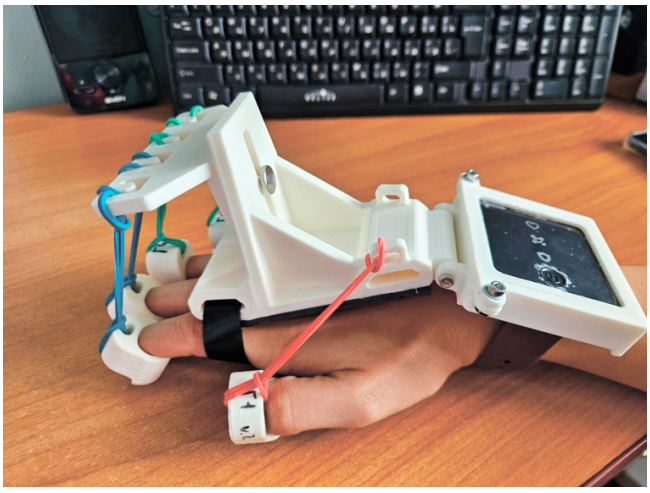


FIG. 1.
Medical simulator "Glove" for correcting of upper limb spasticity

3 points – more pronounced increase in muscle tone across most of the range of movement, with limited passive motor activity;

4 points – significant muscle tension with marked difficulty in passive movement;

5 points – flexion or extension contracture of the limbs.

2) The Frenchay Arm Test for studying the gestural-communicative function of the upper limb (non-verbal communication function) [8]. The method includes 5 tasks: fixing an object (ruler) using the hand, grasping cylindrical objects of various diameters, using a pinch grip, and touching the top of the head.

3) A modified ARAT (Action Research Arm Test) test for assessing the motor activity of the affected limb [18]. This international scale, which provides a detailed assessment of the motor function of the hand and fingers, allows for the evaluation of various types of grip, as well as large movements of the joints, consists of 19 assessed items (tasks), which are divided into four subtests (subtest 1 – ball grip; subtest 2 – cylindrical grip, squeezing an object; subtest 3 – pinch grip; subtest 4 – large movements of the hand – extension and flexion in the elbow and shoulder joints). A standard set of items is provided for performing the testing procedure. The ARAT test has high sensitivity even with minor changes in the pattern of movements of the upper limb, especially in patients with spastic syndromes.

4) The method of V.G. Bosykh and N.T. Pavlovskaya [19] is intended for additional assessment of manual functions in children with different forms of cerebral palsy during their daily activities. During examination of the motor functions of the upper limb, the range of motion in the joints, the position of the hands during walking and performing manual skills, the presence and degree of spasticity, the ability to voluntarily hold and release an object, the development of the main types of grips and their quality, the ability to perform manipulations with objects, their quality and speed of execution, the ability to perform isolated movements of the fingers, and the characteristics of graphic skills are determined. Each hand is assessed separately on a five-point scale.

Statistical analysis

The sample size was not calculated in advance. Statistical processing of the study results was performed using Statistica for Windows version 10.0 (StatSoft, USA). Continuous data were presented as the median (Me) with upper and lower quartiles [25th and 75th percentiles] due to the small sample size in each group (preliminary testing of groups for normal distribution was not performed); qualitative characteristics were presented as absolute values and percentages of observations. Comparability of clinical and demographic parameters between the MG and CG was assessed using the Mann–Whitney U-test. When comparing groups based on qualitative characteristics, the χ^2 test with Yates' correction was used (if the number of observations in any cell was <10). In cases of a small number of observations (up to 5), Fisher's exact test was used. Treatment effectiveness was assessed based on changes in manual function across groups using the Wilcoxon signed-rank test (W) for dependent samples. All differences were considered significant at $p < 0.05$.

Compliance with ethical principles and ethical review of the study

The ethical principles outlined in the World Medical Association Declaration of Helsinki (1964), as amended in 2024 (amended at the 75th General Assembly of the World Medical Association, Helsinki), were observed in the study with patients. All study procedures were conducted only with the informed voluntary consent (IVC) of patients (upon reaching the age of 15 and being recognized as competent) and their legal representatives, signed on the day of hospitalization. The study protocol and accompanying documents (information sheet and IVC) were pre-approved by the local Biomedical Ethics Committee of the Scientific Centre for Family Health and Human Reproduction Problems (Protocol No. 5 dated June 5, 2023).

RESULTS

The motor sphere parameters, specifically muscle tone, motor functions and skills of the affected upper limb, were analyzed in 40 patients with hemiplegic cerebral palsy, assessed before and after an intensive short-term rehabilitation course according to the protocol of this study.

Characteristics of the comparison groups

Before the study began, the MG and CG patients with cerebral palsy were similar in age, sex, severity of motor impairments according to the GMFCS and MACS, and the nature of perinatal CNS pathology. Distribution of patients by the side of the affected limb revealed a predominance of right-hand paresis in the CG (Table 1).

Main results of the study

When comparing the results of the modified Ashworth scale before treatment, no statistically significant differences were found between the MG and CG. Upper limb muscle spasticity was expressed equally in all patients (Me 3 points [25–75%: 2–3] in the MG versus Me 3 points [25–75%: 2–4] in the CG, $p = 0.175$). After a short-term course of intensive comprehensive rehabilitation, patients in the MG achieved significant positive dynamics in these indicators, which was not observed in the CG (Me 2 points [25–75%: 1–2], and Me 3 points [25–75%: 2–4], respectively, $p_w = 0.015$ and $p_w = 0.875$).

A comparative analysis of the efficacy of the comprehensive rehabilitation programs for two groups of patients with spastic hemiplegia is presented in Table 2 and Figure 2.

An analysis of the dynamic changes in motor function after a short-term course of intensive rehabilitation for patients with cerebral palsy at a neurological

hospital revealed that improved motor performance and the development of new motor skills was observed in patients from both groups, accompanied by an increased frequency in the use of alternative movement patterns and greater precision in performing manipulative tasks. However, motivation for bimanual movement in the CG was only observed upon prompting and was very limited. A sustained increase in motivation was observed in only 10 % of children from the CG, while this indicator in the MG reached 55 % ($p = 0.007$), but mainly with mild to moderate severity of movement disorders (GMFCS and MACS levels II-III). A similar distribution of patients in the MG and CG was observed with respect to a reduction in the incidence of the phenomenon of "ignoring" the paretic hand (10 % and 60 %, respectively, $p = 0.003$). However, the efficiency of movements improved only in some patients in the MG, but not in the control. Overall, it should be noted that the dynamics of motor activity indicators in the affected upper limb during

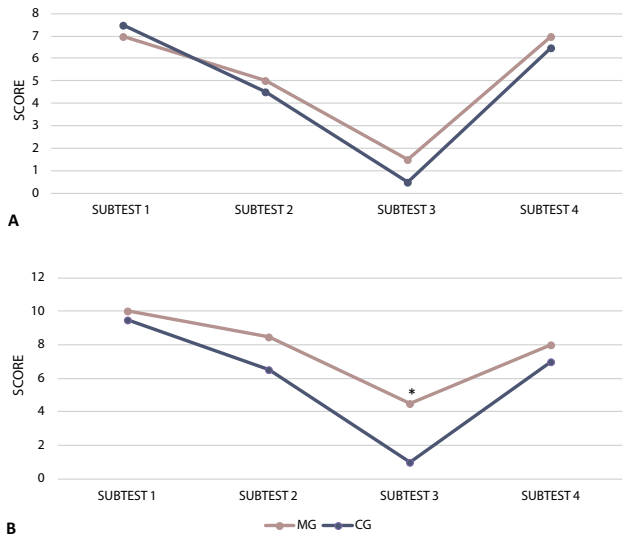
TABLE 1

INITIAL CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF PATIENTS

Indicator	MG ($n = 20$)	CG ($n = 20$)	p-level
Age, years	10[7-12]	9.5[7-12.5]	0.989
Sex:			
girls	8(40)	7(35)	1.000
boys	12(60)	13(65)	1.000
Lateralization of the upper limb lesion:			
right hand	10(50)	15(75)	0.191
left hand	10(50)	5(25)	0.191
Severity of movement disorders			
GMFCS:			
I	-	-	
II	15(75)	14(70)	1.000
III	5(25)	6(30)	1.000
IV	-	-	
V	-	-	
MACS:			
I	-	-	
II	4(20)	5(25)	1.000
III	12(60)	10(50)	0.525
IV	4(20)	5(25)	1.000
V	-	-	
Types of perinatal organic brain damage			
Porencephalic and other cysts, hypoplasia of the corpus callosum and other parts of the brain	7(25)	6(30)	1.000
Periventricular leukomalacia	2(10)	2(10)	0.598
Adreno-, leuko-dystrophy, cystic gliosis changes	3(15)	3(15)	0.658
Hydrocephalus, ventriculomegaly	5(25)	5(25)	0.715
ACVA	2(10)	2(10)	0.598
Hypoxic/toxic-ischemic brain injury	2(10)	3(15)	1.000
Combination of brain pathologies	5(25)	5(25)	0.715

Note. The data are presented as Me [25%–75%] and abs. (%). ACVA – acute cerebrovascular accident; GMFCS – Gross Motor Function Classification System; MACS – Manual Ability Classification System. p – level of statistical significance of differences in groups, taking into account the criteria: 1 – Pearson χ^2 with Yates' correction and 2 – Fisher's exact test.

comprehensive rehabilitation were more intense with the additional use of the new "Glove" device in the exercise therapy program, due to a statistically significant reduction in spasticity in the arm muscles, particularly in the hands and fingers, including their distal regions. This significantly improved manual activity (including the gestural and communicative function of the upper limb according to The Frenchay Arm Test) in terms of not only "large", "undifferentiated", and "immature" movements, primarily due to an increase in range of motion in large joints and the ability to grasp, hold, and release a large object (typical of patients in the control group), but also "fine" motor skills, including improved quality and speed of cylindrical and pinch grasps (Fig. 2). Most patients with spastic hemiplegia who underwent intensive rehabilitation using an improved method for correcting upper limb spasticity also demonstrated significant improvements in their ability to perform isolated finger movements and in their graphic skills using the additional method of V.G. Bosykh and N.T. Pavlovskaya.



** – p < 0,05 – statistically significant differences between groups according to the U-test.*

FIG. 2.
Indicators of ARAT's subtests in the main and control groups. A – pre-treatment; B – post-treatment

DISCUSSION

Summary of the main study findings

The addition of the new "Glove" medical simulator for correcting hand spasticity in the short-term intensive rehabilitation program for children with hemiplegic cerebral palsy resulted in significantly improved treatment outcomes in the neurology department, with a significant reduction in upper limb muscle tone, an increase in the range and precision of movement, including fine-grained movements, and the elimination of the phenomenon of "ignoring" the paretic hand.

Discussion of the main study findings

To date, numerous programs, methods, and devices have been developed for the rehabilitation of motor functions in cerebral palsy, most of which have established a strong reputation in the medical and patient (parent) communities due to their high effectiveness and reduced socioeconomic burden on families and the state. However, the therapeutic effect of many of these is primarily aimed at developing

TABLE 2

ANALYSIS OF DIFFERENCES IN THE SCALES FOR ASSESSING MANUAL SKILLS IN PATIENTS OF THE MAIN AND CONTROL GROUPS BEFORE AND AFTER TREATMENT

Indicator	Period	MG (n = 20)	CG (n = 20)	p_u	p_w MG/p_w CG
The Frenchay Arm Test, score	initially after treatment	3 [2-6.5] 6 [5-8]	4 [2-6.5] 5 [3-8]	0.913 0.061	0.036/ 0.745
ARAT test, total score	initially after treatment	23 [7.5-27.5] 35.5 [17.5-53.5]	21.5 [8-34.5] 24.5 [13-39.5]	0.924 0.116	0.017/ 0.528
Method of V.G. Bosykh and N.T. Pavlovskaya, score	initially after treatment	21 [19.5-28] 31.5 [25.5-35]	25.5 [21-31.5] 28.5 [24-32.5]	0.171 0.328	0.027/ 0.354

Note. The data are presented as Me [25%–75%]. ARAT – Action Research Arm Test, a test of hand motor activity. p_u is the level of statistical significance of differences between the MG and CG according to the Mann–Whitney criterion; p_w is the level of statistical significance of differences in groups according to the Wilcoxon T-criterion.

the muscles of the lower torso and legs and developing a physiological gait pattern [4, 20-22]. At the same time, the theoretical and practical aspects of rehabilitation of children with upper limb impairments remain a pressing and challenging task in pediatric science and clinical neurology. It should be noted that the human hand plays a vital role at all stages of ontogenesis in the development of verticalization and balance, which, in turn, allows the child to free the upper limbs to perform complex manipulations, develop and refine fine differentiated motor acts (including drawing and writing), and self-care skills [15]. Functionally, the hand is the most important part of the upper limb [23]. For children with cerebral palsy, pathognomonic symptoms include pronation of the forearm, flexion contracture of the distal upper limb, and inability to abduct the thumb, which hinders or eliminates manipulation of objects and, in turn, complicates the rehabilitation process and reduces its effectiveness [24]. In severe paresis and organic brain damage, these motor impairments are accompanied by the phenomenon of "ignoring" the paretic hand, as demonstrated in our study. Given the high functional significance of the upper limb in everyday activities, early and complete restoration of its motor activity is a pressing task.

Our study is not a pioneer in this area, including among domestic developments of rehabilitation simulators for restoring upper limb function. The reviews by E.A. Biryukov et al. (2022), Chen Y.P. et al. (2016), and Cardone D. et al. (2025) emphasized the importance of modern rehabilitation technologies for improving upper limb function [25-27]. However, the reviewed studies on this topic, in patients with cerebral palsy, primarily demonstrate the use of robotic simulators and devices equipped with biofeedback or a computer-based neurointerface, where the development of correct upper limb motor patterns is achieved primarily through a passive training and the acquisition of adaptive sensory-motor experience by the child. Our development does not include robotic elements; the child must apply voluntary effort to perform active actions with the upper limb. However, the game-based nature of the training helped to increase motivation for training and its effectiveness, similar to previously created rehabilitation devices. It is worth highlighting four studies in which patients, as in our study, suffered from the hemiplegic form of cerebral palsy and had similar severity of motor impairments according to the GMFSC and MACS [9, 28-30], in one of which [29] the frequency and exposure of intervention using the simulator corresponded to that stated by us (10 days, 30 minutes per day). The authors obtained similar results regarding the improvement of fine differentiated movements of the hand and fingers, the speed and accuracy of manipulations, and the emergence of bimanual activity, that is, a decrease in the frequency of the phenomenon of "learned non-use", as demonstrated in this study in children with spastic hemiplegia. The importance of using functional electrical stimulation (provided for in the developed device) in combination with kinesiotherapy is also confirmed in the study of Kim T-W. et al. (2016) to correct spasticity and stimulate the wrist extensor muscles, and as a result, improve wrist extension and fine motor skills of the hand and fingers [30].

The primary objective of neurorehabilitation for patients with paralytic syndromes is to restore motor function and prevent the development of secondary biomechanical complications. Unfortunately, severe muscle spasticity in cerebral palsy impairs the quality of life of patients and their families, hinders the development of complex motor skills, and complicates rehabilitation measures. There is no single, universally accepted method for correcting it, making scientific research and innovation in this field a priority and a justified approach. This research direction is outlined in the study.

Study limitations

The main limitation of our study was the small sample size of patients with spastic hemiplegia and the small number of participants in the comparison groups, which precludes the generalization of our results to the general population of patients with this form of cerebral palsy. It should be noted that our results are consistent with the hypothesis that comprehensive rehabilitation programs aimed at restoring motor function in cerebral palsy are more effective in children with mild to moderate motor impairments. However, this study's limitation prevented us from analyzing the efficacy of the improved method for correcting upper limb muscle spasticity among patients of all GMFCS functional levels (I-V). Furthermore, in order to achieve the desired treatment outcomes in only a selected group of patients, it is necessary to incorporate specific features into the developed simulator to enhance the rehabilitation process, increase motivation and adherence to treatment, and programmatically analyze the obtained data, such as biofeedback and SOI. Limitations of this study also include the lack of long-term follow-up of the patients treated, which would allow for assessment of the long-term effectiveness of the rehabilitation program. Further research is needed to evaluate the effectiveness of the new medical simulator "Glove", the development and clinical application of updated models, taking into account the identified limitations of this study.

CONCLUSION

The effectiveness of the chosen comprehensive rehabilitation program for children with cerebral palsy determines the subsequent prognosis of the disease, with either regression of motor function impairment or transformation into a permanent motor defect.

To develop the optimal combination of rehabilitation methods and determine the parameters for restorative treatment procedures, it is necessary to analyze the comparative efficacy and evaluate the immediate and long-term results of treatment and rehabilitation methods and devices. In our study, the use of an improved method for correcting upper limb muscle spasticity in patients with hemiplegia demonstrated positive results in terms of reducing abnormal muscle tone in the upper limb, increasing the range and precision of movement, including small and differentiated movements, and eliminating the phenomenon of "ignoring" the paretic arm. Thus, the use of a new medical simulator in the comprehensive treatment of children with hemiparetic cerebral palsy allows for increased efficacy compared to standard rehabilitation methods. However, the long-term efficacy of such training remains unclear and requires evaluation of longer-term simulator usage for self-rehabilitation during the post-hospital period. In this regard, the development of treatment and rehabilitation programs based on new technologies for the non-pharmacological correction of motor dysfunction in children with paralytic syndromes and cerebral palsy, ensuring the continuity of rehabilitation processes through the seamless transition between inpatient and outpatient stages and their rapid implementation into practical health care, are relevant areas of innovative research and development in modern neuropediatrics.

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Conflicts of interest

No potential conflict of interest relevant to this article reported.

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OBSTETRICS AND GYNAECOLOGY

PATHOGENETIC MECHANISMS OF BLOOD-BRAIN BARRIER DYSFUNCTION IN PREECLAMPSIA

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RESUME

Hypertensive disorders during pregnancy are the most difficult and unresolved problems of modern obstetrics. Today, their frequency ranges from 12 to 40 % and has no downward trend. About 60–70 % of maternal deaths in hypertensive disorders occur due to cerebral complications, due to the development of eclampsia, cerebral edema and stroke. Underestimating the severity of the condition, inadequate treatment and delayed delivery are the main causes of maternal morbidity and mortality. Despite significant advances in understanding the main stages of the pathogenesis of preeclampsia, the mechanisms of damage to cerebral vascular endothelial cells, as well as the features of local paracrine and autocrine regulation of cerebrovascular blood flow in proinflammatory and hypoxic conditions remain relevant for further study. This literature review is devoted to the study of the main mechanisms of disruption and/or damage to the blood-brain barrier in preeclampsia. A systematic analysis of modern Russian and foreign literature was carried out using the information databases eLibrary, Scopus, PubMed, MEDLINE and Cochrane Library for the period from January 2010 to December 2024. Information is provided on the role of vascular endothelial growth factor and its receptor system in increasing transcellular transport, as well as close contact proteins in enhancing the paracellular pathway. The mechanisms of impaired autoregulation of cerebral blood flow leading to the development of vasogenic cerebral edema in preeclampsia and eclampsia are described. Understanding the key links in the pathogenesis of damage to the blood-brain barrier in preeclampsia will allow us to further identify reliable and accessible early predictors of the development of cerebral dysfunction in this complication of pregnancy.

Keywords: *preeclampsia, eclampsia, hypertensive disorders during pregnancy, blood-brain barrier, cerebrovascular complications, biomarkers of cerebral dysfunction*

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ПАТОГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ ДИСФУНКЦИИ ГЕМАТОЭНЦЕФАЛИЧЕСКОГО БАРЬЕРА ПРИ ПРЕЭКЛАМПСИИ

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РЕЗЮМЕ

Гипертензивные расстройства во время беременности относятся к наиболее сложным и нерешенным проблемам современного акушерства. На сегодняшний день их частота составляет от 12 до 40 % и не имеет тенденции к снижению. Около 60–70 % материнских смертей при гипертензивных расстройствах происходят из-за церебральных осложнений, вследствие развития эклампсии, отека головного мозга и инсульта. Недооценка степени тяжести состояния, неадекватное лечение и запоздалое родоразрешение являются основной причиной материнской заболеваемости и смертности. Несмотря на значительные успехи в понимании основных этапов патогенеза преэклампсии, механизмы повреждения эндотелиальных клеток сосудов головного мозга, а также особенности локальной паракринной и аутокринной регуляции цереброваскулярного кровотока в провоспалительных и гипоксических условиях, остаются актуальными для дальнейшего изучения. Данный литературный обзор посвящен изучению основных механизмов нарушения и/или повреждения гематоэнцефалического барьера при преэклампсии. Проведен систематический анализ современной отечественной и зарубежной литературы с использованием информационных баз eLibrary, Scopus, PubMed, MEDLINE и Cochrane Library за период с января 2010 г. по декабрь 2024 г. Представлена информация о роли фактора роста эндотелия сосудов и системы его рецепторов в увеличении трансклеточного транспорта, а также белков плотных контактов в усилении паракле точного пути. Описаны механизмы нарушения ауторегуляции мозгового кровотока, ведущие к развитию вазогенного отека головного мозга при преэклампсии и эклампсии. Понимание ключевых звеньев патогенеза повреждения гематоэнцефалического барьера при преэклампсии позволит в дальнейшем определить надежные и доступные ранние предикторы развития церебральной дисфункции при данном осложнении беременности.

Ключевые слова: *преэклампсия, эклампсия, гипертензивные расстройства во время беременности, гематоэнцефалический барьер, цереброваскулярные осложнения, биомаркеры церебральной дисфункции*

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INTRODUCTION

According to modern concepts, preeclampsia is defined as a complication of pregnancy, childbirth and the postpartum period, characterized by an increase in blood pressure after the 20th week of pregnancy (≥ 140 and/or ≥ 90 mm Hg) in combination with proteinuria (protein loss > 0.3 g/day or > 0.3 g/l in 2 portions of urine taken at an interval of 6 hours) and/or at least one other parameter indicating the development of multiple organ failure [1]. Without proper treatment, preeclampsia is associated with severe cerebrovascular complications, including eclampsia (seizures), hemorrhagic and ischemic stroke, posterior reversible encephalopathy syndrome (PRES), and reversible cerebral vasoconstriction syndrome (RCVS) [2, 3, 4]. Magnetic resonance imaging (MRI) has shown that 70–100 % of patients with severe preeclampsia have cerebral edema with evidence of increased intracranial pressure [5]. Cerebrovascular changes are the direct cause of approximately 70 % of maternal deaths [2, 6, 7].

The two-stage concept of preeclampsia development suggests that impaired placentation causes chronic placental ischemia and oxidative stress, which leads to the release of antiangiogenic factors, free radicals, and oxidized lipids into the maternal circulation, contributing to the development of generalized endothelial dysfunction [8, 9]. The results of preclinical and clinical studies have shown that in preeclampsia there is an imbalance between pro- and antiangiogenic factors, characterized by an increase in circulating soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng) levels, with a simultaneous decrease in the concentration of placental growth factor (PlGF) and transforming growth factor β1 (TGF-β1) [10].

According to the proposed model of preeclampsia pathogenesis, cerebrovascular complications are one of the possible manifestations of multisystemic endothelial damage [2, 6, 7]. However, this concept does not fully reflect the pathogenesis of central nervous system dysfunction, as in approximately one third of women, eclampsia may develop against the background of moderate levels of arterial hypertension and in the absence of proteinuria, and cerebral complications may occur after childbirth [8, 11].

In a study conducted by Too G. et al. in 2018, it was reported that the risk of stroke within 60 days after delivery for women who experienced hypertensive disorders during pregnancy was 41.7 % [12]. The exact prevalence of posterior reversible encephalopathy syndrome is not fully understood. However, a retrospective study conducted by Liman T.G. et al. in 2012 showed that PRES was present in more than 90 % of women with eclampsia and approximately 20 % of those with preeclampsia [13]. Eclampsia remains a serious complication of pregnancy, and reliable biomarkers or clinical indicators for predicting the development of seizures do not currently exist [14].

A long-term consequence of preeclampsia and eclampsia is damage to the white matter of the brain, which can be observed on magnetic resonance imaging several years after delivery, which significantly increases the risk of future cognitive impairment and dementia [15, 16]. Despite significant progress in understanding the key stages of preeclampsia pathogenesis, the mechanisms underlying damage to cerebral endothelial cells and the characteristics of local paracrine and autocrine regulation of cerebal blood flow under proinflammatory and hypoxic conditions remain relevant for further study [2, 6, 7].

Assessment of blood-brain barrier permeability in hypertensive disorders during pregnancy

The blood–brain barrier (BBB) is a neurovascular unit that separates brain tissue from the systemic circulation. Components of the neurovascular unit include endothelial cells, pericytes, perivascular nerves, smooth muscle cells, astrocytes, and adjacent neurons [17]. Cerebral endothelial cells have distinct characteristics compared to those in peripheral organs due to their lack of fenestrations. Instead, they are connected to one another through a dense network of tight junctions, which have high electrical resistance and regulate the transport of water-soluble substances, such as nutrients, metabolites, and gases, across the barrier. The BBB serves as a protective barrier that prevents the brain from neurotoxins, neurotransmitters, and macromolecules [18].

BBB disruption plays a central role in the pathogenesis of cerebral complications in women with preeclampsia [6, 18, 19]. Cerebral edema, often observed in severe preeclampsia and eclampsia, is likely due to dysfunction of endothelial cells of the cerebral microcirculation, which leads to increased permeability and fluid perfusion into the brain parenchyma [14]. Increased BBB permeability in preeclampsia may be attributed to a variety of pathogenetic mechanisms: increased transcellular transport without changing the mechanical properties of the BBB (implemented through VEGF and its receptor system); enhanced paracellular pathway (changes in the expression/function of tight junction proteins (TJs)); increased microvascular pressure leading to the formation of vasogenic cerebral edema (impaired cerebral blood flow autoregulation) [6, 18]. Figure 1 schematically illustrates the main pathophysiological mechanisms of increased BBB permeability.

To characterize the pathogenetic mechanisms involved in the development of cerebrovascular complications of preeclampsia, several researchers have developed experimental animal models [20, 21]. Most studies aimed at investigating changes in BBB functionality in humans are primarily conducted using MRI of the brain [22] and assessing the levels of circulating markers of neuroinflammation, neurodegeneration, and endothelial dysfunction in various biological fluids (blood, cerebrospinal fluid, urine, tears) [19, 23, 24].

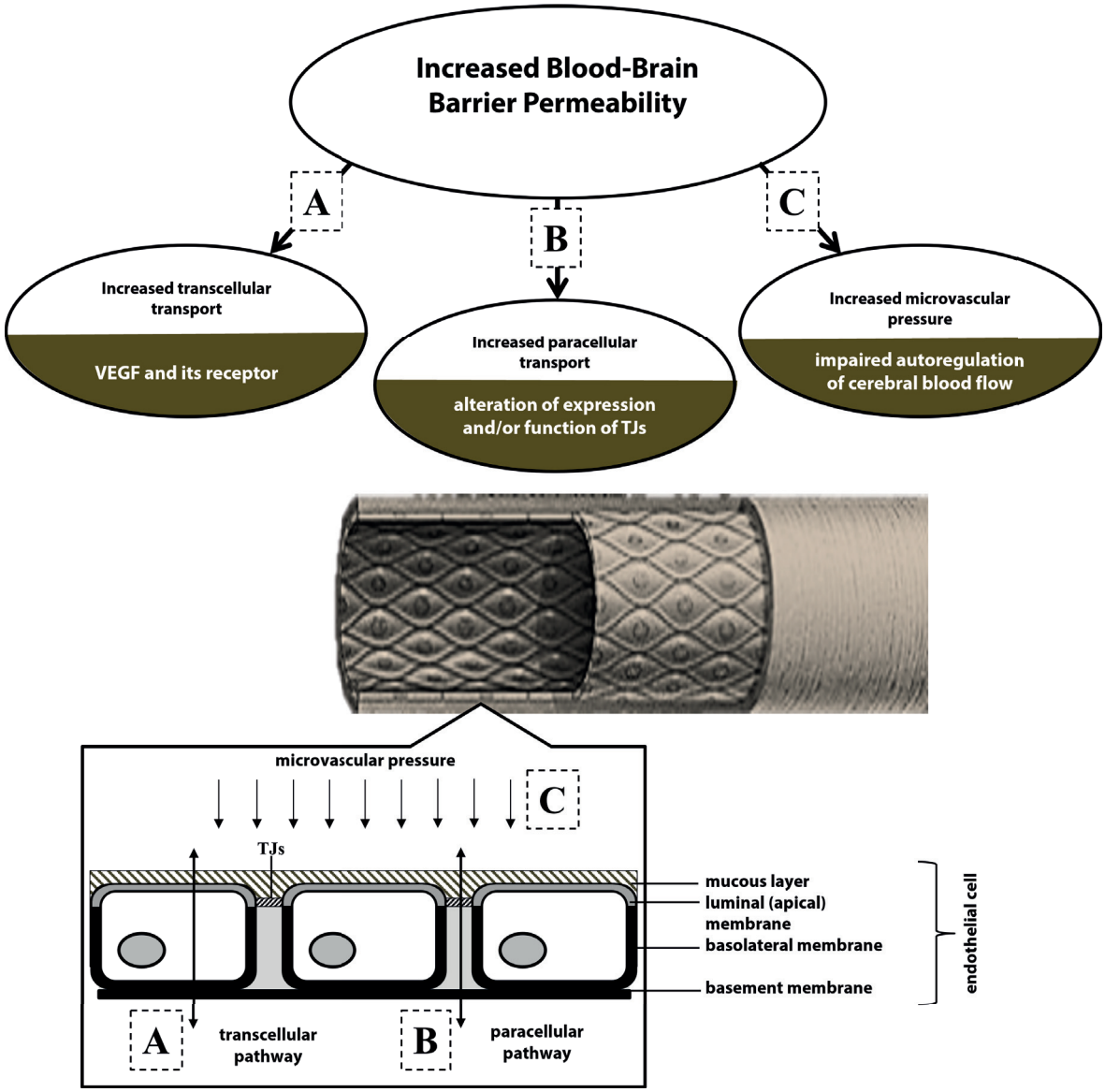

FIG. 1.
The main pathophysiological mechanisms of increased permeability of the blood-brain barrier

It has been established that the levels of neurospecific markers may indicate brain injury prior to the onset of overt neurological symptoms [24].

The results of the studies reviewed are contradictory regarding the disruption of BBB integrity in preeclampsia. In the study conducted by Burwick R.M. et al. in 2019, the levels of albumin, complement proteins C5a, C5b-9, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were measured in paired blood and cerebrospinal fluid samples in patients with preeclampsia, during which no signs of BBB damage and neuroinflammation were observed [19].

According to other data collected by Johnson A.C. et al. (2014) in a study on a rat model of severe preeclampsia, it has been shown that the administration of magnesium sulfate ($MgSO_4$) increased the seizure threshold while maintaining the integrity of the blood-brain barrier. To simulate severe preeclampsia, placental ischemia (decreased uteroplacental perfusion pressure) was created in combination with a high-cholesterol diet. The rats developed arterial hypertension, oxidative stress, endothelial dysfunction, fetal growth retardation, and placental hypoplasia. The seizure threshold was determined by measuring the amount

of pentylenetetrazol (PTZ). Rats that were not administered $MgSO_4$ were more sensitive to PTZ, with a seizure threshold that was 65 % lower than that of the control group ($p < 0.05$). BBB permeability to sodium fluorescein, measured *in vivo*, revealed an increase in rats that had not received $MgSO_4$ treatment, compared to controls ($p < 0.05$) [21].

Calcium-binding protein S100B is a biomarker of BBB activation/damage [23, 24]. This protein affects the proliferation, differentiation, and growth of endothelial cells in the cerebral circulation, as well as calcium homeostasis and intracellular enzymatic activity. A dose-dependent effect of S100B has been demonstrated. At low concentrations, when there is increased BBB permeability without damage to the central nervous system, this cerebral marker has a neuroprotective effect. High concentrations of S100B have been found to be associated with neurotoxicity, inflammation, activation of microglia and astroglia, and increased expression of proinflammatory mediators [25].

The research group led by Friis T. et al. (2022) analyzed the concentration of neuroinflammatory and neurodegenerative markers, including neurofilament light chain (NfL), tau protein (Tau), neuron-specific enolase (NSE), and S100B, in the blood plasma samples of patients with preeclampsia, pregnant women with a normal pregnancy, and non-pregnant women. Plasma concentrations of NfL, Tau, NSE, and S100B were higher ($p < 0.05$) in women with preeclampsia compared to patients in other study groups. The researchers created an *in vitro* BBB model including human cerebral vascular endothelial cells (hCMEC/D3). Increased plasma NfL levels were associated with decreased transendothelial electrical resistance ($p = 0.002$), used in an *in vitro* model to assess BBB integrity [24].

Research aimed at exploring markers of neuroinflammation and neurodenaturation in preeclampsia requires further investigation. We believe that studying the levels of these markers may allow for an indirect assessment of BBB permeability and potentially help develop screening tests to identify individuals at high risk of severe cerebral complications and optimize management and treatment strategies for these patients.

The pathogenic role of VEGF in the cerebrovascular complications of preeclampsia

The VEGF protein family is classified as angiogenic factors that regulate vascular permeability, endothelial cell viability, and participate in vasculogenesis and vasorelaxation by stimulating the synthesis of nitric oxide (NO), including in the cerebral circulatory system. These homodimeric proteins are present in five different isoforms: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PlGF [26]. PlGF regulates angiogenesis via its signaling pathways or by enhancing VEGF-mediated activity. For the development of normal pregnancy, the levels of VEGF and PlGF within the bloodstream rise, but the mechanisms through which the brain and BBB adapt to these changes are unknown [27].

Human vascular endothelial growth factor receptors (VEGFRs) are transmembrane tyrosine kinase structures that include VEGFR1 or Fms-like tyrosine kinase-1 (Flt-1), VEGFR2 or kinase insert domain receptor (KDR), and VEGFR3 or Flt-3 [26]. VEGFR-mediated VEGF signaling to induce vascular permeability has been well studied in peripheral tissues. VEGF has affinity for both Flt-1 and VEGFR2, whereas PlGF binds only to Flt-1 [18].

VEGFR2 has been shown to be expressed in endothelial cells and in the trophoblast layer of the human placenta. This receptor has a more potent tyrosine kinase activity than VEGFR1. VEGFR1 has been found to induce a transient opening of endothelial intercellular junctions, while VEGFR2 seems to act as a major regulator of cellular permeability [27].

Chronic placental ischemia leads to an increase in the level of hypoxia-inducible factor-1-alpha (HIF-1α). HIF-1α has been shown to be oxygen-sensitive and it is rapidly inactivated and degraded under normoxia, while its degradation is inhibited under hypoxic conditions [28]. When HIF-1α binds to HIF-1β, active HIF-1 is formed, which is transferred to the cell nucleus to regulate the expression of various genes, such as sFlt1 and sEng [29].

Several weeks prior to the preeclampsia onset, the placenta overproduces sFlt-1, which is accompanied by an increase in its concentration in the maternal serum [9, 18]. sFlt-1 has been identified as a truncated splice variant of VEGFR-1 and consists of six extracellular IgG-like domains with a unique C-terminus, lacking transmembrane and intracellular domains. *In vivo*, it has been reported that sFlt-1 exists as several isoforms with varying molecular weights between 100 and 145 kDa [18]. sFlt-1 has been found to act as a VEGFR1 decoy receptor, binding both VEGF and PlGF and reducing the levels of their active circulating forms. It also forms a heterodimer with VEGFR2, inhibiting the activation of this receptor [30]. Therefore, it can be proposed that in preeclampsia, sFlt-1 functions as an antagonist of VEGFR2 signaling, balancing the effects of VEGF-mediated signaling by regulating BBB permeability (Fig. 2) [18, 30].

The VEGFR2-mediated signaling pathway that induces BBB permeability has not yet been fully understood. In an *in vitro* experiment, Torres-Vergara P. et al. (2022) used human brain endothelial cells as a BBB model, which were subjected to treatment with plasma derived from women with preeclampsia. The study found that VEGFR2 is involved in BBB disruption by increasing apoptosis and permeability of cerebral endothelial cells. Activation of this receptor occurs due to increased phosphorylation at tyrosine 951 (pY951), and inhibition at tyrosine 1175 (pY1175) [27].

According to a study conducted by Troncoso F. et al. in 2023, infants who experienced preeclampsia during their intrauterine development demonstrate reduced angiogenesis in the brain nuclei. This is associated

with lower circulating VEGF/PlGF/VEGFR2 protein levels, impaired brain endothelial migration, and dysfunctional assembly of F-actin filaments. These changes may predispose to structural and functional alterations in long-term brain development [31].

It has been found that the sFlt1 level in the first trimester is not clearly associated with the development of preeclampsia [32]. According to the study conducted by Nzelu D. et al. in 2020, women with chronic arterial hypertension in the first trimester showed reduced concentrations of PlGF and sFlt-1. Furthermore, these markers had low predictive value for the development of preeclampsia (ROC-AUC = 0.567 [95% CI 0.537–0.615] and 0.546 [95% CI 0.507–0.585], respectively) [10]. The results of first trimester preeclampsia screening based on an algorithm that combines PlGF level assessment with maternal clinical factors, mean arterial pressure, and uterine artery pulsatility index provide consistent and promising results in predicting preeclampsia [33]. Moreover, the assessment of the sFlt1/PlGF ratio in pregnant women also has diagnostic value [34].

It is important to emphasize that sFlt-1 is not the sole factor responsible for the antiangiogenic imbalance in preeclampsia. The role of Endoglin (Eng), which is a TGF-β1 co-receptor, is currently under investigation. The extracellular domain of Eng inhibits TGF-β1 binding to the cell surface, thereby reducing the effect of NO [27]. It has been found that TGF-β1 modulates VEGFR2 signalling in endothelial cells [35].

In a model of HELLP syndrome induced by the daily administration of exogenous sFlt-1 and sEng to pregnant mice, a regional increase in BBB permeability at the posterior cortex was observed [36]. Because the administration of exogenous sFlt-1/sEng leads to the development of a HELLP-like syndrome, other models based on reduced uteroplacental perfusion may be more appropriate for studying cerebrovascular complications associated with preeclampsia. In such models, increased sFlt-1/sEng levels and BBB permeability were detected; however, the mechanism through which these antiangiogenic factors influence the development of cerebrovascular complications remains to be determined [37, 38]. Therefore, we consider further research into sEng as a potential predictor of cerebral complications associated with preeclampsia to be promising.

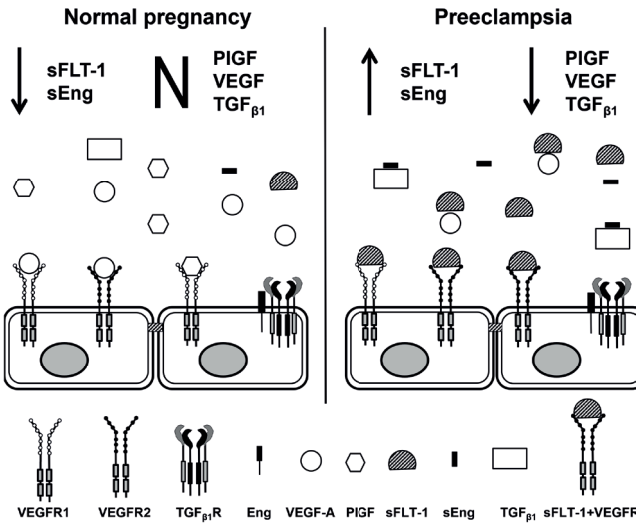

FIG. 2.
The scheme of pro- and antiangiogenic factors interaction in preeclampsia and normal pregnancy

The pathogenetic role of endothelial damage markers and tight junction proteins in the development of cerebrovascular complications of preeclampsia

A key role in the development of preeclampsia is played by endothelial dysfunction, which increases the production of vasoconstrictors – endothelin-1 (EDN-1), sFlt1 and sEng, leading to their imbalance with the vasodilator NO [39, 40]. This imbalance has a negative impact on the brain and eyes in preeclampsia and manifests in the disorder of local hemodynamics, the formation of vasospasm and vascular thrombosis with the development of hypovolemia and tissue ischemia, increasing in severity with disease progression [8, 9, 39].

Pregnancy is associated with significant physiological adaptive changes in the maternal cardiovascular system. NO has been shown to be a soluble gaseous mediator that performs a wide range of physiological functions, including maintaining vascular homeostasis and modulating vascular tone [41]. Reactive oxygen species can influence the maintenance of vascular tone by reducing NO production. According to Matsubara K. et al. (2015), endothelial NO synthase (eNOS), which is constitutively expressed in the vascular endothelium and regulates vascular tone through NO synthesis, is suppressed by excessive production of oxidative stress factors [42]. Inhibition of endothelial NO synthesis leads to dysregulation of vascular tone, platelet and leukocyte adhesion [41]. eNOS and its associated NO synthesis have been linked to maternal endothelial dysfunction, but the precise pathogenesis remains uncertain. Women with severe preeclampsia have lower circulating eNOS levels, which is largely associated with decreased PlGF levels, while women with moderate preeclampsia show a slight increase in these parameters [43]. These findings may indicate that although compensatory increases in eNOS and PlGF levels are observed in moderate preeclampsia, these mechanisms are not activated in severe cases of this disease.

Generalized endothelial dysfunction caused by placental antiangiogenic factors is considered to be the ultimate link in the pathogenesis of preeclampsia [8, 9]. Markers of endothelial damage

and dysfunction include serum concentrations of endothelial activating factors, such as vascular cellular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule type-1 (ICAM-1) and selectins, especially E-selectin; serum levels of endothelial glycocalyx (EG) degradation markers, such as hyaluronan (HA) and syndecan-1 (SDC-1); EDN-1 concentration; levels of circulating endothelial cells (CECs) and circulating endothelial progenitor cells (CEPCs) [44, 45]. Anti-endothelial cell antibodies (AECA) are groups of immunoglobulins IgG, IgM, and IgA produced secondarily in response to endothelial cell injury. The appearance of AECA is related to the severity of proteinuria, and the cytotoxicity to endothelial cells by AECA-positive sera may contribute to the development of endothelial damage in preeclampsia. The IgG-AECA subclass in preeclampsia increases EDN-1 release from endothelial cells, which may affect local vascular tone, including in the brain [46].

It has been found that VCAM-1 and ICAM-1 are among the important factors in the development of local inflammatory changes that promote leukocyte migration and their adhesion to the endothelium [45, 47]. It has been observed that VEGF is involved in increasing the expression of these adhesion molecules on endothelial cells, both *in vivo* and *in vitro*. Adhesion of leukocytes to the vascular endothelium and an increase in leukostasis followed by capillary occlusion and endothelial cell apoptosis lead to increased permeability and destruction of the BBB [39]. Plasma levels of ICAM-1 and VCAM-1 increase in preeclampsia and may be used as laboratory markers for the development of this condition [45, 47, 48].

The key components of intercellular proteins TJs are transmembrane proteins: occludin (Ocln), claudin (Cldn), tricellulin, and junctional adhesion molecules (JAMs), which form complex threads and control the permeability characteristics of paracellular transport [49, 50, 51]. These proteins are involved in the regulation of proliferation, differentiation, and polarization of epithelial cells. Tight junction proteins prevent the tissue fluid diffusion through the epithelium and regulate the permeability of ions, small hydrophilic molecules, and even macromolecules, thereby maintaining the difference in the composition of the apical and basolateral membranes [52].

To regulate cell adhesion, paracellular transport, and surface-to-internal signaling, TJs are associated with cytoplasmic adapter, scaffold, cytoskeletal, and signaling proteins that form a structural link to the actin cytoskeleton. The best-studied cytoplasmic adapter protein, Zonula occludens (ZO-1), has several domains: the PDZ domain (PSD-95/Discs large/ZO-1 homologous) interacts with Cldn and other adapter proteins, ZO-2 and ZO-3, the GUK domain (Guanylate kinase homology) interacts with Ocln, and the SH3 domain interacts with signaling proteins [51].

Reduced TJs expression leads to increased BBB permeability and the development of vasogenic cerebral edema with an increase in fluid volume in the extracellular space. Cldn has been shown to increase transendothelial electrical resistance of the BBB, primarily by reducing cation permeability through it [53]. Initially, several Cldn (-1, -3, -5, and -12) were thought to be expressed in the BBB, but more recent studies indicate that only Cldn-5 is the dominant component of the cell membrane, with limited expression and the contribution of other Cldn to maintaining BBB homeostasis and integrity [54]. Results from Greene C. et al. (2022) show that chronic suppression of Cldn-5 in the central nervous system caused spontaneous seizures in mice with severe neuroinflammation. Epilepsy alters the integrity of the BBB by modulating Cldn-5, which promotes a local inflammatory response, activation of cell adhesion molecules, and immune cell infiltration of the brain parenchyma [54]. We consider further research into the Cldn-5 role in the development of seizures in eclampsia to be promising.

Additionally, the 65 kDa transmembrane protein Ocln is of significant research interest, as it is considered a marker of BBB integrity [49, 55]. According to current data, Ocln comprises two extracellular domains and one intracellular domain. The first extracellular domain (ECL1) has a very high concentration of tyrosine and glycine residues. The tyrosine residues are involved in forming hydrophobic interactions and H-bonds, while glycine residues provide flexibility. The second extracellular domain (ECL2) is sensitive to hypoxia, is rich in tyrosine residues, and contains two cysteines that form disulfide bridges in an oxidizing environment. Compared to ECL1, ECL2 is the main binding domain that interacts with other tight junctions and regulates their function. The intracellular C-terminal domain of Ocln is rich in serine, threonine, and tyrosine residues and directly binds to ZO-1 and the actin cytoskeleton [55]. Ocln expression is regulated by signaling pathways such as nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), protein kinase C (PKC), RhoK, and ERK1/2. Factors regulating the functions of Ocln protein in maintaining BBB permeability include matrix metalloproteinases 2 and 9 (MMP-2, -9), as well as various proinflammatory cytokines [55].

BBB permeability is associated with Ocln phosphorylation, including VEGF-induced phosphorylation, at serine/threonine or tyrosine [55]. The results obtained by Ni Y. et al. (2017) demonstrated that TNF-α induces Ocln phosphorylation in a human cerebral endothelial cell line (hCMEC/D3) by transiently stimulating the p38MAPK and ERK1/2 pathways, leading to increased BBB permeability and disruption [56]. The study conducted by Zhang Y. et al. (2019) demonstrated that TNF-α suppresses Ocln expression by activating the HIF-1α/VEGF/VEGFR-2/ERK signaling pathway [57]. MMP-9 and IL-1β-induced expression in pericytes suppressed Ocln expression in a BBB model and led to increased BBB permeability. This process was regulated by the NOTCH3/NF-κB signaling

pathway [58]. A study conducted by Kanayasu-Toyoda T. et al. (2018) reported the role of Cldn and Ocln in neovascularization and angiogenesis. The deficiency of these transmembrane proteins has been associated with inhibition of brain endothelial cell proliferation, which can lead to long-term microvascular impairment and the development of neurological dysfunction [59].

An experimental study conducted by Clayton A.M. et al. (2019) on preeclampsia models in rats subjected to placental ischemia showed the presence of edema in the posterior part of the brain 2 months after birth. A decrease in Ocln expression, an increase in the levels of anti-inflammatory cytokines IL-4 and IL-10, and a simultaneous significant increase in pro-inflammatory cytokines IL-17, IL-1α, IL-1β, leptin, and MIP-2 (CXCL2) were detected in this area of the brain [60]. However, the obtained results did not allow us to determine the primary mechanisms in the development of cerebral edema. Thus, a decrease in Cldn-1 expression leads to a decrease in transendothelial electrical resistance with an increase in the fluid volume in the extracellular space and the development of vasogenic cerebral edema. Neuroinflammation processes are accompanied by increased fluid transport into the cell through water channels, which leads to cell swelling and the potential development of cytotoxic cerebral edema [60].

The modulation of paracellular transport through targeting TJs has been proposed as a potential drug delivery system for treating brain diseases; however, this approach has several limitations and is still under development. Further preclinical studies will help to evaluate the potential of tight junction proteins as a therapeutic target for cerebrovascular conditions with impaired BBB integrity, including hypertension-related disorders during pregnancy [51, 61].

The pathogenetic mechanisms of impaired autoregulation of cerebral circulation in preeclampsia

The high metabolic demands of the brain require a relatively constant cerebral blood flow. Its autoregulation is accomplished through myogenic, neurogenic, metabolic, and endothelial control. Myogenic control involves changes in vessel diameter due to contraction of smooth muscle cells in response to increased blood pressure. Neurogenic control is performed by perivascular nerves [62]. Metabolic control is initiated in response to changes in carbon dioxide and oxygen levels and is closely linked to neuronal activity, a process known as functional hyperemia or neurovascular coupling. Endothelial control is realized through the production of vasoactive factors that regulate vascular tone and should normally be in mutual balance [45, 63]. Figure 3 illustrates the mechanisms of cerebral blood flow autoregulation.

The regulation of cerebral blood flow is essential for meeting the metabolic demands of the brain and ensuring normal brain function. In situations

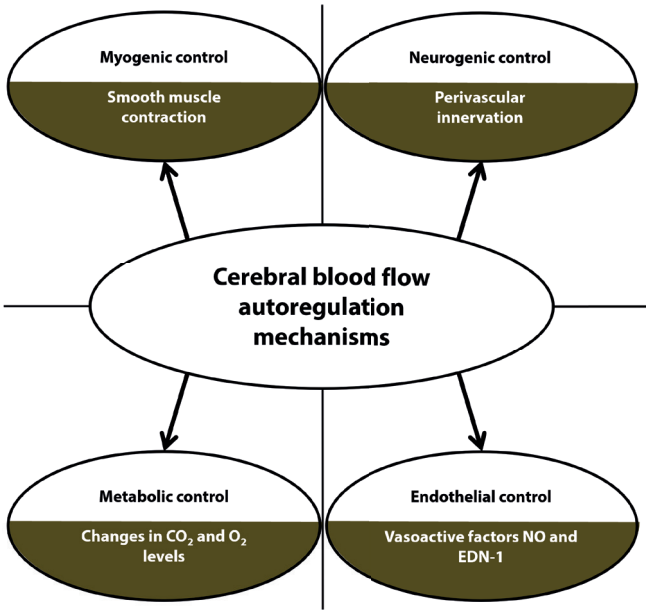

FIG. 3.
Mechanisms of autoregulation of cerebral blood flow

where blood flow to the brain is insufficient, such as in cases of ischemic stroke or hypovolemia due to hemorrhage, ischemic brain injury may occur. Conversely, hyperperfusion due to decreased cerebrovascular resistance may lead to disruption of the blood-brain barrier and vasogenic edema, which is often observed in severe preeclampsia and eclampsia [2-4]. One of the primary mechanisms that regulate cerebral blood flow involves changes in cerebrovascular resistance, which is inversely proportional to the diameter of the blood vessels. Normally, cerebral blood flow is maintained at approximately 50 ml/100 g of brain tissue per minute with a cerebral perfusion pressure of approximately 60–160 mmHg [63, 64]. When cerebral perfusion pressure deviates from the specified reference values, the autoregulation of cerebral blood flow becomes impaired, and the flow becomes linearly dependent on the mean arterial pressure. In cases of acute arterial hypertension, which can occur in severe preeclampsia among other conditions, increased intravascular pressure may overcome the myogenic vasoconstriction of arteries and arterioles, leading to a loss of their ability to maintain vascular resistance [14]. The resulting loss of autoregulation and hyperperfusion can lead to damage to the vascular endothelium, resulting in the development of vasogenic cerebral edema [64].

Transcranial Doppler sonography is used to assess changes in cerebral blood flow velocity, as well

as to calculate cerebrovascular resistance and cerebral perfusion pressure in women with preeclampsia and eclampsia [3, 4]. It has been found that in both women with preeclampsia and women with systemic hypertension, the cerebral perfusion pressure is significantly higher compared to pregnant women with normal blood pressure. Moreover, the cerebrovascular resistance index also increases, indicating the preservation of cerebral blood flow autoregulation. In addition, it has been demonstrated that cerebral blood flow velocity increases in preeclamptic patients compared to those with normal pregnancies [64]. A number of studies have reported a decrease in cerebrovascular resistance in combination with signs of cerebral edema, as indicated by computed tomography and/or MRI data [2, 6, 7]. These data suggest that in most women with preeclampsia there is adequate autoregulation of cerebral blood flow. However, in cases where there is decreased cardiovascular regulation and an autoregulatory breakthrough, excessive perfusion injury, cerebral edema, and neurological symptoms are observed [6, 65].

In a study conducted by van Veen T.R. et al. (2013), cerebral blood flow velocity was measured using transcranial Doppler ultrasonography in pregnant women with gestational hypertension, chronic hypertension, and preeclampsia. No statistically significant relationship was found between the autoregulation index and blood pressure, which, according to the authors, indicates the development of an autoregulatory breakthrough and hyperperfusion without excessive hypertension [66]. A decrease in cerebrovascular resistance in cases of preeclampsia may potentially expose the maternal brain to a significant increase in cerebral perfusion pressure due to the lack of hypertensive adaptation of cerebral arteries. In non-pregnant women, chronic hypertension results in a compensatory decrease in the diameter of the arterial lumen, which increases cerebrovascular resistance and shifts the autoregulation curve towards higher blood pressure values [39, 63, 67].

During normal pregnancy, the maternal vascular resistance reduces, leading to a slight decrease in blood pressure [39]. However, in women with preeclampsia, these adaptive mechanisms do not function sufficiently. Although the exact mechanism of these disturbances remains unclear, it is believed that altered MMP production and/or activity play an important role in the inappropriate vascular remodeling process [32, 39, 68]. These zinc-dependent proteases are produced as precursors that are cleaved into active forms with variable tissue expression, distribution, and substrate specificity. MMP activity is regulated by endogenous tissue inhibitors of metalloproteinases (TIMPs) and altered MMP/TIMP ratios [68, 69]. MMPs have been demonstrated to degrade extracellular matrix proteins, including collagen and elastin [70]. During normal pregnancy, MMPs are involved in the remodeling of uterine and vascular tissue [70, 71]. Changes in the expression/activity of MMP-2 and MMP-9 may lead to decreased vasodilation and increased vasoconstriction with the development of hypertensive disorders during pregnancy [71, 72]. In the study conducted by Timokhina E. et al. (2021), threshold values of MMP-2 and MMP-9 were established to predict the development of preeclampsia in the first trimester [69]. The study conducted by Rao R.S. et al. (2023) revealed significantly increased expression of the EDN-1 and MMP-9 genes in patients with preeclampsia [73]. Understanding the role of MMPs in the remodeling and functioning of the vascular system in pregnant women can help develop new approaches to the prediction and treatment of preeclampsia [68, 69, 73]. Figure 4 illustrates a schematic representation of cerebrovascular changes associated with arterial hypertension, normal pregnancy, and hypertensive disorders during pregnancy. As arterial hypertension progresses, the wall thickness of cerebral vessels increases, and the lumen diameter decreases. During pregnancy, adaptive external (muscular) remodeling occurs, which leads to a slight expansion of the vascular lumen. In chronic arterial hypertension against the background of pregnancy, internal (endothelial) remodeling of cerebral vessels occurs. Preeclampsia is a condition characterized by abnormal internal (endothelial) remodeling in response to increased blood pressure, which probably contributes to increased hydrostatic pressure, which can damage microvessels, and lead to disruption of the BBB, microbleeding, an increase in glial cell numbers and chronic neuroinflammation and neuronal damage (Fig. 4) [63, 74].

CONCLUSION

Women with a history of preeclampsia and/or eclampsia are at an increased risk of developing neurological disorders, including cognitive decline and dementia, which may occur months or even years after delivery. Preclinical and clinical studies have demonstrated that impaired blood-brain barrier permeability plays a key role in the development of central nervous system dysfunction in preeclampsia. The main mechanisms inducing neuroinflammation and neurodegeneration include increased transcellular (mediated by vascular endothelial growth factor and its receptor system) and paracellular (associated with altered expression and function of tight junction proteins) transport, as well as impaired cerebral blood flow autoregulation. These mechanisms lead to impaired cerebral blood flow autoregulation, resulting in hyperperfusion and the development of vasogenic cerebral edema. Although significant progress has been made in understanding the key aspects of preeclampsia pathogenesis, the mechanisms that cause brain endothelial cell damage, as well as the local paracrine and autocrine regulation of cerebral blood flow,

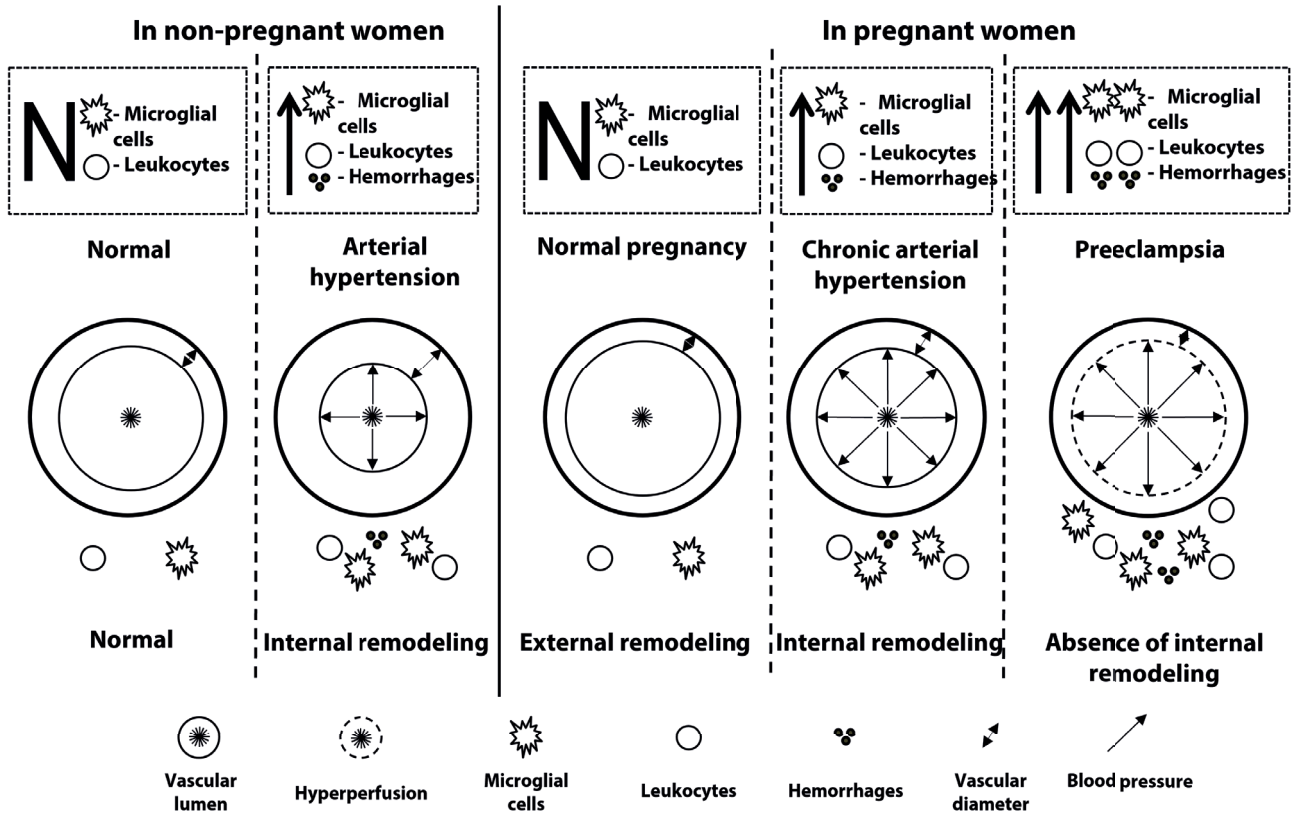

FIG.4.
Cerebrovascular changes associated with arterial hypertension, pregnancy and preeclampsia

continue to be highly relevant for future research. Understanding the key factor for the development of new approaches to the diagnosis and treatment of cerebrovascular complications associated with preeclampsia. This could significantly improve outcomes for both mothers and their newborns.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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POSTTRANSLATIONAL MODIFICATIONS AND ITS ROLE IN HABITUAL MISCARRIAGE: PROGNOSIS, DIAGNOSIS AND NEW APPROACHES TO THERAPY

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RESUME

The prevalence of recurrent pregnancy loss (RPL) in women ranges from 1 to 5 %. Among the known causes of RPL, the role of post-translational protein modifications (PTMP) has been studied in recent years. These are protein structure transformations that complete the formation of their molecule or participate in the regulation of the functions of this molecule, catalyzed by specific enzymes.
The aim. *To assess the role of PTMP in the pathogenesis of RPL, as well as to determine potential biomarkers and therapeutic targets of RPL.*
Material. *A search of publications by keywords was conducted in the electronic databases PubMed/MEDLINE and Google Scholar, published before December 2024.*
Results. *PTMB plays an important role in the processes of trophoblast invasion, endometrial decidualization and embryo implantation, which makes them significant for understanding reproductive dysfunction. The use of mass spectrometry to study PTMB opens up new possibilities for the diagnosis and prognosis of RPL. Epigenetic therapy of RPL demonstrates efficacy and a lower probability of side effects compared to traditional methods. Despite significant prospects, research in this area is accompanied by difficulties associated with heterogeneity of terminology and ethical issues.*
Conclusion. *PTMB in the context of RPL can contribute to the improvement of diagnostic and therapeutic strategies in reproductive medicine. Further development of methodologies for studying PTMB is needed.*

Key words: *recurrent miscarriage; posttranslational protein modifications; mass spectrometry, epigenetic therapy*

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ПОСТТРАНСЛЯЦИОННЫЕ МОДИФИКАЦИИ БЕЛКОВ И ИХ РОЛЬ В ПРИВЫЧНОМ НЕВЫНАШИВАНИИ БЕРЕМЕННОСТИ: ПРОГНОЗЫ И ДИАГНОСТИКА

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РЕЗЮМЕ

Распространенность привычного невынашивания беременности (ПНБ) у женщин по всему миру составляет от 1 до 5 %. Среди известных причин ПНБ в последние годы изучается роль посттрансляционных модификаций белков (ПТМБ) – превращения структуры белков, завершающие формирование их молекулы или участвующие в регуляции функций этой молекулы, и катализируемые специфическими ферментами.

Цель. *Оценить роль ПТМБ в патогенезе ПНБ, а также определить потенциальные биомаркеры и терапевтические мишени ПНБ.*

Материал. *Проведен поиск публикаций по ключевым словам в электронных базах данных PubMed/MEDLINE и Google Scholar, опубликованных до декабря 2024 г.*

Результаты. *ПТМБ играют важную роль в процессах инвазии трофобласта, децидуализации эндометрия и имплантации эмбриона, что делает их значимыми для понимания нарушений репродуктивной функции. Использование масс-спектрометрии для исследования ПТМБ открывает новые возможности для диагностики и прогноза ПНБ. Эпигенетическая терапия ПНБ демонстрирует эффективность и меньшую вероятность побочных эффектов по сравнению с традиционными методами. Несмотря на значимые перспективы, исследования в этой области сопровождаются трудностями, связанными с неоднородностью терминологии и этическими вопросами.*

Заключение. *ПТМБ в контексте ПНБ может способствовать улучшению диагностических и терапевтических стратегий в репродуктивной медицине. Необходимы дальнейшие разработки методологий для изучения ПТМБ.*

Ключевые слова: *привычное невынашивание беременности, посттрансляционные модификации белков; масс-спектрометрия, эпигенетическая терапия*

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INTRODUCTION

Recurrent pregnancy loss (RPL), or habitual miscarriage, is a woman's history of two or more clinical pregnancy losses before 22 weeks of gestation, according to Russian clinical guidelines [1]. The European Society of Human Reproduction and Embryology (ESHRE) defines RPL as two or more pregnancy losses before 24 weeks [2]. The prevalence of RPL ranges from 1 % to 5 %, but its true incidence is difficult to estimate due to heterogeneity in definitions and criteria [3]. The etiology of RPL remains unresolved and includes many modifiable and non-modifiable factors. Even after a thorough assessment of the etiology and risk factors for RPL, up to 75 % of cases remain unexplained [3].

Achieving satisfactory pregnancy outcomes through available treatment methods remains a complex and challenging process, particularly in cases of unexplained recurrent miscarriages. Furthermore, RPL causes significant suffering to many families and results in serious socio-economic losses [3].

In recent years, the importance of post-translational modifications (PTMs) of proteins in various physiological and pathological processes has become known [4]. PTMs of proteins are transformations of protein structure catalyzed by specific enzymes that complete the formation of a protein molecule or participate in the regulation of its functions. PTMs of proteins are the process of adding or removing chemical groups from amino acid residues in a polypeptide chain, which increases the functional diversity of proteins and is defined as modification of amino acid side chains after protein synthesis [5]. These modifications influence cell growth and differentiation, participate in maintaining the integrity of the cell cycle and apoptosis, and regulate numerous biological processes. Research into PTMs of proteins is actively conducted in the context of oncological, cardiovascular, and metabolic diseases [6].

Pregnancy is the result of the interplay of multiple regulatory systems, and an abnormality at any of these stages can lead to pregnancy termination. Recent genetic studies have confirmed that the frequency of aneuploidy in RPL and sporadic miscarriages is not statistically significantly different. This indicates that the underlying mechanisms of sporadic miscarriage and RPL may be analogous [7].

PTMs of proteins play an important role in regulating embryo implantation, embryonic development, placental formation, and the maternal and fetal immune response, which is crucial for understanding the pathological mechanisms of RPL [5]. Studying PTMs of proteins may shed light on the role of modified proteins in the RPL pathogenesis and facilitate the development of more effective diagnostic/prognostic tools and more targeted treatments. However, the number of studies examining the role of PTMs of proteins in RPL remains limited to date, and the data obtained are not systematized, which serves as the basis for this review.

THE AIM OF THE REVIEW

To assess the role of PTMs of proteins in the pathogenesis of RPL, as well as to determine potential biomarkers and therapeutic targets of RPL.

MATERIALS AND METHODS

Publication search strategy

We searched PubMed/MEDLINE and Google Scholar for publications. The search strategy included the following keywords and their combinations in Russian and English: привычное невынашивание беременности; постранслящионные модификации белков; гликозилирование; фосфорилирование; сумоилирование; убиквитинирование; метилирование; ацетилирование; пальмитоилирование; (miscarriage; pregnancy loss; posttranslational modifications; glycosylation; phosphorylation; sumoylation; ubiquitination; methylation; acetylation; palmitoylation). The search was performed among studies published up to December 2024.

All authors independently screened the titles and abstracts of the identified articles. When relevant studies were identified, the full text of the corresponding article was retrieved. Duplicates and incomplete versions of articles were excluded. Full-text versions of articles were assessed for compliance with the following inclusion criteria: the article was published in English or Russian between 2014 and 2024; it was published in a peer-reviewed scientific journal; the article is a literature review, experimental study, or clinical trial that contains the specified keywords; the article describes the role of the specific PTMs of proteins in reproductive function.

RESULTS AND DISCUSSION

PTMs of proteins are a non-template process and are responsible for the formation of multiple protein forms. Approximately 400 types of PTMs of proteins reactions are known, each affecting a limited range of proteins. It has now been established that protein synthesis does not end at the ribosomes; afterward, the next stage of protein transformation begins is processing, or PTMs of proteins. After a peptide (protein) chain has been released from the ribosome, it assumes its biologically active form, i.e., folds in a specific manner. However, this process is not always possible until the newly formed polypeptide chain undergoes processing, which is the final stage of protein biosynthesis. PTMs of proteins occur in the rough endoplasmic

reticulum, where ribosomes are located on its surface, as well as in the Golgi complex. The functional significance of PTMs of proteins reactions is that they enable the activity of a protein or entire groups of proteins to be controlled in response to the changing cellular requirements. The specificity of these interactions opens up the possibility of selectively influencing the processing and, consequently, the function of specific proteins [8].

Advances in mass spectrometry over the past two decades have significantly expanded the number of known PTMs of proteins in biology, and as instrumentation continues to improve, this number is likely to continue to grow. The following is a description of some PTMs in proteins that have already been studied in detail.

GLYCOSYLATION

Glycosylation is a common and complex process in PTMs of proteins. It is based on a mechanism through which certain amino acid residues in proteins are linked to carbohydrates, forming glycosidic bonds under the influence of enzymes called glycosyltransferases, which mediate various biological functions and modulate protein activity [9].

There are several types of glycosylation, including N-, O-, C-, S-, and P-glycosylation. Each type of glycosylation has its own unique characteristics and functions, and can influence the stability, longevity and functional activity of proteins. These processes are also important for cell adhesion and interactions between cells in the immune system.

O-Glucosamination (O-GlcNAcylation) is a common PTM of proteins that significantly influences the functional properties of proteins. This process is regulated by two important enzymes: O-GlcNAc transferase (OGT), which adds the glucosamine residue, and O-Glucosaminase (OGA), which removes it. O-Glucosamination plays a crucial role in maintaining genomic stability, epigenetic regulation, regulation of protein synthesis and degradation, metabolic pathways, signaling cascades, and apoptosis. Research suggests that OGT may be associated with various pathologies, including adverse changes in fetal nervous system development [10]. This emphasizes the significance of O-Glucosaminylation in understanding not only typical physiological processes, but also the pathological mechanisms underlying numerous diseases.

OGA expression is essential for embryonic and fetal viability. In the study conducted by de Lima Castro M. et al. (2023), an increase in perinatal mortality was observed among experimental mice with the OGA gene deleted. This phenomenon is likely associated with the dynamics of circulating glucose levels and a decrease in glycogen storage in the liver, indicating the sensitivity of glycosylation to the metabolic state of the body [11].

Hypoxia that occurs during placental development is one of the main causes of various pregnancy complications, vascular placental abnormalities, and miscarriage [12]. Increased O-Glucosamination caused by OGA loss has a significant impact on placental function. This can lead to weakened vascularization in the area between the mother's blood vessels and the placenta [13]. Ruane P.T. et al. suggested that O-Glucosamination promotes accelerated trophoblast differentiation [14]. Additionally, Liu J. et al. suggest that cystathionine γ-lyase (CSE) and nuclear receptor subfamily 4, group A, member 3 (NR4A3) are activated by high levels of O-Glucosamination; this activation suppresses trophoblast syncytialization and leads to H_2S production [15].

O-Glucosamination serves as a key regulator of transcriptional activity. Aquaporin-3 (AQP3) expression is enhanced by O-Glucosamination, which interacts with transcription factor protein 1 (SP1). A decrease in human placental trophoblast migration is observed with AQP3 inhibition. One of the targets of O-Glucosamination at Ser40 is a histone H_2A variant, which is essential for trophoblast stem cell differentiation [16]. Hypoxia-inducible factor-1 alpha (HIF-1α) activity, which is crucial for placental vascular development, increases with decreased O-Glucosamination levels [17].

Placental growth and glucose and amino acid transport are primarily controlled by two key protein kinases: AMP – activated protein kinase (AMPK) and the mammalian target of rapamycin (mTOR). An important enzyme in the hexosamine biosynthetic pathway (HBP) is fructose-6-phosphate amidotransferase, also known as glutamine: fructose-6-phosphate amidotransferase (GFAT). This enzyme plays a critical role in controlling trophoblast proliferation via the PI3K/Akt/mTOR signaling pathway, which is necessary for maintaining optimal nutrient balance in the placenta [18].

AMPK regulates the localization, expression, and selectivity of OGT. It has the ability to directly or indirectly suppress mTOR activity and phosphorylate GFAT protein, reducing its activity. In the human placenta, it shapes the mTOR signaling pathway and maintains OGT levels, thereby influencing trophoblast differentiation [19].

Poor embryo quality and endometrial dysfunction are considered the main factors leading to RPL. During oocyte maturation, OGA expression increases and O-Glucosamination levels decrease. O-Glucosamination improves cell proliferative, migratory, and invasive abilities, as well as cell adhesion, which facilitates successful embryo implantation by regulating endometrial receptivity [20].

There is evidence that O-Glucosamination may be associated with the development of chronic inflammatory processes in the placenta. Dysfunction in the regulation of the hexosamine signaling pathway (HSP) and O-Glucosamination may be the mechanism responsible for the embryotoxic effects caused by hyperglycemia [21]. Therefore, reduced glycosylation

of the prominin-1 protein may also negatively impact the ability of the blastocyst to implant in the uterus.

N-glycosylation. Within the context of N-glycosylation, the most active enzymes are N-acetylglucosamine transferases V (GnT-V) and III (GnTIII). Although the role of GnT-III during pregnancy in healthy women and RPL has not been fully elucidated, GnT-V is believed to influence trophoblast invasion by altering β1,6-GlcNAc levels on integrin α5β1. N-glycosylation, a key regulator of intercellular communication, plays an important role in the normal function of the immune system.

Yu M. et al. found that N-glycosylation influences endometrial receptivity [22]. Some studies have also shown that alpha-1,3-mannosyltransferase (ALG3) and components of the oligomeric Golgi complex 5 (COG5) may lead to congenital disorders of glycosylation [23, 24]. These glycosylation mechanisms may be closely linked to the pathogenesis of RPL.

Protein O-fucosylation. Protein O-fucosyltransferase 1 (poFUT1) is a key enzyme that catalyzes the O-fucosylation of proteins that affect embryo implantation. This enzyme regulates cyclin protein production and activates the MAPK and PI3K/Akt signaling pathways, which promotes trophoblast proliferation [25]. Epiregulin enhances poFUT1 expression by increasing the O-fucosylation of plasminogen activator and activating the PI3K/Akt signaling pathway. This, in turn, promotes the epithelial-mesenchymal transition (EMT) of the trophoblast and improves embryo implantation.

PoFUT1 also positively correlates with O-fucosylation of the Notch1 molecule within certain limits. A decrease in poFUT1 activity is accompanied by a decrease in Notch1 activity, which leads to a decrease in the transcriptional activity of prolactin and insulin-like growth factor binding protein-1 (IGFBP1), as well as to impaired decidualization of endometrial stromal cells [26]. Fucosyltransferase IV (FUT4) plays an important role in the biosynthesis of α1,3-fucosylated glycans carried by glycoproteins. The miR-200c/FUT4/α-1,3-fucosylation (LeY)/CD44/Wnt/β-catenin signaling cascade significantly contributes to uterine receptivity. MiR-200c inhibits α-1,3-fucosylation, while LeY activates CD44 by interacting with FUT4, leading to inhibition of the Wnt/β-catenin signaling pathway and decreased endometrial receptivity [27].

Thus, protein glycosylation significantly influences the functions of trophoblast, decidual stromal cells, and decidual immune cells, playing an important role in maintaining immunological tolerance during pregnancy. Therefore, studies of protein glycosylation processes are of significant interest in understanding the immunopathogenesis of RPL.

PHOSPHORYLATION

Phosphorylation is the most common modification of PTMs in proteins. It has been suggested that abnormal placentation or impaired trophoblast invasion may be the main causes of RPL in women [28]. Decreased endometrial plasticity is also associated with RPL. Patients with RPL exhibit a significant decrease in the expression levels of exocyst complex component 2 (SEC5) in decidual macrophages, which inhibits M2 polarization and STAT6 phosphorylation [29]. M2 cells, in addition to reducing the inflammatory response, play an important role in tissue repair and maintaining fetal immune stability throughout pregnancy.

Extravillous trophoblasts (EVT) are actively stimulated to proliferate and invade when decidual macrophages polarize into M2 *in vitro*. Formyl peptide receptor 2 (FPR2) can regulate trophoblast functions through the PI3K/AKT signaling pathway [30]. The ability of EVTs and primary cell lines to migrate and invade is significantly reduced by high levels of ezrin protein and its activated phosphorylated form. According to Gao L. et al., increased levels of trophoblast-produced lactic acid in the decidua of women with RPL can induce macrophage polarization in M1, which occurs via the HIF-1α/SRC/LDHA pathway. RPL is also associated with abnormal β3-integrin expression [31].

Cai X. et al. demonstrated that phosphorylated Nur77 protein controls endometrial receptivity via the β3-integrin/FAK pathway [32]. STAT3 hyperphosphorylation is observed in RPL, which inhibits the proliferation of regulatory T lymphocytes (Treg) and reduces the secretion of transforming growth factor (TGF)-1β and interleukin (IL)-10 [33]. High levels of SPARCL protein are responsible for decreased ERK phosphorylation and Fos and Jun expression, which suppresses EVTs migration and invasion [34]. By suppressing STAT3 phosphorylation, insufficient indoleamine 2,3-dioxygenase (IDO) activity can impair trophoblast proliferation and migration, ultimately leading to RPL.

The activity of various signaling pathways is regulated through modifications in phosphorylation. Due to the significant impact of protein phosphorylation on most vital processes, it is crucial to develop methods for targeting specific phosphorylated molecules. Continued developments in phosphorylation technology and research are opening up new opportunities for the diagnosis and treatment of RPL.

SUMOYLATION

Sumoylation involves the addition of small ubiquitin-like modifiers (SUMO) to specific targets in a covalent and reversible manner. Four different SUMO subtypes have been identified. Notably, they appear to exhibit spatial specificity: SUMO-1 is localized to the nuclear envelope of oocytes, while SUMO-2 and SUMO-3 are located intranuclearly. During meiosis, SUMO-1 is predominantly localized

to the spindle poles, while SUMO-2 and SUMO-3 are concentrated in the centrosome [35]. These observations suggest a specific role for SUMO in oocyte development.

Sumoylation is regulated by the sentinel-specific protease (SENP) family [35]. Septin2 can be modified by SUMO; septins are required for chromosome congression and meiotic progression [35].

Jones K.T. noted that if securin remained unchanged, meiotic progression via the anaphase-promoting complex (APC) would be hampered [36]. In transgenic mouse models, knockdown of the desumoylation enzymes SENP1 and SENP2 results in pregnancies with nonviable embryos, as well as abnormal placental trophoblast differentiation and cell proliferation [37]. Yu H.I. et al. found that SENP2-mediated extraembryonic and embryonic development requires SUMO2/3 [38]. A study conducted by Huang C.J. et al. showed that SENP7 deficiency results in progressive embryonic transformation, with these embryos exhibiting varying degrees of DNA damage and difficulty in progressing to the blastocyst stage [39]. Sumoylation is essential for oocyte maturation and is critical for controlling the activity of cytoskeletal proteins [40], but its specific molecular mechanism remains unclear. Studies have shown that the absence of UCB9 in chicken cells leads to the cumulative accumulation of chromosomal abnormalities [41]. Nacerddine K. et al. noted that embryos lacking UCB9 died due to chromosome segregation defects [42].

Polo-like kinase 1 (PLK1), a member of the polo-like and serine/threonine kinase family, plays an important role in the phosphorylation of serine-137 and threonine-210, which significantly affects the activity of spindle checkpoints. PLK1's function in organizing microtubules and spindle poles is linked to SUMO-1, and its localization and kinetochore function in PLK1 are modified and regulated by SUMO-2/3 [43].

Errors in egg meiosis and cell cycle regulation can predispose eggs to aneuploidy, potentially leading to miscarriage. Thus, SUMO studies provide a new theoretical basis for screening euploid embryos, thereby expanding our understanding of embryonic development.

UBIQUITINATION

Ubiquitination is a post-translational modification process that involves the covalent attachment of ubiquitin to target proteins through a series of enzymatic reactions. Ubiquitination regulates various cellular processes, such as DNA repair, the cell cycle, autophagy, and transcriptional regulation. The enzymes responsible for ubiquitination are divided into three classes: ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3). These enzymes are responsible for the activation, binding, and ligation of ubiquitin, ensuring the normal course of ubiquitination. E1 proteins activate ubiquitin using ATP, with UBA1 being a member of the E1 family and playing a key role in fertilization. E2 proteins determine the specific mode of ubiquitin chain attachment, while E3s link a target protein to a specific E2, allowing for the selection of the type of protein that is ubiquitinated. Deubiquitinating enzymes (DUBs) include several classes, such as ubiquitin-specific proteases (USPs), ovarian tumor proteases (OTUs), ubiquitin carboxyl-terminal hydrolases (UCHs), Josephin/MPN domain-associated metallopeptidases (JAMMs), and monocyte chemotactic protein-inducible proteins (MCPIPs) [44].

USP25 and USP36 are members of the deubiquitinating enzyme (DUB) family. A study conducted by Ding J. et al. showed that USP25 levels are reduced in placental villous tissue from patients with RPL. The miR-27a-R3p/USP25 axis may influence trophoblast migration and invasion by controlling downstream Wnt signaling [45]. This finding highlights the importance of USP25 in the process of trophoblast invasion and possible mechanisms through which it participates in the RPL pathogenesis.

Furthermore, it has been suggested that another deubiquitinating enzyme, USP2a, may deubiquitinate β-catenin, thus promoting trophoblast invasion through the PI3K/Akt/GSK3β/β-catenin pathway [46]. Collectively, these findings suggest a potential role for USP2a in the regulation of processes essential for normal trophoblast development.

USP36, through its regulation of DHX33–DEAH box RNA helicase, significantly contributes to ribosomal RNA synthesis and mRNA translation. Additionally, it controls nucleolar activity through deubiquitinization of proteins such as nucleophosmin/B23 and fibrillarin. USP36 deficiency at the morula stage induces apoptosis, which, in turn, can cause preimplantation death [47]. These data highlight the importance of DUBs in regulating key processes in reproductive biology and indicate their potential role in reproductive disorders.

E3 ubiquitin ligases are key components of the ubiquitin-protease system, playing an important role in the regulation of invasion and migration of human placental trophoblasts. Such E3 ligases include β-TrCP, Fbxw8, Cullin family proteins, and Cbl family proteins. These ligases are involved in the control of the trophoblast cell cycle, including apoptosis, proliferation, and differentiation. Trophoblast apoptosis is regulated by proteins such as Mcl-1 and MDM2, while proliferation and differentiation depend on Fbxw8 [48]. MDM2 is also required for maintaining cell cycle integrity, highlighting its importance in cellular regulation. Underregulation of SKP2 protein in decidual tissue has been associated with RPL.

Wu L. et al. suggest that MALAT1, an antisense transcript associated with lung adenocarcinoma metastasis, may recruit an E3 ligase to participate

in trophoblast invasion [49]. Furthermore, E3 ubiquitination of MIB2 plays an important role in the control of oocyte meiosis by activating DLL3, which regulates oocyte meiosis through the AKT pathway [50].

Oocyte maturation is closely linked to oocyte ubiquitination processes, which play an important role in the regulation of meiosis. Cyclin B1 is a protein essential for this process. Ubiquitination of Beclin 1, an important regulator of autophagy, promotes Vps34 activity, but the Wiskott–Aldrich syndrome protein (WASP) inhibits Beclin 1 ubiquitination, leading to Vps34 inactivation and inhibition of autophagy [51]. Furthermore, it was recently found that lnc-HZ08 promotes PI3K ubiquitination and degradation, which suppresses trophoblast growth through activation of the PI3K/pAkt/p21/CDK2 pathway, which in turn can lead to miscarriage [52].

Another study found that an OTU deubiquitinase, which has specificity for linear linkages, can activate the linear ubiquitin chain assembly machinery (LUBAC). This mechanism prevents autoubiquitination, which is associated with linear polyubiquitin, and is linked to cell death and type I interferon production [53]. Importantly, many physiological processes in the body, such as autophagy, cellular metabolism, and apoptosis, are mediated by protein ubiquitination.

However, despite significant progress in understanding the role of ubiquitination in various cellular processes, further research is needed to identify the impact of ubiquitination on RPL and potential therapeutic options.

METHYLATION

Protein methylation is an enzymatic process in which methyl groups are transferred to specific amino acid residues in proteins. Common targets for methylation include lysine, arginine, histidine, cysteine, and asparagine. This modification can influence protein function, their interactions with other molecules, and the regulation of various cellular processes.

Lysine residues can undergo different levels of methylation: monomethylation, dimethylation, and trimethylation. Conversely, arginine residues can be monomethylated, as well as symmetrically or asymmetrically dimethylated. These differences in the methylation process influence the functional properties of proteins and their roles in cellular processes.

Protein methylation can be classified into two main categories depending on which proteins are modified: histone and non-histone. Histone methylation is largely associated with the regulation of gene transcription, as it influences chromatin structure and the accessibility of DNA to transcription machinery. Non-histone methylation, in turn, affects all proteins and plays a crucial role in various cellular functions, including transcriptional signaling, the cell cycle, and metabolism.

Non-histone methylation, regulated by protein arginine methyltransferases (PRMTs) and protein lysine methyltransferases, is an important mechanism that influences cellular signaling pathways, protein stability, and mRNA translation, and is involved in many critical biological processes. Arginine methyltransferase 1, 3, and 6 have been identified within the female reproductive system, indicating their potential role in the regulation of reproductive functions [54].

Studies have shown that PRMT1 plays a crucial role in repairing damaged DNA, and mouse embryos that have lack of this protein do not survive. The absence of PRMT3 also leads to reduced embryo size and delayed growth and development [55]. These data indicate that arginine methyltransferases play a critical role in normal embryonic development and may be associated with RPL.

Research has shown a link between PRMT3, asymmetric dimethylarginine (ADMA), and nitric oxide (NO), where ADMA, by inhibiting nitric oxide synthase (NOS), is formed as a result of arginine methylation in PRMT proteins [56]. A recent study has shown that women with RPL have reduced NOS activity compared to control subjects. This may adversely affect pregnancy outcomes [56].

Furthermore, methylation of CXC, Rab, and CAAX proteins is completed by a reaction catalyzed by isoprenylcysteine carboxylmethyltransferase (LCMT). Studies have shown that LCMT-deficient embryos die during the middle stages of gestation. However, the precise mechanism through which LCMT affects embryonic development is still not fully understood [57].

Histone methylation plays a crucial role in the regulation of gene expression and maintenance of genomic stability, which in turn significantly affects the embryonic development prior to implantation. The methylation of histones such as H3K4, H3K27, H3K9, and H3K36 is associated with important processes that occur during the early stages of mammalian embryonic development [58]. Methylation of the H3K9 residue, in particular, is involved in maintaining genomic stability and in repressing the expression of cell type-specific genes. Abnormalities in H3K9me3 reprogramming may lead to impaired genomic activation in zygotes, highlighting its importance for proper embryonic development [59]. G9a, a key enzyme responsible for H3K9 methylation, plays an important role in processes associated with hypoxia, cancer, and early embryonic development. Studies have shown that G9aMT expression and methylated histone H3-K9 levels were significantly lower in fresh endometrial decidual tissue from women with RPL compared to average levels [60]. However, it remains unclear how exactly H3-K9 methylation levels and G9a activity relate to RPL. Understanding this interaction may be critical for developing new approaches to diagnosing and treating conditions associated with RPL. Further research in this area is required

to clarify the precise mechanisms of histone methylation in relation to reproductive biology and its influence on pregnancy outcomes.

DNA methylation has been suggested as a potential mechanism that contributes to RPL development [61]. However, histone H3K27 methylation also plays a significant role in DNA methylation-independent processes associated with imprinting. Specifically, the H3K27me3 modification modulates gene expression by suppressing its activity and influencing cellular differentiation, as well as contributing to the development and progression of various diseases.

During embryonic development, dynamic changes in H3K27me3 may indicate the choice of cellular differentiation pathways. This marker is also involved in the regulation of bivalent genes, maintaining the pluripotency of embryonic stem cells. H3K27me3 has been identified as an imprinting marker, XIST, which plays an important role in X-chromosome inactivation [62].

Interestingly, loss of H19/IGF2 imprinting has been observed in the decidua of patients with RPL. This discrepancy appears to be closely linked to a deficiency in the inhibitory histone marker H3K27me3 [63]. This methylation imbalance may indicate a potential predisposition to RPL.

Fatima N. et al. used a structural equation model to substantiate the correlation between methyltransferases and embryonic development in patients with RPL [64]. Such studies highlight the complexity of the molecular mechanisms associated with methylation and demonstrate that methylated protein modifications may have unpredictable hidden implications for RPL therapy. This opens up new perspectives for developing treatment approaches and understanding the causes of RPL.

ACETYLATION

Acetylation is the process of transferring acetyl groups to the lysine residues or N-terminus of a protein. This mechanism is particularly important in regulating histone activity, where histone acetyltransferases and deacetylases (HDACs) maintain cellular homeostasis. Histone acetylation is associated with the activation of gene expression, while deacetylation often leads to gene silencing.

Studies have shown that inhibiting HDAC enzyme activity with trichostatin A may limit trophoblast invasion. Moreover, trichostatin A also promotes decidualization of endometrial stromal cells, which is essential for maintaining normal reproductive function [65].

Histone acetylation is a crucial process that regulates cytokine expression. ATP citrate lyase (ACLY) is an important regulator of this process. A study conducted by Chen X. et al. showed a significant decrease in ACLY levels in the chorionic villi of placentas in patients with RPL compared to the control group. This decrease leads to inhibition of histone acetylation and causes an imbalance in the ratio of M2 and M1 macrophages, which may negatively affect immune responses in the placenta [66].

Additionally, Wang P. et al. noted that patients with RPL have decreased HDAC levels in chorionic villi and increased transcriptional activity of the transcription factor EB (TFEB). Increased TFEB activity leads to excessive activation of autophagy, which may suppress trophoblast growth [67]. This suggests that disturbances in acetylation mechanisms and their regulators may contribute to the development of RPL.

Class I HDACs (histone acetyl-independent deacetylases), including HDAC1, HDAC2, HDAC3, and HDAC8, play important roles in preimplantation embryonic development and other vital processes such as checkpoint activation and DNA repair. These enzymes are involved in maintaining DNA methylation homeostasis and regulating gene expression, which is critical for normal embryonic development. HDAC1 and HDAC2 promote genome-wide DNA methylation; embryos with impaired function of these HDACs are destined to die at the morula stage [68]. This underscores their importance in early embryonic development, when proper methylation is essential for normal cellular differentiation and genomic stability.

HDAC3 deficiency also has consequences: as shown in a study conducted by Bhaskara S. et al., its deficiency leads to prolongation of the S-phase of the cell cycle and DNA damage [69]. This suggests that HDAC3 has a critical role in cell cycle control and maintaining genomic integrity in cells.

Furthermore, a study conducted by Kim T.H. et al. noted decreased HDAC3 expression in the uterus of patients with endometriosis-induced infertility [70]. This opens up new perspectives for understanding the connection between changes in HDAC activity and reproductive disorders, which could lead to significant insights into the development of new therapeutic approaches.

Overall, these data highlight the critical importance of class I HDACs for embryonic development and reproductive function, as well as the need for further study of their role in RPL.

Non-histone acetylation is an important process in which acetyl groups are attached to lysine residues of proteins other than histones. This process is carried out by lysine acetyltransferases (KATs) and lysine deacetylases (KDACs), which play a key role in regulating protein functionality in cells [71]. KAT families can be classified into three main groups: GCN5, CBP/p300, and MYST, each with its own specific functions and mechanisms of action. These enzymes are involved in the acetylation of various proteins, including transcription factors, enzymes responsible for metabolism, and proteins

involved in cell signaling, thereby influencing a variety of cellular processes. Lysine deacetylases (KDACs), on the other hand, are divided into two main classes: Zn^{2+}-dependent and NAD^{+}-dependent sirtuin deacetylases. Zn^{2+}-dependent KDACs, such as HDAC1 and HDAC2, play a role in deacetylation, leading to the suppression of gene expression, while NAD^{+}-dependent sirtuin deacetylases (e.g., SIRT1) regulate various cellular processes, including metabolism and aging. Although KAT and KDAC have been studied, many aspects of their interactions with specific substrates and the mechanisms they use to regulate protein functionality remain uncertain [71]. Further research in this area is expected to better understand the role of non-histone acetylation in various physiological and pathophysiological processes, including RPL.

The discovery of α-tubulin acetylation and the transcription factor p53 has been an important step in our understanding of the role of non-histone acetylation in cellular processes. For example, post-ovulatory oocyte aging is associated with abnormal α-tubulin acetylation, which may impact female fertility [72]. Studies have shown that defects in α-tubulin acetylation mechanisms lead to impaired meiotic spindle assembly in oocytes and sperm, thereby reducing fertility and contributing to abnormalities in the morphology of female and male gametes. These findings suggest specific aspects that are relevant to germ cells [73].

KAT6A, a lysine acetyltransferase, plays an important role in regulating the expression of a number of developmental genes, including genes responsible for the formation of the heart and nervous system [74]. Abnormal protein acetylation has also been observed in infants with congenital heart defects [75].

Studies of mitochondrial deacetylases, such as Sirt3, have shown that they can modulate oxidative stress in blood vessels and exert a protective effect on endothelial function [76].

Therefore, numerous studies highlight that acetylation significantly influences embryonic development through transcription, translation, and protein interaction mechanisms. These processes may play a crucial role in RPL development, providing new theoretical foundations and approaches for further research in this area. Understanding the impact of non-histone acetylation on reproductive health creates new opportunities for the development of therapeutic approaches aimed at improving pregnancy outcomes and offspring health.

PALMITOYLATION

Palmitoylation, or S-palmitoylation, is an important PTM in proteins that results in the addition of palmitic acid to proteins. This process is mediated by enzymes such as palmitoyltransferases and depalmitoylases. Palmitoylation influences the subcellular localization, stability, and functional activity of proteins, which in turn may play a critical role in cellular signaling and homeostasis [77]. This modification is particularly important for regulating cellular activity, including cell differentiation and apoptosis. Understanding the mechanism of palmitoylation may aid in the development of new therapeutic approaches for the treatment of these pathologies.

Interestingly, some studies have found a direct correlation between RPL and the palmitoylation process [78-80]. This may open up new horizons for studying the mechanisms underlying RPL and facilitating the search for new solutions.

THE POTENTIAL OF PTMs IN PROTEINS IN THE PREDICTION OF RECURRENT PREGNANCY LOSS

Omics technologies, including genomics, epigenomics, transcriptomics, proteomics, and metabolomics, provide a holistic and comprehensive approach to studying biological systems. Proteomics, which includes the study of PTMs in proteins, the subject of this review, is the systematic and comprehensive study of the types, structures, and functions of proteins expressed within cells or tissues. Proteomic methods used to analyze PTMs in proteins can be divided into antibody-based and mass spectrometry (MS)-based analyses. Protein microarrays, immunohistochemistry, and Western blotting have demonstrated widespread popularity as effective tools for antibody-based analysis of PTMs in proteins. MS-based analysis is also a powerful method for studying PTMs in proteins. However, most proteomic studies investigating RPL have been performed using 2D-DIGE or quantitative methods such as iTRAQ in combination with MS-based approaches. Through the investigation of the relative associations between protein modifications and physiopathological changes, biomarkers for disease diagnosis can be identified. By examining and integrating data obtained through various omics approaches, it is possible to uncover and gain a more profound understanding of underlying molecular interactions and their related longitudinal effects [6, 15].

Although RPL pathogenesis is somewhat understood, specific diagnostic biomarkers and potential regulatory targets for RPL have not been identified. Therefore, researchers have carried out various omics studies using decidual tissue, villous tissue, and blood from patients with RPL. Several studies have so far provided insight into the potential use of PTMs in proteins markers for RPL prognosis.

OPG and Syndecan-1 transcript and protein expression, which were significantly lower in decidual samples from women with RPL than in women with normal pregnancies, are likely markers of RPL [6, 15].

PTMs IN PROTEINS AND NEW APPROACHES TO THE TREATMENT OF RECURRENT PREGNANCY LOSS

Epigenomics, the study of epigenetic modifications at the genome level, is closely related to PTMs in proteins. The most important and well-studied epigenetic modification is DNA methylation. Current epigenetic studies of RPL primarily focus on DNA methylation [54-57]. Epigenetic mechanisms are well-established in fetal and maternal pathophysiology. A new RPL risk gene, *CREB5*, was identified, and Yu M. et al. showed that its hypomethylation increased its expression and caused trophoblast cell dysfunction, leading to recurrent pregnancy loss [22]. Environmental factors that cause *CREB5* hypomethylation should be the focus of further research, as this may suggest approaches to causal interventions to prevent RPL [22]. Epigenetic therapy involves the application of medications or other methods to target these epigenetic processes. Methylation analyses have identified new molecular targets for epigenetic therapy. In therapeutic approaches, dCas9 may serve as a targetable platform for various effector proteins. However, given the current limitations, only a few epigenetic medications have been introduced into clinical practice so far. Further research into the field of epigenetic therapy is therefore required.

CONCLUSION

PTMs in proteins play a significant role in the pathophysiological mechanisms of RPL, affecting processes such as trophoblast invasion and implantation. The use of mass spectrometry has provided new opportunities for their investigation, allowing for the identification of post-translational modifications that can be used as biomarkers. Epigenetic therapies may offer more targeted and fewer adverse effects compared to conventional RPL treatments, emphasizing the need for continued research into the relationship between PTMs in proteins and reproductive health. However, research in this area faces challenges, including inconsistent terminology and ethical concerns, which hinder scientific collaboration and require the development of new methodologies to better understand this field.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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UNDER WHAT CONDITIONS IS UTERINE MYOMA IN WOMEN OF REPRODUCTIVE AGE ASSOCIATED WITH THE USE OF COMBINED ORAL CONTRACEPTIVES?

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RESUME

Uterine myoma (UM) is a common benign tumor of smooth muscle cells of the myometrium, which is often associated with metabolic disorders. Hormonal contraceptives are used to control the duration and volume of menstrual bleeding in UM. At the same time, data on the relationship between the use of combined oral contraceptives (COCs) and uterine myoma are contradictory.

The aim. *To identify the relationship between uterine fibroids and the use of combined oral contraceptives in women of reproductive age, taking into account their ethnicity and the presence of metabolic disorders.*

Materials and methods. *The results of a re-analysis of a cross-sectional study conducted earlier in Eastern Siberia (2016–2019) are presented. A total of 1347 women of reproductive age (34.33 ± 6.37 years) were included in the study, of which 198 participants had uterine fibroids. The study methods included a questionnaire survey, general clinical and gynecological examinations, pelvic ultrasound, and statistical analysis.*

Results. *It was found that an increase in the likelihood of detecting uterine fibroids is associated with the use of COCs in the presence of metabolic syndrome and only in the Caucasian subpopulation (OR 3.287; 95% CI (1.490; 7.253)). The use of COCs is a factor associated with uterine fibroids in women with a BMI of more than 30 kg/m^2, due to the subpopulation of Caucasian ethnicity, for whom the likelihood of having uterine fibroids is 6 times higher when using COCs than when not using COCs (OR 6.253, 95% CI (1.857; 21.054)). For Caucasians, the association between COC use and uterine fibroids was also demonstrated in patients with a BMI of less than 25 kg/m^2 (OR 2.521; 95% CI (1.255; 5.064).*

Conclusion. *In women of reproductive age, the association between uterine fibroids and the use of combined oral contraceptives is observed in women of Caucasian ethnicity. The presence of metabolic disorders is a key co-factor in the association between uterine fibroids and the use of hormonal contraceptives.*

Keywords: *uterine fibroids, ethnicity, combined oral contraceptives, body mass index, and metabolic syndrome*

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ПРИ КАКИХ УСЛОВИЯХ МИОМА МАТКИ У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА АССОЦИИРОВАНА С ПРИЕМОМ КОМБИНИРОВАННЫХ ОРАЛЬНЫХ КОНТРАЦЕПТИВОВ?

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РЕЗЮМЕ

Миома матки (ММ) — распространенная доброкачественная опухоль из гладкомышечных клеток миометрия, которая часто ассоциирована с метаболическими нарушениями. Гормональные контрацептивы используются для контроля за длительностью и объёмом менструальной кровопотери при ММ. В то же время, данные о взаимосвязи приёма комбинированных оральных контрацептивов (КОК) и миомы матки противоречивы.

Цель исследования. *Выявить связь миомы матки и приёма комбинированных оральных контрацептивов у женщин репродуктивного возраста с учетом этнической принадлежности и наличия метаболических нарушений.*

Материалы и методы. *Представлены результаты ре-анализа проведённого ранее в Восточной Сибири кросс-секционного исследования (2016–2019 г.). Всего в исследование было включено 1347 женщин репродуктивного возраста (34,33 ± 6,37 лет), из которых 198 участниц имели миому матки. Методы исследования: анкетный опрос, общеклиническое и гинекологическое исследование, УЗИ органов малого таза, статистические методы анализа.*

Результаты. *Установлено, что увеличение вероятности обнаружения миомы матки связано с приемом КОК при условии наличия метаболического синдрома и только в субпопуляции европеоидов (ОШ 3,287; 95% ДИ (1,490; 7,253)). Приём КОК является фактором, ассоциированным с миомой матки, у женщин с ИМТ более 30 кг/м^2 за счет субпопуляции европеоидной этнической принадлежности, для которых вероятность наличия ММ при использовании КОК в 6 раз выше, чем без применения КОК (ОШ 6,253, 95% ДИ (1,857; 21,054)). Для женщин европеоидной этногруппы связь приема КОК и миомы матки продемонстрирована также при ИМТ менее 25 кг/м^2 (ОШ 2,521; 95% ДИ (1,255; 5,064).*

Заключение. *В репродуктивном возрасте ассоциация миомы матки и приёма КОК характерна для женщин европеоидной этнической принадлежности. Основным вмешивающимся фактором для реализации потенциала роста миомы матки с применением гормональных контрацептивов является наличие метаболических нарушений.*

Ключевые слова: *миома матки, этническая принадлежность, комбинированные оральные контрацептивы, индекс массы тела, метаболический синдром*

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Uterine myoma (uterine leiomyoma, uterine fibroid) is a benign tumor that originates from the muscular layer of the uterus (myometrium) [1]. According to population studies, its prevalence reaches 14.7 % [2]. Risk factors for developing UM include certain ethnicities, older age, menstrual and reproductive history, and the presence of metabolic disorders [3]. The main symptoms reported by patients with uterine myoma include menstrual cycle disorders, in particular, abnormal uterine bleeding [4]. To reduce menstrual blood loss and duration, obstetrician-gynecologists often prescribe hormonal contraceptive methods for women who are not trying to conceive [1, 5, 6, 7]. At the same time, the impact of modern low- and micro-dose COCs on the size and number of myomatous nodes, as well as their growth, is still a subject of debate [8, 9]. Therefore, it has been established that when triphasic COCs are used in patients with interstitial uterine myomatous nodes, there is a significant reduction in the size of these nodes after 12 months. In contrast, previously healthy women of reproductive age who do not use COCs are more likely to be diagnosed with uterine myoma for the first time compared to healthy women who are taking these medications [7]. In their review, Krzyżanowski J. et al. concluded that further studies are needed to confirm the potential protective role of COCs with regard to the risk of uterine myoma [8]. Other researchers believe that COCs do not diminish uterine fibroid volume or uterine size. Moreover, they have minimal effects on other fibroid-related symptoms, making their use for fibroid treatment limited [9]. In contrast, our study demonstrated association between the use of COCs and the development of uterine fibroids [3]. The heterogeneity of the data available may be attributed to the multifactorial nature of uterine fibroids. When interpreting associations between these fibroids and COCs use, it is essential to consider the potential impact of metabolic disorders and ethnic background.

THE AIM OF THE STUDY

To identify the relationship between uterine fibroids and the use of combined oral contraceptives in women of reproductive age, taking into account their ethnicity and the presence of metabolic disorders.

MATERIALS AND METHODS

The article presents the results of a re-analysis of data collected between 2016 and 2019 as part of a cross-sectional epidemiological study [3]. Women residing in Irkutsk, Bokhan (Irkutsk Region), and Ulan-Ude (Republic of Buryatia), who were undergoing annual health check-ups at their workplaces, were invited to take part in the study.

Inclusion criteria: reproductive age (18–44 years inclusive) and informed consent to participate in the study. The study excluded women who were currently pregnant or breastfeeding, those who had undergone bilateral hysterectomy and/or appendages, endometrial ablation, and/or uterine artery embolization, or who refused to participate in the study. A total of 1,347 women (mean age 34.33 ± 6.37 years) were enrolled in the study. The ethnic distribution was as follows: 867 (64.37 %) were Caucasian, 361 (26.80 %) were Asian, and 119 (8.83 %) were mixed Caucasian-Asian participants. The main characteristics of the study population are presented in Table 1.

One hundred ninety-eight out of 1,347 study participants had uterine fibroids. No significant differences in the composition of the contraceptives used were found between the groups of women with and without uterine fibroids who were taking COCs (Table 2).

The study methods included a questionnaire, general medical examination, anthropometric assessment (including body mass index (BMI) calculation), blood pressure measurement, gynecological examination, and pelvic ultrasound using the Mindray M7 (MINDRAY, China) transvaginal (5.0–8.0 MHz) and transabdominal (2.5–5.0 MHz) transducers.

Biochemical testing methods: serum glucose and triglyceride levels were measured spectrophotometrically using commercially available BioSystems reagent kits on a BTS350 biochemical analyzer (Spain). Total cholesterol and HDL-C levels were also measured spectrophotometrically using the same commercial reagent kits and the same analyzer. These measurements were necessary for diagnosing metabolic syndrome. Metabolic syndrome was diagnosed in accordance with the NCEP ATP III criteria (Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults) criteria (2001) [10] in the presence of 3 out of 5 criteria: an increased waist circumference, increased fasting glucose levels, triglycerides levels ≥ 1.7 mmol/L (≥ 150 mg/dL) or the use of medications to manage this condition, HDL cholesterol levels < 1.04 mmol/L (< 50 mg/dL), SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or the treatment of previously diagnosed hypertension. Fasting plasma glucose was assessed using optimized criteria published in 2004, with values ≥ 5.6 mmol/l (≥ 100 mg/dl) [11]. Waist circumference was measured according to the diagnostic criteria proposed by the International Diabetes Federation (2006) [12]. These criteria define a WC ≥ 80 cm as an indicator of metabolic syndrome, which is consistent with the consensus criteria established by the Russian Association of Cardiologists [13]. The characteristics of anthropometric measurements and the main parameters that characterize the presence or absence of metabolic syndrome in women with and without uterine fibroids are presented in Table 2.

The study was conducted in accordance with the ethical guidelines outlined in the World Medical Association's Declaration of Helsinki (1964, as amended in Brazil in October 2013), and the study protocol was approved

by the Biomedical Ethics Committee of the Scientific Center for Family Health and Human Reproduction Problems (protocol No. 2.1 dated February 24, 2016).

Statistical Analysis

The sample size calculation was carried out using the interactive software "PS: Power and Sample Size Calculation" version 3.1.2 (Vanderbilt University, USA, 2014). Data entry and storage was performed using the REDCap information system, hosted on the server of the Scientific Center for Family Health and Human Reproduction Problems [14]. Logistic regression models were employed in the study. The results of the analysis are presented in the form of odds ratios (ORs) and 95% confidence intervals (CIs) for factors considered potentially significant relative to the hypotheses tested, and to assess their contribution to the risk/anti-risk process. Data analysis was conducted using statistical methods implemented in R, version 4.0.3 (R Core Team 2024).

RESULTS

As a result of a re-analysis of data from a previously conducted epidemiological study [2], it has been found

TABLE 1

AGE, ANTHROPOMETRIC PARAMETERS AND BLOOD PRESSURE OF WOMEN INCLUDED IN THE STUDY WITH AND WITHOUT UTERINE FIBROIDS

Parameter	All women *N* = 1347	Women with uterine myoma *N* = 198	Women without uterine myoma *N* = 1149	*p*
	Mean±Std.Dev Median (Lower Q;Upper Q)			
Age, years	34.33 ± 6.37	38.95 ± 4.34	33.54 ± 6.32	<0.001*
Height, cm	163.09±6.00 163.00 (159.00; 167.00)	162.55±6.11 162.00 (159.00; 166.00)	163.19±5.98 163.20 (159.00; 167.00)	0.164*
Body weight, kg	68.42±15.13 65.90 (57.50; 76.20)	72.45±16.17 68.30 (61.20; 80.20)	67.72±14.84 64.90 (57.00; 75.45)	<0.001**
BMI, kg/m^2	25.73±5.53 24.73 (21.55; 28.53)	27.43±5.96 26.27 (23.46; 30.36)	25.43±5.40 24.44 (21.36; 28.29)	<0.001**
BMI, kg/m^2, n/N (%)				<0.001**
< 18.5	50/1345 (3.72)	3/197 (1.52)	47/1148 (4.09)	
≥ 18.5 and < 25	656/1345 (48.77)	75/197 (38.07)	581/1148 (50.61)	
≥ 25 and <30	375/1345(27.88)	63/197 (31.98)	312/1148 (27.18)	
≥ 30 and <35	165/1345(12.27)	30/197 (15.23)	135/1148 (11.76)	
≥ 35 and <40	69/1345(5.13)	16/197 (8.12)	53/1148 (4.62)	
≥ 40	30/1345(2.23)	10/197 (5.08)	20/1148 (1.74)	
Waist circumference, cm	78.29±12.85 76.00 (69.00; 85.00)	81.65±13.11 80.00 (72.00; 88.00)	77.73±12.73 76.00 (68.00; 85.00)	<0.001**
Systolic blood pressure, mmHg	122.65±13.86 122.00 (113.00; 130.00)	128.17±16.61 127.00 (118.00; 138.00)	121.69±13.11 121.00 (113.00; 129.00)	<0.001**
Diastolic blood pressure, mmHg	78.93±9.958 79.00 (72.00; 85.00)	82.39±10.75 82.00 (75.00; 88.00)	78.33±9.69 78.00 (71.00; 84.00)	<0.001**
Glucose >5.6, mmol/l	1093/1347 (81.14%)	163/198 (82.32%)	930/1149 (80.94%)	0.646
HDL <1.2, mmol/L	865/1347 (64.22%)	124/198 (62.63%)	741/1149 (64.49%)	0.613
TG ≥1.7, mmol/l	67/1347 (4.97%)	15/198 (7.58%)	52/1149 (4.53%)	0.068

Note. * *t*–test, ** U-test, *** χ^2 test.

TABLE 2

COMPOSITION OF COCs IN WOMEN WITH AND WITHOUT UTERINE FIBROIDS TAKING COCs

Types of COCs	All women taking COCs n/N, % *N* = 133	Women with uterine myoma taking COCs n/N, % *N* = 19	Women without uterine myoma taking COCs n/N, % *N* = 114	*p*
Estradiol hemihydrate + Nomegestrol acetate	1/133 (0.75%)	0/19 (0.00%)	1/114 (0.88%)	0.682
Estradiol valerate + Dienogest	2/133 (1.5%)	1/19 (5.26%)	1/114 (0.88%)	0.147
Ethinyl estradiol + Gestodene	32/133 (24.06%)	6/19 (31.58%)	26/114 (22.81%)	0.408
Ethinylestradiol + Desogestrel	30/133 (22.56%)	3/19 (15.79%)	27/114 (23.68%)	0.446
Ethinylestradiol + Drosperidone	24/133 (18.05%)	2/19 (10.53%)	22/114 (19.30%)	0.357
Ethinylestradiol + Dienogest	17/133 (12.78%)	3/19 (15.79%)	14/114 (12.28%)	0.671
Ethinylestradiol + Levonorgestrel	14/133 (10.53%)	1/19 (5.26%)	13/114 (11.40%)	0.419
Ethinylestradiol + Cyproterone acetate	5/133 (3.76%)	1/19 (5.26%)	4/114 (3.51%)	0.710
Ethinylestradiol + Chlormadinone acetate	3/133 (2.26%)	1/19 (5.26%)	2/114 (1.75%)	0.340
The composition of COCs is unknown	5/133 (3.76%)	1/19 (5.26%)	4/114 (3.51%)	0.710

that among the general population, the use of COCs is associated with uterine fibroids, particularly among individuals with a BMI ≥ 30 kg/m^2 (OR 4.795, 95% CI (1.997; 11.517)), mainly due to Caucasians with a BMI ≥ 30 kg/m^2, for whom the risk of having UM when using COCs is 6 times higher than without using COCs (OR 6.253 95% CI (1.857; 21.054). A feature of women of Caucasian ethnicity is the association of UM and the use of COCs even among women with a normal (less than 25 kg/m^2) BMI (OR 2.521; 95% CI (1.255; 5.064)) (Fig. 1).

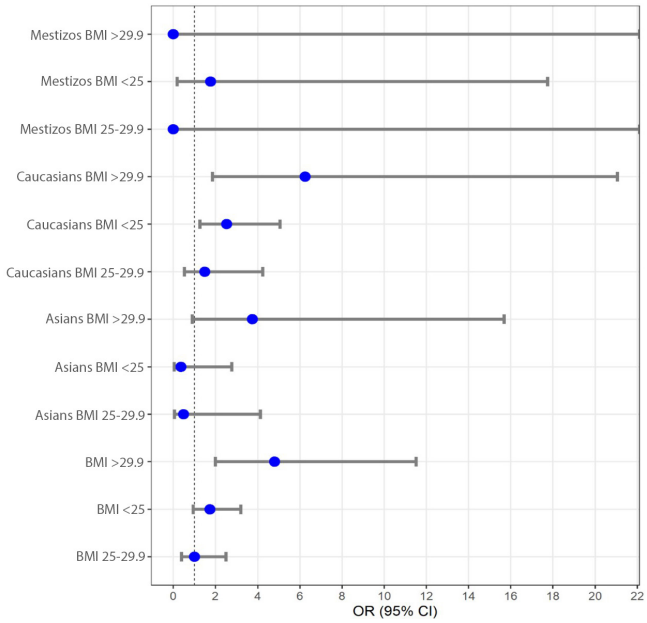
This study confirmed the previously reported association between UM and the presence of metabolic syndrome. When examining the association between UM and COC use, we found that this association was specific to women with MetS (OR 2.285; 95; CI (1.231; 4.242)), and was stronger in Caucasian women (OR 3.287; 95% CI (1.490; 7.253)) (Fig. 2).

DISCUSSION

This study investigated the relationship between uterine fibroids and COC use, depending on the presence or absence of metabolic disorders, among women from the main ethnic subgroups in Eastern Siberia. The study included women of reproductive age. A positive association was observed between the presence of uterine fibroids and the use of COCs among women with a BMI ≥ 30 kg/m^2. According to one hypothesis regarding the development of uterine fibroids, estrogens play a primary role in their pathogenesis. Since adipose tissue serves as a depot for steroid hormones, primarily estrogens, the risk of uterine fibroid development naturally increases in individuals with metabolic disorders such as overweight and obesity [15]. This likely explains the positive association observed between uterine fibroids and COC use among women with a BMI ≥ 30 kg/m^2. Elevated BMI has previously been identified as potential risk factor for uterine fibroids [16], but this study is the first to demonstrate its role as a confounding factor in the association between COC use and MM. Further analysis revealed that this association is predominantly present in Caucasian women. Nevertheless, our data suggest that in Caucasian women, an association between MM and COC use can be observed even among women with a BMI below 25 kg/m^2.

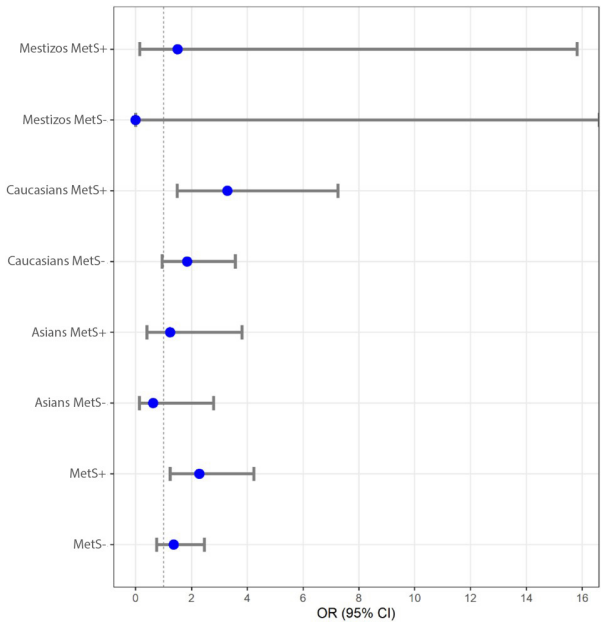
This study confirmed the previously reported association between MM and metabolic syndrome, which has been shown to occur even with in individuals with normal BMI values. Therefore, the possible role of MetS as a potential modifying factor in the association between MM and COC use was explored. Results showed that the association between MM and COC use is specific to women with MetS, particularly those of Caucasian ethnicity. Strengths of this study include a large sample size, lack of selection bias (non-hospital-based participants), and multi-ethnic composition of the participants. This study is the first to examine the association between uterine fibroids and COC use, while considering the participants' ethnic background and the presence or absence of common metabolic conditions.

However, given that the study design did not involve long-term follow-up of patients, but rather a single, time-sensitive analysis, the data collected do not



Abbreviations: BMI – body mass index, OR – odds ratio, CI – confidence intervals.

FIG. 1.
Associations of MM with the use of COCs, depending on BMI, in the general population and in different ethnic groups



Abbreviations: MetS (metabolic syndrome), OR (odds ratio), CI (confidential intervals).

FIG. 2.
Associations between uterine fibroids and the use of COCs, depending on the presence of metabolic syndrome in the general population and in different ethnic groups

allow for drawing conclusions about causality when discussing the associations between COC use and the presence of uterine fibroids.

CONCLUSION

Therefore, it has been determined that during the reproductive age, the correlation between uterine fibroids and COC use is primarily observed in Caucasian women. A significant contributing factor to the association between uterine fibroids and the hormonal contraceptive use is the presence of metabolic disorders. Large-scale prospective studies are needed to clarify the potential role of COCs in the development of uterine fibroids.

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Conflicts of interest

No potential conflict of interest relevant to this article reported.

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INTERNAL DISEASES

THE INFLUENCE OF BLOOD GROUPS ON PREDISPOSITION TO CERTAIN DISEASES: MOLECULAR MECHANISMS AND CLINICAL IMPLICATIONS (BRIEF-REVIEW)

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RESUME

The problem of early diagnosis and detection of diseases predictors of various etiologies is relevant. Blood type can act as such a predictor. The research for the relationship between blood type and predisposition to certain diseases will make it possible to identify risk groups for a particular disease and develop preventive measures. One such predictor could become blood type. The relationship between infectious (Cholera, the plague, tuberculosis, smallpox etc.) and non-communicable (oncological, neurodegenerative, cardiovascular, dental diseases etc.) AB0 blood type and other systems such as Rhesus, Lewis is being discussed. Although considerable advancements have been achieved in investigating the mechanisms that facilitate this connection, the inquiry remains unresolved. This review examines the current state of the problem and the alleged mechanisms of the association of various blood groups with a predisposition to certain diseases. The relationship between blood type and oncological diseases has been most studied. The relationship of blood type is discussed not only with certain diseases, but also with typological personality traits, temperament, and response to stressful factors that can predispose to the development of somatic and mental illnesses. Studying the influence of blood groups on predisposition to the development of dental diseases is largely devoted to the relationship of blood type AB0 with periodontal health. There are studies examining the prevalence of caries in people with different blood types. We analyzed more than 100 articles indexed in RSCI, PubMed, and Scopus, mainly over the past 10 years. Forty eight sources were used for the article, of which 16 were published in the last 5 years. Works published earlier than 2005 were excluded from the analysis.

Key words: *blood groups, antigens of the AB0 system, predisposition to diseases, infectious, somatic and dental diseases, blood*

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ВЛИЯНИЕ ГРУПП КРОВИ НА ПРЕДРАСПОЛОЖЕННОСТЬ К НЕКОТОРЫМ ЗАБОЛЕВАНИЯМ: МОЛЕКУЛЯРНЫЕ МЕХАНИЗМЫ И КЛИНИЧЕСКИЕ ИМПЛИКАЦИИ (КРАТКИЙ ОБЗОР)

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РЕЗЮМЕ

Проблема ранней диагностики и выявления предикторов заболеваний различной этиологии является актуальной. Группа крови может выступать в качестве такого предиктора. Поиск взаимосвязи между группой крови и предрасположенностью к определённым заболеваниям позволит выявлять группы риска по конкретному заболеванию и разрабатывать профилактические меры. Обсуждается взаимосвязь между инфекционными и неинфекционными заболеваниями и группой крови AB0 и другими системами, такими как резус-фактор, система Льюиса. Несмотря на значительный прогресс в изучении механизмов реализации этой взаимосвязи, вопрос остаётся открытым. В обзоре рассматривается современное состояние проблемы и предполагаемые механизмы связи различных групп крови с предрасположенностью к определённым заболеваниям. Наиболее изучена связь между группой крови и онкологическими заболеваниями. Обсуждается связь группы крови не только с определёнными заболеваниями, но и с типологическими чертами личности, темпераментом и реакцией на стрессовые факторы, которые могут предрасполагать к развитию соматических и психических заболеваний. Исследование влияния групп крови на предрасположенность к развитию стоматологических заболеваний посвящены, в основном, связи группы крови AB0 со здоровьем пародонта. Существуют исследования, изучающие распространённость кариеса у людей с разными группами крови. Мы проанализировали более 100 статей, индексированных в RSCI, PubMed и Scopus, в основном за последние 10 лет. Для статьи было использовано 48 источников, из которых 16 опубликованы за последние 5 лет. Работы, опубликованные ранее 2005 года, из анализа исключались.

Ключевые слова: *группы крови, антигены системы AB0, предрасположенность к заболеваниям, инфекционные, соматические и стоматологические заболевания, кровь*

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INTRODUCTION

Currently, the problem of early diagnosis and detection of predictors of pathological conditions and diseases of various etiologies is acute. Paradoxically, blood type can act as such a predictor. The search for a relationship between blood type and predisposition to certain diseases has been going on for several decades, but the question remains open. The solution to this issue will make it possible to identify risk groups and develop preventive measures for certain diseases, since almost everyone undergoes a routine blood type examination according to the AB0 system and the Rh factor. Blood system antigens are an important individual, species, and population characteristic, reflecting the diversity and peculiarities of maintaining the body's homeostasis [1]. The antigens of the AB0 blood group system, discovered by K. Landsteiner, are expressed not only on erythrocytes, but also on leukocytes, platelets, epithelial and endothelial cells, and various types of neurons [2], which makes it legitimate right to use the term histo-blood group, emphasizing the systemic nature of the response. Presently, the relationship between infectious and non-communicable diseases and blood type is being discussed not only according to the AB0 system [3-6], but also according to Rhesus, Lewis and others systems [3, 6]. However, despite the fact that there are many studies [7-10] that show statistical correlations between blood groups and certain diseases, there is currently no consensus on the exact mechanisms of this association.

More than 100 articles indexed in RSCI, PubMed, and Scopus were analyzed, mainly over the past 10 years. A total of 48 references were utilized in this study, among which 16 were published within the last five years. Any works published prior to 2005 were excluded from the analysis.

THE AIM

To analyze modern scientific literature containing theories and studies that explain the mechanisms of conjugation between different blood groups and predisposition to certain diseases.

Oncological diseases

The interrelation of blood type and cancer is the most studied [3, 4, 11, 12]; mechanisms for the implementation of such interrelation are proposed. Studies conducted in the 1950s have shown that risk of stomach cancer development is about 20 % higher [4, 5, 12, 13] in people with blood type II (A) compared to people with blood type I (0). People with blood type IV (AB) are more susceptible to this disease [4, 13]. It has been proven [5] that the antigen A presence in people of blood groups II and IV negatively affects the production of hydrochloric acid, which reduces antibacterial protection. In this regard, individuals with blood type II(A) possess significantly increased rates of *H. pylori* infection than those without this antigen. It is known that *H. pylori* is one of the numerous factors which can cause metaplasia of the gastric epithelium [4, 5]. Also, the individuals with blood groups II (A) and IV(AB) have a decrease in the production of intercellular adhesion molecule type 1, which reduces antitumor immunity [3]. However, these are not the only factors contributing to the high incidence of cancer in people of blood type II (A).

The antigens of the AB0 and H-antigen systems have a leading role in oncogenesis, metastasis, prognosis of the tumor process [4, 5]. They can be observed in epitheliocytes of the digestive system, respiratory, urinary and reproductive systems [2, 5]. Tumor cells, especially of epithelial origin, can also express antigen A or a similar antigen. With malignancy of the tumor, the number of such antigens decreases or absent at all. This happens because the transcription of A-transferase is suppressed due to DNA methylation in the region of the gene responsible for the expression of antigen A. The smaller the antigen, the greater the malignancy of the tumor. The loss of antigens A and, to a lesser extent, the loss of antigen B are proportional to the metastatic potential of the tumor [5], because a lack of these antigens blocks the immune antitumor response. Those tumors where A or A-like antigens are present will be perceived as alien and interact with antibodies, which will lead to an attack on tumor tissue.

Individuals with blood type II(A) do not have an immune reaction to the A-antigen. Therefore, malignant cells with the A-antigen or similar antigens will not be recognized as allogenic, so such cells will not be destroyed by the immune system. Thus, the absence of antigen A in people with blood group I(0) can be considered as a factor of antitumor protection against epithelial malignancies, such as cancer of the reproductive system in men and for women, intestinal cancer, pancreatic cancer, which is also more common in people without I(0) blood group [4, 5, 6].

Also, the normal expression (Fig. 1) of antigens A, B or H [14] changes in patients with lymphoma or leukemia.

Modern literature addresses two mechanisms through which these antigens are lost (Fig. 2) [4].The first mechanism is due to the chromosomal translocation of the region of chromosome 9 responsible for information about A- or B-transferases. The activity of A- and B-transferases, individually or both at the same time, is inhibited, which leads to an increase in antigen H, which is no longer transformed into antigens A and B. Breakdown can also occur

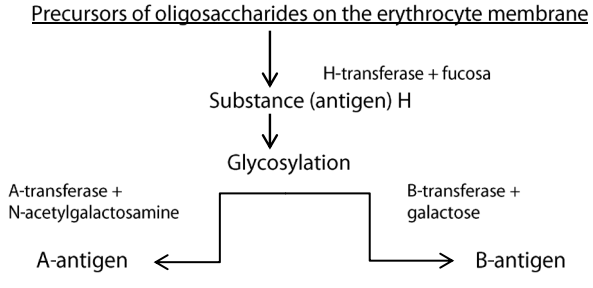

FIG. 1.
Formation of A, B and H antigens on human erythrocytes

at the level of formation of H-antigen, as a precursor of antigens A and B (the second possible mechanism). For example, by reducing the amount or activity of H-transferase. Thus, the suppression of the expression of A- and B-antigens can be considered as a predictor of malignant diseases of the blood system and act as a factor that allows assessing the dynamics of the disease. It has been shown that normal expression of antigens A and B by blood cells occurs during remission. With the recurrence of leukemia or lymphoma, such expression decreases or cells that have lost A- and B-antigen reappear [4].

At the same time, the predominance of blood group II (A) was not revealed in patients with brain tumors [9], a slight predominance of III(B) was found, which the authors of the study explained by the relative isolation of the tumor from the general immune system. In tumors, there is not only a connection with the AB0 antigen system, but also with the Lewis system [4, 5]. The antigen Le^b is an antigen associated with colon adenocarcinoma, and the Lewis system antigens (Le^a and Le^b) are co-expressed in tumor tissue. Therefore, the relationship of blood type with predisposition to certain oncological diseases can be considered proven. However, the variability of the localization of tumor growth and their diversity provide a wide field for discussion.

Metabolic disorders. Hyperlipidemia

People with blood type II(A) have decreased serum levels of apo-lipoprotein B-48, which is involved in the formation of chylomicrons [5, 15]. This may be due to the genetically determined low activity of intestinal alkaline phosphotase (I-ALP). It is believed that this enzyme is essential for the crossing of chylomicrons from the intestine into the blood. Due to this, representatives of the II(A) blood group have a lower level of cholesterol in the blood serum than those of the owners of other groups. However, that data need to be clarified due to the fact that the inheritance of metabolic disorders is multi-factor and is not managed by a single gene. Some studies have shown that blood groups II(A) and III(B) contain lower levels of HDL and higher levels of LDL, total cholesterol and triglycerides. The blood group IV(AB) protected against hyperlipidemia [16].

Diabetes mellitus (Type 2 diabetes)

There is currently no clear association of the risk of developing type 2 diabetes mellitus (DM2) with the blood type [5, 16]. According to a study by Fagherazzi G. et al., there is no connection between the Rh blood type and the possible development of DM2 [5]. According to the AB0 system, people with blood type I(0) have the lowest risk of developing DM2 [17-19], and those with blood type III(B) have the highest risk [20, 21]. A possible protective effect in individuals with blood type I(0) is associated with the lack of activity (or low activity) of transferases, namely glycosyltransferase [14]. It is known that in the presence of active glycosyltransferase, the level of inflammatory mediators is higher [21]. This leads to the development of immune and inflammatory reactions, which play a significant role in the development of DM2. When assessing blood groups according to the Rhesus and AB0 system, the highest risk

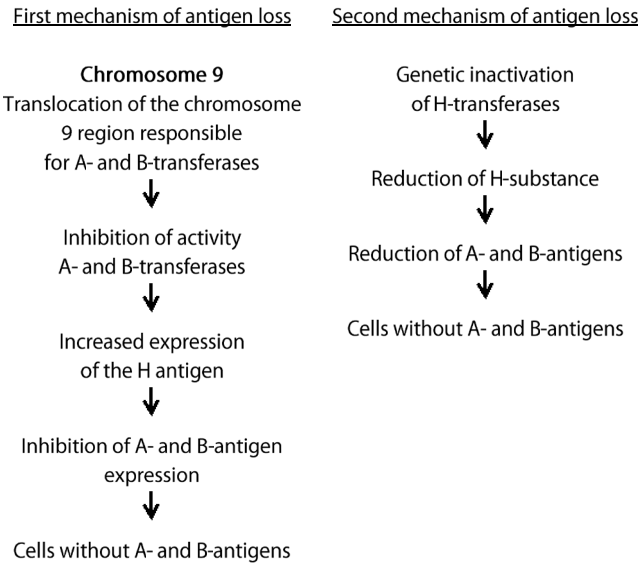

FIG. 2.
Mechanisms of antigen loss at malignant diseases of the blood system

was also found in people with blood group III(B) Rh+ [5, 20]. Nevertheless, research undertaken in different nations has not demonstrated a similar correlation.[20, 21]. Perhaps the metabolic status [1, 22] (lipid profile, fasting glucose level, etc.) is important, influencing the implementation of the mechanisms of diabetes mellitus development.

Psychological status and nervous system disorders

The relationship of blood type is discussed not only with certain diseases, but also with typological personality traits, temperaments, and response to stressful factors [23-26], which in turn may predispose to the development of not only somatic, but also mental illnesses [3]. One of the first theories of the conjugation of blood type and psychological status was proposed in the 30s of the last century by T. Furakawa [25], and discussions on this issue continue to this day. For example, there have been attempts to link blood type and aggression (external (verbal and physical) or internal (negativism, resentment, guilt)) [23]. Representatives of blood groups I(0) and II(A) had a tendency to direct aggression directed at another person, while representatives of blood groups III(B) and IV(AB) had more frequent manifestations of internal aggression. These studies are based on the assumption that blood type is a marker of biochemical individuality [23, 24], which can manifest itself in behavioral reactions. The authors propose that the schematic representation outlined is essential to understanding the interplay between blood type and the body's inclination towards specific ratios of hormones and neurotransmitters, including cortisol, catecholamines, dopamine, and gamma-aminobutyric acid (GABA), which subsequently influence behavioral outcomes. Nevertheless, such conclusions also have an ethical aspect. Historically experience shows that attempts to find "ideal" biological markers (including racial theories) have led to scientifically unsound conclusions.

This warns against similar simplistic interpretations of blood type data.

Individuals with blood type IV(AB) have a higher risk of stroke and cognitive impairment [5, 11, 27, 28] in both men and women. Such cognitive impairments can occur not only as a result of stroke, but also in its absence, for example, due to neurodegenerative diseases [27]. A higher risk of stroke and cognitive impairment was noted in the carriers of blood group IV(AB) in all age groups [5, 27]. Similarly, the proportion of mental disorders in people with blood type IV(AB) is almost 3 times higher than the average in the population [25]. This could be attributed, among other factors, to psychological traits, the degree of synthesis, and the balance of neurotransmitters previously discussed. Although research data are contradictory [27], most of them indicate that people with blood type IV(AB) are more likely to have Alzheimer's disease [5]. Alzheimer's disease is based on pathological activity and impaired elimination of beta-amyloid and tau proteins, which have a toxic effect on brain tissue and disrupt the formation of neuronal connections. One of the reasons leading to a violation of the elimination of pathological proteins is genetic. It can be assumed that inherited biochemical features associated with blood type can influence the pathogenesis of neurodegenerative diseases.

Research indicates that individuals with the I(0) blood group, as classified by the ABO blood group system, tend to possess a significantly greater volume of gray matter in the brain when compared to other blood groups [27]. Perhaps this is a shielding factor against neurodegenerative diseases, including Alzheimer's disease, in which number of neurons of the brain progressively decreases. The protective role of blood group I(0) in the aging of not only the brain, but also the body as a whole is discussed [29, 30]. This may be due to the fact that the plasma levels of von Willebrand factor (vWF) and factor VIII (FVIII) are lower in people with the first blood group than in people with other blood groups [27, 31, 32]. It may reduce risks of thrombosis in development of vascular pathologies during aging.

Infectious diseases

Researches have shown [6] that blood group I(0) has a high resistance to most infectious agents compared to other blood groups. However, when exposed to *Mycobacterium tuberculosis*, vibrio cholera, or *Yersinia pestis*, the risk of infection in people with blood type I(0) is quite high [3]. They are more likely to have a severe, progressive course of these infections. The antigens of some bacteria are similar to those of blood groups, and this largely determines the immune response to these antigens [14]. Thus, people with blood group III(B) are more likely than those with groups I(0) and II(A) to have an infectious process caused by *E. coli*, since the B antigen is similar to the antigen of the microorganism, therefore, the immune response does not develop or is insufficient. For the same reason, people with blood type IV(AB) have a high probability of escherichiosis. Statistically, the carriers of this group are more likely to have severe forms of smallpox and salmonellosis, and people with blood type II(A), in addition to smallpox, often have an infection caused by *Pseudomonas aeruginosa* [3, 6]. Probably it is due to the affinity of pathogens to blood group antigens [3], which are expressed not only on erythrocytes, but as well as on epithelial cells. There is a version that the prevalence of a certain blood type in a given territory is largely due to natural selection due to epidemics raging in a particular region or country. For example, the inhabitants of West Africa have practically no Duffy antigen, which was the result of selection providing protection against Plasmodium vivax [6]. However, the variety of strains of viruses and bacteria, as well as the variety of adhesives used by them, does not allow us to make an unambiguous conclusion about the connection of a blood group with a particular disease. Rather, it is worth talking about the tropicity of a particular pathogen to a certain antigen that determines the blood group.

In recent years, the relevance between blood type AB0, Rh factor and susceptibility to coronavirus infection (COVID-19) has been studied [33-36]. It was found that blood group II(A) is associated with an increased infection risk, severe and even fatal course of the disease, while those with group I(0) are characterized by resistance of the bronchopulmonary system to coronavirus or, in the presence of infection, relatively mild course of the disease. It is assumed that the SARS-CoV-2 virus is able to bind directly to antigen A, which is located on epithelial cells of the respiratory tract, which increases the viral load [8]. In addition, individuals with blood type II(A) have not natural immunity to polysaccharides A, which leads to a lack of immune response and a more severe course of infection. Individuals with blood type II(A) have a higher level of von Willebrand factor [5, 31, 33], which is a possible cause of thrombotic complications.

Dental diseases

Studies of the blood groups influence on predisposition to the dental diseases development are largely devoted to the relationship between the blood group and periodontal health [37-39]. However, the results of the observations vary significantly. For example, a study of the results of the D. Mostafa research [37], which evaluated the condition of 1126 patients with chronic periodontitis, revealed an increased risk of developing an inflammatory process in periodontitis in people with blood type I(0). A possible mechanism explaining this phenomenon is a reduced level of IgA in the oral fluid in patients with blood type I(0), which makes the anti-infective protection of the oral cavity vulnerable. On the contrary, Gurpur Prakash Pai and co-authors [38] noted the highest percentage of people with healthy periodontitis among the owners of blood group I(0). At the same time, gingivitis and periodontitis in their work were more often diagnosed in subjects with A(II) and B(III) blood groups [38]. This is probably due to the fact that antigens A and B, which are also present on mucosal epithelial cells, act as receptors for the fixation of tropic bacteria.

According to other data [39], the 61-kDa bacterial adhesive protein is considered as a tropic for the H antigen, which is a precursor of the B and A antigens. The expression

of the H antigen precursor is carried out mainly by cerebrospinal cells; however, it can also occur in non-keratinized epithelium, including the epithelium of the oral mucosa. Individuals with blood type I(0) have the highest amount of H antigen, including in the gum tissues, which, according to researchers, may contribute to the attachment of gram-negative bacteria and a greater risk of developing an inflammatory process [39].

There are studies examining the prevalence of caries in people with different blood types [40, 41, 42]. It has been established that individuals with different blood groups have different saliva composition parameters; therefore, their resistance to various infectious agents differs, which affects the development of caries [41, 42]. According to studies, the incidence of caries was statistically higher among people with blood type III(B) ($p<0.05$) [41] and with Rh-positive blood type IV(AB) [42].

Some studies assessing the risks of developing various types of cancer of the oropharyngeal region also suggest taking into account the phenotype of the patient's blood [43, 44]. Since blood antigens A/B, precursors, or related antigens (H, Lewis, Ii) are expressed in endodermal epithelial cells, where most cancers occur, the blood group can detect tumor-related glycosylation changes. There is evidence of the relationship between blood type and the propensity to develop oral potentially malignant disorder [45]. It was revealed that people with blood type "B" were 1.46 times more susceptible to acquiring oral potentially malignant disorder, such as leukoplakia and lichen planus [45]. The authors suggest that blood group antigens on the cell surface play a role in protecting mucous membranes, and suggest informing people with blood group B who have bad habits that they are more likely to develop oral potentially malignant disorder.

Other somatic diseases

Blood type III(B) is a predictor of severe rheumatoid disease due to the higher frequency of the haptoglobin 2-2 phenotype [46], which predisposes to a clinical variant with a tendency to frequent and prolonged exacerbation. Belonging to blood group III(B) is associated with a higher risk of arterial hypertension compared to other blood groups according to the AB0 system [7, 16].

The relationship between the AB0 blood group system and coagulation abnormalities is associated with the function of von Willebrand factor (vWF), which serves as the transport protein for factor VIII (FVIII) [11, 28, 31, 32, 47]. Von Willebrand factor participates in both primary (vascular-platelet) and secondary (coagulation) hemostasis. A decrease in its quantity and activity is accompanied by a risk of bleeding (persons with blood type I(0)) [11, 31]. This risk must be taken into account when performing surgical interventions, especially long-term ones, such as joint replacement. Similarly, in people with blood type I(0), a decrease in prothrombin (FII) and proconvertin (FVII) levels was noted, which indicates the peculiarity of both the external and internal pathways of coagulation hemostasis in these subjects [31]. A decrease in the level of coagulation factors contributes to the development of bleeding, but at the same time protects against excessive thrombosis, which occurs in atherosclerosis, coronary heart disease, thrombophlebitis, etc. [27, 48]. Increased activity of the coagulation system is of great importance in the pathogenesis of heart attacks and other "vascular" disasters. The H-antigen present on erythrocytes of group I(0) affects the metabolism and duration of action of vWF, shortening the time of its activity [31]. A longer half-life, therefore, a higher concentration of vWF and the coagulation factor FVIII carried by it in the blood plasma of other groups, especially II(A), lead to an increased likelihood of thrombosis and thromboembolism. However, according to a study by O.A. Gusyakova, et al. [31], in individuals with blood type II(A), there is a compensatory increase in the activity of anticoagulant and fibrinolytic systems, which prevent the development of thrombosis for a long time.

The development of cardiovascular diseases (coronary heart disease, arterial hypertension, etc.) is facilitated by the influence of blood group antigens on erythrocyte aggregation [7]. An increase in the ability to aggregate leads to an increase in blood viscosity, increased peripheral resistance to blood flow and the risk of thrombosis. The negative charge of the erythrocyte membrane, which also depends on the expressed antigens, enhances their mutual repulsion and increases resistance to aggregation. Individuals with blood type I(0) who have a "basic" antigen have a lower risk of cardiovascular pathologies [7]. There is also evidence that the genes that determine the AB0 blood type are associated with the genes responsible for the expression of tumor necrosis factor (TNF), which has a significant effect on endothelial function, capillary permeability and coagulation [7].

CONCLUSION

The review does not include all diseases and conditions in which there is a link between them and blood type. The association of blood type with the development of schizophrenia [3], HIV infection [6] and others is discussed [1, 5, 11]. Modern research suggests mechanisms for this coupling, but existing theories and proposed mechanisms need to be clarified. Blood group antigens are important genetic and immunological factors that affect the level of pro-inflammatory and anti-inflammatory agents, the state of the coagulation and anticoagulation systems, and response characteristics. The review can help in the development of screening programs and the individualization of preventive measures. For example, people with blood type 1 who are predisposed to bleeding may be advised to conduct an in-depth study of coagulation hemostasis before surgery. For people with blood groups 2 and 4 with an increased risk of developing stomach cancer, it is advisable to undergo a medical examination with the mandatory inclusion of fibrogastroduodenoscopy in the study plan. For people with blood type 3, especially Rh-positive ones, it is possible to include earlier monitoring of blood pressure and glycemia in the examination plan. Further research

to establish the mechanisms of the relationship between blood type and pathological conditions will shed light on many links in the pathogenesis of various diseases. Blood group antigens may become markers of the prenosological diagnosis of certain conditions [4, 10, 19, 22], that makes it advisable to include the blood type in predictive diagnostic algorithms. This will make it possible to develop preventive measures and carry out early diagnosis of many diseases.

Conflict of interest

The authors declare that they have no competing interests.

Author's contributions

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CIRCULATING IMMUNE COMPLEXES IN THE PATHOGENESIS OF POST-COVID JOINT SYNDROME

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RESUME

Background. *A common manifestation of the post-COVID syndrome is damage to the articular apparatus. Considering the role of circulating immune complexes in the occurrence of postinfectious and immune lesions of joints, as well as their participation in the immunopathogenesis of the acute period of infection, it can be assumed that they are involved in the formation of joint syndrome after COVID-infection.*
The aim. *To assess the involvement of circulating immune complexes in the pathogenesis of various clinical variants of post-COVID joint syndrome.*
Materials and methods. *Sixty two patients with post-COVID syndrome and complaints of damage to the musculoskeletal system were examined. All patients had suffered coronavirus infection during the previous 12 months. All patients underwent radiographic and ultrasound examination of the joints. In the blood serum the total content of IgM, IgG and IgE was determined. Circulating immune complexes in peripheral blood were determined by precipitation method.*
Results. *The post-COVID joint syndrome in the examined patients manifested itself in four variants, which differed clinically and had different immunological characteristics. High levels of circulating immune complexes were detected in arthralgia, arthritis, and the onset of arthropathy and were accompanied by elevated titers of IgM and IgG. With the progression of arthropathy, the circulating immune complexes content in the blood of patients often corresponds to the borderline level with low IgM and IgG values.*
An increased IgE titer was recorded in the blood of patients with arthritis, onset and progression of arthropathy, and there were no manifestations of allergy and the allergic history was negative in the majority of the examined.
Conclusion. *Thus, the immunocomplex mechanism of damage plays an important role in the pathogenesis of arthralgia, arthritis and the onset of osteoarthropathy, but not its progression in post-COVID syndrome. IgE is actively involved in the formation of arthritis, the progression of osteoarthropathy, and especially in its onset.*

Key words: *post-COVID syndrome; post-COVID joint syndrome; circulating immune complexes; immunoglobulins; mast cell activation syndrome*

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РОЛЬ ЦИРКУЛИРУЮЩИХ ИММУННЫХ КОМПЛЕКСОВ В ПАТОГЕНЕЗЕ ПОСТКОВИДНОГО СУСТАВНОГО СИНДРОМА

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РЕЗЮМЕ

Частым проявлением постковидного синдрома является повреждение суставного аппарата. Учитывая роль циркулирующих иммунных комплексов в возникновении постинфекционных и иммунных поражений суставов, а также их участие в иммунопатогенезе острого периода инфекции, можно предположить их причастность к формированию суставного синдрома после COVID-инфекции.
Цель исследования: *оценить роль циркулирующих иммунных комплексов в патогенезе различных клинических вариантов постковидного суставного синдрома.*
Методы. *Обследовано 62 пациента с постковидным синдромом и жалобами на поражение мышечно-суставного аппарата. Перенесенная COVID-19-инфекция была подтверждена лабораторно. Всем пациентам проведено инструментальное обследование: рентгенография и ультразвуковое исследование суставов. В сыворотке крови оценивали общее содержание IgM, IgG и IgE. Уровень циркулирующих иммунных комплексов в периферической крови определяли методом преципитации.*
Результаты. *Суставной синдром в постковидном периоде у обследованных пациентов клинически проявлялся в виде четырех вариантов: изолированной артралгии, артрита, дебюта и прогрессирования артропатии. Высокие уровни циркулирующих иммунных комплексов были выявлены при артралгии, артрите и дебюте артропатии и сопровождались повышенными титрами IgM и IgG. При прогрессировании артропатии содержание циркулирующих иммунных комплексов в крови у пациентов зачастую соответствовало пограничному уровню при невысоких значениях IgM и IgG.*
Повышенный титр IgE зафиксирован в крови у пациентов с артритом, дебютом и прогрессированием артропатии, причем проявления аллергии отсутствовали и аллергологический анамнез был отрицательным у большинства обследованных.
Заключение. *Таким образом, иммунокомплексный механизм повреждения играет важную роль в патогенезе артралгии, артрита и дебюта остеоартропатии, но не ее прогрессирования при постковидном синдроме. В формировании артрита, а также при прогрессировании остеоартропатии и, особенно, при ее дебюте принимают активное участие IgE.*

Ключевые слова: *постковидный синдром; постковидный суставной синдром; циркулирующие иммунные комплексы; иммуноглобулины; синдром активации тучных клеток*

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INTRODUCTION

After the acute phase of SARS-CoV-2 infection, some patients may experience post-COVID syndrome (PCS). In addition to respiratory, cardiovascular, and neurological damage, joint pathology may occur, persisting and worsening over several months [1]. The incidence of joint damage in the post-COVID period (PCP) reaches 65 % [2]. Joint syndrome (JS) manifests in 80 % of cases and progresses in 20 % [3]. The development of JS depends on the severity of the acute COVID-19 infection [4]. Risk factors for JS in post-COVID patients include female gender, older age, pre-existing arthralgia, prolonged hospitalization, and a history of joint pain at the onset of the infection [5, 6]. Another significant risk factor for JS in PCP is a high body mass index [7].

Researchers' opinions on the nature of the post-COVID joint syndrome are highly contradictory. The syndrome develops in the context of high acute-phase reactant levels (ESR, CRP, and IL-6), yet the titers of antinuclear antibodies and antibodies to cyclic citrullinated peptides, as well as C3 and C4 complement system components, have changed insignificantly. This suggests that there is excess inflammation associated with the COVID-19 infection rather than autoimmune activation [8, 9]. However, the high probability of transformation of unspecified arthritis into various rheumatic conditions in 49 % of patients (most commonly into early rheumatoid arthritis), as well as exacerbation of underlying disease in 83.4 % of those with advanced rheumatoid arthritis, and significant increase in immune activity due to antinuclear antibodies in systemic connective tissue disorders do not allow us to exclude the role of autoimmune mechanism in the pathogenesis of post-COVID joint damage [10].

One of the significant mechanisms of immune tissue damage is the immune complex mechanism. This mechanism involves the formation and circulation of immune complexes, which are composed of specific immunoglobulins, complement components, and antigens. Immune complexes are formed when there is an excess of antigen, both from exogenous sources (such as viruses) and endogenous sources (products of damaged cells and tissues). The deposition of large numbers of immune complexes in tissues can initiate an enhanced signaling cascade mediated by Fc-gamma receptors. This ultimately leads to the development of vasculitis, glomerulonephritis, and arthritis in the setting of acute COVID-19. Moreover, soluble circulating immune complexes (CICs) have been found in the blood of critically ill patients with acute COVID-19, and their levels correlate with disease severity [11]. Soluble circulating immune complexes (CICs), containing IgG, have been detected in approximately 80 % of patients with severe and critical COVID-19 at levels comparable to those seen in active systemic lupus erythematosus. CICs may form before the development of a specific humoral response to SARS-CoV-2, and through excessive activation of Fc-gamma receptors, they can cause impaired immune responses in susceptible patients [12]. Given the role of CICs in the immunopathogenesis of acute COVID-19, it is possible that they may also contribute to the development of post-COVID-19 arthritis syndrome.

THE AIM OF THE STUDY

To assess the role of circulating immune complexes in the pathogenesis of various clinical manifestations of post-COVID joint syndrome.

MATERIALS AND METHODS

Study Design and Setting

The study was conducted at the outpatient clinic of the E.M. Niginsky Consultative and Diagnostic Clinic in Tyumen between 2021 and 2023. A total of 62 patients were included in the study: 19 male patients (mean age 48.84 ± 13.97 years) and 43 female patients (mean age 44.53 ± 12.47 years). All participants had signs of a joint syndrome that developed following COVID-19 infection. All patients had a laboratory-confirmed COVID-19 infection (a positive SARS-CoV-2 RNA PCR result in their medical records or a positive IgG antibody titer to SARS-CoV-2 after the acute phase of the disease had resolved and in case of asymptomatic infection). Based on the persistent asthenia following COVID-19, the diagnosis of post-acute COVID-19 syndrome (PCS) was made. The duration of the latest acute phase of infection was as follows: 1–3 months (n = 12); 3–6 months (n = 18); 6–12 months (n = 16); and 12–15 months (n = 16).

Exclusion criteria: the presence of any chronic diseases that may have triggered or exacerbated general asthenia during the PCP; lack of laboratory confirmation for a prior COVID-19 infection; refusal to participate in the study.

All patients underwent instrumental examinations, including radiography and ultrasonography of the joints.

The white blood cell count and differential in the complete blood count were determined using a Mindray BC-2800 hematology 3-frequency analyzer (Hemalight 1270, USA). Blood biochemistry parameters: C-reactive protein (CRP) and fibrinogen were measured using a Mindray BS-240Pro biochemistry analyzer (China). To assess total IgM and IgG levels in serum, a standard reagent kit from Protein Contour LLC (Russia) was used.

The analysis was conducted in accordance with the manufacturer's guidelines. Results were obtained using a Multiskan photometer (Labsystems, Finland). Total immunoglobulin E (total IgE) levels in serum were measured using an ELISA assay method and results were recorded on a Multiskan SkyHigh reader (Thermo FS, Finland). Laboratory values from healthy individuals of the same age served as a control.

Circulating immune complex (CIC) levels in peripheral blood were measured using PEG precipitation and results were recorded on an Infinity F50 ELISA reader (Austria). According to the method used, if the CIC concentration was less than 3.2 μg/ml, the result was considered negative; if the concentration was 3.3–5.0 μg/ml, the result was classified as borderline; and if the CIC level exceeded 5.0 μg/ml, the sample was considered positive.

Ethical review. The study has been conducted in compliance with the ethical standards established in accordance with the World Medical Association's Declaration of Helsinki. This is confirmed by the extract from the minutes of the local Ethics Committee meeting. The study protocol has been approved by the independent Ethics Committee of the Ilizarov National Medical Research Centre for Traumatology and Orthopedics (protocol No. 2(72) dated October 7, 2022). All participants included in the study signed voluntary written informed consent.

Statistical analysis of the results was conducted using Microsoft Excel (Microsoft Office, USA) and the Statistica 10.0 package (StatSoft, Inc., USA). A sample size was not pre-calculated. The normality of variable distribution was verified using the Shapiro – Wilk test. The data are presented as median and interquartile range Me [Q25; Q75], categorical data as frequencies and percentages. Statistical significance of intergroup differences in quantitative variables was determined using the Mann – Whitney U-test. Differences in the compared parameters were considered statistically significant at $p < 0.05$.

RESULTS

Most patients with joint syndrome (56 %, $n = 35$) experienced the acute phase of COVID-19 with mild or no symptoms. In 36 % ($n = 22$) of these cases, the acute phase was moderate, with evidence of interstitial viral pneumonia, and therefore full treatment was administered. Only 8 % ($n = 5$) of patients experienced a severe acute phase, requiring hospitalization for treatment.

Joint syndrome in the PKP patients examined manifested clinically in four different ways.

Isolated arthralgia, which was not accompanied by visual signs of joint inflammation or changes in instrumental examination, was reported by 14 women with an average age of 33.64 ± 9.11 years and 1 man, aged 27 years. Arthralgia typically manifested 1–3 months following recovery. Patients most frequently reported pain in the wrists (47 %), ankles (26 %), knees (20 %), and feet (7 %). In 76 % of cases, arthralgia affected only a single joint. In the peripheral blood, despite the normal number of leukocytes, unchanged leukogram and acute phase indices corresponding to the standards (ESR values, as well as CRP and fibrinogen), IgM and IgG titers were high (Table 1). Additionally, CIC levels were detected in blood samples from all patients except for one, exceeding the reference range (Table 2).

Postinflammatory arthritis (PIA) without cartilage destruction was observed in 30 patients: 17 women aged 47.41 ± 10.82 years and 13 men aged 45.3 ± 11.14 years. The period from COVID-19 to the onset of joint syndrome ranged from 2 to 6 months. The most commonly affected joints were the knee (39 %) and ankle (36 %), followed by the proximal and distal interphalangeal joints (34 %), the hip (10 %), the elbow (6 %), and the shoulder (4 %). All signs of inflammation were locally present: pain, swelling, hyperemia, and varying degrees of joint mobility impairment. Instrumental examination (X-ray, ultrasound of the affected joints) revealed signs of synovitis without evidence of cartilage destruction. Joint inflammation was associated with elevated acute-phase reactant levels, while white blood cell counts remained within normal ranges. IgM, IgG, and IgE titers were elevated, and circulating immune complex (CIC) levels were significantly increased in all patients (Tables 1 and 2).

Osteoarthritis with cartilage destruction, detected through instrumental examination, developed in 8 patients 6–8 months after acute COVID-19. The disease manifested as acute monoarthritis in large joints, including the knees, hips, wrists, and interphalangeal joints. Local signs of inflammation were accompanied by generalized polyarthralgia and polymyalgia. Examination revealed deformity of the affected joints and limited mobility. Instrumental examination showed signs of synovitis in nearly all cases, along with developing cartilage destruction. Increased blood levels of CRP, fibrinogen, and ESR were not accompanied by leukocytosis. However, IgM, IgG, and particularly IgE titers were elevated. The number of circulating immune complexes (CIC) was also increased (Table 2).

The joint syndrome, which was present in the period prior to COVID, progressed in 9 patients (2 men aged 59 and 68 years and 7 women with a median age of 54.7 [39.0; 72.0] years). Polyarticular symmetric lesions were more typical of the progressive joint syndrome. Ultrasound examination of the affected joints frequently revealed signs of synovitis (in 90 % of cases), osteoarthritis (in 44 %), and tenosynovitis (in 22 %). Joint radiography showed narrowing of the joint space and the presence of osteophytes. Destructive changes were seen in both knee joints in 4 out of 9 patients (44 %), ankle joints in 4 patients (44 %), wrist and elbow joints in another 4 cases (44 %), and hip joints in 3 patients (33 %). Elevated levels of acute-phase reactants in peripheral blood also indicated the presence of alterative inflammation. The total white blood cell count remained stable, but eosinophilia was noted in some cases. The IgM titer was below the expected level, and IgG titer values were not significantly different from those of the control group, but total IgE levels were elevated. The circulating immune complex (CIC) levels were within the normal range (4.29 [3.1; 5.7] μg/ml) and were significantly lower than those observed in other cases of joint syndrome.

TABLE 1

THE IMMUNOGLOBULIN CONTENTS IN PERIPHERAL BLOOD IN PATIENTS WITH VARIOUS TYPES OF POST-COVID JOINT SYNDROME, ME [Q25; Q75]

	Group I	Group II	Group III	Group IV	Group V	*p*			
	Isolated arthralgia, *n* = 15	Arthritis, *n* = 30	Debut of arthropathy, *n* = 8	Progression of arthropathy, *n* = 9	Healthy individuals (control), *n* = 25	Groups I-V	Groups II-V	Groups III-V	Groups IV-V
ESR, mm/h	7.9 [3–11]	11.7 [6–16]	16.3 [5–23]	13.4 [6–19]	6.3 [1–8]	0.162	0.007	0.000	0.001
IgM, g/l	2.27 [1.5; 3.4]	2.625 [1.9; 2.9]	2.6 [1.6; 3.4]	1.13 [0.9; 2.0]	1.39 [0.99; 1.5]	0.008	0.001	0.004	0.010
IgG, g/l	14.46 [11.5; 16.0]	12.27 [7.5; 22.9]	13.28 [11.7; 20.0]	12.44 [5.5; 12.5]	11.03 [10.2; 13.6]	0.008	0.040	0.005	0.050
Total IgE, IU/ml	40.97 [6.0; 31.0]	97.53 [25.0; 112.0]	148.82 [40.1; 172.0]	118.56 [25.4; 265.4]	32.54 [5.0; 76]	0.060	0.001	0.000	0.000

Note. *p* is the level of statistical significance for the differences between the control and treatment groups based on the Mann – Whitney U-test.

TABLE 2

THE CONTENT OF CIRCULATING IMMUNE COMPLEXES (CIC) IN PERIPHERAL BLOOD IN PATIENTS WITH VARIOUS TYPES OF POST-COVID JOINT SYNDROME, ME [Q25; Q75]

Indicator	Group I Isolated arthralgia, *n* = 4	Group II Arthritis, *n* = 5	Group III Debut of arthropathy, *n* = 6	Group IV Progression of arthropathy, *n* = 6	*p*					
					Groups I-II	Groups I-III	Groups I-IV	Groups II-III	Groups II-IV	Groups III-IV
CIC, µg/ml	8.05 [1.67; 11.45]	11.45 [9.33; 12.98]	8.58 [6.23; 14.27]	4.29 [3.1; 5.7]	0.391	0.165	0.0140	0.120	0.008	0.005

DISCUSSION

Women predominated among the patients with post-COVID-19 syndrome: 43 out of 62 presenting with complaints of joint pain, as reported in the literature [5, 6]. However, in most cases, the patients experienced initial symptoms and their development did not depend on age or the severity of the COVID-19 infection they had.

Based on clinical, laboratory, and instrumental examinations, four distinct types of post-COVID syndrome have been identified, each with its own underlying mechanism.

In our study, high levels of CICs were detected in patients with arthralgia, arthritis, and the onset of arthropathy. These findings suggest a possible role for CICs in the development of these joint conditions. CICs are known to cause tissue damage through various mechanisms. In the form of complexes with antigens, IgG and IgM antibodies activate the classical pathway of the complement system, which leads to the development of inflammation through its damaging effects. Independent of the complement, IgG-containing CICs can bind to Fc receptors expressed on various cell types, including macrophages, neutrophils, eosinophils, and platelets, leading to the release of inflammatory mediators. Through direct interaction with neutrophils via Fc receptors and activation of platelets and endothelial cells, CICs can induce neutrophil

extracellular trap (NETosis) [13]. Moreover, the pattern of chemokine secretion by macrophages is dependent on the characteristics of CICs [14]. As the arthropathy progresses, the levels of CIC, as well as IgG and IgM in patient blood, often correspond to the borderline level, indicating a reduced contribution of the immune complex pathway to the destructive process formation.

Elevated IgE titers in the blood of patients with arthritis, as well as the onset and progression of arthropathy, deserve special attention. Although most of the individuals examined did not exhibit any allergic symptoms and had a negative history of allergy, recent research has demonstrated the existence of IgE autoantibodies, and their elevated production is not linked to an increased incidence of atopic conditions in patients. IgE plays a crucial role in immune response by stimulating the secretion of type I interferons from plasmacytoid dendritic cells, attracting basophils to lymph nodes, and activating both B and T cell-mediated adaptive immune responses. Immune complexes with DNA-specific IgE antibodies stimulate plasmacytoid dendritic cells and induce a powerful differentiation of B lymphocytes and the formation of plasma cells. This process subsequently leads to the development of autoimmune humoral responses [15]. Furthermore, immune complexes formed by IgE and low-molecular weight proteins can enhance specific reactions of CD4+ T cells, thereby stimulating the Th2 immune response [16].

IgE is a trigger for mast cell activation, which can lead to the development of a secondary mast cell activation syndrome (SMAS) [17]. As suggested by numerous authors, SMAS may be one of the mechanisms underlying the formation of PCS [18, 19].

Mast cells are abundantly present in the inflamed synovial tissue. Although there is no direct evidence that mast cells themselves synthesize IL-17, it has been shown that they actively take up exogenously produced IL-17 through receptor-mediated endocytosis. This exogenous IL-17 is stored within intracellular granules and can be subsequently released in a biologically active form [20]. Mast cells represent the predominant population that expresses IL-17 within the synovial tissues during inflammation, particularly in reactive arthritis compared to rheumatoid arthritis [21-23]. The number of IL-17A-positive mast cells expressing IL-17A within target tissues correlates inversely with the level of inflammation, suggesting a role for this cytokine in mediating the inflammatory response [24, 25]. IL-17A is a proinflammatory cytokine that has the additional ability to stimulate angiogenesis and osteoclastogenesis [26].

CONCLUSION

Thus, the immune complex mechanism of injury plays a significant role in the development of isolated arthralgia, arthritis, and the onset of osteoarthropathy in post-COVID-19 joint syndrome, although it does not appear to be involved in the progression of the osteoarthritic process. High IgE titers during episodes of arthritis and the onset and progression of arthropathy in patients may be interpreted as a manifestation of an IgE-dependent autoimmune mechanism mediated by mast cell activation syndrome. The obtained results allow us to justify an individualized approach to treatment depending on the type of post-COVID-19 joint syndrome. To better predict the development and course of post-COVID-19 manifestations, further research is needed to elucidate the initial immune system changes that occur following infection.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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GENETICS, PROTEOMICS AND METABOLOMICS

ASSOCIATION BETWEEN VARIANTS OF *PNPLA3* (rs738409), *UCP2* (rs660339) AND *HFE* (rs1800562, rs1800730, rs1799945) GENES AND CHANGES IN THE FUNCTIONING OF THE LIPID PEROXIDATION – ANTIOXIDANT DEFENSE SYSTEM IN PLASMA IN NON-ALCOHOLIC FATTY LIVER DISEASE PATIENTS

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RESUME

Currently reaching epidemic proportions, non-alcoholic fatty liver disease (NAFLD) particularly affects individuals of employable age. The pathogenesis of NAFLD involves a combination of hereditary factors and external influences that collectively disrupt lipid and carbohydrate metabolic pathways and impair the balance between lipid peroxidation and antioxidant protection mechanisms. To date, there has been limited exploration of the possible relationship between these pathological changes and specific variants of the PNPLA3, UCP2, and HFE genes.

The aim. *To examine the association between some markers of the LPO-AOD system in plasma depending on polymorphic variants of the PNPLA3, UCP2 and HFE genes.*

Materials and methods. *For this study, we collected whole blood samples from 116 patients with NAFLD (65 with steatosis and 51 with steatohepatitis) and 100 healthy volunteers. All participants had peripheral venous blood collected for subsequent molecular genetic and biochemical analysis.*

Results. *Our findings indicate that in steatosis, catalase activity was elevated in carriers of the rs660339 TT genotype, while SOD activity was reduced in those with the rs738409 GG variant.*

For steatohepatitis patients, ceruloplasmin levels were altered in opposite directions based on genotype: the rs1800730 TT variant was associated with lower levels, whereas the rs660339 TT genotype was linked to higher levels.

Conclusions. *Polymorphisms rs738409 of the PNPLA3 gene, rs1800730 of the HFE gene and rs660339 of the UCP2 gene are associated with an imbalance in the LPO-AOD system, which may be caused by an increase of the iron level and a change in the antioxidant activity of the UCP2 protein, as well as an increase in the production of prooxidants.*

Key words: *steatosis, steatohepatitis, PNPLA3, HFE, UCP2, lipid peroxidation, antioxidant defense*

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ВЗАИМОСВЯЗЬ НОСИТЕЛЬСТВА ВАРИАНТОВ ГЕНОВ *PNPLA3* (rs738409), *UCP2* (rs660339) И *HFE* (rs1800562, rs1800730, rs1799945) С НЕКОТОРЫМИ ПОКАЗАТЕЛЯМИ СИСТЕМЫ «ПЕРЕКИСНОЕ ОКИСЛЕНИЕ ЛИПИДОВ – АНТИОКСИДАНТНАЯ ЗАЩИТА» У БОЛЬНЫХ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ

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РЕЗЮМЕ

Неалкогольная жировая болезнь печени (НАЖБП) — это заболевание, принимающее в настоящее время размах эпидемии среди населения трудоспособного возраста. Патогенез НАЖБП обусловлен сочетанным воздействием экзогенных факторов и генетической предрасположенности, что приводит к комплексным нарушениям липидного и углеводного обмена, а также дисфункции системы перекисного окисления липидов и антиоксидантной защиты. Влияние полиморфизмов генов PNPLA3, UCP2 и HFE на указанные процессы остается малоизученным.

Целью исследования. *Изучение взаимосвязи некоторых показателей системы «ПОЛ-АОЗ» в плазме в зависимости от носительства отдельных полиморфных вариантов генов PNPLA3, UCP2 и HFE.*

Материалы и методы. *В исследование включены 216 участников, из которых 116 пациентов с верифицированным диагнозом НАЖБП (65 – со стеатозом, 51 – со стеатогепатитом) и 100 условно здоровых лиц контрольной группы. У всех участников проводился забор периферической венозной крови для последующего молекулярно-генетического и биохимического анализа.*

Результаты. *Выявлена зависимость между генетическими вариантами и активностью ферментов антиоксидантной системы у пациентов с различными формами НАЖБП. В группе со стеатозом было установлено статистически значимое повышение каталазной активности у носителей гомозиготного генотипа TT (rs660339), тогда как у пациентов с вариантом GG (rs738409) наблюдалось снижение активности супероксиддисмутазы (СОД).*

У больных стеатогепатитом зафиксированы разнонаправленные изменения концентрации церулоплазмина. Носители гомозиготы TT (rs1800730) демонстрировали снижение уровня данного показателя, в то время как у пациентов с генотипом TT полиморфизма rs660339 отмечалось его достоверное повышение.

Заключение: *Полиморфизмы rs738409 гена PNPLA3, rs1800730 гена HFE и rs660339 гена UCP2 связаны с дисбалансом в системе «ПОЛ-АОЗ», что может быть вызвано нарушением уровня железа и изменением антиоксидантной активности белка UCP2, а также повышением выработки прооксидантов.*

Ключевые слова: *стеатоз, стеатогепатит, PNPLA3, HFE, UCP2, перекисное окисление липидов, антиоксидантная защита*

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INTRODUCTION

The obesity epidemic, resulting from a sedentary lifestyle and consumption of high-calorie foods, is affecting an increasing number of people of all ages worldwide each year [1]. Abdominal obesity, which leads to insulin resistance and dyslipidemia, is a risk factor for non-alcoholic fatty liver disease (NAFLD). This disease is associated with the accumulation of fat in the liver and gradual damage to hepatocytes, increasing the risk of progression to more severe stages, such as steatohepatitis, fibrosis, and cirrhosis. In some cases, it can even lead to hepatocellular carcinoma [2, 3].

According to various studies, the prevalence of NAFLD varies between 17 % and 35 %, with the condition most commonly affecting middle-aged individuals who are part of the working population.

The development of non-alcoholic fatty liver disease is a complex process influenced by various external factors, such as dietary habits and physical activity, as well as hereditary predisposition [4, 5]. Large-scale studies have shown that certain genetic variations play a key role in the development and progression of this pathology. They affect genes that regulate lipid, carbohydrate, and micronutrient metabolism, particularly iron metabolism [6, 7, 8]. The rs738409 genetic variant in the *PNPLA3* gene has been identified as a significant contributor to NAFLD development. This gene encodes for adiponutrin, a protein that plays a crucial role in hepatic lipid metabolism by participating in the formation of lipid droplets and exhibiting activity as an acetyltransferase and retinol esterase. Individuals with the GG genotype of this variant have an increased risk of developing NAFLD and experiencing a more severe clinical course [9, 10, 11].

The *UCP2* gene and its impact on NAFLD have been relatively understood. The protein encoded by the *UCP2* gene, which belongs to the uncoupling protein family, plays a role in regulating insulin secretion, antioxidant system function, and lipid metabolism. The rs660339 (Val55Ala) polymorphism has been suggested as a potential predictor for NAFLD development. This polymorphism may indirectly influence certain pathogenesis pathways associated with NAFLD [12].

As previously stated, NAFLD progression may be linked to gene variants that are not directly related to lipid and carbohydrate metabolism, such as the *HFE* gene. Its polymorphisms (rs1800562, rs1800730, and rs1799945) have been associated with the inability of the HFE protein to interact with the transferrin receptor. This disrupts the signaling pathway and leads to excessive iron uptake by cells. Researchers have linked this to a more adverse prognosis for NAFLD and an increased risk of hepatocellular carcinoma development [13, 14]. Furthermore, increased iron levels in liver cells can contribute to oxidative stress. The increased lipid peroxidation of hepatocytes, imbalanced antioxidant activity, and development of ferroptosis influence the pathogenesis of NAFLD.

Excess iron in hepatocytes can lead to oxidative stress, which is a significant factor in the development of NAFLD. An imbalance in the function of the various components of the body's antioxidant defense system enhances the harmful effects of intracellular iron on liver cells and can result in ferroptosis.

Lipid peroxidation processes in patients with NAFLD have been previously studied, and it has been found that patients with steatohepatitis experience higher levels of oxidative stress compared to those with steatosis. Membrane lipid peroxidation can be primarily explained by the excessive fat accumulation in hepatocytes, which leads to mitochondrial dysfunction as the cells attempt to utilize this fat. This process also results in the formation of a significant number of reactive oxygen species, or free radicals [15, 16]. However, recent studies have demonstrated the influence of ferroptosis on the imbalance between prooxidants and antioxidants in cells and plasma in the development of NAFLD. Ferroptosis is a type of cell death that is closely associated with increased intracellular iron concentration and dysfunction of glutathione peroxidase. Increased iron levels in hepatocytes lead to an increase in the number of spontaneous Fenton reactions with intracellular lipids. The ongoing lipid peroxidation processes suppress individual components of the hepatocyte antioxidant system, which causes cell damage and progression of NAFLD [17, 18]. Although this aspect has not been thoroughly investigated, it is known that elevated plasma iron levels and the occurrence of ferroptotic processes in patients with NAFLD are linked to a more unfavorable prognosis [19].

We hypothesize that investigating the associations between *PNPLA3, UCP2*, and *HFE* gene variants and plasma levels of LPO-AOD in patients with steatohepatitis and steatosis associated with NAFLD may be linked to the related disturbances in iron and lipid metabolism. This could indirectly contribute to the development of lipid peroxidation, which could further elucidate the impact of these genetic variants on the pathogenesis of the disease.

THE AIM OF THE STUDY

To investigate the correlation between certain parameters of the LPO-AOD system in plasma and the presence of specific polymorphic variants of the *PNPLA3, UCP2*, and *HFE* genes.

MATERIALS AND METHODS

The study population consisted of 116 patients with a verified diagnosis of non-alcoholic fatty liver disease (43 men and 73 women) who were treated at the internal medicine department of the Krasnoyarsk Science Centre of the Siberian Branch of Russian Academy of Science in 2021–2022. The age range of the participants

was between 21 and 88 years old, with a median age of 62.3 ± 2 years.

The diagnosis of non-alcoholic fatty liver disease and inclusion in the study group were based on the identification of metabolic disorders (BMI > 30 kg/m^2 and changes in carbohydrate and lipid metabolism), the presence of a cytolytic syndrome (increased ALT and AST with a decreased de Ritis coefficient), and characteristic ultrasound changes in liver tissue, including increased echogenicity and the "white liver" phenomenon [20].

The study excluded patients with a history of viral hepatitis, a significant history of alcohol consumption (as confirmed by the CAGE questionnaire), or parasitic infestations. Patients also had to be willing to participate in the study.

Based on their clinical presentation, the gastroenterologist divided the patients with NAFLD into two groups: a group with steatosis (n = 65, mean age 47.4 ± 4 years) and a group with steatohepatitis (n = 51, mean age 47.4 ± 4 years).

Genetic methods were used to assess the presence of *PNPLA3* (rs738409), *UCP2* (rs660339), and *HFE* (rs1800562, rs1799945, rs1800730) variants within the study population. Genomic DNA was extracted from blood leukocytes using the DNA-sorb-B kit (Central Research Institute of Epidemiology, Rospotrebnadzor, Russia). Genotyping was conducted via RT-PCR using hydrolysis probes on a LightCycler 96 thermocycler (Roche, Switzerland) using commercial kits from TestGen LLC (Russia). Following this, lipid peroxidation-antioxidant defense system parameters were measured in blood plasma using a Genesys 10s UV-Vis spectrophotometer (Thermo Fisher Scientific, USA). Malondialdehyde concentration was determined by measuring the colored product formed in the reaction with 2-thiobarbituric acid, employing a wavelength of 532/600 nm [21]. Superoxide dismutase (SOD) activity was assessed through the autoxidation reaction involving adrenaline, by measuring the concentration increase of the product within the sample at 347 nm wavelength [22]. Catalase activity was measured using a reaction with ammonium molybdate, which produces a chromogen with a maximum at 410 nm [23]. Ceruloplasmin concentration was determined by measuring the amount of n-phenylenediamine that reacted with the protein, compared to a blank sample, at a wavelength of 530 nm [24].

All studies were conducted in accordance with the principles of biomedical ethics and approved by the local ethics committee of the Federal Research Center of the Krasnoyarsk Science Centre of the Siberian Branch of the Russian Academy of Science (Protocol No. 4 dated April 12, 2021).

Data analysis was performed using the software STATISTICA and SPSS v.26. Following testing the sample for normality (Shapiro – Wilk test) and rejecting the hypothesis of normality, a nonparametric Mann – Whitney U-test was employed to compare groups. A χ^2 test was utilized to assess whether the observed genotype frequencies conformed to those predicted by the Hardy – Weinberg equilibrium equation. Data are presented as medians with interquartile ranges [Q25-Q75].

RESULTS

In our previous studies, we identified a discrepancy in the lipid peroxidation-antioxidant defense system (LPO-AOD) in plasma among patients with steatosis and steatohepatitis. Additionally, we determined the distribution patterns of specific polymorphic variants of the *PNPLA3, UCP2*, and *HFE* genes linked to the development of particular clinical forms of NAFLD. A test for compliance with the Hardy – Weinberg equilibrium law of genetics revealed no significant differences between the observed values and the expected values (p > 0.05).

It should be noted that in all study groups, there were no individuals with the homozygous TT genotype of the rs1800562 polymorphism, and no statistically significant differences in the frequency of the rs1799945 polymorphism were detected [25, 26]. The influence of genetic factors on the function of the antioxidant system and production of lipid peroxides may occur in two ways: directly, through changes in the functional activity of proteins associated with polymorphic variants in genes encoding antioxidant system proteins, or indirectly, via changes in signaling pathways and cellular metabolism that can lead to an imbalance in oxidative stress.

In this regard, further analysis was conducted to investigate the impact of polymorphic variants rs738409 (*PNPLA3*), rs660339 (*UCP2*) and rs1800730 (*HFE*) on parameters of the LPO-AOD system in patients with steatosis and steatohepatitis (Table 1).

Malondialdehyde (MDA) is a lipid peroxidation product, that is normally formed during prostaglandin synthesis, and functions as a secondary messenger. In pathological lipid peroxidation, MDA serves as a stable reaction product and can be used to assess the severity of the process in different diseases [16].

Superoxide dismutase (SOD) is an antioxidant enzyme that plays a role in the body's defense against oxidative stress by eliminating superoxide anion radicals. Reduced SOD activity may contribute to impaired function of the LPO-AOD system in NAFLD.

Catalase is also a component of the antioxidant system and catalyzes the decomposition of hydrogen peroxide, converting it into water and oxygen. Reduced catalase activity has been suggested as a potential risk factor for insulin resistance development [27].

Ceruloplasmin is a copper-containing plasma protein that is involved in iron transport, and it also exhibits oxidase and glutathione peroxidase activities, making it an antioxidant in plasma [28].

Statistical analysis has revealed significant alterations in antioxidant enzyme activity among individuals with specific genotypes. For example, in patients with steatosis who carry the homozygous GG genotype

(rs738409), superoxide dismutase (SOD) activity was decreased by 1.2-fold, while catalase activity was increased by six-fold. Odds ratio analysis has confirmed a correlation between the CC+CG allele variants and an opposite trend, namely increased SOD activity and reduced catalase levels.

Among patients with steatosis, those carrying the homozygous TT genotype of the rs660339 UCP2 polymorphism demonstrated a threefold reduction in catalase activity. Odds ratio calculations indicate that the presence of this particular genotype significantly increases the probability of enhanced activity of this enzyme.

Patients with the TT genotype of the rs1800730 polymorphism in the *HFE* gene showed divergent changes in antioxidant enzyme levels: a 1.5-fold decrease in SOD activity, while catalase activity was 6-fold higher compared to patients with the AA and AT variants. Calculation of the odds ratio revealed no correlation between these changes and the presence of the rs1800730 polymorphism.

The analysis revealed a significant reduction in superoxide dismutase (SOD) activity in patients with steatosis who carry the GG genotype of the rs738409 polymorphism in the *PNPLA3* gene. An increase in catalase levels was observed in carriers of the TT genotype of the rs1800730 polymorphism, GG homozygotes (rs738409), and individuals with the TT variant of the rs660339 polymorphism. No statistically significant changes in plasma malondialdehyde (MDA) and ceruloplasmin concentrations were found depending on the studied genetic variants.

The next phase of the study focused on analyzing various parameters of the lipid peroxidation system, which is the body's natural antioxidant defense, in plasma. This included measuring levels of MDA, SOD, catalase, and ceruloplasmin in the blood samples of patients with steatohepatitis. The relationship between these parameters and the presence of specific genetic polymorphisms in the *HFE, UCP2*, and *PNPLA3* genes was investigated (Table 2).

Individuals carrying of the GG variant of the rs738409 polymorphism in the *PNPLA3* gene and steatohepatitis exhibited a 1.3-fold elevation in ceruloplasmin concentrations. However, the odds ratio (OR) showed no significant association observed between ceruloplasmin levels and the specific variant of the rs738409 polymorphism.

Based on the findings, individuals with the TT genotype (rs660339 in the *UCP2* gene) exhibited abnormalities in the activity of essential antioxidant enzymes. In comparison to the CC and CT genotypes, they demonstrated a four-fold reduction in SOD activity and a two-fold increase in ceruloplasmin concentrations. Furthermore, MDA levels in these patients were reduced by 1.5-fold. Statistical analysis using the OR revealed that the TT genotype was associated with elevated ceruloplasmin levels.

Patients with the homozygous TT (rs1800730) variant showed a two-fold increase in SOD activity compared to patients with the AA and AT genotypes, with a simultaneous 1.5-fold reduction in ceruloplasmin levels in these patients. The odds ratio revealed a significant association between the presence of the TT (rs1800730) genotype and reduced ceruloplasmin concentration.

An analysis of markers related to the lipid peroxidation system, which is an antioxidant defense system,

TABLE 1

MARKERS OF THE LPO-AOD SYSTEM IN PLASMA IN STEATOSIS PATIENTS-CARRIERS OF VARIANTS OF THE *PNPLA3* (rs738409), *UCP2* (rs660339) AND *HFE* (rs1800830) GENES

Gene	Genotypes	MDA µmol/g protein		SOD units/min*ml		Catalase µmol/s* mg protein		Ceruloplasmin mg/l	
		Me	[Q25-Q75]	Me	[Q25-Q75]	Me	[Q25-Q75]	Me	[Q25-Q75]
PNPLA3	**CC+CG**	1	0.5–1.7	186	63–321	0.01	0.002–0.03	233	140–317
(rs738409)	**GG**	0.9	0.6–1.3	155	70–204	0.06	0.01–0.1	229	120–352
OR (CI 95%)		**0.04 (0.01-0.32)**		**0.02 (0.001-0.14)**		**0.1 (0.01-0.86)**		0.8 (0.44–1.46)	
p		0.51		**0.01**		**0.01**		0.77	
UCP2	**CC+CT**	0.8	0.5–1.6	185	66–320	0.01	0.002–0.02	238	139–315
(rs660339)	**TT**	1	0.5–2.4	163	35–394	0.03	0.01–0.1	229	130–340
OR (CI 95%)		0.47 (0.19–1.15)		2.28 (1.07–4.85)		**6.8 (1.84-25.1)**		0.84 (0.42–1.68)	
p		0.73		0.62		**0.003**		0.70	
HFE	**AA+AT**	0.95	0.48–1.73	188.4	63.4–335.2	0.01	0.002–0.03	231	138–310
(rs1800730)	**TT**	0.8	0.6–1.3	123	35–204	0.04	0.01–0.05	212	144–352
OR (CI 95%)		**0.05 (0.01-0.36)**		0.71 (0.04–11.65)		1.79 (0.65–4.92)		1.71 (0.92–3.18)	
p		0.36		**>0.001**		**>0.001**		0.79	

TABLE 2

MARKERS OF THE LPO-AOD SYSTEM IN PLASMA IN STEATOHEPATITS PATIENTS-CARRIERS OF VARIANTS OF THE *PNPLA3* (rs738409), *UCP2* (rs660339) AND *HFE* (rs1800830) GENES

Gene	Genotypes	MDA µmol/g protein		SOD units/min*ml		Catalase µmol/s* mg protein		Ceruloplasmin mg/l	
		Me	[Q25-Q75]	Me	[Q25-Q75]	Me	[Q25-Q75]	Me	[Q25-Q75]
PNPLA3	**CC+CG**	1.1	0.7–2.2	200	24–371	0.04	0.02–0.06	210	99–309
(rs738409)	**GG**	1	0.8–1.2	266	245–288	0.07	0.01–0.1	269	207–330
OR (CI 95%)		0.33 (0.03–3.51)		1.17 (0.28–4.87)		**6.5 (1.13-37.4)**		1.29 (0.33–4.97)	
p		0.05		0.14		0.87		**0.03**	
UCP2	**CC+CT**	1.1	0.8–2.36	245	138–386	0.04	0.01–0.05	175	94–277
(rs660339)	**TT**	0.7	0.1–1.2	60	54–160	0.05	0.04–0.07	321	290–330
OR (CI 95%)		1.13 (0.21–6.05)		0.5 (0.07–3.85)		0.9 (0.1–7.78)		**15 (2.02-111.18)**	
p		**0.04**		**0.005**		0.07		**0.001**	
HFE	**AA+AT**	1.1	0.7–2.3	181	11.1–344	0.04	0.02–0.6	249	114–318
(rs1800730)	**TT**	0.8	0.3–1.5	349	203–393	0.03	0.01–0.04	156	88–223
OR (CI 95%)		**36 (3.67-352.66)**		2.8 (0.62–12.6)		0.33 (0.03–3.68)		**0.08 (0.01-0.8)**	
p		0.154		**0.02**		0.074		**0.04**	

in patients with steatohepatitis has revealed a statistically significant association with changes in ceruloplasmin levels in plasma, depending on the presence of certain genetic variations. Patients with the TT genotype of the rs1800730 polymorphism in the *HFE* gene exhibited a decrease in ceruloplasmin, while those with the TT genotype of the rs660339 polymorphism in the *UCP2* gene exhibited an increase. There were no significant associations between the carriage of the polymorphic variants of *PNPLA3, UCP2*, and *HFE* genes and other parameters studied (MDA, SOD, and catalase).

DISCUSSION

The imbalance of the LPO-AOD system in NAFLD is due to several factors. Primarily, it is caused by the excessive accumulation of lipids within cells, leading to mitochondrial dysfunction and an increase in cellular ROS levels. Additionally, excessive fat can cause chronic inflammation, which exacerbates the imbalance of the antioxidant defense system and leads to pro-oxidation. Iron overload in hepatocytes may also contribute to the development of a prooxidant condition. The development of this cascade may be influenced, among other factors, by genetic factors.

According to the data obtained, individuals with the GG genotype of the rs738409 polymorphism and steatosis were found to have reduced SOD activity. However, among patients with steatohepatitis, this genetic variant was not linked to any significant alterations in the functioning of the LPO-AOD system. Moreover, the TT genotype of the rs660339 polymorphism among patients with steatosis was associated with elevated catalase activity. Among patients with both steatosis and the TT genotype, ceruloplasmin levels were increased.

A clear correlation has been established: carriers of the TT variant of the rs1800730 polymorphism and steatohepatitis show decreased ceruloplasmin concentrations. In contrast, no correlation has been found between the studied genetic marker and the LPO-AOD system parameters for cases of steatosis.

Adiponutrin, a product of the *PNPLA3* gene, influences various aspects of lipid metabolism within the liver. When its function is impaired, it leads to an excessive lipid accumulation by hepatocytes, resulting in the development of fatty liver disease and eventually steatohepatitis. Fatty cell infiltration caused by adiponutrin dysfunction likely leads to an increase in β-oxidation. Increased oxidation, in turn, increases the production of ROS, particularly the superoxide anion radical. The excessive superoxide anion radicals can inhibit SOD activity, which may be a contributing factor to the decreased activity seen in patients with steatosis and those carrying the GG genotype of the rs738409 polymorphism.

The effect of the rs738409 polymorphism on oxidative stress development in patients with steatosis has not been previously investigated. For the first time we have demonstrated a decrease in SOD activity in this patient group associated with carriage of a particular variant of the *PNPLA3* gene. This finding may explain the decreased SOD activity

observed in patients with NAFLD, which was also reported by Javed A. et al. [16].

The impact of the rs660339 polymorphism in the *UCP2* gene on the development of steatohepatitis in NAFLD may be related to the fact that the substitution of alanine to valine at position 55 disrupts the functional activity of the UCP2 protein. This may lead to altered uncoupling activity, which indirectly affects the regulation of ROS, insulin secretion, and lipid metabolism. The relationship between the rs660339 variant in the *UCP2* gene and alterations in the LPO-AOD system in plasma among patients with steatosis and steatohepatitis has not yet been investigated. It is hypothesized that these changes may result from the active role of *UCP2* in controlling ROS production and the disruption caused by the Ala55Val substitution. This impairment may be offset by increased catalase activity in patients with steatosis who carry the TT variant (rs660339), as shown in our study. Additionally, in patients with steatohepatitis and the TT genotype, we observed elevated ceruloplasmin levels, which may be associated with severe oxidative stress and the antioxidant function of ceruloplasmin as a ferroxidase and glutathione peroxidase.

The role of the rs1800730 polymorphism in the development and progression of NAFLD has received the least attention in research. However, the contribution of polymorphic variants of the *HFE* gene and elevated iron levels to the development of oxidative stress in other pathologies, such as pulmonary fibrosis, has been established, as well as an effect on ceruloplasmin activity reduction, as reported in the studies of Sangiuolo F., Laine F., and Stevens R. [29, 30, 31].

Our study emphasizes the significance of alterations in the α1 domain structure linked to this polymorphic site and their influence on the development of a particular clinical form of NAFLD. The reduced plasma ceruloplasmin levels observed in patients with steatohepatitis who carry the TT genotype might be linked to impaired iron metabolism and a probable substrate inhibition of the expression of this protein. Although connection between the rs1800730 polymorphism and alterations in antioxidant defense indicators in patients with steatohepatitis has not been investigated, Xia Z. et al. have demonstrated that reduced ceruloplasmin levels in patients with NAFLD correlate with a worse prognosis, further supporting our study and expanding our comprehension of the potential mechanism behind this phenomenon [32].

Thus, variants in the *PNPLA3, UCP2,* and *HFE* genes are linked to opposing alterations in the function of the LPO-AOD system, specifically its antioxidant component, depending on the clinical form.

CONCLUSION

In patients with steatosis, there is a characteristic relationship between polymorphisms and changes in enzymatic activity: rs660339 (TT) is associated with alterations in catalase activity, whereas rs738409 (GG) is linked to suppression of SOD activity. Conversely, in steatohepatitis, the polymorphisms have the opposite effect on ceruloplasmin levels: rs1800730 (TT) correlates with a reduction, while rs660339 (TT) correlates with an increase.

The rs1800730 polymorphism within the *HFE* gene and the rs660339 polymorphism in the *UCP2* gene have been associated with an imbalance in the LPO-AOD system, which may contribute to dysregulation of iron levels and alterations in the antioxidant activity of the UCP2 protein.

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Conflicts of interest

No potential conflict of interest relevant to this article reported.

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INFECTIOUS DISEASES

FATAL CASE OF HEMORRHAGIC FEVER WITH RENAL SYNDROME ASSOCIATED WITH HANTAVIRUS SEOUL

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RESUME

Seoul orthohantavirus is one of the causative agents of hemorrhagic fever with renal syndrome (HFRS) in the Russian Far East. Foci of SEOV in Norway rats have been identified in the cities of Vladivostok and Khabarovsk.

The aim. *Study of a clinical case of HFRS with a fatal outcome, from Komsomolsk-on-Amur in 2025.*

Materials and methods. *Samples of blood serum and autopsy material (blood, lung, spleen, liver, kidney tissues) from a resident of Komsomolsk-on-Amur with a clinical diagnosis of HFRS were examined using enzyme-linked immunosorbent assay (ELISA) and reverse transcription-polymerase chain reaction (RT-PCR) followed by sequencing.*

Results. *The laboratory studies confirmed the clinical diagnosis. Antibodies to hantaviruses in a titer of 1:3200 (IgM) and 1:1600 (IgG) were detected by the ELISA in the blood serum. SEOV RNA was detected in blood serum and autopsy material (blood, lung, spleen, liver, kidney tissues) studying by the RT-PCR and using the OM-Screen-GLPS-RV test system. Analysis of genome fragments showed high homology of SEOV from Komsomolsk-on-Amur with virus strains previously identified in Khabarovsk, as well as those widespread in China. Genetic evidence of human infection, associated with the Seoul virus circulating in the city of Komsomolsk-on-Amur has been obtained, and two hypotheses have been put forward for the formation of the focus: importation with infected rats from China or Khabarovsk, and the possible existence of a mainland variant of the virus in a vast territory, including the eastern regions of China and Khabarovsk Krai.*

Conclusion. *Third urban focus of Seoul hantavirus was detected in Russia. The fatal outcome of HFRS could be caused by a comorbidity: chronic alcohol intoxication with multiple organ manifestations.*

Keywords: *hantavirus, Seoul virus, HFRS, Russia*

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ЛЕТАЛЬНЫЙ СЛУЧАЙ ГЕМОРРАГИЧЕСКОЙ ЛИХОРАДКИ С ПОЧЕЧНЫМ СИНДРОМОМ, ОБУСЛОВЛЕННЫЙ ЗАРАЖЕНИЕМ ХАНТАВИРУСОМ СЕУЛ

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РЕЗЮМЕ

Ортохантавирус Сеул (SEOV) является одним из возбудителей геморрагической лихорадки с почечным синдромом (ГЛПС) на Дальнем Востоке России. Очаги циркуляции SEOV в серых крысах выявлены в городах Владивосток и Хабаровск.

Цель работы. *Исследование клинического случая ГЛПС с летальным исходом, выявленного в г. Комсомольске-на-Амуре в 2025 году.*

Материалы и методы. *Образцы сыворотки крови и аутопсийного материала (кровь, ткани легких, селезенки, печени, почек) от жительницы г. Комсомольска-на-Амуре с предварительным диагнозом «ГЛПС, завершившаяся летальным исходом», были исследованы методами иммуноферментного анализа (ИФА) и обратной транскрипции – полимеразной цепной реакции (ОТ-ПЦР) с последующим секвенированием.*

Результаты. *Проведенные исследования подтвердили клинический диагноз. Методом ИФА в сыворотке крови обнаружены антитела к хантавирусам в титре 1:3200 (IgM) и 1:1600 (IgG). При исследовании методом ОТ-ПЦР с использованием тест-системы «ОМ-Скрин-ГЛПС-РВ» в сыворотке крови и аутопсийном материале (крови, тканях легких, селезенки, печени, почек) выявлена РНК SEOV. Анализ фрагментов генома показал высокую гомологию SEOV из Комсомольска-на-Амуре с вариантами вируса, выявленными ранее в Хабаровске, а также широко распространенными в Китае. Впервые получено генетическое доказательство инфицирования человека вирусом Сеул, циркулирующим в г. Комсомольске-на-Амуре, и выдвинуты две гипотезы формирования очага: завоз с инфицированными крысами из Китая либо Хабаровска и возможное существование материкового варианта вируса на обширной территории, включающей восточные районы Китая и Хабаровский край.*

Заключение. *В РФ выявлен третий городской очаг хантавируса Сеул. Летальный исход ГЛПС мог быть обусловлен фоновым заболеванием: хронической алкогольной интоксикацией с полиорганными проявлениями.*

Ключевые слова: *хантавирус, вирус Сеул, ГЛПС, Россия*

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INTRODUCTION

Hemorrhagic fever with renal syndrome (HFRS) is a potentially life-threatening infectious disease of humans that has been reported in various regions of Russia [1]. In the Far Eastern region, HFRS is caused by the Hantaan (HTNV), Amur (AMRV), and Seoul (SEOV) orthohantaviruses, which circulate among the stripped field mouse (*Apodemus agrarius*), Korean field mouse (*Apodemus peninsulae*), and Norway rat (*Rattus norvegicus*), respectively [2, 3]. Infection with HTNV and AMRV viruses can occur when humans visit natural foci, while SEOV forms urban foci of infection [4]. Global trade and human migration have contributed to the spread of the SEOV worldwide, including the emergence of two foci in the Far East [4-6]. Based on the genetic similarity between the SEOV variants from patients and Norway rats in these outbreaks and previously published data, it can be assumed that the virus was introduced to the port city of Vladivostok through infected rats on ships originating from Southeast Asian countries (Cambodia, Vietnam and Singapore). The outbreak in the city of Khabarovsk and the neighboring village of Priamursky, is associated with another variant of the SEOV, which is linked to cargo transportation from China [4, 6].

HFRS is characterized by a variety of clinical manifestations, ranging from mild febrile forms to more severe forms with systemic damage of small blood vessels, hemorrhagic diathesis, hemodynamic abnormalities, renal failure, and in severe cases, multi-organ failure [7]. HFRS variants associated with SEOV tend to be mild to moderate in severity, although severe clinical forms of the disease have been identified in 5.7 % of cases in Vladivostok [6, 8, 9].

The aim of this study was to analyze a fatal case of HFSR that occurred in Komsomolsk-on-Amur.

MATERIALS AND METHODS

The clinical diagnosis of HFRS was confirmed based on data from a laboratory study of the patient's blood serum using enzyme-linked immunosorbent assay (ELISA) with the VectoHanta-IgG and VectoHanta-IgM reagent kits (Vector-Best, Russia) and reverse transcription polymerase chain reaction (RT-PCR) with the OM-Screen-HFRS-RV reagent kit (Synthol, Russia). In addition, autopsy samples (blood, lung tissue, spleen, liver, and kidneys) were analyzed using RT-PCR with the same kit to further confirm the diagnosis.

RNA was isolated from blood samples using the RIBOprep kit (Central Research Institute of Epidemiology, Russia). Viral cDNA was synthesized using the M-MuLV-RH reverse transcriptase (Dia-M, Russia). Two-round amplification products were generated according to a standard protocol using a series of previously described primers for the L- and S-segments of the genome [4, 10], and Taq DNA polymerase Hot Start (Dia-M, Russia). The resulting amplicons were separated by electrophoresis on a 1.2 % agarose gel and then purified using the Zymoclean Gel DNA Recovery Kit (Zymo Research, USA). Sanger DNA sequencing was conducted using an ABI Prism 310 genetic analyzer (Applied Biosystems, USA).

Nucleotide sequence alignment was conducted using the ClustalW algorithm in the Mega5 software. Neighbor-joining (NJ) method was employed to generate phylogenetic trees. The calculations were performed for 1,000 iterations.

Approval for the study was obtained from the Ethics Committee of the State Research Center of Virology and Biotechnology «Vector» of Rospotrebnadzor on February 10, 2025 (protocol no. 12).

A CLINICAL CASE

Patient H., a 41-year-old resident of Komsomolsk-on-Amur, was admitted to the Infectious Diseases Department No. 1 of the M.I. Shevchuk City Hospital on January 31, 2025. The patient complained of fever, generalized weakness, and back pain.

The patient's medical history reveals that, as a homeless person, she resided in a basement apartment between December 2024 and January 2025. During this time, she was exposed to a significant number of mice and rats, and her living conditions were substandard. The patient did not adhere to personal hygiene practices and relied on meltwater for drinking. On January 28th, 2025, she became acutely ill, presenting with fever (38.9–40°C), chills, severe general weakness, and a feeling of heaviness in her lower back. Additionally, she experienced a decrease in urine output. Upon admission, a physical examination revealed several findings. The patient exhibited swelling and hyperemia (excessive blood flow) of the face, neck, and collar zone, as well as scleral injection (blood vessels in the white of the eyes) and conjunctival hyperemia. Furthermore, a positive Pasternatsky sign was observed on both sides, indicating possible kidney involvement. A complete blood count showed moderate thrombocytopenia (97 $\times$ 10^9/L). The patient was admitted to the hospital with a preliminary diagnosis of hemorrhagic fever with renal syndrome (HFRS). Upon admission to the hospital, the patient gave informed consent in accordance with Article 20 of Federal Law No. 323-FZ dated November 21, 2011 «On the Basics of Public Health Care in the Russian Federation».

During the first day of admission, there was a significant decline in the patient's condition. The platelet count decreased to 57 x 10^9/L, lower back pain increased, anuria (no urine output through the catheter after saline infusion) developed, there were a single episode of vomiting containing blood, muscle pain, hypotension, and dyspnea. The patient was immediately transferred to the intensive care unit for further monitoring and treatment.

Within the next 24 hours, despite continued pathogenetic and symptomatic treatment, multiple organ dysfunction (renal, hepatic, respiratory, and cardiovascular)

deteriorated, leading to somnolence and coma. On February 2, 2025, death was recorded.

The sanitary and epidemiological investigation into the given case of a severe and fatal course of HFRS was conducted by the Epidemiology Department of the Center for Hygiene and Epidemiology in the Khabarovsk region (Komsomolsk-on-Amur).

Laboratory analysis results

Serum samples and autopsy materials were used to confirm the clinical diagnosis through laboratory testing. A vital serum sample collected on February 1, 2025, revealed specific antibodies to hantaviruses at titer levels of 1:3200 (IgM) and 1:1600 (IgG) using ELISA. In the autopsy material, the titers of specific antibodies to hantaviruses in the blood were 1:1600 for IgM and 1:1400 for IgG. The SEOV RNA was detected in the serum samples as well as in the autopsy materials (blood, lung, spleen, liver and kidney tissue) using RT-PCR.

Based on clinical, laboratory and pathological findings, the final diagnosis was hemorrhagic fever with renal syndrome in the anuric stage, which was severe, as confirmed by laboratory tests.

The underlying condition was chronic alcohol-induced intoxication, which had led to multiple organ complications, including alcoholic cardiomyopathy, chronic pancreatitis, and alcoholic hepatitis.

Complications of the underlying condition: grade 3 infection-related toxic shock. Renal nephritis, acute kidney failure. Hemorrhagic syndrome: mucosal and parenchymal organ hemorrhages. Hemorrhagic gastritis and enterocolitis. Pulmonary edema. Meningeal and brain tissue edema with brainstem displacement. Dystrophic and necrobiotic changes in parenchymal organs.

Phylogenetic analysis results

RT-PCR analysis using the OM-Screen-HFRS-RV reagent kit enabled us to identify the viral species responsible for HFRS. However, it did not permit us to compare the genome sequence of the virus with previously identified strains from various parts of the world to determine the genetic variant of SEOV and its origin. To this end, blood samples obtained from the patient during her hospital stay and at the time of autopsy were utilized to extract and sequence fragments from the L and S genome segments.

Phylogenetic analysis of the L-segment sequence fragment (346 nt) revealed that the isolate from Komsomolsk-on-Amur is consistent with the same SEOV strain that has previously been identified in patients and brown rats from Khabarovsk and surrounding areas. However, it differs from the VDV strain of SEOV identified in Vladivostok (Fig.). The nucleotide sequence divergence between SEOV isolates from Komsomolsk and Vladivostok was 4.7–5.0 %. The nucleotide differences between the Khabarovsk, Komsomolsk, and Chinese SEOV isolates were 0.3–1.2 %. The encoded amino acid sequences were identical for all isolates.

Genetic analysis of the S-segment fragment (760 nt) has also revealed a close relationship between the SEOV virus isolated from a patient in Komsomolsk-on-Amur and isolates from Norway rats and patients in Khabarovsk and China. A comparison of nucleotide sequences revealed the highest level of similarity with isolates from Khabarovsk patient samples, HU977/Russia/2019, and Priamursk patient samples, HU1619/Russia/2018, with 99.7 % and 100 % identity, respectively, at the amino acid level of the nucleocapsid protein encoded by these sequences. Similarity with isolates from China reached 99.5 % at the nucleotide level and 100 % at the amino acid level.

The data presented allow us to propose two hypotheses regarding the origin of the previously unreported urban focus of SEOV in Komsomolsk-on-Amur: the importation of infected rats with food products from either Khabarovsk or China, and the possible existence of this mainland variant of the virus in a wide area, including the eastern regions of China and the Khabarovsk region.

DISCUSSION

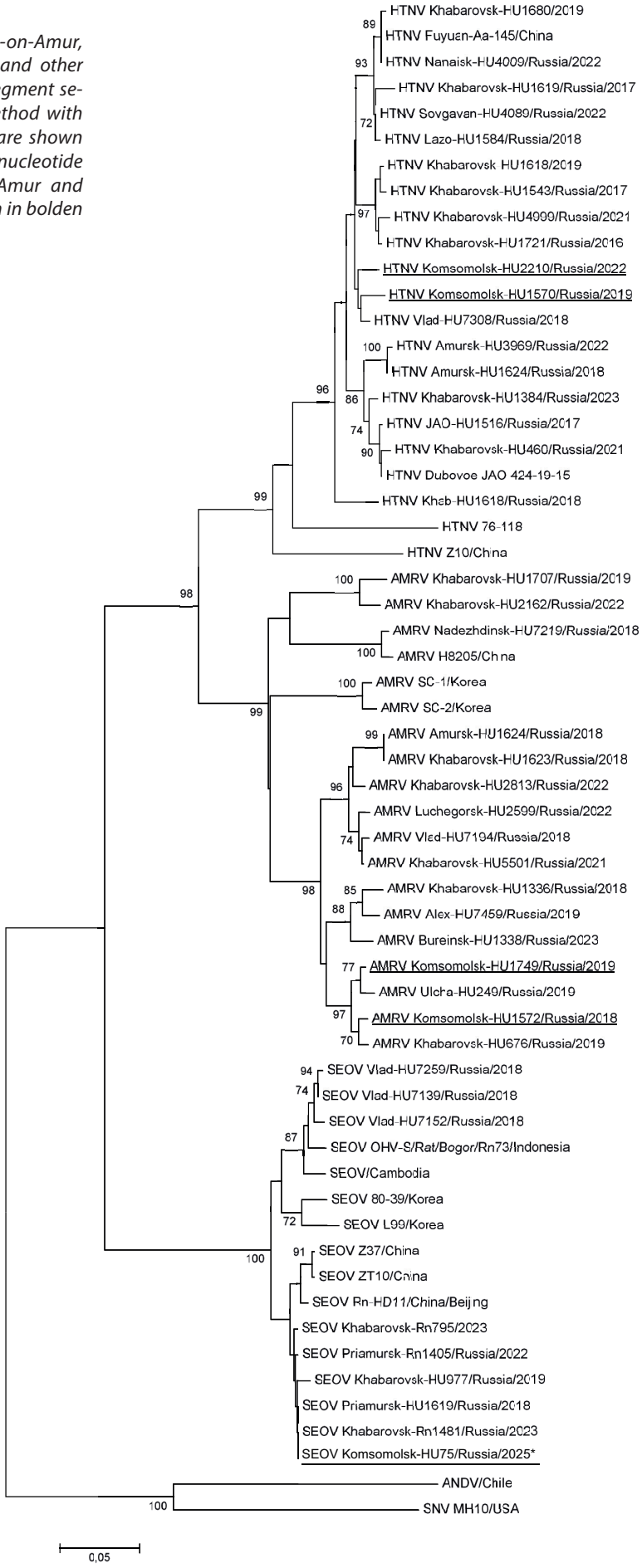
The Russian Far East is part of the high-risk area for HFRS, where three pathogenic orthohantaviruses have been identified as responsible for HFRS cases: HTNV, AMRV, and SEOV [2, 3]. Only two of these viruses, AMRV (isolates Komsomolsk-HU1572/Russia/2018 and Komsomolsk-HU1749/Russia/2019) and HTNV (Komsomolsk-HU1570/Russia/2019 and Komsomolsk-HU2210/Russia/2022), have been previously identified in infected residents of Komsomolsk-on-Amur and the surrounding area.

This is the first documented case of SEOV hantavirus infection in a patient with HFRS who had not travelled outside of Komsomolsk-on-Amur, and it has been genetically confirmed.

Over 80 % of HFRS cases associated with HTNV and AMRV have a severe or moderate course, whereas in cases of SEOV infection the proportion of severe forms does not exceed 5.7 %, with a mortality rate in Asia of less than 1 % [6, 9, 11]. However, the clinical case presented demonstrates a severe and complicated form of HFRS caused by SEOV, with a fatal outcome on the sixth day. Most likely, the fatal course of the disease was related to an aggravated pre-morbid background. It is known that hyperproduction of pro-inflammatory cytokines in combination with suppression of the cellular immune response plays a crucial role in the pathogenesis of severe HFRS forms, contributing to the development of systemic immune inflammation in the microvasculature of the kidneys, lungs, liver, myocardium, and brain. The rapid development of coagulopathy, accompanied by platelet depletion and disruption of microcirculation and central hemodynamics, as well as uncontrolled vascular responses (toxic shock), leads to multiple organ failure and irreversible destructive processes [12, 13]. Chronic ethanol intoxication, in addition to toxic multiple organ dysfunction, has also been shown to suppress Th1 lymphocyte activity and lead to an increase in blood

FIG.

Phylogenetic tree of new strain identified in Komsomolsk-on-Amur, in relationship to hantavirus strains from far-eastern and other regions of the world. Tree was based on the partial L-segment sequences (346 bp). The trees were generated by NJ method with 1000 bootstrap replicates, bootstrap values (> 70 %) are shown at relevant nodes. The scale bar depicts the number of nucleotide substitutions per site. Strains from Komsomolsk-on-Amur and Komsomolsk district are underlined, new strain is shown in bolden lettering and asterisk (*)



levels of pro-inflammatory (IL-6) cytokines and a decrease in anti-inflammatory cytokine levels (IL-10) [14, 15]. This can enhance the systemic immune-mediated damage caused by the etiological agent of HFRS.

Previously, cases of HFRS caused by SEOV infection had not been reported in Komsomolsk-on-Amur. This is likely due to the fact that standard laboratory diagnostics using ELISA do not allow for differentiation of pathogen types, and the more recently implemented differential diagnostic system based on RT-PCR has not yet been widely adopted in practical healthcare. It has also been demonstrated that the reported incidence of HFRS does not fully represent the actual prevalence of the pathogens, primarily due to undiagnosed cases of mild or asymptomatic infections, which constitute a significant portion of the epidemic process [16, 17]. This is particularly true for SEOV-associated variants of HFRS, which often present as mild clinical forms [6, 8, 11].

CONCLUSION

Therefore, for the first time, we have obtained genetic confirmation of human infection with SEOV circulating in Komsomolsk-on-Amur. We have also determined that the identified SEOV isolate belongs to a genotype previously identified in Khabarovsk and its surrounding areas, which is prevalent in China.

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Conflicts of interest

No potential conflict of interest relevant to this article reported.

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INDICATORS OF IMMUNOCOMPETENT BLOOD CELLS OF EXPERIMENTAL ANIMALS IMMUNIZED AGAINST PLAGUE ON THE BACKGROUND OF IMMUNOMODULATION

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RESUME

The strategy of specific prophylaxis of plague for epidemic indications accepted in the Russian Federation, while having positive experience, needs to be improved. The solution to one of the problems is the use of vaccines together with adjuvants. The ability of the selenium-containing preparation 974zh to increase the immunogenicity of live plague vaccine was demonstrated.

The aim of the work. *To evaluate the subpopulation composition of blood cells in animals immunized by Y. pestis EV on the background of immunomodulation.*

Materials and methods. *In the study we used 100 white mice. Blood served as a material for the study. The phenotype of lymphocytes was determined on a flow cytofluorimeter using antibodies to markers CD45, CD44, CD3, CD19, CD4, CD8, CD25, CD62L, I-A/I-E (MHC II).*

Results. *Evaluation of cellular immunity revealed a statistically significant increase in monocytes on day 7 and a decrease in lymphocytes on day 3 in mice immunized with Y. pestis EV at doses of 10^3 CFU and 10^4 CFU in combination with 974zh. When co-injected with Y. pestis EV (10^3 CFU) and 974zh, unlike Y. pestis EV at different doses, no decrease in $CD3^+CD4^+CD8^-CD25^+$ cells was detected.*

Conclusion. *Thus, the adjuvant property of 974zh has been established, contributing to an increase in the immunogenic properties of the Y. pestis EV vaccine strain, regardless of the dose. The use of Y. pestis EV at a dose of 10^3 CFU to reduce the bacterial load is appropriate.*

Key words: *Yersinia pestis, organoselenium compound, lymphocytes, subpopulation composition*

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ПОКАЗАТЕЛИ ИММУНОКОМПЕТЕНТНЫХ КЛЕТОК КРОВИ ЭКСПЕРИМЕНТАЛЬНЫХ ЖИВОТНЫХ, ИММУНИЗИРОВАННЫХ ПРОТИВ ЧУМЫ НА ФОНЕ ИММУНОМОДУЛЯЦИИ

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РЕЗЮМЕ

Принятая в Российской Федерации стратегия проведения специфической профилактики чумы по эпидемическим показаниям, несмотря на положительный опыт, нуждается в совершенствовании. Решением одной из проблем является применение вакцин совместно с адъювантами. Продемонстрирована способность селенсодержащего препарата 974zh повышать иммуногенность живой чумной сухой вакцины.

Цель работы. *Оценка субпопуляционного состава клеток крови животных, иммунизированных Y. pestis EV на фоне иммуномодуляции.*

Материалы и методы. *Биомоделями служили 100 белых мышей, материалом для исследования – кровь. Фенотип лимфоцитов определяли на проточном цитофлуориметре с использованием антител к маркерам CD45, CD44, CD3, CD19, CD4, CD8, CD25, CD62L, I-A/I-E (MHC II).*

Результаты. *При оценке клеточного иммунитета выявлено статистически значимое увеличение моноцитов на 7 сутки и снижение лимфоцитов на 3 сутки у мышей, иммунизированных Y. pestis EV дозами 10^3 КОЕ и 10^4 КОЕ в сочетании с 974zh. Отмечено повышение $CD3^+CD4^+CD8^-CD25^+$ клеток в опытной группе животных при сочетанном введении Y. pestis EV (10^3 КОЕ) и 974zh.*

Заключение. *Таким образом, установлено адъювантное свойство препарата 974zh, способствующее повышению иммуногенных свойств вакцинного штамма Y. pestis EV не зависимо от дозы. Поэтому для уменьшения бактериальной нагрузки целесообразно использовать Y. pestis EV в дозе 10^3 КОЕ.*

Ключевые слова: *Yersinia pestis, селеноорганическое соединение, лимфоциты, субпопуляционный состав*

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INTRODUCTION

Plague is an infectious disease caused by the *Yersinia pestis* bacteria. Although the infection is rare in the modern world, it remains a public health concern. Vaccination plays a significant role in controlling the spread of plague. Plague vaccination is administered according to the preventive vaccination schedule approved by the Ministry of Health of the Russian Federation, Order No. 1122n dated December 6, 2021. This vaccination is recommended for individuals temporarily or permanently residing in areas where plague outbreaks occur, as well as for those working with live plague pathogens. A licensed live plague vaccine (LPV) is used in the Russian Federation for specific plague prevention [1]. Long-term experience in the immunological monitoring of individuals vaccinated against plague living in the areas of three natural plague foci (Caspian sandy, Gorno-Altai highlands, and Tuva mountains) has demonstrated the efficacy of using live subunit vaccines [2]. At the same time, most vaccine preparations based on weakened; repeatedly passaged microorganisms can be reactogenic and cause allergic reactions. In contrast, subunit vaccines are safer but have lower immunogenicity [3]. To address the issues of vaccine reactogenicity and low subunit vaccine immunogenicity, adjuvants have been used [4]. The search for adjuvants that can activate innate immune responses, reduce antigen load, trigger and enhance adaptive immune response remains a significant and promising area of research [5].

We have previously demonstrated the immunomodulatory properties of the experimental synthetic organoselenium compound 2,6-dipyridinium-9-selenabicyclo[3.3.1]nonane dibromide (974zh) [6], which increases the immunogenicity of the *Y. pestis* EV NIIEG vaccine strain, even when the immunizing dose is reduced, and also reduces allergic reactions and enhances the immune response to the vaccine [7, 8].

Considering the potential of drug 974zh to enhance the immunogenicity of the *Y. pestis* EV NIIEG vaccine strain, a study of the cellular composition of blood lymphocytes utilizing flow cytometry would allow us to determine the characteristics of the impact of this medication on the cellular aspect of immunity [9].

THE AIM OF THE STUDY

To assess the subpopulation composition of blood cells in immunized white mice with *Y. pestis* EV NIIEG in the context of immunomodulation using the drug 974zh.

MATERIALS AND METHODS

The work with the *Y. pestis* EV vaccine strain and experimental animals was conducted in accordance with the SanPiN 3.3686-21 «Sanitary and Epidemiological Requirements for the Prevention of Infectious Diseases», as well as the requirements of Directive 2010/63/EU on the protection of animals used for scientific purposes, and the «Rules of Good Laboratory Practice», approved by Order No. 199n of the Ministry of Health dated April 1, 2016. The study was approved by the local ethics committee of the institution (protocol No. 7, dated November 15, 2021).

The study focused on the synthetic organoselenium compound 1,5-diparidinonium-9-selenobicyclo [3.3.1] nonane dibromide (1-[6-(1-pyridinium)-9-selenabicyclo[3.3.1]non-2-yl]pyridinium dibromide (974zh). This compound was synthesized in the laboratory of organochalcogen compounds at the A.E. Favorsky Institute of Chemistry of the Siberian Branch of the Russian Academy of Sciences, and it was used in conjunction with the *Y. pestis* vaccine strain EV line NIIEG.

The study involved 100 outbred, white mice of both sexes, weighing 18–22 g, obtained from the Irkutsk Anti-Plague Research Institute (RD 42-26-3…3738, State Research Center for Virology and Biotechnology "Vector", Novosibirsk). The animals were divided into five groups, each consisting of 20 individuals. The first group (group I) received a subcutaneous injection of 0.5 ml of *Y. pestis* EV at a dose of 10^4 CFU. The second group (group II) received a combination of *Y. pestis* EV (10^4 CFU) and 974zh, at a dose of 2.5 mg/kg. The third group (group III) received *Y. pestis* EV at a dose of 10^3 CFU. Group IV received a combination of both *Y. pestis* EV (10^3 CFU) and 974zh (2.5 mg/kg). Animals in the control group received an isotonic sodium chloride solution pH 7.2 (0.5 ml). Research and data collection were conducted on days 3, 7, 14, and 21. Heparinized blood samples were used for the study.

To determine the phenotype of lymphocytes, a panel of monoclonal antibodies (mAbs) from Becton Dickinson (USA), specific for the markers CD45, CD44, CD3, CD19, CD4, CD8, CD25, CD62L, I-A/I-E (MHC II), were utilized.

A blood cell subpopulation analysis was conducted using a BD FACSCanto™ II flow cytometer and BD Diva 6.0 software. Statistical analysis of the obtained data was performed using nonparametric methods and Statistica 6.0 software. The results are presented as median values and interquartile ranges (IQR). Differences were considered statistically significant at $p < 0.05$.

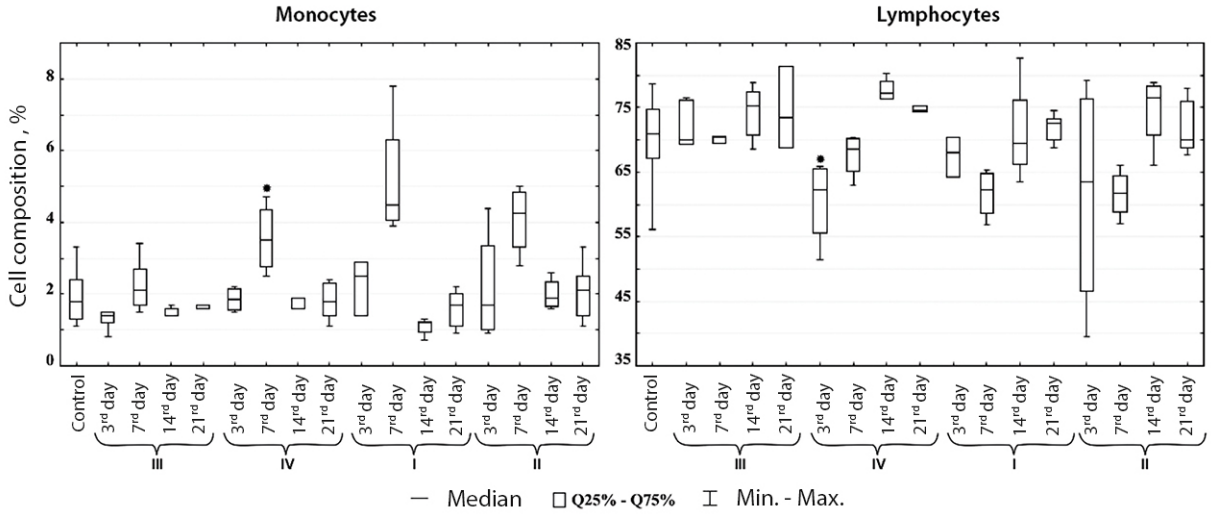
RESULTS AND DISCUSSION

In group IV of the experimental animals, a statistically significant increase ($p < 0.05$) in the percentage of monocytes was observed on day 7, by 1.7-fold (3.5 (2.8–4.4)%) compared to group III (2.1 (1.7–2.7)%) and a decrease in lymphocytes by 1.2-fold (62.3 (55.5–65.4)%) on day 3. Groups I and II showed a similar change in these indicators on day 7, which was not statistically significantly different from the values in group IV (Fig. 1).

During the experiment, an increase in the number of T-lymphocytes and a decrease in B-lymphocytes were observed in animals from experimental groups I and III on the third day, with no statistically significant differences between the groups.

It was demonstrated that the expression levels of CD44 and CD62L molecules on the surface of T-lymphocytes (naive $CD3^+CD44^-CD62L^+$) in group IV on day 21 were statistically significantly lower by 1.2-fold ($p < 0.05$) compared to those in group II of animals. The proportion of naive T-cells was (78.0 (64.7–78.3)%) in experimental group IV and (83.4 (80.5–83.7)%) in group II (Fig. 2).

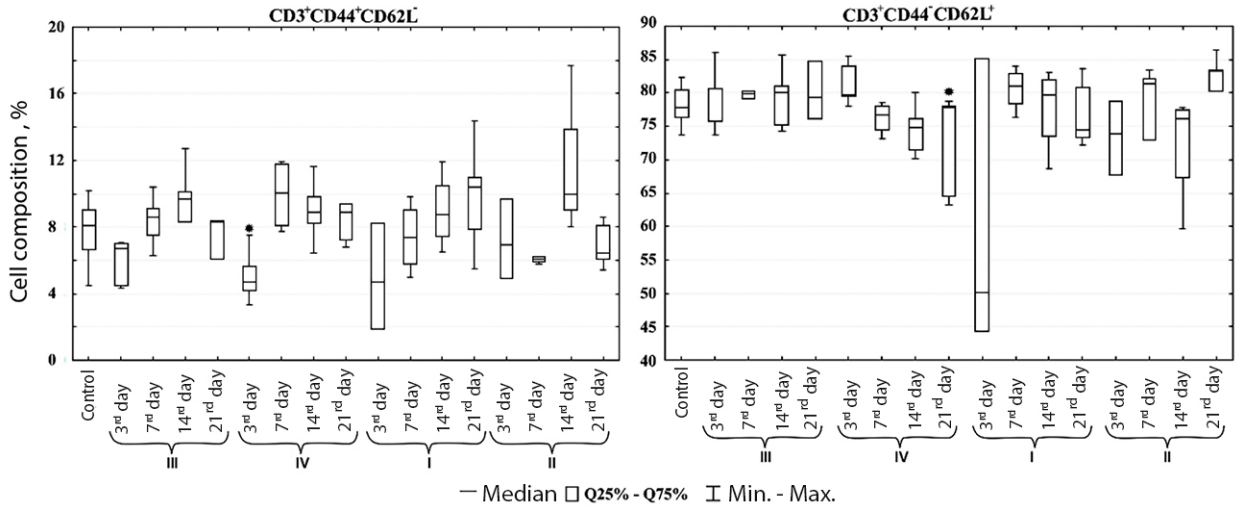
A statistically significant decrease of $CD3^+CD4^+CD8^-CD44^+CD62L^-$ cells by 1.7-fold was observed on day 3 in group IV, compared to the control group (6.5 (4.6–6.8)%). A statistically significant increase in the number of these cells was detected in the blood of animals from group II on day 14 (8.3 (7.5–10.5)%),



Note. I – *Y. pestis* EV at a dose of 10^4 CFU, II – *Y. pestis* EV at a dose of 10^4 CFU in combination with 974zh, III – *Y. pestis* EV at a dose of 10^3 CFU, and IV – *Y. pestis* EV at a dose of 10^3 CFU in combination with 974zh; * – $p < 0.05$ compared to group III.

FIG. 1.

Dynamics of the content of monocytes and lymphocytes in the blood of experimental animals at different stages of the experiment with immunization with Y. pestis EV in different doses and with combined administration with 974zh, Me (Q25%–Q75%)



Note. I – *Y. pestis* EV at a dose of 10^4 CFU, II – *Y. pestis* EV at a dose of 10^4 CFU in combination with 974zh, III – *Y. pestis* EV at a dose of 10^3 CFU, and IV – *Y. pestis* EV at a dose of 10^3 CFU in combination with 974zh; * – $p < 0.05$ compared to group II.

FIG. 2.

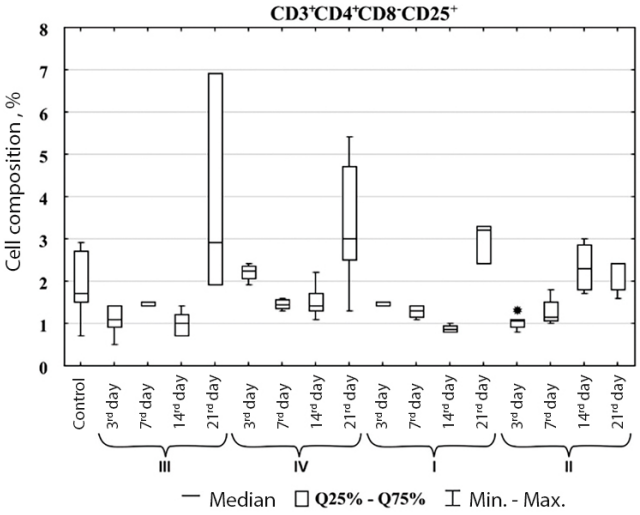
Expression of adhesion molecules CD44 and CD62L on T-lymphocytes, Me (Q25%–Q75%)

which is 1.3-fold higher than the values in the control group ($p < 0.05$). No changes were observed in the $CD8^+$ population (naive T-lymphocytes, memory T-cells).

In experimental groups I, II, and III, during the determination of the dynamics of circulating activated helper T-lymphocytes in the blood of experimental animals, a statistically significant reduction in $CD3^+CD4^+CD8^-CD25^+$ cells was observed on days 3, 7, and 14. A comparative analysis of these parameters between groups II and IV revealed that on the third day of the study, the content of these cells in animals of group II was 2.1-fold lower than that in animals of group IV ($p < 0.05$). This difference is likely associated with a higher antigen load in group II (Fig. 3).

The number of activated T-helpers ($CD3^+CD4^+CD8^-CD44^-CD62L^+CD25^+$ – and $CD3^+CD4^+CD8^-CD44^+CD62L^-CD25^+$– cells) in the blood of white mice from all experimental groups on day 3 was significantly lower than the control values. On day 14 of the immunogenic process, regardless of the dose of *Y. pestis* EV administered, there was a tendency towards an increased number of activated naive T-helpers in experimental animals from groups I and III (Fig. 4).

It is worth noting that in group II of animals on day 14 and group IV on day 7, there was an increase in the number of memory helper T-cells expressing $CD25^+$ (Fig. 4).

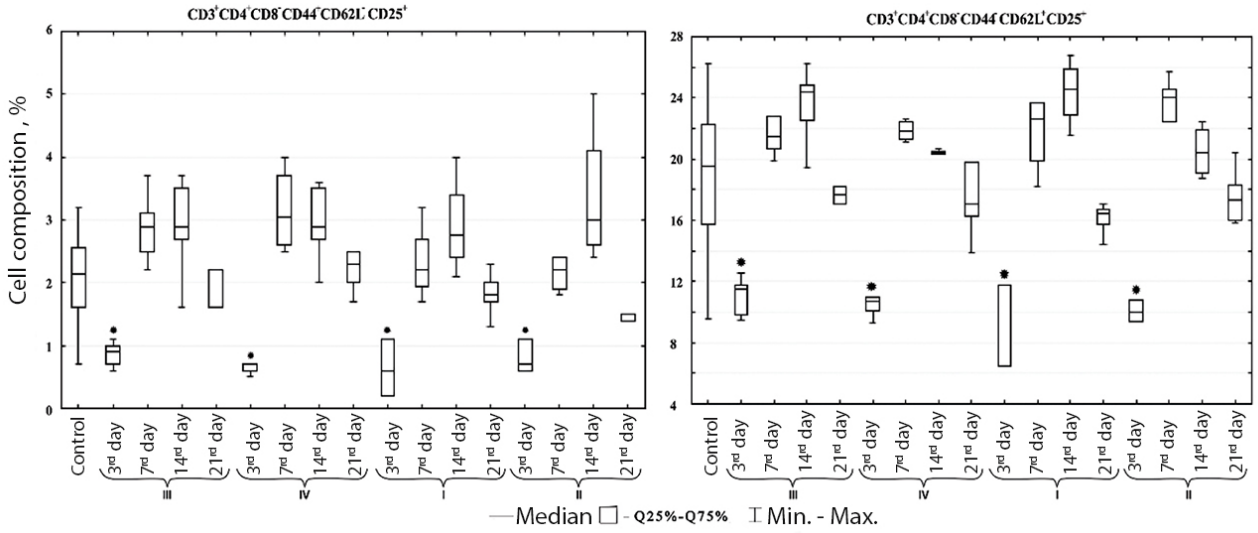


Note. I – *Y. pestis* EV at a dose of 10^4 CFU, II – *Y. pestis* EV at a dose of 10^4 CFU in combination with 974zh, III – *Y. pestis* EV at a dose of 10^3 CFU, and IV – *Y. pestis* EV at a dose of 10^3 CFU in combination with 974zh; * – $p < 0.05$ compared to group IV.

FIG. 3.
Dynamics of the content of circulating $CD25^+$-activated helper T-lymphocytes, Me (Q25%–Q75%)

CONCLUSION

The study has demonstrated the immunomodulatory effects of the organoselenium compound 974zh on innate immune cell activation, even with a reduced immunizing dose of the *Y. pestis* EV vaccine strain. This compound has been shown to influence the composition of blood cell populations in experimental animals, regardless of the dose of vaccine used (10^3 or 10^4 CFU). Importantly, there was no decrease in the number of $CD3^+CD4^+CD8^-CD25^+$ cells when 974zh was combined with *Y. pestis* at a dose of 10^3 CFU.



Note. I – *Y. pestis* EV at a dose of 10^4 CFU, II – *Y. pestis* EV at a dose of 10^4 CFU in combination with 974zh, III – *Y. pestis* EV at a dose of 10^3 CFU, and IV – *Y. pestis* EV at a dose of 10^3 CFU in combination with 974zh; * – $p < 0.05$ compared to control.

FIG. 4.
Content of activated $CD25^+$ T helper lymphocytes in the blood of white mice Me (Q25%–Q75%)

Therefore, the adjuvant effect of 974zh has been demonstrated, enhancing the immunogenicity of the *Y. pestis* EV vaccine strain, regardless of dose. Therefore, in order to reduce the bacterial burden, it is recommended to use *Y. pestis* EV at a dose of 10^3 CFU.

Based on the available information regarding the effect of drug 974zh on the immunogenic and protective activity of the *Yersinia pestis* EV NIIEG vaccine strain, as well as our findings, it is evident that further research is needed to pathogenetically substantiate its impact on the cells of the macroorganism's immune system.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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CARDIOLOGY

COMPARATIVE ANALYSIS OF MORPHOMETRIC DATA ON INTERNAL DIAMETERS OF SEGMENTS FORMING BIFURCATIONS IN CORROSION CASTS OF HUMAN CORONARY ARTERIES AND THEIR CALCULATION USING CONTEMPORARY METHODS

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RESUME

Background. *The study of human coronary arteries (HCA) as a fractal system composed of arterial bifurcations (AB) has proven promising and effectiveness in the development of digital methods for diagnosing and treating vascular pathology. However, at present, there is no consensus among researchers regarding the theory of the optimal structure of HCA bifurcations and the methodology for calculating the internal diameters of arterial segments (AS) that form these bifurcations under normal conditions.*
Objective. *To conduct a comparative analysis of morphometric data from real normal HCA and contemporary numerical modeling methods for calculating diameters of segments forming AB.*
Methods. *A comparative study was carried out on the internal diameters of 2,072 AS comprising 1,078 AB from 60 corrosion casts of HCA obtained from hearts of both sexes, aged 36 to 74 years, without signs of pathology. Morphometric measurements were compared with values calculated using established equations, proposed by Mette S. Olufsen and G. Finet.*
Results. *It was found that the internal diameters of AS forming HCA bifurcations, obtained by morphometry of corrosion casts and by calculations using the equations of Mette S. Olufsen and G. Finet, differ significantly.*
Conclusion. *For numerical modeling of realistic HCA geometry as a fractal structure composed of heterogeneous AB, the use of the equations proposed Mette S. Olufsen and G. Finet would not be appropriate. At present, there is no universally accepted theory of the optimal structure of HCA bifurcations, and consequently, no established technology for numerical modeling of realistic vascular geometry.*

Keywords: *human heart, coronary arteries, fractal system, bifurcation*

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СРАВНИТЕЛЬНЫЙ АНАЛИЗ РЕЗУЛЬТАТОВ МОРФОМЕТРИИ ВНУТРЕННИХ ДИАМЕТРОВ СЕГМЕНТОВ, СОСТАВЛЯЮЩИХ БИФУРКАЦИЮ КОРРОЗИОННЫХ ПРЕПАРАТОВ РЕАЛЬНЫХ ВЕНЕЧНЫХ АРТЕРИЙ СЕРДЦА ЧЕЛОВЕКА И СОВРЕМЕННЫХ МЕТОДИК ИХ РАСЧЕТОВ

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РЕЗЮМЕ

Обоснование. *Исследование венечных артерий сердца человека (ВАСЧ) как фрактальной системы, состоящей их артериальных бифуркаций (АБ), доказали свою перспективность и эффективность при разработке цифровых методов диагностики и лечения сосудистой патологии. Однако в настоящее время среди исследователей нет единого мнения о теории оптимального строения АБ ВАСЧ и технологии расчета величин внутренних диаметров артериальных сегментов (АС), составляющих АБ ВАСЧ в норме.*

Цель. *Провести сравнительный анализ результатов морфометрии реальных ВАСЧ в норме и современных методик численного моделирования диаметров сегментов, входящих в состав АБ.*

Методы. *Проведено сравнительное исследование величин внутренних диаметров 2072 АС, составляющих 1078 АБ, 60-ти коррозионных препаратов ВАСЧ сердец лиц обоего пола в возрасте от 36 до 74 лет, без признаков патологии, полученных путем морфометрии и значений данных показателей, рассчитанных с использованием известных уравнений, предложенных Mette S. Olufsen и G. Finet.*

Результаты. *Установлено, что величины внутренних диаметров АС, входящих в состав АБ ВАСЧ, полученные путем морфометрии коррозионных препаратов и расчетным путем с использованием уравнений, предложенных Mette S. Olufsen и G. Finet, значимо отличаются.*

Заключение. *Для численного моделирования реалистичной геометрии ВАСЧ, как фрактальной структуры, состоящей из разнородных АБ, будет не правильным решением использование уравнений Mette S. Olufsen и G. Finet. Сегодня можно говорить об отсутствии общепризнанной теории оптимального строения АБ ВАСЧ и, соответственно, технологии численного моделирования реалистичной геометрии русла.*

Ключевые слова: *сердце человека, венечные артерии, фрактальная система, бифуркация*

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BACKGROUND

Following the paradigm of modern scientific research and the requirements of theoretical and clinical medicine, traditional morphology is increasingly undergoing digitalization [1]. In today's world, a simple verbal (qualitative) description of anatomical structures is no longer sufficient; medical theory and practice require a quantitative (digital) representation. This trend is directly reflected in the study of vascular beds in vital human organs, such as the heart, brain, kidneys, etc. The arterial beds of these organs can be considered as fractal (self-similar) systems, with the structural and functional unit (fractal) being a bifurcation. A bifurcation is a section of a vascular bed that consists of a parent vessel (D), two daughter (d_{max}, d_{min}) vessels, and the point where they join. Extensive research has been conducted on numerical modeling (a computer-based research method that performs calculations based on a specific mathematical model to simulate real-world physical objects or processes) of an arterial bifurcation (AB) [2-4]. From a theoretical perspective, this approach enables a quantitative description of the structure and function of the bed as a whole, as well as its individual components [5-7]. From a clinical perspective, the AB is a focus of attention for diagnosticians and interventional radiologists, as it is the most likely site for vascular damage [8, 9].

Such studies have already demonstrated their potential and efficacy in the development of digital diagnostic and therapeutic approaches for vascular pathology [8, 9]. However, there is currently a lack of consensus among researchers on the optimal design of the HCA bifurcation model and the corresponding technology for calculating the inner diameters of the arterial segments (AS) that comprise the HCA bifurcations in normal conditions. The theoretical data often diverge significantly from the morphometric findings of real-world objects. This has guided the direction of this study.

THE AIM OF THE STUDY

To conduct a comparative analysis of the results of morphometric data of actual normal HCA and modern numerical modeling techniques for the diameters of the segments included in AB.

METHODS

Study design

A comparative study was conducted on the internal diameters of the segments constituting the HCA bifurcations, which were previously obtained through the morphometry of actual anatomical specimens [10] and numerical modeling. This study adheres to the ethical standards set forth in 1964 Declaration of Helsinki and its subsequent revisions. Ethical approval was granted by the local ethics committee at the Medical Institute of A.A. Kadyrov Chechen State University (Protocol No. 258/24-77, dated October 16, 2023).

Eligibility criteria

Inclusion criteria: Individuals of both sexes, aged 36–74 years, who died from non-vascular accidental causes; heart weight 250–350 g in women, and 300–400 g in men; and with no external organ damage.

Exclusion criteria: Age <36 years and >74 years; mechanical organ damage; history of diseases that may cause vascular injury; visually detectable vascular deformities and anomalies; heart weight <250 g and >350 g in women, and <300 g and >400 g in men.

The study involved 60 samples of HCA corrosion preparations, which were manufactured according to a standard method [10]. Following morphometric analysis, numerical characteristics of the internal diameters of the AS were obtained: D is the internal diameter of the maternal (proximal) AS (mm); d_{max} is the diameter of the larger daughter (distal) AS (mm); d_{min} is the diameter of the smaller daughter AS (mm), which constitute the AB of the corrosion preparations of actual HCA.

To obtain the calculated values of d_{max} and d_{min}, methods based on the previously described patterns were employed:

1) according to Mette S. Olufsen, et al., 2000 [11]:

$$d_{max(Olufsen)} = 0{,}9D;\ d_{min(Olufsen)} = 0{,}6D \quad (1)$$

2) according to G. Finet, et al., 2008 [12]:

$$d_{max(Finet)} = \frac{D}{0{,}678} - d_{min(Finet)};\ d_{min(Finet)} = \frac{D}{0{,}678} - d_{max(Finet)} \quad (2)$$

A comparative analysis of the values of the studied parameters was conducted, using both morphometric measurements and equations (1) and (2). To assess the distribution of these values, the Kolmogorov – Smirnov test was applied, with a significance level of $p < 0.05$. Non-parametric methods of analysis were used (Wilcoxon signed-rank test). Median values, 95% confidence intervals (using asymptotic methods), interquartile ranges (25–75%), as well as minimum (min) and maximum (max) values of the studied parameter were calculated. Statistical analyses were conducted using the R programming language, employing the medianCI function provided by the MKinfer package: medianCI (x, method = "asymptotic").

RESULTS

The study included 1,078 AB, consisting of 2,072 AS, without signs of pathology. The findings are presented in Tables 1 and 2. It was found that the distributions of the studied parameters, including the internal diameters of AS (D – maternal (proximal), d_{max} – larger daughter (distal), and d_{min} – smaller daughter (distal)), which were obtained through morphometric analysis of the HCA and using equations (1) and (2), do not follow the normal distribution pattern (Table 1). This finding was taken

into consideration when selecting subsequent methods for statistical analysis.

The values of the parameters studied, obtained through morphometric analysis and using equations (1) and (2), are presented in Table 2.

The data in Table 2 clearly demonstrate that the values of the internal diameter of the larger and smaller daughter (distal) branches of the AB, obtained through morphometric analysis, significantly differ from the values of this parameter calculated using equations (1) and (2) ($p < 0.05$, where p represents the significance level for differences as determined by the Wilcoxon signed-rank test (here and further in the text).

A comparative analysis (Table 2) of the values of medians (Me) and 95% confidence intervals [CI 95%] of the internal diameters of the daughter (distal) AS (d_{max} and d_{min}), obtained from corrosion preparations of HCA from real anatomical specimens and using equations (1) and (2), convincingly demonstrates significant differences ($p < 0.05$) between the values of the studied parameters obtained through morphometric analysis and those calculated using these equations. It has been established that the measurements (Me [CI 95%], mm) of the larger and smaller daughter (distal) AS obtained through morphometric analysis (d_{max} = 0.60 [0.60; 0.70], mm and d_{min} = 0.40 [0.40; 0.50], mm, respectively) are significantly lower ($p < 0.001$ and $p < 0.001$, respectively) than the corresponding measurements (Me [CI 95%]) obtained using the equation (1) ($d_{max(Olufsen)}$ = 0.63 [0.63; 0.72], mm and $d_{min(Olufsen)}$ = 0.42 [0.42; 0.48], mm, respectively). The significance level for differences in the measurements (Me [CI 95%]) of the internal diameter of the larger daughter (distal) AS, obtained through morphometric analysis (d_{max} = 0.60 [0.60; 0.70] mm) and using the equation (2) ($d_{max(Finet)}$ = 0.60 [0.60; 0.69], mm), is $p = 0.033$, although it can be visually observed that both measurements tend to converge. On the other hand, the measurement (Me [CI 95%]) of the internal diameter of the smaller daughter (distal) branch of the AB, obtained through morphometric analysis (d_{min} = 0.40 [0.40; 0.50], mm), is noticeably and significantly higher ($p < 0.001$) than the value of the corresponding parameter ($d_{min(Finet)}$ = 0.34 [0.34; 0.38], mm), obtained using equation (2).

It has been established (Table 2) that the interquartile range (IQR) of the internal diameter of the larger daughter (distal) AS, obtained through morphometric analysis (d_{max} = 0.80 mm) is significantly higher than the values of this parameter calculated using equation (1) ($d_{max(Olufsen)}$ = 0.72 mm) and equation (2) ($d_{max(Finet)}$ = 0.72 mm). Comparison of the interquartile range values of the internal diameters of the smaller daughter (distal) AS showed

TABLE 1

RESULTS OF TESTING THE DISTRIBUTION OF THE VALUES OF THE STUDIED INDICATORS FOR COMPLIANCE WITH THE NORMAL DISTRIBUTION LAW

Parameter	Kolmogorov – Smirnov test statistics	*p*
D	0.17	<0.001
d_{max}	0.18	<0.001
d_{min}	0.18	<0.001
$d_{max(Olufsen)}$	0.17	<0.001
$d_{min(Olufsen)}$	0.17	<0.001
$d_{max(Finet)}$	0.17	<0.001
$d_{min(Finet)}$	0.15	<0.001

Note. D – diameter of maternal (proximal) AS, morphometry; d_{max} – diameter of larger daughter (distal) AS, morphometry; d_{min} – diameter of smaller daughter (distal) AS, morphometry; $d_{max(Olufsen)}$ – diameter of larger daughter (distal) AS, equation (1); $d_{min(Olufsen)}$ – diameter of smaller daughter (distal) AS, equation (1); $d_{max(Finet)}$ – diameter of larger daughter (distal) AS, equation (2); $d_{min(Finet)}$ – diameter of smaller daughter (distal) AS, equation (2); p – significance level for differences.

TABLE 2

VALUES OF THE STUDIED PARAMETERS OBTAINED BY MORPHOMETRY AND USING EQUATIONS (1) AND (2) (*n* = 2072)

No.	Parameter	Values of the parameter			
		Me	CI 95%	Interquartile range (IQR) (25–75%)	Minimum and maximum (min; max)
1	D (mm)	0.70	0.70; 0.80	0.80	0.10; 7.50
2	d_{max} (mm)	0.60	0.60; 0.70	0.80	0.10; 5.10
3	d_{min} (mm)	0.40	0.40; 0.50	0.40	0.10; 3.50
4	$d_{max(Olufsen)}$ (mm)	0.63	0.63; 0.72	0.72	0.09; 6.75
5	$d_{min(Olufsen)}$ (mm)	0.42	0.42; 0.48	0.48	0.06; 4.50
6	$d_{max(Finet)}$ (mm)	0.60	0.60; 0.69	0.72	0.06; 6.69
7	$d_{min(Finet)}$ (mm)	0.34	0.34; 0.38	0.33	0.06; 2.64

Note. D – diameter of maternal (proximal) AS, morphometry; d_{max} – diameter of larger daughter (distal) AS, morphometry; d_{min} – diameter of smaller daughter (distal) AS, morphometry; $d_{max(Olufsen)}$ – diameter of larger daughter (distal) AS, equation (1); $d_{min(Olufsen)}$ – diameter of smaller daughter (distal) AS, equation (1); $d_{max(Finet)}$ – diameter of larger daughter (distal) AS, equation (2); $d_{min(Finet)}$ – diameter of smaller daughter (distal) AS, equation (2); Me, median; [CI 95%], 95% confidence interval; IQR – interquartile range (25–75%); min – minimum value of the parameter studied; max – maximum value of the parameter studied; *n* – number of AS studied.

that the morphometric value (d_{min} = 0.40 mm) is lower than that calculated using equation (1) ($d_{min(Olufsen)}$ = 0.48 mm), but higher than the corresponding IQR value calculated using equation (2) ($d_{min(Finet)}$ = 0.33 mm).

The minimum values (Table 2) of the internal diameters of the larger daughter (distal) AS $d_{max(Olufsen)}$ (min = 0.09 mm) and $d_{max(Finet)}$ (min = 0.06 mm), obtained by calculations, are significantly lower than the d_{max} (min = 0.10 mm) parameter obtained through morphometric analysis. On the other hand, the maximum value of the internal diameter of the larger daughter (distal) branch AB, obtained through morphometric analysis d_{max} (max = 5.10 mm), is significantly lower than $d_{max(Olufsen)}$ (max = 6.75 mm) and $d_{max(Finet)}$ (max = 6.69 mm). The opposite pattern is observed with respect to the minimum diameter of the smaller daughter (distal) branch AB. The minimum value of d_{min} (min = 0.10 mm), obtained through morphometric analysis, is significantly greater than those calculated using equation (1) $d_{min(Olufsen)}$ (min = 0.06 mm) and equation (2) $d_{min(Finet)}$ (min = 0.06 mm). With regard to the maximum value of the smaller daughter (distal) branch of AB, it is not entirely clear. The maximum value of the smaller daughter (distal) branch of AB d_{min} (max = 3.50 mm) is less than $d_{min(Olufsen)}$ (max = 4.50 mm) and greater than $d_{min(Finet)}$ (max = 2.64 mm).

DISCUSSION

Mette S. Olufsen et al., 2000 [11] determined the values of the internal diameters of AS that comprise the HCA bifurcations: the internal diameter of the proximal AS – D, the internal diameter of the larger distal AS – d_{max}, the internal diameter of the smaller distal AS – d_{min}, based on the power law:

$$D^{\xi} = d_{max}^{\xi} + d_{min}^{\xi} \quad (3)$$

This law is based on the principles outlined in the works of C.D. Murray, M. Zamir, and H.B.M. Uylings [13, 14], which are based on the concept of "minimum energy" in the arterial system. The equation is valid for laminar flow, where ξ = 3.0 [15], and for turbulent flow, where ξ = 2.33 [16]. In the study by [17], it was found that for the HCA bifurcations, the characteristic value of ξ = 2.76. According to data from a systematic review conducted by Taylor et al., the optimal index for the relationship between blood flow and vessel diameter in coronary arteries is 2.39 [18]. In combination with equations for calculating the area ratio (η) ($\eta = \frac{d_{max}^2 + d_{min}^2}{D^2}$) and asymmetry ratio (γ) ($\gamma = \left(\frac{d_{min}}{d_{max}}\right)^2$),

$$d_{max} = \alpha D; d_{min} = \beta D; D_{k,n} = \alpha^k \beta^{n-k} D \quad (4)$$

arteries (d_{max} and d_{min}) relative to the diameter of the parent (proximal) artery (D)

where α and β are constants that characterize the asymmetry of the AB, *n* is the generation number (the division level of a newly formed set of AS), and *n* = 0 corresponds to an AS that is at the beginning of a channel. In each generation, up to 2^n vessels can exist. Within generation *n*, there can only be *n* + 1 AS of different sizes. This corresponds to *k* possible choices for the scale factor α, and *n* – *k* choices for the scale factor β, where $0 \le k \le n$. The HCA continues to branch until any AS has a diameter that is less than some specified minimum value (d_{min}). The asymmetry of the AB (γ) was determined using the following equation [19]:

$$\eta = \frac{1+\gamma}{\left(1+\gamma^{\frac{\xi}{2}}\right)^{\frac{\xi}{2}}} \quad (5)$$

$$\alpha = \left(1+\gamma^{\frac{\xi}{2}}\right)^{-\frac{1}{\xi}} = 0{,}9 \;\&\; \beta = \alpha\sqrt{\gamma} = 0{,}6 \quad (6)$$

where η is the area coefficient and γ is the asymmetry coefficient. Using the values of η = 1.16 and γ = 0.41 as well as ξ = 2.76 [14], the values of α and β can be determined:

G. Finet et al., 2008 [12] derived the equation through a study on the fractal geometry of the HCA bifurcations. The researchers measured the diameter of the parent AS (D) as well as the two daughter AS (d_{max} and d_{min}), that comprise 173 AB in the HCA radiographs of 59 patients without cardiovascular pathology. They found that the ratio $R = {}^{D}/_{d_{max} + d_{min}}$ remains constant at 0.678 regardless of the observation scale. This finding confirms the fractal nature of the HCA bifurcations.

However, the results of this study suggest that it is not possible to obtain, through calculation using equations (1) and (2), values of the studied parameters that correspond to real morphometric data. This may indicate that the "minimum cost" principle [13, 14] is not suitable for numerical modeling of the structure of real HCA as fractal systems, at least for the section of the HCA studied in this research, which is the epicardial and transmural AS from the origin of the coronary artery to the level of the hemomicrocirculatory bed (up to 0.1 mm).

The majority of scientific studies on the HCA bifurcations are based on a fundamental biological principle described in 1926 by Murray's law (C.D. Murray), which relates the form and function of these branched networks [13]. This law is founded on the principle of minimizing the work required to generate and maintain blood flow, as well as the energy needed to overcome viscous resistance [20]. This principle applies to both the epicardial and transmural systems of the HCA, which are composed of structural and functional units known as AB.

It is believed that the primary function of AB is blood transportation [21, 22]. However, this statement, which appears to be true for the proximal segments of the HCA, contrasts with the perfusing vessels of the distal segments, where a rapid increase in cross-sectional area (i.e., the increase in the total diameter of the vessels), contributes to a slower blood flow and less efficient substrate exchange [23, 24]. There is also compelling evidence that AB, in addition to transporting blood, also serve as the distribution and support system for an organ, acting as its soft skeleton. It should be noted that, in most studies, morphometric characteristics of AB focus on the ratio of internal diameters of the AS, rather than their lengths. However, it would be incorrect to assess hemodynamics and other functions of AB without considering the lengths of AS. In addition, the obtained results may be attributed to the fact that, as demonstrated by modern morphological studies, the AB population in all areas of the HCA (both distal and proximal sections), is heterogeneous. Previous studies have identified four types of AB: 1 – complete asymmetry, $D \neq d_{max} \neq d_{min}$; 2 – lateral asymmetry, $D = d_{max}$ and $d_{max} \neq d_{min}$; 3 – one-sided symmetry – $D \neq d_{max} \neq d_{min}$ and $d_{max} = d_{min}$; 4 – complete symmetry, $D = d_{max} = d_{min}$ in the composition of the HCA [25]. This, to some extent, explains the significant differences between the values of the studied parameters calculated and those obtained through morphometric analysis.

For discussion purposes. In the absence of a widely accepted theory on the structure and function of the HCA, the use of machine learning models appears to be a valid approach for numerical modeling the realistic geometry of the HCA. These models can be based on both classical regression techniques and neural network architectures, which are trained on morphometric measurement data. The channel geometry can be modeled as a fractal or pseudo-fractal system composed of structurally diverse AB.

CONCLUSION

Considering the above, it can be stated that at present, there is no unified, universally accepted theory on the optimal design of the HCA bifurcations and the methodology for numerically modeling the realistic geometry of the HCA.

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Conflicts of interest

No potential conflict of interest relevant to this article reported.

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MORPHOLOGY, PHYSIOLOGY AND PATHOPHYSIOLOGY

LIPOPOLYSACCHARIDE-BINDING SYSTEMS IN THE PATHOGENESIS OF VASCULAR COMPLICATIONS IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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RESUME

Rationale. *Disturbance of glycemia in type 1 diabetes mellitus (DM1) leads to the development of oxidative stress and damage to the barrier organs for lipopolysaccharide (LPS), which is accompanied by its increased translocation into the systemic bloodstream, inducing vascular damage.*
The aim. *Determination of the influence of the level of major lipopolysaccharide-binding systems on the risk of macro- and microvascular complications of DM1.*
Materials and methods. *The study included 92 patients with a verified diagnosis of type 1 diabetes mellitus. Patients underwent examination of biomaterial (blood plasma) by enzyme-linked immunosorbent assay (ELISA) to determine the level of lipopolysaccharide-binding protein (LBP), bactericidal permeability-increasing protein (BPI) and sCD14, as well as a marker of systemic inflammation – CRP. ROC-analysis with ROC-curve construction was used to assess the quality of the prognostic model efficiency, as well as to find the optimal point (cut-off point) of the threshold value of the level of the investigated markers.*
Results. *ROC-analysis revealed statistically significant patterns of relationship between peripheral blood LBP level and risk of arterial hypertension (AH) in patients with DM1 ($p = 0.014$), as well as relationship between peripheral blood LBP and sCD14 level and risk of diabetic nephropathy (DN) in patients with DM1 ($p = 0.042$ and $p = 0.048$).*
Conclusion. *We have revealed a statistically significant influence of LBP and sCD14 concentrations on the development of vascular lesions in DM1, with a decrease in the level of the main LPS-binding systems accompanied by an increased risk of AH and DN. Lipopolysaccharide of Gram-negative flora plays an important role in the development of complications of DM1, which is largely due to the peculiarities of the response to LPS under conditions of hyperglycemia and dysfunction of the normal response to LPS, accompanied by protective reactions and subsequent clearance of LPS.*

Key words: *type 1 diabetes mellitus, complications, nephropathy, arterial hypertension, endotoxin, lipopolysaccharide, imbalance*

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ЛИПОПОЛИСАХАРИД-СВЯЗЫВАЮЩИЕ СИСТЕМЫ В ПАТОГЕНЕЗЕ СОСУДИСТЫХ ОСЛОЖНЕНИЙ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 1-ГО ТИПА

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РЕЗЮМЕ

Обоснование. *Нарушение гликемии при сахарном диабете 1-го типа (СД1) приводит к развитию окислительного стресса и повреждению барьерных органов для липополисахарида (ЛПС), что сопровождается повышенной его транслокацией в системный кровоток, индуцируя сосудистое поражение.*

Цель исследования. *Определение влияния уровня основных липополисахарид-связывающих систем на риск развития макро- и микрососудистых осложнений СД1.*

Материалы и методы. *В исследование было включено 92 пациента с верифицированным диагнозом Сахарный диабет 1-го типа. Пациентам было проведено исследование биоматериала (плазмы крови) методом иммуноферментного анализа (ИФА) для определения уровня липополисахарид-связывающего белка (ЛСБ), бактерицидного белка, повышающего проницаемость (BPI) и sCD14, а также маркера системного воспаления – СРБ. Для оценки качества эффективности прогностической модели, а также для нахождения оптимальной точки (точка cut-off) порогового значения уровня исследуемых маркеров применялся ROC-анализ с построением ROC-кривой.*

Результаты. *В результате ROC-анализа выявлены статистически значимые модели взаимосвязи уровня ЛСБ периферической крови с риском развития артериальной гипертензии (АГ) у пациентов с СД1 (p = 0,014), а также взаимосвязи уровня ЛСБ и sCD14 периферической крови с риском развития диабетической нефропатии (ДН) у пациентов с СД1 (p = 0,042 и p = 0,048).*

Заключение. *Нами выявлено наличие статистически значимого влияния концентрации ЛСБ и sCD14 на развитие сосудистых поражений у пациентов с СД1, при этом снижение уровня основных ЛПС-связывающих систем сопровождается повышением риска развития АГ и ДН. Липополисахарид грамотрицательной флоры играет важную роль в развитии осложнений СД1, что во многом связано с особенностями ответа на ЛПС в условиях гипергликемии и нарушения функции нормального ответа на ЛПС, сопровождающегося защитными реакциями и последующим клиренсом ЛПС.*

Ключевые слова: *сахарный диабет 1-го типа, осложнения, нефропатия, артериальная гипертензия, эндотоксин, липополисахарид, дисбаланс*

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Recent studies have shown that the number of individuals suffering from type 1 diabetes mellitus (DM1) in Russia has reached 277,100 and is continuing to increase [1]. Specifically, the mortality rate among women with DM1 is worsening, with the average age at death over the last 12 years decreasing from 62.1 to 56 years [1]. Individuals with DM1 face a significantly increased risk of developing high blood pressure at a younger age compared to healthy individuals. In the group of young individuals with DM1, there is an increased prevalence of arterial hypertension (AH) (4–7 %), compared to those without diabetes (1–5 %) [2]. This is due to factors such as long-term hyperglycemia, development of diabetic nephropathy, oxidative stress, lipid metabolism disorders, and damage to the vascular structure. Hypertension contributes to the development of both micro- and macrovascular complications in patients with DM1 [3].

In most cases, hypertension in people with DM1 begins to manifest concurrently with the onset of albuminuria, suggesting a renal origin for the hypertension. However, it is important to note that the development of hypertension in individuals with DM1 cannot be solely attributed to nephropathy development [4]. Thus, diabetic nephropathy does not appear to be a universal factor contributing to hypertension in those with DM1. Additionally, hypertension development in these patients is influenced by other factors such as oxidative stress, advanced glycation end product exposure, endotoxin exposure, and intracellular lipoprotein accumulation, leading to endothelial dysfunction [5]. These processes can contribute to the development of vascular lesions and increase the risk of hypertension.

In real-world clinical practice, achieving optimal glycemic control is not feasible for all patients due to various factors. A combination of abnormal blood glucose levels, low-grade inflammation, and lipid metabolism disorders can lead to oxidative stress and vascular damage, increasing the risk of cardiovascular complications in individuals with DM1 [6]. Damage to vital organs, especially the small intestine, and changes in the intestinal microbiome can result in increased translocation of bacterial components, such as lipopolysaccharides (endotoxins) from gram-negative bacteria, into the lymphatic and circulatory systems. This can lead to the development of "metabolic endotoxemia" [7].

Even at relatively low levels of LPS, a sustained activation of the signaling pathways associated with soluble CD14 receptors (sCD14) and toll-like receptors 4 (TLR4) has been observed [8]. This is linked to prolonged low-grade inflammation, alterations in the extracellular matrix architecture of the pancreas, endothelial dysfunction, and vascular inflammation.

In 2011, a study conducted by Russian researchers found that LPS levels in the blood of individuals with newly diagnosed DM1 were ten-fold higher than in healthy individuals [9]. This indicates that people with DM1 are exposed to an increased level of endotoxin. To date, there have been only a limited number of studies investigating the issue of endotoxinemia and LPS-binding mechanisms in individuals with DM1 [10-13]. These studies have primarily focused on analyzing LPS levels, LPS antibodies (EndoCAb), and the level of systemic inflammation. However, they have not addressed the relationship between LPS and vascular damage in these patients.

In this regard, **the aim of our study** was to investigate the impact of the levels of key lipopolysaccharide-binding proteins on the risk of macro- and microvascular complications in patients with type 1 diabetes mellitus.

MATERIALS AND METHODS

The study involved 92 patients diagnosed with type 1 diabetes mellitus who were admitted to the Endocrinology Department of the N.A. Semashko Republican Clinical Hospital in Simferopol for treatment. All patients underwent a blood plasma sample upon admission to the study.

Inclusion criteria for the study group with type 1 diabetes was a confirmed diagnosis of this condition.

Exclusion criteria included patients over the age of 50, pregnant women, individuals with a history of cancer, inflammatory bowel disease, clinical signs of acute inflammation or fever (Table 1).

Data on the presence of comorbid conditions were collected from medical records of previous hospitalizations (outpatient charts).

Patients underwent an enzyme-linked immunosorbent assay (ELISA) test of their blood plasma to measure levels of the main lipopolysaccharide-binding proteins (lipopolysaccharide-binding protein (LBP), bactericidal permeability-increasing protein (BPI), and sCD14) as well as the systemic inflammation marker CRP.

The concentrations of LBP (ng/ml), BPI (pg/ml), sCD14 (pg/ml), and CRP (mg/l) in blood plasma were measured using a quantitative, highly sensitive ELISA test manufactured by Cloud Clone Corporation (Wuhan, Hubei, China).

The studies were conducted in compliance with the Helsinki Declaration as revised in 2013, and all respondents provided written informed consent prior to participating in the study. The study (Protocol No. 10) was approved by the local ethics committee of the V.I. Vernadsky Crimean Federal University (Simferopol) on October 10, 2024.

RESULTS AND DISCUSSION

As a result of the ROC analysis of the relationship between peripheral blood LBP level and the risk of hypertension in patients with DM1, the area under the ROC curve was 0.771 ± 0.084, with a 95% CI: 0.605–0.936. The model was statistically significant (p = 0.014) (Fig. 1). The cut-off value for serum LBP concentration at the optimal point was 5.65 mg/l. If the LBP level was less than or equal to this value, there was a high risk of developing hypertension. The sensitivity and specificity of the method were 80.0 % and 70.8 %, respectively.

The ROC models for the effects of sCD14, BPI, and CRP were not statistically significant ($p > 0.05$).

In a ROC analysis of the relationship between peripheral blood LBP and sCD14 levels and the risk of developing DN in patients with DM1, the area under the ROC curve for LBP and sCD14 were 0.740 ± 0.099 with 95% CI: 0.547–0.934 and 0.702 ± 0.097 with 95% CI: 0.511–0.893, respectively. These models were statistically significant ($p = 0.042$ and $p = 0.048$) (Fig. 2). The cut-off values for serum LBP concentration at the cut-off point was 6.81 mg/l. The cut-off value for sCD14 was 10.6 pg/ml. At LBP and sCD14 levels less than or equal to these values, a high risk of DN was predicted. The sensitivity and specificity of the method for LBP were 69.2 % and 75.0 %, respectively. For sCD14, the sensitivity and specificity of the method were 73.1 % and 75.0 %, respectively.

ROC curve models for the effects of BPI and CRP were not statistically significant ($p > 0.05$).

The results of our study confirm the impact of the main lipopolysaccharide-binding systems, specifically LPS and sCD14, on the risk of developing DN and hypertension in patients with DM1. Intriguingly, there is a negative correlation: the lower the levels of LPS-binding systems are, the greater the risk of hypertension.

According to the literature, the levels of LPS in the blood of patients with DM1 significantly exceed those of healthy individuals and are correlated with inflammation levels [10-13]. Despite this increased LPS, however, Aravindhan V. et al. did not find statistical differences in sCD14 levels between patients with DM1 and the control group ($p = 0.61$). Moreover, the LBP level was even significantly lower in the group of patients with DM1 ($p < 0.001$). Additionally, the authors observed an increase in the levels of proinflammatory cytokines such as interleukin-6 (IL-6), IL-1β, tumor necrosis factor-α (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with DM1, and a direct correlation between LPS levels and TNF-α levels ($r = 0.312$; $p = 0.009$), IL-6 levels ($r = 0.245$; $p = 0.041$) and IL-1β levels ($r = 0.428$; $p < 0.001$) [10].

The CD14 receptor may play a significant role in the impact of LPS on endothelial function and the progression of atherosclerotic changes. Based on the literature, levels of soluble CD14 (sCD14) have been shown to directly correlate with the formation of atheromatous plaques in carotid arteries, as well as with measures of aortic stiffness [14]. It is thought that CD14 is not expressed on endothelial cells, and the primary interaction with LPS occurs through sCD14 [15]. However, there have been reports of CD14 expression *in vitro* in endothelial cells from human umbilical veins [16], as well as on the surfaces of smooth muscle cells in coronary arteries [17].

A study has also found a possible association between serum LBP levels and carotid intimal thickness, which is a common marker of atherosclerosis disease. This suggests that serum LBP may play a role in the development of this condition [18]. Other studies have indicated that infections with a low LBP/CD14 ratio are also linked to the development of atherosclerosis [15]. Additionally, a previous study found that a low LBP/CD14 ratio is linked to activation of smooth muscle and endothelial cells in human coronary arteries [17].

However, CD14 is not the sole mediator of LPS effects on vascular cells. A study found that LPS effects on dermal microvascular endothelial cells were mediated by TLR4, which was expressed on these cells [19]. Atherosclerotic plaques, studied in various animal models and in humans, confirmed TLR4 expression, particularly on inflammatory macrophages and endothelial cells [20]. Furthermore, studies have demonstrated that TLR4 is expressed on both smooth muscle and endothelial cells in human coronary arteries and saphenous veins [21].

TABLE 1

CHARACTERISTICS OF THE PATIENTS INCLUDED IN THE STUDY

Signs	DM1 ($n = 92$) 1
Sex — Male abs. (%)	45 (48.91)
Sex — Male abs. (%)	47 (51.09)
Age (full years) Me [Q1;Q3]	34,5 [23.0; 47.0]
BMI, kg/m^2 Me [Q1;Q3]	23.0 [21.0; 26.7]
Achievement of target HbA1c levels, abs. (%)	16 (18.0)
Achievement of LDL target levels, abs. (%)	20 (21.7)
IHD: angina pectoris, abs. (%)	6 (6.52)
Angiopathy of the lower extremities, abs. (%)	38 (41.3)
AG, abs. (%)	32 (34.78)
Nephropathy, abs. (%)	73 (79.3)
Retinopathy, abs. (%)	68 (73.9)
Polyneuropathy, abs. (%)	66 (71.7)
Duration of illness (in full years) Me [Q1, Q3]	9.0 [4.0; 19.0]
Statins intake, abs. (%)	3 (3.3)
Angiotensin-converting enzyme inhibitor use, abs. (%)	15 (16.3)
Calcium antagonist intake, abs. (%)	7 (7.6)
Diuretic intake, abs. (%)	11 (12.0)
Beta-blocker intake, abs. (%)	7 (7.6)

Note. BMI – body mass index, IHD – ischemic heart disease, AG – arterial hypertension.

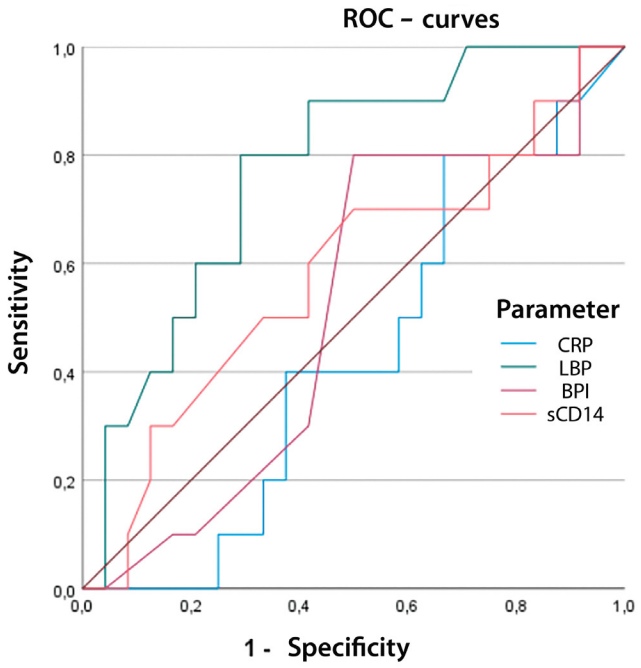

FIG. 1.
ROC-curves of the dependence of the risk of arterial hypertension on the level of lipopolysaccharide-binding systems

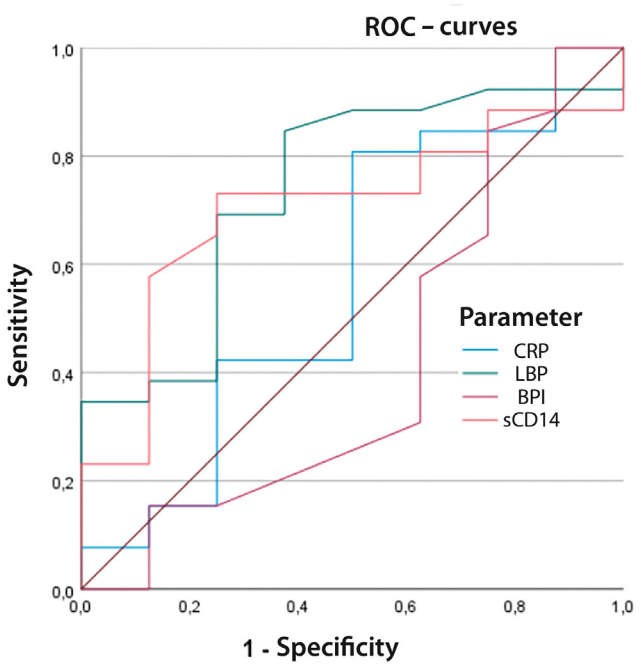

FIG. 2.
ROC-curves of the dependence of the risk of diabetic nephropathy on the level of lipopolysaccharide-binding systems

It has been postulated that LBP in combination with high-density lipoprotein (HDL) interacts with stabilin to mediate a series of metabolic reactions resulting in the inactivation and breakdown of LPS [22]. However, the exact physiological pathway and participants in these processes have not yet been fully established. This hypothesis is further supported by evidence of HDL dysfunction in patients with DM1, indicating that the LBP-HDL complex may lack the necessary anti-inflammatory properties. There is also evidence of increased intestinal permeability in individuals with CD14 deficiency, which could lead to increased LPS translocation into the portal and systemic circulations, increasing LPS concentrations and potentially damaging vascular endothelium [23].

In our view, patients with DM1 experience a "depletion" or imbalance in LPS-binding systems, which lead to reduced clearance and elimination of LPS, resulting in direct vascular damage associated with LPS. This phenomenon of "depletion", on the one hand, may be a consequence of increased concentrations of circulating LPS in the bloodstream of patients with DM1 and excessive consumption of LPS-binding system components. On the other hand, prolonged hyperglycemia in these patients can lead to protein glycation, disrupting its conformation and functional activity, potentially affecting LPS and sCD14 [24].

CONCLUSION

We have found a statistically significant impact of LPS and sCD14 levels on the development of vascular complications in patients with DM1. Reduced levels of the primary LPS-binding proteins are associated with an increased risk of hypertension and respiratory dysfunction. Gram-negative lipopolysaccharide plays a crucial role in the pathogenesis of complications in this condition, primarily due to its specific effects under conditions of elevated glucose levels and impaired normal responses to LPS, including protective mechanisms and subsequent clearance of LPS.

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Conflicts of interest

No potential conflict of interest relevant to this article reported.

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SERUM PHOSPHOLIPID AND SELECTED OXYLIPIN LEVELS IN SECOND-TRIMESTER PREGNANT WOMEN WITH COVID-19

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RESUME

Background. *The inflammatory response in coronavirus disease 2019 (COVID-19) markedly alters lipid metabolism. However, the phospholipid and oxylipin profile of pregnant women with COVID-19, stratified by disease severity, remains insufficiently studied.*

The aim. *To assess second-trimester serum levels of phospholipids, arachidonic acid, and the oxylipins 12- and 15-hydroxyeicosatetraenoic acids (12-HETE, 15-HETE) in women with COVID-19 according to clinical severity.*

Methods. *The study enrolled 88 pregnant women at 14–16 weeks of gestation with confirmed COVID-19. Patients with moderate disease (n = 42) formed subgroup 1; those with mild disease (n = 46), subgroup 2. A control group comprised 40 second-trimester pregnant women without COVID-19. Serum phospholipids were quantified by thin-layer chromatography; 12-HETE and 15-HETE by enzyme-linked immunosorbent assay; and arachidonic acid by gas–liquid chromatography.*

Results. *Compared with the mild-disease subgroup, women with moderate COVID-19 and control group showed significantly higher serum concentrations of sphingomyelin, lysophosphatidylcholine, arachidonic acid, 12-HETE, and 15-HETE, and lower levels of phosphatidylcholine and phosphatidylethanolamine ($p < 0.001$ for all comparisons).*

Conclusion. *The development of COVID-19 in second-trimester pregnant women is associated with severity-dependent alterations in serum phospholipids, arachidonic acid, and oxylipins. These changes may reflect the intensity of pulmonary inflammation and underscore the need to optimise therapeutic approaches in this patient population.*

Keywords: *COVID-19, pregnancy, phospholipids, arachidonic acid, 12-hydroxyeicosatetraenoic acid, 15-hydroxyeicosatetraenoic acid*

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ПОКАЗАТЕЛИ ФОСФОЛИПИДОВ И НЕКОТОРЫХ ОКСИЛИПИНОВ В СЫВОРОТКЕ КРОВИ БЕРЕМЕННЫХ С COVID-19 ВО ВТОРОМ ТРИМЕСТРЕ

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РЕЗЮМЕ

Обоснование. *Воспалительный процесс при COVID-19 значительно модифицирует метаболизм липидов. Однако состав фосфолипидов и оксилипинов у беременных с COVID-19 в зависимости от тяжести течения заболевания изучен недостаточно, что актуализирует тематику исследований.*

Цель исследования. *Дать оценку содержания сывороточных фосфолипидов, арахидоновой кислоты, оксилипинов (12- и 15-гидроксиэйкозатетраеновой кислот) во втором триместре у женщин в зависимости от степени тяжести COVID-19.*

Методы. *В основную группу исследования включены 88 беременных с COVID-19 во втором триместре (14–16 недель). Пациентки со среднетяжелым течением COVID-19 (n = 42) составили 1 подгруппу; легким течением (n = 46) – 2 подгруппу. Сорок беременных во втором триместре, без COVID-19, вошли в контрольную группу. В крови определяли концентрацию фосфолипидов методом тонкослойной хроматографии; 12- и 15-гидроксиэйкозатетраеновых кислот методом иммуноферментного анализа; арахидоновой кислоты – методом газо-жидкостной хроматографии.*

Результаты. *При сравнительном анализе результатов исследования было выявлено, что у женщин со среднетяжелым течением COVID-19 по сравнению с легким течением заболевания и контрольной группой в сыворотке крови наблюдались статистически значимо более высокие показатели сфингомиелина, лизофосфатидилхолина, арахидоновой кислоты, 12- и 15-гидроксиэйкозатетраеновых кислот при низких значениях фосфатидилхолина и фосфатидилэтаноламина (p < 0,001).*

Заключение. *Развитие COVID-19 у беременных во втором триместре ассоциировано с изменением содержания фосфолипидов, арахидоновой кислоты и оксилипинов в сыворотке крови, зависимое от тяжести патологического процесса. Выявленные нарушения в составе фосфолипидов и оксилипинов у беременных с COVID-19 могут потенциально отражать тяжесть течения воспалительного процесса в бронхолегочной системе и диктуют необходимость оптимизации терапевтических подходов в данной группе пациентов.*

Ключевые слова. *COVID-19, беременность, фосфолипиды, арахидоновая кислота, 12-гидроксиэйкозатетраеновая кислота, 15-гидроксиэйкозатетраеновая кислота*

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BACKGROUND

Lipids and their metabolites have been shown to be a diverse group of molecules involved in regulating inflammation in pulmonary diseases [1], including COVID-19. Lipids play a significant role in the life-cycle of the SARS-CoV-2 virus [2], serving as receptors or facilitating the entry of viruses into cells. They are also involved in viral replication complexes and energy production for efficient viral replication. They regulate the distribution of viral proteins within the cell and play a role in the assembly, transportation, and release of viral particles [3]. In addition, it has been demonstrated that lipid mediators, such as sphingolipids, lysophospholipids, and products of polyunsaturated fatty acid (PUFA) oxidation – oxylipins – can regulate the host immune response to viral infection [2].

Oxylipins are ligands for various receptor systems. They interact with peroxisome proliferator-activated receptors (PPARs), which are involved in the regulation of lipid homeostasis and inflammatory processes [4]. In addition, oxidized fatty acids serve as monocyte adhesion molecules. Lysophosphatidylcholines act as a strong chemoattractant for macrophages and T lymphocytes. They stimulate the expression of adhesion molecules and cytokines while disrupting endothelial function. Therefore, both lysophosphatidylcholines and oxidized fatty acids (oxylipins) are considered inflammatory mediators [5].

Oxylipins are synthesized from PUFAs, which are constituents of phospholipids, via a series of multiple oxidative reactions catalyzed by specific enzymes (cyclooxygenases, lipoxygenases (LOX) or cytochrome P450 monooxygenases). Additionally, enzyme-independent reactions may occur in the presence of reactive oxygen species (ROS) [6]. Pathological conditions associated with inflammation are thought to be linked to an imbalance between ω-3 (eicosapentaenoic and docosahexaenoic) and ω-6 (arachidonic) PUFA levels, leading to the overproduction of pro-inflammatory lipid mediators (ω-6 oxylipin derivatives, such as prostaglandins and hydroxyeicosatetraenoic acid, HETE) and the underproduction of pro-resolution (ω-3 oxylipin derivatives) molecules [4].

The main metabolite generated by 12-LOX is 12-HETE, which plays a role in various biological processes, including platelet activation and GPR31-mediated regulation of pro-inflammatory mediator production [7, 8]. Another oxylipin synthesized as a result of the enzymatic metabolism of arachidonic acid via 15-LOX is 15-HETE, which is generated during periods of hypoxia and exerts an inhibitory effect on sirtuin-mediated apoptosis in smooth muscle cells of the pulmonary artery by increasing the expression of pro-apoptotic proteins, such as Bcl-2 and Bel-xL [9].

There are several studies in the literature examining the impact of SARS-CoV-2 infection on the metabolism of oxylipins produced by LOX. It has been demonstrated that SARS-CoV-2 disrupts the metabolic pathways of arachidonic acid conversion, leading to an imbalance between pro-inflammatory oxylipins (12-HETE and 20-HETE), and anti-inflammatory oxylipins (epoxyeicosatrienoic acid) [10, 11]. However, these findings were obtained in non-pregnant individuals. Limited information is available on how the severity of COVID-19 affects oxylipin metabolism in pregnant women. These results support the study of lipid mediator roles in the pathogenesis of COVID-19 in pregnant women, depending on the extent of the pathological process.

THE AIM OF THE STUDY

To evaluate the levels of serum phospholipids, arachidonic acid, and oxylipins (12-HETE and 15-HETE) in pregnant women in the second trimester, depending on the severity of COVID-19 infection.

MATERIALS AND METHODS

Study design and setting

A prospective cohort study was conducted among 128 pregnant women who were hospitalized in the pulmonology department of the Blagoveshchensk City Clinical Hospital in the Amur Region. Of these, 88 women with COVID-19 in the second trimester (14-16 weeks gestation) were included in the study group, which was then divided into two subgroups based on the severity of COVID-19: subgroup 1 (n = 42) for women with moderate COVID-19 and subgroup 2 (n = 46) for women with mild COVID-19. The severity of COVID-19 was determined in accordance with relevant regulatory documents, such as the clinical guidelines "Organization of Medical Care for Pregnant Women, Women in Labor, and Newborns with Novel Coronavirus Infection (COVID-19)", version 5, published on December 28, 2021.

Inclusion criteria for the main study group were: pregnancy in the second trimester (14–16 weeks), confirmed case of COVID-19 infection (U07.1), presence of clinical symptoms of respiratory disease, signs of viral pneumonia (if indicated by computed tomography) for patients in subgroup 1, signed informed consent from participants to participate in the study and publication of its results in open sources, availability and accessibility of medical records for collection of research information, age of reproductive capacity, and singleton pregnancy. Exclusion criteria included: decompensated chronic somatic diseases, HIV infection, malignancies, and mental disorders.

The average age of participants in subgroup 1 was 29.0 (24.0; 33.0) years, and in subgroup 2 it was 31.0 (26.0; 34.0) years. No statistically significant difference was found between the two groups. The two groups were comparable in terms of age.

Thirty-six patients in subgroup 1 (85.71 %) and 39 patients in subgroup 2 (84.78 %) were married. This determined the comparability of the two groups ($p > 0.05$).

The parity of pregnancy among women in both groups did not differ significantly. In subgroup 1, there

were slightly fewer primigravid women compared to subgroup 2, with 18 (42.86 %) and 20 (43.48 %), respectively ($p > 0.05$).

The control group consisted of 40 pregnant women in their second trimester (14–16 weeks) with a negative COVID-19 status who were seen at the antenatal clinic No. 2 of the Blagoveshchensk City Clinical Hospital in the Amur Region. These patients were aged 30.0 (25.0; 34.0) years. Inclusion criteria for the control group required that the women were in their second trimester (14–16 weeks), had a singleton pregnancy, had no history of COVID-19 infection, had negative nasopharyngeal swab test for SARS-CoV-2 at the time of testing, and did not have a history of acute respiratory viral infection at the time of the examination. Exclusion criteria were the same as those for the study group.

ETHICAL REVIEW

The study has been conducted in accordance with the guidelines of the Declaration of Helsinki (2013), and has been approved by the local ethics committee of the Blagoveshchensk Scientific Center for Fundamental Pediatrics and Pedagogical Research (Protocol No. 172, dated October 12, 2021). All participants have provided informed voluntary consent to participate in the study (in accordance with the Federal Law "On the Fundamentals of Protection of Citizens' Health in the Russian Federation" dated November 21, 2011, No. 323-FZ, as amended December 30, 2021).

Study duration, description, and data collection

The study period for data collection and analysis was from 2022 to 2023.

Peripheral venous blood samples were collected for laboratory analysis. Blood was drawn upon admission to the hospital, after COVID-19 infection had been confirmed through medical diagnosis, using venipuncture in the morning, on an empty stomach. Standard vacuum systems without anticoagulants (Guangzhou Improve Medical Instruments Co., Ltd, China) were used to collect the blood samples. Serum was obtained from the collected blood samples by centrifuging them for 15 minutes at a speed of 1500 g, and then stored at -70°C until analysis.

Serum phospholipid levels (% of the total) were determined in peripheral blood samples after preliminary lipid extraction [12] using a thin-layer chromatography method. The resulting lipid extracts were separated into individual phospholipid components on thin-layer silica gel plates (Supelco, Germany). Two-dimensional thin-layer chromatographic analysis and identification of the individual phospholipids were performed using the protocol described by J. Kirchner [13].

Arachidonic acid concentration was measured by gas-liquid chromatography using a Crystal 2000M chromatograph (Russia), equipped with a flame ionization detector. Peaks were counted and identified using the Chromatec Analytic 2.5 software and hardware package (Russia). Quantitative chromatogram analysis was performed by internal normalization, which involved determining the area of each analyzed component's peak and calculating its relative percentage of the total area of peaks corresponding to higher fatty acids in the sample.

The levels of bioactive metabolites of arachidonic acid (12-HETE and 15-HETE) in serum samples were analyzed using an enzyme-linked immunosorbent assay (ELISA). Laboratory analyses were carried out using Enzo Life Sciences (USA) reagent kits, following the manufacturer's guidelines, on a StatFax 2100 ELISA (USA).

Statistical analysis

Statistical data processing was conducted using the standard IBM SPSS Statistics v.23.0 software (Statistical Package for the Social Sciences, USA). The sample size was not pre-determined. To test whether the observed sample followed a normal distribution, the Kolmogorov – Smirnov and Shapiro – Wilk tests were employed. Quantitative indicators are reported as Me (Q1; Q3), where Me represents the median and Q1 and Q3 denote the first and third quartiles, respectively. Categorical data is presented as proportions, frequencies, and percentages. For paired comparisons of normally distributed quantitative data between independent groups, a Student's *t*-test was utilized. When comparing groups with non-normal distributions, a non-parametric Mann – Whitney U-test was implemented. Null hypotheses were assessed at a critical significance level of 0.05.

RESULTS AND DISCUSSION

Phospholipids and bioactive metabolites derived from (oxylipins) are of significant interest in the context of COVID-19 research. These compounds form the basis for pulmonary surfactant and play a crucial role in inflammation, maintenance of lung cell integrity, and the viral life cycle [14].

Previous studies have demonstrated that SARS-CoV-2 replication during pregnancy is linked to high levels of phospholipase A2 activity, as well as an imbalance in the prooxidant-antioxidant system. This is characterized by a reduction in the total antioxidant capacity of the serum and an increase in oxidative modification products of biomolecules, as indicated by the levels of diene conjugates and TBA-active products, as well as 8-isoprostane. This oxidative stress may contribute to lung damage and may depend on the severity of the condition [15, 16]. These findings suggest that the composition of phospholipids may be affected by the development of this condition.

A comparative analysis of the study findings revealed differences in the quantitative composition of individual phospholipid fractions in the blood serum of women in the control and study groups. The levels of serum phospholipid subclasses varied depending on the severity of COVID-19 symptoms among participants in the study group (Table 1).

In subgroup 1, the median concentrations of phosphatidylcholine (Pc) and phosphatidylethanolamine (Pe) in the blood serum were decreased by 1.5-fold ($p < 0.001$)

and 1.7-fold ($p < 0.001$), respectively, compared to the control group. In subgroup 2, these values were lower than in the control by 1.2-fold ($p < 0.001$) and 1.3-fold ($p < 0.001$), respectively (Table 1). At the same time, the median level of lysophosphatidylcholine (Lpc) increased by 2.3-fold in subgroup 1 ($p < 0.001$), and by 1.7-fold in subgroup 2 ($p < 0.001$) when compared to the corresponding value in the control group (Table 1).

A decrease in the concentrations of Pe and Pc, accompanied by an increase in the Lpc levels in the blood serum of pregnant women with COVID-19, can be attributed to the intensification of lipid peroxidation and oxidative stress in these patients, as previously demonstrated [15, 16]. The oxidative stress observed in COVID-19 patients may contribute to increased phospholipase A2 activity or reduced Lpc reacylation, resulting in a higher concentration of this lipid.

The findings of Kagan V.E. et al. (2017), were completely unexpected, as they demonstrated that Pe, which contains a large number of arachidonic acyl chains, is a target for lipoxygenase. Lipoxygenase oxidizes unsaturated acyl chains to produce cytotoxic lipid hydroperoxides, leading to ferroptosis [17]. Other researchers have also shown that ferroptosis is one of the primary mechanisms of cell death in lungs infected with SARS-CoV-2. This occurs due to impaired iron metabolism regulation, activation of iron-dependent lipid peroxidation, reduction in phospholipid levels containing polyunsaturated acyl "tails", and accumulation of lysophospholipids. In particular, the accumulation of Lpc leads to increased alveolar epithelial permeability, destruction of pulmonary surfactant, and activation of pro-inflammatory processes [18].

According to current research, increased Lpc levels in COVID-19 patients may increase the risk of inflammation by activating NADPH oxidase in human neutrophils [19]. Additionally, lysophospholipids and arachidonic acid can enhance the production of pro-inflammatory cytokines (IL-8, IL-6, and IL-1β) in epithelial cells and monocytes, contributing to the development and persistence of the "inflammatory/cytokine storm" in COVID-19 patients [20]. This, in turn, can lead to disturbances in arachidonic acid metabolism, resulting in an imbalance between pro-inflammatory oxylipins such as 15-HETE and 20-HETE [11, 20]. Therefore, these findings suggest a potential pathogenic role for lysophospholipids and arachidonic acid in initiating or exacerbating COVID-19 disease.

A similar pattern of change was observed for sphingomyelin (Sph) with median values in the blood serum of women in subgroup 1 increasing by 1.8-fold ($p < 0.001$), and in subgroup 2 increasing by 1.4-fold ($p < 0.001$), when compared to the same parameter in the control group (Table 1).

According to international studies, Sph is not directly linked to COVID-19. However, Sph is an important component of membrane lipid rafts, play a role in signal transduction and activation of the immune system [21]. Specifically, proteins targeted by (angiotensin-converting enzyme 2 and membrane-associated proteases) are embedded in these lipid rafts and contribute to viral infection [22]. On the other hand, Sph has been the most extensively studied lipid associated with high-density lipoproteins (HDL). HDL with Sph plays a crucial role in the body's immune response, inhibiting the production of cytokines and chemokines by monocytes and macrophages. Additionally, HDL contains various proteins with antioxidant properties, such as paraoxonase 1, apolipoprotein A1 (apoA1), lipoprotein-associated phospholipase, and glutathione peroxidase 3. HDL is also able to inhibit apoptosis in endothelial cells through activation of the Akt/eNOS and apoA1 pathways, as well as sphingosine-1-phosphate [23]. Recent studies have demonstrated that HDL plays a protective role against severe complications of COVID-19 by regulating the immune response and reducing the severity of inflammatory

TABLE 1

CHANGES IN PERIPHERAL-BLOOD CONCENTRATIONS OF PHOSPHOLIPIDS, 12-HETE, 15-HETE, AND ARACHIDONIC ACID IN THE STUDY GROUPS

Parameter	Control group	Main study group	
		Subgroup 1	Subgroup 2
Pc, %	39.49 (36.79; 42.18)	26.82 (25.88; 27.25), $p < 0.001$	34.17 (33.28; 35.05), $p < 0.001$
Lpc, %	5.29 (5.0; 5.55)	12.0 (11.56; 12.48), $p < 0.001$	8.79 (8.44; 9.14), $p < 0.001$
Pe, %	31.12 (30.34; 31.89)	17.96 (17.30; 18.62), $p < 0.001$	24.14 (23.60; 24.68), $p < 0.001$
Sph, %	24.10 (23.64; 24.49)	43.22 (42.41; 44.05), $p < 0.001$	32.90 (32.0; 33.80), $p < 0.001$
12-HETE, ng/ml	1.81 (1.74; 1.89)	4.84 (4.78; 4.91), $p < 0.001$	3.69 (3.63; 3.74), $p < 0.001$
15-HETE, ng/ml	1.68 (1.63; 1.73)	3.84 (3.75; 3.93), $p < 0.001$	3.17 (3.07; 3.27), $p < 0.001$
Arachidonic acid, %	3.83 (3.77; 3.90)	5.77 (5.69; 5.85), $p < 0.001$	4.38 (4.29; 4.47), $p < 0.001$

Note. *p* – significance of the differences between subgroups within the main group and the control group.

responses. Sph, as a component of HDL, contributes indirectly to these functions [24].

It should be noted that Sph and its precursor, ceramide, have been implicated in the mechanisms of programmed cell death (apoptosis) under various pathophysiological conditions, including those associated with COVID-19. Studies by international researchers have demonstrated a clear correlation between increased Sph levels and the risk of mortality among patients infected with the SARS-CoV-2 virus. Apoptosis, a process that occurs early on, may contribute to the initiation of lung damage, leading to loss of pulmonary function and respiratory failure [25].

Consequently, phospholipid levels were dependent on the severity of COVID-19. The concentrations of Pc and Pe decreased significantly with increasing severity of the pathological process, whereas Lpc and Sph levels increased significantly depending on the severity of COVID-19.

Oxylipins, which are products of arachidonic acid lipoxygenase metabolism, have been shown to play a significant role in regulating inflammation and oxidative stress. This is achieved through both direct and indirect effects on cells and tissues, including modulation of vascular tone (vasoconstriction and vasodilation) and immune function [26].

As our observations indicate, when analyzing the levels of oxylipins in the blood serum of pregnant women infected with COVID-19 during the second trimester, there are changes in lipid metabolism, as presented in Table 1.

Based on the results of the study, the median concentration of 12-HETE increased by 2.7-fold ($p < 0.001$) in pregnant women in subgroup 1, and by 2-fold ($p < 0.001$) in subgroup 2, compared with the control group (Table 1). The same trend was observed for 15-HETE, with median values increasing by 2.3-fold ($p < 0.001$), and 1.9-fold ($p < 0.001$), respectively, in subgroups 1 and 2 compared to control values (Table 1). These findings suggest increased activity of 12- and 15-lipoxygenase enzymes, as well as activation of lipid peroxidation and oxidative stress in these subgroups.

An increase in the levels of 12-HETE and 15-HETE was observed against the background of high concentrations of arachidonic acid. The median value of arachidonic acid in subgroup 1 increased by 1.51-fold ($p < 0.001$), and in subgroup 2 it increased by 1.14-fold ($p < 0.001$) (Table 1).

The obtained data indicate that exposure to SARS-CoV-2 has significantly increased the concentrations of arachidonic acid metabolites (oxylipins), specifically 12-HETE and 15-HETE, in the blood serum of pregnant women with COVID-19. This increase was most pronounced in cases of moderate disease severity, which may indicate increased activity of 12- and 15-lipoxygenase enzymes, activation of lipid peroxidation pathways, and the development of oxidative stress. Our findings are consistent with those of international researchers, who have also reported elevated levels of 12-HETE in the blood plasma of COVID-19 patients [27]. 12-HETE is known to play a role in various physiological and pathobiological processes, acting as a chemotactic agent for neutrophils and smooth muscle cells and as a mitogen for endothelial cells [28, 29]. In addition, it has been shown to induce the expression of endothelial cell adhesion molecules, tissue factor on monocytes, and TNF-α in macrophages [29].

In general, HETEs are known for their pro-inflammatory and pro-apoptotic properties [30], suggesting their direct involvement in the development of inflammation in pregnant women with COVID-19. However, recent research has identified some HETEs as anti-inflammatory mediators. For example, 15-HETE, which was found to be elevated in the COVID-19 group compared to healthy controls, is a PPARγ ligand that can reduce inflammation by inhibiting nuclear factor-κB and modulating macrophage activity towards an anti-inflammatory phenotype. Additionally, 15-HETE serves as a precursor for lipoxin A4. Lipoxins, in contrast to classical pro-inflammatory arachidonic acid derivatives, exhibit potent anti-inflammatory and resolution-promoting properties. Additionally, 15-HETE undergoes further oxidation to 15-oxo-eicosatetraenoic acid, a class of oxylipins with anti-inflammatory activity [30]. Therefore, our data indicate the simultaneous production of both pro-inflammatory and anti-inflammatory oxylipins, and/or a shift in the temporal expression of lipid mediators towards an anti-inflammatory response, as part of a process known as lipid class switching [31].

Therefore, the findings have allowed us to identify certain trends in changes in the levels of arachidonic acid and its products of lipoxygenase metabolism, oxylipins (12-HETE and 15-HETE), which are key mediators in the pathophysiology of various intra- and intercellular processes, including inflammation associated with COVID-19.

CONCLUSION

The study suggests that the development of COVID-19 during the second trimester of pregnancy is associated with alterations in the levels of phospholipids, arachidonic acid, and oxylipins in the peripheral blood serum. These changes may be related to the severity of the disease process. The identified abnormalities in phospholipid and oxylipin metabolism in pregnant women with COVID-19 could potentially reflect the intensity of the inflammatory response in the respiratory system and could guide the optimization of therapeutic strategies for this patient group.

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Conflicts of interest

No potential conflict of interest relevant to this article reported.

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OPHTHALMOLOGY

DIAGNOSTIC CAPABILITIES OF COMPUTER ACCOMMODOGRAPHY IN MIDDLE-AGED (PRESBYOPIC) INDIVIDUALS

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RESUME

Background. *Presbyopia research aims to improve the quality of life of the aging population by correcting near vision and timely addressing accommodative disorders in presbyopes, particularly when combined with hypermetropic and myopic refraction.*
The aim. *To assess the parameters of computer accommodography in individuals aged 45–59 with presbyopia combined with hypermetropic and myopic refraction.*
Methods. *A cross-sectional study was conducted on a random sample of Arkhangelsk population aged 45–59 (n = 69), including ophthalmological examination with a comprehensive accommodation assessment. Data of 127 eyes were analysed. Participants were divided into five groups: those diagnosed with myopia (mild, moderate, and high degree), those with presbyopia (with emmetropia), and those with presbyopia accompanied by hypermetropia (refraction up to 3.0 D inclusive).*
Results. *In 32.3% of cases (41 eyes), no ocular pathology was detected except for presbyopia. Myopic refraction was found in 46.5% of cases (59 eyes), with an average refraction of 3.26±0.13 D in this group. When comparing groups on quantitative accommodogram parameters, the highest microfluctuation coefficient (up to +3.0 D inclusive) was in participants with moderate myopia and in those with age-related presbyopia combined with hypermetropia, the lowest – in participants with presbyopia (with emmetropia) and in groups with mild and high myopia (p = 0.028). Microfluctuation coefficient was the most stable was in individuals without visual organ pathology, with the exception of age-related presbyopia, and among participants with mild myopia (p = 0.017).*
Conclusion. *The use of computer accommodography in ophthalmological practice can significantly expand diagnostic capabilities for identifying accommodative changes in middle-aged individuals.*

Keywords: *presbyopia, computer accommodography, healthy aging, myopia, hypermetropia*

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ДИАГНОСТИЧЕСКИЕ ВОЗМОЖНОСТИ КОМПЬЮТЕРНОЙ АККОМОДОГРАФИИ У ЛИЦ СРЕДНЕГО (ПРЕСБИОПИЧЕСКОГО) ВОЗРАСТА

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РЕЗЮМЕ

Обоснование. *Изучение пресбиопии направлено на улучшение качества жизни стареющего населения посредством коррекции зрения вблизи и своевременной коррекции аккомодационных нарушений у пресбиопов, в особенности сочетающихся с гиперметропической и миопической рефракцией.*

Цель исследования. *Оценить основные параметры компьютерной аккомодографии у лиц 45–59 лет с пресбиопией в сочетании с гиперметропической и миопической рефракцией.*

Методы. *Проведено поперечное исследование случайной выборки населения г. Архангельска 45–59 лет (n = 69), включавшее офтальмологическое обследование с комплексным исследованием аккомодации. В анализ включены данные 127 глаз. Участники были разделены на 5 групп: лица с установленным диагнозом «миопия» (слабой, средней и высокой степени), лица с пресбиопией (с эмметропией) и лица, у которых пресбиопия сопровождалась гиперметропией с величиной рефракции до 3,0 дптр включительно.*

Результаты. *В 32,3 % случаев (41 глаз) не было выявлено патологии органа зрения за исключением пресбиопии. Наличие миопической рефракции выявлено в 46,5 % случаев (59 глаз) и среднее значение рефракции в данной группе участников составило -3,26 ± 0,13 диоптрий. При сравнении групп по количественным параметрам аккомодограмм коэффициент микрофлюктуации был наиболее высок (до +3,0 дптр, включительно) в группах участников с миопией средней степени и у лиц с возрастной пресбиопией в сочетании с гиперметропией, наиболее низким – у участников пресбиопов с эмметропией, и в группах миопии слабой и высокой степеней (p = 0,028). Коэффициент микрофлюктуации был наиболее устойчив среди лиц без патологии органа зрения, за исключением возрастной пресбиопии, и у участников с миопией слабой степени (p = 0,017).*

Заключение. *Применение компьютерной аккомодографии в офтальмологической практике может значительно расширить диагностические возможности в части определения аккомодационных изменений у лиц среднего возраста.*

Ключевые слова: *пресбиопия, компьютерная аккомодография, здоровое старение, миопия, гиперметропия*

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BACKGROUND

According to the World Health Organization's first World Report on Vision [1], globally, at least 2.2 billion people are visually impaired. In the context of aging, the study of presbyopia is significant in assessing the decline of organ-specific functions. Presbyopia is a natural process of age-related vision change that occurs due to changes in the accommodative ability of the eye.

According to data published in 2020, globally, over half a billion people are visually impaired caused by uncorrected presbyopia. This number is expected to increase due to aging population [2, 3]. Despite the prevalence of this issue, research on the development of presbyopia continues to be relevant, as the underlying mechanism remains unclear. One theory that has been proposed is the Helmholtz theory of accommodation. This theory suggests that changes in lens shape occur due to alterations in the diameter of the ciliary muscle. Presbyopia is then explained by the ongoing enlargement of the equatorial region of the lens and the inability of the ciliary muscles to stretch the ligaments in that area [4].

Presbyopia is a condition characterized by a decrease in binocular interaction due to a decrease in accommodation [5]. In individuals with presbyopia, the size of the fusion field is reduced both in length and width. A more significant reduction in the field occurs as a result of losses in the area of convergence. The most significant impairment of binocular vision in individuals with presbyopia is observed in those with hyperopia [6]. In young individuals, additional accommodation takes place due to convergence when stimuli are presented at a close distance. This is less evident in older individuals as the target is typically visible at a distance of approximately half a meter and the need for convergence is lower. Increased need for convergence may also lead to further constriction of the pupil and an associated increase in depth of field [7].

Various diagnostic methods are employed to detect presbyopia. Accommodative testing is the most accurate method for evaluating accommodation, assisting to assess the magnitude of the accommodative response and microfluctuations. In presbyopic individuals, these parameters decline with age, approaching zero at about the age of 50–55 years of age [8].

In the literature, presbyopia has been described solely as a reduction in accommodative capacity [9]. The visual system is a complex functional network, the efficient operation of which depends on the proper functioning of its various components. Any impairment in one of these components should be accompanied by efforts to compensate for or adapt to it. However, the mechanisms involved in the development of presbyopia have not been thoroughly investigated. The literature lacks systematic information on the alteration of pupillary diaphragm function, and there are no data available on changes in binocular interaction levels or on the impact of the accommodative-refractive component, which are essential aspects of visual perception [10].

Ongoing research into presbyopia is aimed at improving the quality of life for the aging population and achieving full correction of near vision. Additionally, it aims to address the timely and early treatment of accommodative issues in individuals with presbyopia who have hyperopic or myopic refractive errors [11]. Therefore, it is relevant to assess the prevalence of accommodative problems among middle-aged adults who do not have ophthalmological conditions and have a history of hyperopia or myopia.

Our previous study has shown that the parameters of computer accommodography can complement traditional methods of accommodation research. We have presented these parameters in young adults and students without any ophthalmological pathologies, as well as in those with a normal accommodative response [12]. The scientific literature lacks data on these parameters for the accommodation research of middle-aged individuals.

THE AIM OF THE STUDY

To assess the main parameters of computer accommodography in individuals aged 45–59 years with presbyopia, in combination with hypermetropic and myopic refraction.

METHODS

A cross-sectional study was conducted among a random sample of Arkhangelsk residents aged 45–59 years who participated in the "Biomarkers of Individual Viability in Residents of the European North of Russia" study (hereinafter referred to as IIV). The study was conducted at the Clinical and Diagnostic Outpatient Clinic of the Northern State Medical University (Arkhangelsk) from March 1 to May 31, 2024. Participants for IIV were selected from among residents of Arkhangelsk who were previously included in a random population sample for the "Know Your Heart" study conducted in 2015–2017. The sample was formed on the basis of an anonymized database of city resident addresses provided by the regional mandatory health insurance fund [13]. Participants were contacted through telephone and mail communication with 1,014 "Know Your Heart" participants aged 45–59 years who had resided in the Arkhangelsk region for over 10 years. Exclusion criteria included the presence of mental illness, acute infection symptoms, or exacerbation of chronic conditions (hypertensive crises, fever, pain of any origin) on the day before or immediately prior to the examination. Consequently, 612 individuals underwent the IJI exam, which included an ophthalmological examination.

Inclusion criteria for the additional examination using computer accommodography included individuals aged 45–59 years who met the criteria for health groups 1 and 2 for outpatient observation by an ophthalmologist. These groups included individuals with certain disease groups

and individual nosological entities, excluding refractive errors. This means that study participants were only individuals with refractive errors, and individuals with other visual pathologies were excluded from the study. Exclusion criteria included a history of acute cerebrovascular accidents and traumatic brain injuries, as well as certain ophthalmological conditions (such as established diagnoses according to the International Classification of Diseases 10th Revision (ICD-10) codes for diseases of the eye and adnexa except for refractive and accommodative disorders (H52)). Other exclusion criteria also included a history of previous keratorefractive surgeries, the presence of partial optic nerve atrophy in both eyes, and uninformative data from computer accommodography tests. Of the total number of participants, 74 individuals were examined using a computer-based assessment. Based on the inclusion and exclusion criteria, 69 male and female participants aged 45–59 years were selected for the study.

The ophthalmological examination of the participants involved assessing uncorrected visual acuity (UCVA) ranging from 0 to 1.0 conventional units (c.u.) using the Sivtsev – Golovin charts (Golovin S.S. and Sivtsev D.A., 1928). Best-corrected visual acuity (BCVA) parameters were also assessed. Clinical refraction was performed using automatic refractometry. Based on the examination findings, an initial ophthalmologist's examination (appendix to form 025/U-07 approved by the Order of the Ministry of Health, dated August 30, 2007 No. 710) was conducted in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Based on the results of a thorough study of accommodation, qualitative changes in the positive portion of the accommodative amplitude (PPAV in diopters) were evaluated, as well as the values of the main accommodative coefficients – the accommodative response coefficient (ARC), growth coefficient (GC), microfluctuation coefficient (MFC), and others. The study of the accommodative capacity of the eye was conducted using an objective computerized accommodation method employing the Acomoref-2 (Righton, Japan). In accordance with the instructions provided by the manufacturer [14], the acquired accommodograms were classified into the following categories: 1 – normal appearance; 2 – presbyopia; 3 – presbyopia accompanied by accommodative strain; 4 – phenomena related to computer vision syndrome; 5 – habitually excessive accommodative strain; and 6 – accommodative spasm. In five instances (five eyes), the data obtained from computer accommodography were not informative, and therefore, in accordance with the exclusion criteria, these instances were not incorporated into the study.

The graphical representation of the accommodogram generated using the Acomoref-2 includes a color spectrum, in which the severity of high-frequency fluctuations is indicated from green (normal) to red (indicating increased tension of the ciliary muscle) [15]. Additionally, the accommodogram demonstrates the nature of the accommodative response (AR, color columns) in relation to the presented accommodative stimulus (AS, contour columns). A typical accommodogram will display an increasing, steady curve, with AR being less than the accommodative stimulus. The color spectrum of microfluctuations will be predominantly green and yellow-green, with possible isolated instances of red towards the end of the maximum accommodative effort. An accommodogram indicating habitually excessive tension and accommodation spasm will demonstrate an unstable, increasing curve, with a red-orange color spectrum. The accommodogram in presbyopia exhibits a significantly reduced AR, a "flattened" curve resembling a plateau, and a predominance of green color spectrum. In cases of accommodative strain associated with presbyopia, the accommodative response is further diminished, with the accommodogram displaying a plateau-like curve and a yellowish-reddish color spectrum.

The study participants were divided into 5 groups: those with a confirmed diagnosis of myopia (mild, moderate, and high), those with presbyopia in combination with emmetropia (referred to hereafter as the "no pathology" group, or the comparison group), and those whose presbyopic condition was accompanied by hyperopia of up to 3.0 D inclusive. The severity of myopia was determined based on autorefractometric data and categorized as follows: mild, between -0.5 and -3.0 D; moderate, between -3.25 and -6.0 D; and high, over -6.25 D [16].

Categorical variables were presented as absolute values (abs.) and percentages (%). Comparisons of proportions in groups were performed using the Pearson's χ^2 test. The normality of the distribution of continuous variables was assessed using the Shapiro – Wilk test. Given the distribution pattern of the analyzed characteristics, results are presented as medians (Me) with values of the 25th and 75th percentiles (P25-P75). Continuous variable comparisons between men and women were performed using the Mann – Whitney U-test, and comparisons between the five groups were performed using the Kruskal – Wallis H-test. Differences were considered statistically significant at $p < 0.05$. For further pairwise comparisons between groups with and without ophthalmic pathologies, the Mann – Whitney U-test with Bonferroni correction was used, with differences considered statistically significant at $p < 0.0125$. Statistical analysis was conducted using Stata version 18.0 (StataCorp, USA, Texas, College Station).

The study was approved by the local ethics committee of the Northern State Medical University of the Ministry of Health of the Russian Federation (Arkhangelsk) (Protocol No. 03/04-23, dated April 26, 2023). All participants in the study provided voluntary informed consent.

RESULTS

A total of 69 participants aged 45–59 years were included in the study, with an average age of 51.5 years. The sample consisted of 127 eyes, 44 of which were male and 83 were female, and 64 were right eyes and 63 were left eyes. All eyes met the inclusion criteria and did not meet any exclusion criteria.

In 32.3 % of cases (41 eyes), emmetropic refraction combined with presbyopia was observed (Table 1). Myopic

refraction was present in 46.5 % of cases (59 eyes). The largest number of participants was in the group ophthalmologic pathology (32.3 %) and with a diagnosis of "mild myopia" (26.0 %), as well as in the group with hypermetropic refraction up to +3.0 D (21.3 %). The average myopic refractive error in the examined participants with myopia was -3.26 ± 0.13 diopters.

The main parameters assessed during the ophthalmological examination, including the parameters of computer accommodography (UCVA, BCVA, near visual acuity, autorefractometry, etc.), are presented in Table 2. The analyzed groups differed in UCVA ($p < 0.001$). The parameters in the groups with myopia and with presbyopia and hyperopia were lower compared to the group without pathology. After excluding participants without pathology, differences in BCVA were observed ($p < 0.001$), with individuals with myopia having reduced values for this parameter. Differences were also found in near visual acuity ($p < 0.001$), with the lowest values determined in the group with presbyopia and hyperopia. When assessing the positive part of accommodation volume, it was found to be 0 (0; 0) D in all groups of study participants.

When assessing the microfluctuation coefficient (MFC), it was observed that the highest reduction frequency was seen in the groups of participants with moderate myopia and participants with age-related presbyopia in combination with hyperopia up to +3.0 D inclusive. The lowest MFC values were found in presbyopic participants with emmetropia, as well as in groups with mild and severe myopia ($p = 0.028$) (Table 2 and Fig. 1). The stability of the σMFC was lowest in individuals with mild myopia, as well as those without visual organ pathology ($p = 0.017$) (Table 2).

In pairwise comparisons between the group without pathology and other groups, statistically significant differences were observed for the MFC parameter in comparison with the group of participants whose presbyopia was accompanied by hyperopia ($p = 0.008$) and the group of participants with moderate myopia ($p = 0.010$). Significant differences were also observed for the σMFC parameter in the group with moderate myopia ($p = 0.008$).

When analyzing the accommodogram data (Fig. 2), participants with moderate and high myopia were grouped together due to the limited number of participants in each category. The four groups under study exhibited the following types of accommodative disorders: presbyopia, presbyopia with accommodative strain, computer vision syndrome, habitually excessive accommodative strain, and accommodative spasm. The distribution of these four types of disorders among the four groups did not reach statistical significance ($p = 0.123$). It is worth noting, however, that the accommodative responses of individuals without visual impairment most frequently corresponded to presbyopic accommodative response (46.3 %) and presbyopic response with accommodative strain (29.3 %). In 5 cases (12.2 %), a normal accommodative response was observed, and among individuals with presbyopia and hyperopic refractive errors, the majority of accommodative responses demonstrated presbyopic strain (44.4 %). In the group of participants with mild myopia, the presbyopic accommodative type was most commonly observed (57.6 %). Among participants with moderate and high myopia, presbyopia with accommodative strain predominated (46.3 %).

DISCUSSION

The study revealed a decrease in visual function in the group of participants with presbyopia and hyperopia, compared to those without ophthalmopathology. This was true for all participants, except for those with presbyopia, who experienced an increase in their degree of refractive error, and as a result, a corresponding decrease in central vision.

Near visual acuity was decreased in all groups, which can be attributed to the age of the study participants. The lowest near visual acuity was observed in the presbyopic and hyperopic groups, which is explained by the presence of hyperopia in these individuals, further reducing near visual acuity. Given the reduced

TABLE 1

GENDER DISTRIBUTION OF CASES (EYES) BY SEVERITY OF REFRACTIVE DISORDERS

Groups	Sex		Total *n* = 127
	Male *n* = 44	Female *n* = 83	
	abs. (%)	abs. (%)	abs. (%)
Presbyopia and emmetropia	18 (14.2%)	23 (18.1%)	41 (32.3%)
Presbyopia and hyperopia up to +3.0 D inclusive	12 (9.4%)	15 (11.8%)	27 (21.3%)
Mild myopia	7 (5.5%)	26 (20.5%)	33 (26.0%)
Moderate myopia	4 (3.1%)	13 (10.2%)	17 (13.4%)
High myopia	3 (2.4%)	6 (4.8%)	9 (7.1%)

TABLE 2

KEY STUDY PARAMETERS, INCLUDING COMPUTER ACCOMMODOGRAPHY DATA, IN INDIVIDUALS AGED 45–59 YEARS

Characteristics	Presbyopia and emmetropia *n* = 41	Presbyopia and hyperopia *n* = 27	Myopia			*p**
			Mild myopia *n* = 33	Moderate myopia *n* = 17	High myopia *n* = 9	
	Me (25; 75)	Me (25; 75)	Me (25; 75)	Me (25; 75)	Me (25; 75)	
Indicators of visual acuity for distance and near vision, as well as accommodation						
Uncorrected visual acuity, c.u., as measured using the Sivtsev-Golovin chart	1.00 (0.90; 1.00)	0.70 (0.40; 0.80)	0.20 (0.10; 0.30)	0.05 (0.04; 0.05)	0.02 (0.01; 0.10)	<0.001
Best-corrected visual acuity, c.u., as measured using the Sivtsev-Golovin chart	–	1.0 (1.0; 1.0)	1.0 (0.9; 1.0)	1.0 (0.8; 1.0)	0.9 (0.5; 0.9)	<0.001
Near visual acuity, c.u.	0.5 (0.3; 0.5)	0.3 (0.2; 0.3)	0.7 (0.5; 0.8)	0.5 (0.2; 0.6)	0.5 (0.1; 0.9)	<0.001
Autorefractometry:						
- spherical component, D	+0.5 (+0.25; +0.75)	+1.75 (+1.5; +2.5)	-1.25 (-2.0; -0.75)	-4.25 (-4.75; -3.5)	-7.5 (-10.0; -6.5)	<0.001
- cylindrical component, D	-0.25 (-0.75; -0.25)	-0.5 (-0.75; -0.25)	-0.5 (-0.75; -0.25)	-0.5 (-0.75; -0.5)	-1.0 (-1.25; -0.75)	0.001
Intraocular pressure, mmHg	14.0 (12.0; 16.0)	14.0 (12.0; 16.0)	16.0 (14.0; 18.0)	15.0 (14.0; 17.0)	14.0 (13.0; 19.0)	0.076
Positive portion of the accommodative amplitude, D	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.559
The parameters of computer accommodography						
Accommodative response coefficient (ARC), c.u.	0.04 (-0.01; 0.14)	0.12 (-0.06; 0.32)	0.03 (-0.16; 0.14)	0.09 (-0.06; 0.16)	0.02 (-0.09; 0.18)	0.509
Coefficient of stability of the accommodative response coefficient (σARC), c.u.	0.09 (0.06; 0.24)	0.19 (0.11; 0.34)	0.13 (0.08; 0.20)	0.12 (0.07; 0.19)	0.12 (0.09 0.14)	0.077
Accommodogram growth coefficient (AGC), c.u.	0.43 (0.29; 0.57)	0.57 (0.43; 0.57)	0.43 (0.43; 0.57)	0.43 (0.43; 0.57)	0.57 (0.43; 0.57)	0.448
Microfluctuation coefficient (MFC), μF/min	54.6 (51.1; 56.9)	58.5** (54.3; 61.8)	55.0 (52.8; 59.0)	59.2** (55.2; 61.1)	55.3 (54.3; 56.7)	0.028
Coefficient of stability of the microfluctuation coefficient (σMFC), c.u.	3.47 (2.79; 4.21)	3.62 (3.14; 4.41)	3.14 (2.65; 3.73)	4.97** (3.80; 5.23)	4.06 (2.57; 5.03)	0.017

Note. * Comparison of parameter values between groups using the Kruskal – Wallis test. ** Significant differences observed in the pairwise comparisons of the groups with the group without ophthalmic pathology, after applying the Bonferroni correction and considering a critical significance level of $p < 0.0125$.

near visual acuity in this age range, assessing accommodative capacity by determining accommodation reserve is not practical. Therefore, our study employed computer-based accommodation testing, which allowed us to compare the analyzed groups based on microfluctuation coefficients and their stability indices. These findings support the usefulness of this method in identifying accommodative disorders in presbyopic individuals.

When assessing the type of accommodative responses, a normal accommodative response was found in only in 5 out of 127 cases. This is consistent with literature data, which indicate that accommodation weakens significantly after the age of 45 [17]. The study of accommodative function in individuals aged 45 to 59 years allowed us to identify various types of accommodative disorders. These findings indicate that, in addition to the presbyopia that is traditionally mentioned in scientific literature, other types of abnormalities can occur at this age. Previous studies have demonstrated that in a significant number of patients, even those over the age of 60, signs

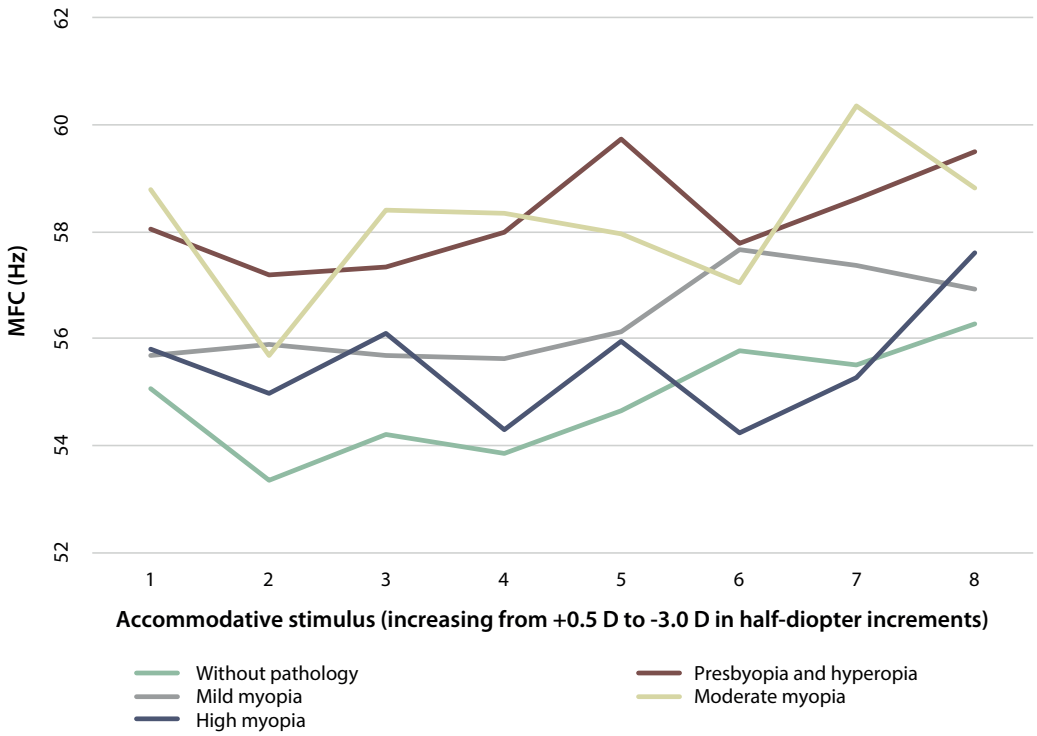

FIG. 1.
Microfluctuation changes with increasing accommodative stimulus in study participants aged 45–59 years without ophthalmopathology and in groups with different degrees of myopia

of functional accommodation are detectable. In particular, according to the findings of E.L. Shalygina, accommodative responses in the age group of 46–50 years were noted in 49 % of cases, while in the group of 51–55 years they were seen in 17 %. The presence of accommodative microfluctuations was reported in 58 % of individuals aged between 46 and 50 and 21 % of those aged 56 to 60 [18]. Additionally, I.G. Ovechkin et al. emphasized that the presence of accommodative responses and microfluctuations among individuals over the age of 55 and even 60 indicates the need for further, in-depth research into this topic [19]. Nevertheless, the prevalence of accommodative disorders among middle-aged people has not been investigated.

The accommodative capacity of the eye has been widely studied in patients who have undergone cataract phacoemulsification and implantation of various intraocular lens (IOL) types (monofocal, multifocal, accommodating) [20]. The implantation of monofocal and trifocal IOLs has been associated with a significant decrease in the MFC (by 3.8–4.4 %) and MFC stability (by 26.5–31.4 %). These changes are believed to reflect a shift in the accommodative system of the eye from a "normal" to a "habitually excessive accommodation tension" state, as reported by the authors [21]. The study identified specific features of accommodative responses in individuals after phacoemulsification, indicating the sensitivity of the MFC and MFC stability (σMFC) indices in this age group. These findings were also reflected in our own study.

The findings regarding changes in the MFC indices and MFC stability (σMFC) may be considered predictive of accommodative dysfunction in individuals aged 45–59 years and potentially in older patients. This suggests a potential avenue for further investigation of these parameters.

Therefore, the identified computer-based accommodation parameters can assist in identifying accommodative disorders in individuals with presbyopia, necessitating timely treatment. The greatest risks for the development of accommodative disorders were observed in groups of participants with presbyopia in combination with moderate to high hyperopia and myopia, warranting special attention during the examination of patients with these characteristics. The increased prevalence of accommodative disorders in these groups may be partially attributed to the presence of refractive errors.

The traditional method of assessing accommodative function through the determination of the positive component of the accommodative volume, as illustrated by the findings of this study, has been found to be insufficiently informative. A computerized accommodationography technique, which not only provides a visual representation of the accommodative process but also allows for the quantification of a range of parameters, may represent a complementary approach for the identification of accommodative disorders in this population.

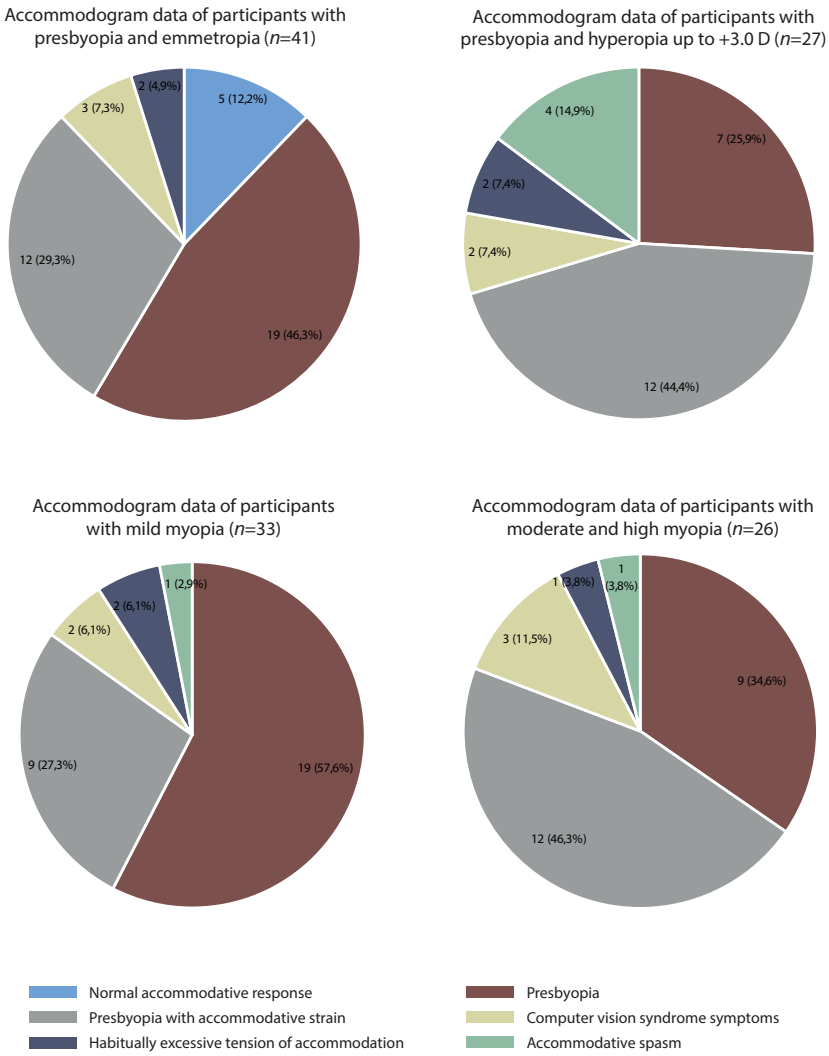

FIG. 2.
Distribution of accommodation disorders based on computer accommodography findings in participant groups (number of analyzed accommodograms, abs., %)

CONCLUSION

Computer-based accommodation parameters can significantly enhance diagnostic capabilities for detecting accommodative changes in middle-aged individuals. Our study has demonstrated that accommodative alterations in individuals aged 45–59 years encompass more than simply the traditionally described presbyopia. The coefficients of microfluctuations and stability of microfluctuations were identified as the most sensitive quantitative parameters in accommodograms. These parameters may be considered predictors of accommodative abnormalities in middle-aged patients, and potentially in older individuals as well, paving the way for further research.

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Conflicts of interest

No potential conflict of interest relevant to this article reported.

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EVALUATION OF THE EFFECTIVENESS OF COMBINATION TREATMENT FOR COATS' RETINITIS

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RESUME

The aim of this study *is to evaluate the efficacy of a combined treatment modality for Coats' disease, integrating anti-angiogenic therapy with retinal laser photocoagulation.*
The presented clinical case illustrates the advantages of a combined, staged treatment approach for Coats' disease. A marked increase in exudative manifestations within the macular region and along the inferior-temporal vascular arcade, observed following the initial session of retinal laser photocoagulation (which included barrier and delimiting applications to the macula), would have precluded subsequent laser intervention without a significant risk of complications. Consequently, the administration of anti-VEGF agents as adjuvant therapy proved optimal for establishing favorable conditions for the next stage of laser photocoagulation. Given that the clinical course of Coats' disease in adult patients is frequently associated with hypercholesterolemia, performing a lipid profile and initiating appropriate corrective measures for any identified dyslipidemia is essential. This management also contributes to the reduction of cholesterol exudation. Thus, the implemented combined, staged treatment regimen in this patient resulted in the stabilization of the pathological process and the preservation of high visual acuity.
Conclusion. *Laser photocoagulation remains the primary treatment for Coats' disease. However, the use of anti-VEGF agents, either as neoadjuvant or adjuvant therapy, facilitates the stabilization of the pathological process and aids in the preservation of the patient's maximum potential visual function.*

Key words: *Coats' disease, retinal arterial macroaneurysm, retinal edema, retinal laser coagulation, angiogenesis inhibitors.*

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ОЦЕНКА ЭФФЕКТИВНОСТИ КОМБИНИРОВАННОГО ЛЕЧЕНИЯ РЕТИНИТА КОАТСА

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РЕЗЮМЕ

Целью данной работы *является оценка эффективности комбинированного лечения ретинита Коатса с применением антиангиогенной терапии и лазеркоагуляции сетчатки.*
На примере клинического случая показаны преимущества комбинированного поэтапного лечения ретинита Коатса. Выраженное усиление экссудативных проявлений в макулярной области и по ходу нижне-височной сосудистой аркады после лазеркоагуляции сетчатки (отграничительная, барраж макулы) не позволило бы провести следующий этап лазерного лечения без серьёзных осложнений. Поэтому применение анти-VEGF препаратов в качестве адъювантной терапии оптимально для создания благоприятных условий для следующего этапа лазеркоагуляции. Учитывая, что течение ретинита Коатса у взрослых пациентов часто ассоциировано с гиперхолестеринемией, необходимо проведение липидограммы и назначение адекватной коррекции выявленных нарушений, что также способствует снижению экссудации холестерина. Таким образом, комбинированное поэтапное лечение ретинита Коатса у данной пациентки позволило стабилизировать патологический процесс и сохранить высокую остроту зрения.
Заключение*. Основным методом лечения ретинита Коатса остаётся лазеркоагуляция. Однако применение анти-VEGF препаратов в качестве неоадъювантной либо адъювантной терапии способствует стабилизации патологического процесса и сохранению максимально возможного зрения у пациента.*

Ключевые слова: *ретинит Коатса, ретинальная артериальная макроаневризма, отёк сетчатки, лазеркоагуляция сетчатки, ингибиторы ангиогенеза*

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Exudative retinitis, also known as Coats' disease, is a rare idiopathic eye disease characterized by telangiectasia, micro- and macroaneurysms of the retinal vessels, and the deposition of hard exudates (intra- and subretinal).

The disease was first described in 1908 by ophthalmologist G. Coats. Coats' retinitis is most often diagnosed in the first or second decade of life, with the majority of cases occurring between the ages of 3 and 9. In 90 % of cases, Coats' retinitis is unilateral, with only 10 % of patients experiencing bilateral involvement. Men are more commonly affected by Coats' retinitis, although no differences in clinical presentation have been identified between men and women [1, 2]. No racial or ethnic predisposition to Coats' retinitis has been identified. In adults, the disease may be associated with hypercholesterolemia [3].

The etiology and pathogenesis of Coats' disease are unknown. Initial theories suggested an infectious origin for the disease. Toxoplasmosis has also been hypothesized as a possible cause. A.C. Woods and J.R. Duke proposed an inflammatory theory based on the presence of atrophic lesions in the chorioretina of patients with Coats' disease. However, failure of anti-inflammatory and hormone therapy has not supported these theories [3].

In previous studies (P. Genkova, 1986, G.L. Skuta, 1987), genetic defects have not been identified. However, there is currently literature on a potential genetic predisposition for the development of Coats' retinitis. A cytogenetic examination of children with Coats' disease revealed a pericentric inversion of chromosome 3 in one case and a partial deletion of chromosome 13 in another [3]. Furthermore, it has been suggested that the vascular changes associated with Coats' disease may be similar to those caused by mutations in the NDP gene, which is located on the X chromosome and encodes norrin. This may explain why Coats' retinitis predominantly affects men, as estrogen inhibits the expression of NDP in women [2].

Currently, the leading theory for the pathogenesis of Coats' disease is vascular. This condition is thought to be caused by a primary lesion to the retinal vasculature, which disrupts the blood-retina barrier, leading to lipid exudation, retinal ischemia, and VEGF activation [1, 2, 4].

There is no universally accepted classification system for Coats' retinitis. However, the most commonly used classification is that proposed by Shields J.L. et al. (2000), which divides the disease into five stages: stage 1 – retinal telangiectasia, stage 2 – telangiectasia and exudation, stage 3A – subtotal exudative retinal detachment, stage 3B – total retinal detachment, stage 4 – total retinal detachment and glaucoma, stage 5 – terminal stage [5].

Russian ophthalmologists use I.M. Mosin's classification system in their clinical practice:

I. Initial stage

A. Vascular malformations (micro- and macroaneurysms, arteriovenous shunts, telangiectasia), foci of solid exudates in the central and peripheral retina;

B. Vascular malformations and protruding foci of solid exudates in the macula and periphery.

II. Advanced stage

A. Localized protruding deposits of solid exudate at the posterior pole. Limited exudative retinal detachment (less than 2 squares in extent).

B. Extensive, tumor-like solid exudative deposits. Subtotal exudative retinal detachment (2-3 squares in extent). Posterior vitreous detachment.

III. Far-advanced stage

A. Total retinal detachment. Subretinal membranes.

B. Uveitis, cataracts, and rubeosis iridis

IV. Terminal stage

A. Neovascular glaucoma.

B. Subatrophy of the eyeball (phthisis) [6].

According to I.M. Mosin, 96 % of children who do not receive treatment for Coats' disease develop total retinal detachment, uveitis, and complicated cataracts within several years. Additionally, 57–75 % of these patients develop secondary glaucoma [6]. Without timely and appropriate treatment, the prognosis for visual outcomes is unfavorable [7].

Currently, the treatment of Coats' retinitis presents significant challenges due to the absence of a unified therapeutic approach. In the early stages of the disease (stages 1A, B and 2A), the primary treatment method remains laser coagulation of the retina to shut off areas of non-perfusion and obliterate vascular abnormalities in order to reduce or prevent further exudation. However, the use of laser coagulation as the sole treatment, even in the initial stages of the disease, does not always lead to stabilization of the process or improved visual acuity. Consequently, research into new methods or combination therapies for Coats' retinitis treatment continues.

THE AIM OF THE STUDY

To evaluate the efficacy of a combined treatment modality for Coats' disease, integrating anti-angiogenic therapy with retinal laser photocoagulation.

A CLINICAL CASE

Patient P., born in 1989, visited the Irkutsk Branch of S.N. Fyodorov Eye Microsurgery Federal State Institution due to complaints of blurred distance and near vision in the right eye. When working at close range, the patient noted letter loss and visual distortion. These symptoms had been present for the past three weeks. The patient reported that she was in good physical health and had given birth to a healthy child two years prior without complications.

The visual acuity for the right eye when turning is 0.6 cyl (-) 0.5 D ax 87° = 1.0, and the left eye is 1.0.

Upon examination of both eyes, the anterior segments were found to be unremarkable. In the fundus

of the right eye, the optic disc was observed to be pale pink with clear borders and a central deep excavation measuring 0.5 DD. In the macular region, deposits of solid exudate, calcifications, and edema were noted. Along the temporal vascular arcades, particularly the inferior temporal arcade, retinal edema, multiple fusiform retinal arterial macroaneurysms and deposits of solid exudate were present. The venules in the inferior temporal quadrant were tortuous and their course was not always traceable. An atrophic lesion was also noted at the extreme periphery of the retina at 7 o'clock (Fig. 1A). In the fundus of the left eye, the optic disc was similarly pale pink with clear margins and a central, deep excavation measuring 0.5 DD, with preserved reflexes in the macular region. The retinal periphery was considered quiet, and the a:b ratio was 2:3.

The results of the additional examinations

Optical coherence tomography (OCT) OD: foveal profile distortion. A juxtafoveal intraretinal hyperreflective lesion was blocking the underlying retina. In addition, there were macroaneurysms present above the lesion and along the inferotemporal vascular arcade, as well as intraretinal edema and deposits of solid exudates (Fig. 1B and 1C).

Fluorescein angiography (FA) OU – the time taken for the dye to transit was unchanged and the vascular bed was completely filled. OD – choroidal filling appeared to be uneven. The caliber of the arterial vessels was also uneven, with narrowing followed by dilation in the superior and inferior temporal and inferior nasal branches of the central retinal artery, and multiple saccular and fusiform aneurysmal dilatations were present. These were more pronounced in the inferior temporal branch of the central retinal artery system. Perifoveal capillary perfusion in the inferotemporal segment was decreased. Dye extravasation around the aneurysms was moderate, and the dye impregnated the retina and accumulated in intraretinal cysts (Fig. 2A and 2B).

Lipidogram: cholesterol – 6.68 mmol/l, high-density lipoprotein cholesterol (HDL) – 1.38 mmol/l, low-density lipoprotein cholesterol (LDL) – 5.13 mmol/l, triglycerides – 0.93 mmol/l. A lipid profile correction has been prescribed by the therapist due to dyslipidemia – rosuvastatin (Crestor), 5 mg, once daily.

A follow-up examination has revealed a significantly negative trend in the pathological changes. Within 2 weeks, the best-corrected visual acuity of the right eye has decreased to 0.65, due to increased retinal edema in the macular region and along the inferior temporal vascular arcade. Based on these findings, it has been decided to proceed with the initial stage of laser retinal coagulation on the right eye in order to establish an artificial barrier and prevent further progression of the observed changes. Laser coagulation was performed using an ELLEX laser system

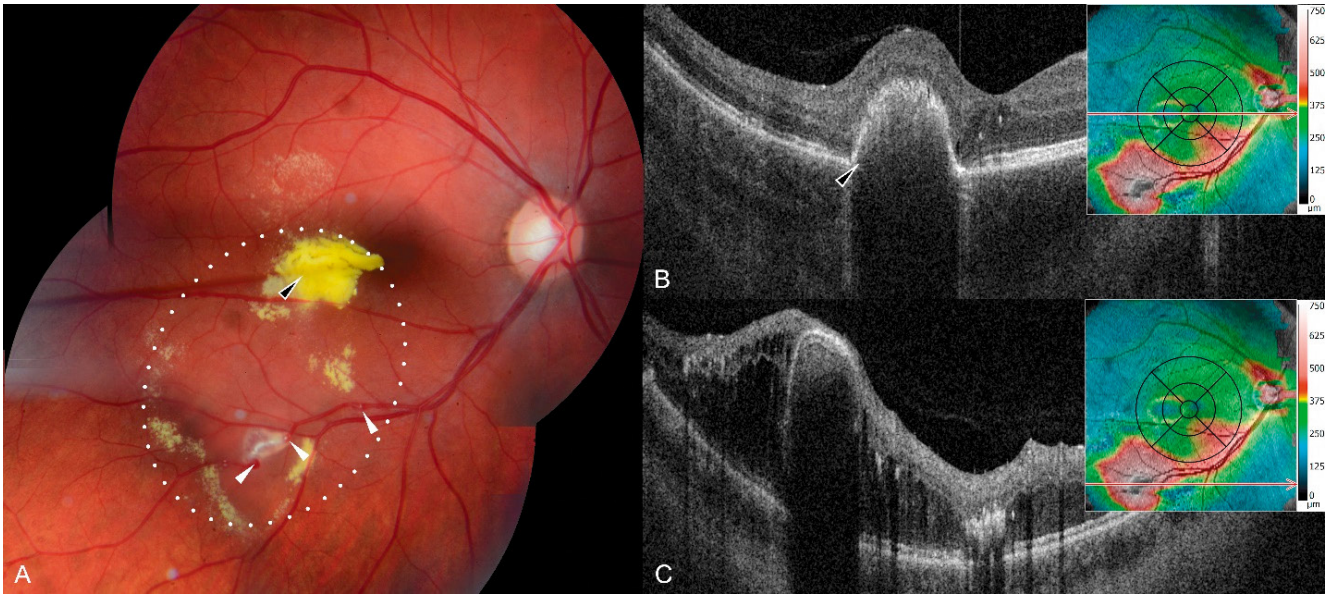

FIG. 1.
A. *Fundus image: white arrows indicate retinal arterial macroaneurysms, black arrow with white outline indicates hard exudate deposits in the macular area, retinal edema is indicated by a dotted elliptical line.* ***B.*** *OCT. Horizontal B-scan through the center with a retinal thickness map. Foveal profile deformation. Juxtafoveal intraretinal hyperreflective lesion blocking the underlying retina is indicated by a black arrow with white outline.* ***C.*** *Horizontal B-scan along the inferotemporal vascular arcade through a retinal arterial macroaneurysm with a retinal thickness map*

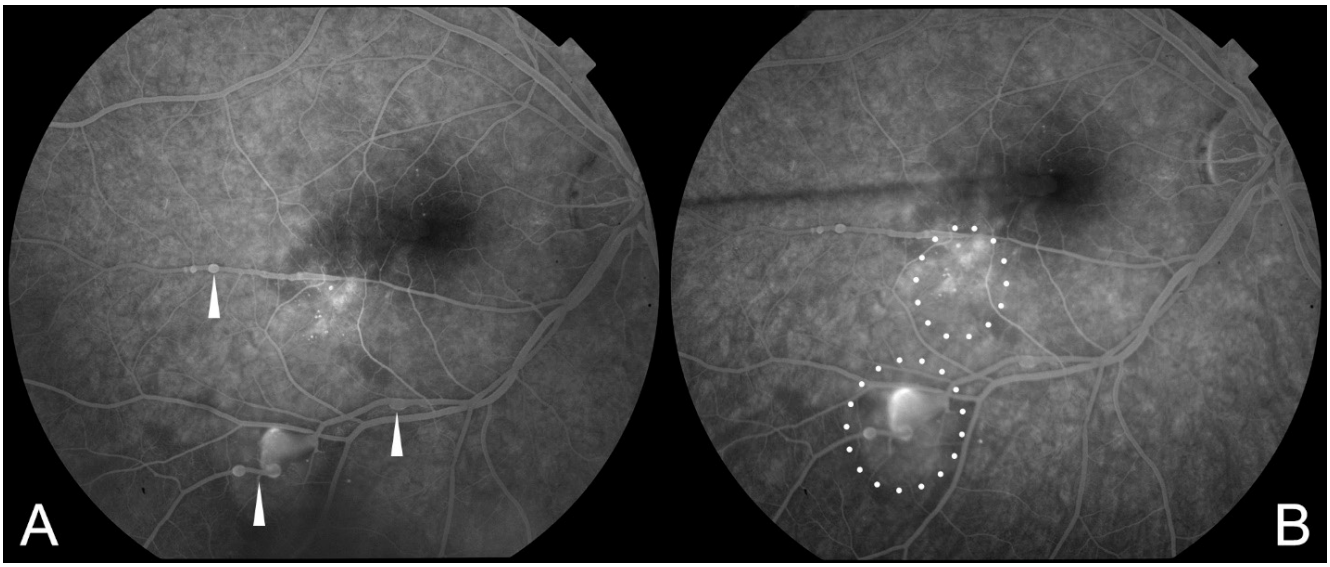

FIG. 2.
A. FAG *– white arrows point to multiple saccular and fusiform aneurysmal dilatations (macroaneurysms), most prominent in the inferior temporal branch of the central retinal artery.* ***B*** *– elliptical dots indicate moderate dye extravasation in the projection of the aneurysms*

with a wavelength of 561 nm. The following coagulation parameters were used: a power between 110 and 150 mW, an exposure time of 0.02 sec, a spot diameter between 100 and 200 μm, and a total of 502 coagulates. During the initial stage, the coagulates were applied along the inferior temporal vascular arcade and within the macular region in a horseshoe-shaped pattern that opened towards the fovea.

At the one-month follow-up visit, the patient reported a continued decline in visual acuity in the right eye, which had decreased to 0.3. Ophthalmoscopic examination revealed an increase in retinal edema in the macular region and along the inferior temporal vascular arcade. In the macular area, pigmented coagulates were observed in a horseshoe-shaped pattern, extending to the foveal area, and along the inferior temporal arcade. Multiple retinal arterial macroaneurysms were identified along the vascular arcades (primarily the inferior temporal arcades), along with the presence of solid exudates and vessels of uneven caliber (Fig. 3).

Given the increasing retinal edema and decreasing visual acuity, it was recommended to use anti-VEGF therapy to improve the resorption of subretinal fluid and solid exudates, followed by laser coagulation of retinal arterial macroaneurysms. The decision to administer intravitreal angiogenesis inhibitors was taken after consultation and approval from the local ethics committee. Written informed consent for the surgical intervention was obtained from the patient. Five monthly intravitreal injections of aflibercept (Eylea) were administered. Anti-VEGF therapy led to complete resorption of subretinal fluid and partial resorption of solid exudates. The visual acuity in the right eye improved to 0.8. Blood tests showed a reduction in total cholesterol levels to 3.4 mmol/l, with no abnormal fractions.

Three months later, the patient experienced a recurrence of increased retinal edema and solid exudate deposits in the inferior temporal arcade and macular region. The visual acuity in the right eye had decreased to 0.3. Blood tests revealed an elevation in total cholesterol levels to 6.8 mmol/l. The patient had discontinued rosuvastatin therapy (Crestor) without consulting her healthcare provider. Her physician recommended rosuvastatin (Roxera) 5 mg daily in order to manage dyslipidemia.

Laser coagulation of macroaneurysms was performed using an ELLEX laser system with a wavelength of 561 nm and coagulation parameters: a power of 130 mW, an exposure time of 0.2 sec, a spot diameter of 200 μm (the spot diameter overlaps the diameter of the macroaneurysm), and a total of 12 coagulates. The coagulates were applied to projections of two macroaneurysms located along the inferotemporal vascular arcade.

After 3 weeks of examination following laser coagulation of the patient's macroaneurysms, she reported an improvement in her vision. The visual acuity in the right eye had increased to 0.95. Upon ophthalmoscopic examination of the fundus in the right eye, a pale pink, centrally deepened optic disc was observed, measuring 0.5 DD, with no retinal edema in the macular region. Dyspigmentation, solid exudates, and pigmentary coagulates were also noted. Along the inferior temporal vascular arcade, retinal arterial macroaneurysms were present, as well as minor

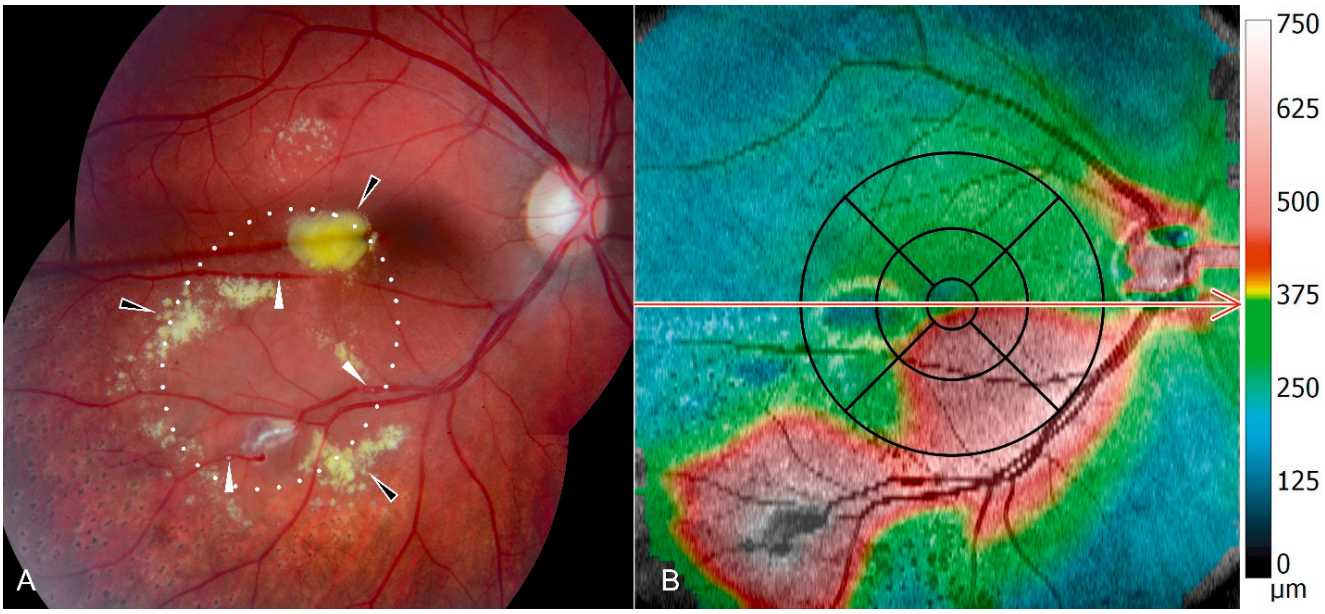

FIG. 3.
A. *– fundus image: white arrows indicate retinal arterial macroaneurysms, black arrows with a white outline indicate hard exudate deposits in the macular area, retinal edema is indicated by a dotted elliptical line.* ***B.*** *OCT – retinal thickness map*

retinal edema and deposits of solid exudates and pigmentary coagulates. At the site of the macroaneurysm coagulation, subretinal hemorrhage was observed during ophthalmoscopy, which may have resulted from a rupture in the macroaneurysm's wall following laser treatment. Additionally, an atrophic focus was noted at the extreme peripheral edge of the retina, at 7 o'clock position (Fig. 4).

Consecutive restrictive (barrier) laser coagulation, five injections of aflibercept, and laser coagulation of macroaneurysms allowed us to stabilize the pathological process and achieve resorption of macular edema and solid exudates (Fig. 5).

According to the fluoroscopic examination, dye extravasation in the aneurysm projections is moderate, approaching a mild level. The dye has penetrated the retina and there is no evidence of accumulation in intraretinal cyst formations. Transient fluorescence can be observed in the projection of the coagulates (Fig. 6).

Given the minor extravasation of the dye, it is recommended to continue dynamic observation. When the patient returned 6 months after fluorescein angiography, the visual acuity in the right left eyes was 1.0. Ophthalmoscopic examination of the fundus in the right eye showed that the optic disc had a pale pink color with a deep central excavation of 0.5 DD. There was no retinal edema in the macular region, dyspigmentation or pigmentary coagulates. Minor retinal edema, solid exudate deposits, retinal arterial macroaneurysms, and pigmentary coagulates persisted along the inferior temporal vascular arcade. An atrophic lesion was observed at the periphery of the retina at 7 o'clock. In the fundus of the left eye, the optic disc appeared to be pale pink with well-defined borders and a deep central excavation measuring 0.5 DD. Reflexes within the macular region were retained. The peripheral retina appeared to be calm. The a:b ratio was 2:3. Further observation is recommended. If there is an increase in exudation from retinal arterial microaneurysms, further treatment options should be considered (Fig. 7).

DISCUSSION

Currently, there is no standardized approach to the management of Coats' retinitis. The choice of therapy is at the discretion of the physician and depends on the severity of the disease. Different treatment modalities are employed at various stages of Coats' retinitis: laser photocoagulation, cryotherapy of the retina and retinal vessels, intravitreal administration of angiogenesis inhibitors, corticosteroids, and in advanced cases, vitreoretinal surgery. For neovascular glaucoma, transscleral cyclophotocoagulation with a diode laser is performed, and in certain cases (painful subatrophy), the eye may be enucleated [3, 7, 8]. Efforts at conservative therapy (corticosteroids, antibiotics) have been unsuccessful. In the initial stages of Coats' retinitis treatment, the aim is to obliterate vascular changes (micro- and macroaneurysms, telangiectasia), shut off areas of non-perfusion, in order

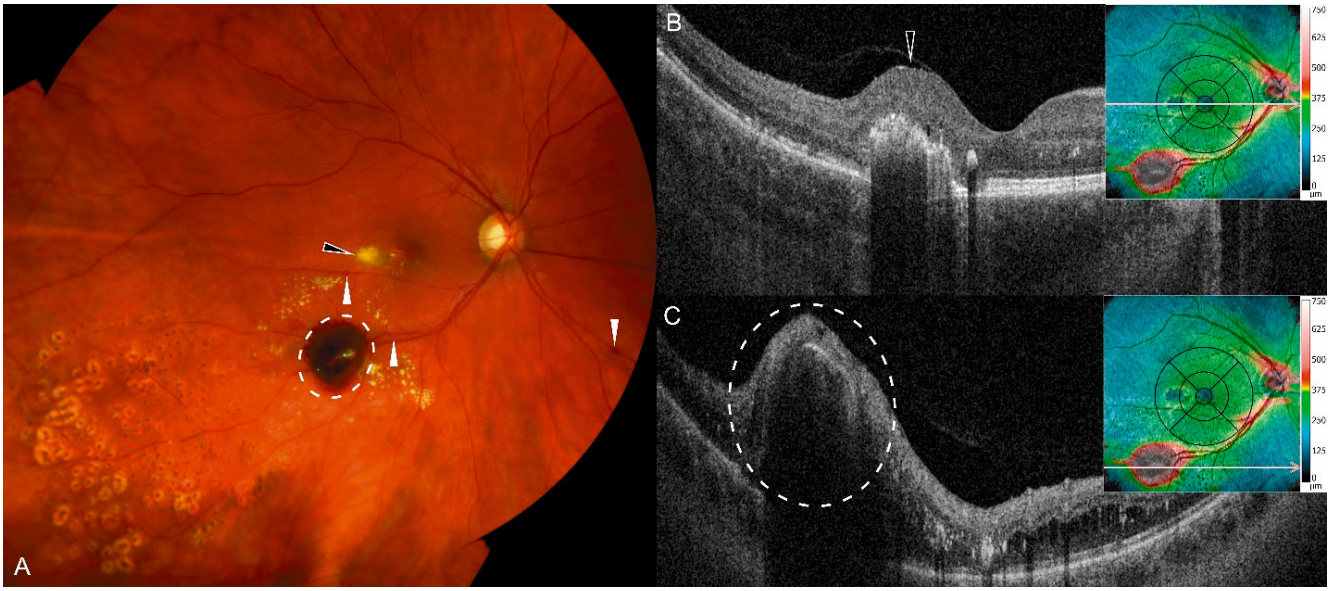

FIG. 4.
A. *– fundus image: white arrows point to retinal arterial macroaneurysms, black arrow with white outline points to hard exudate deposits in the macular area, subretinal hemorrhage is indicated by the dotted line in the form of an ellipse.* ***B.*** *OCT. Horizontal B-scan through the center with a retinal thickness map. Deformation of the fovealar profile. Juxtafoveolar intraretinal hyperreflective lesion (hard exudates) blocking the underlying retina is indicated by a black arrow with a white outline.* ***C.*** *OCT. Horizontal B-scan along the inferotemporal vascular arcade through the retinal arterial macroaneurysm with a retinal thickness map. The hyperreflective protruding lesion (blood) blocking the underlying tissues is indicated by the dotted line in the form of an ellipse*

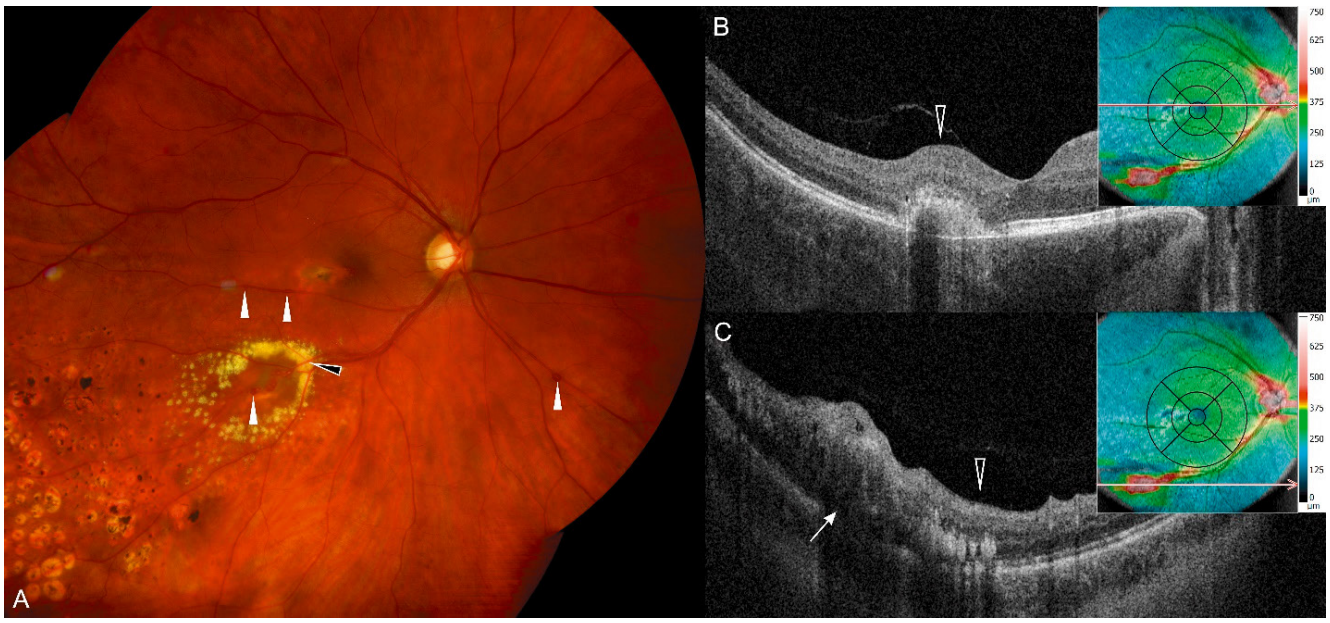

FIG. 5.
A. *– fundus image: white arrows point to retinal arterial macroaneurysms, black arrow with white outline points to hard exudate deposits along the inferotemporal arcade.* ***B.*** *OCT. Horizontal B-scan through the center with retinal thickness map. Deformation of the fovealar profile. Juxtafovealar intraretinal hyperreflective lesion blocking the underlying retina is indicated by a black arrow with white outline.* ***C.*** *OCT. Horizontal B-scan along the inferotemporal vascular arcade through the retinal arterial macroaneurysm with retinal thickness map. The white arrow points to destruction of the outer retinal layers*

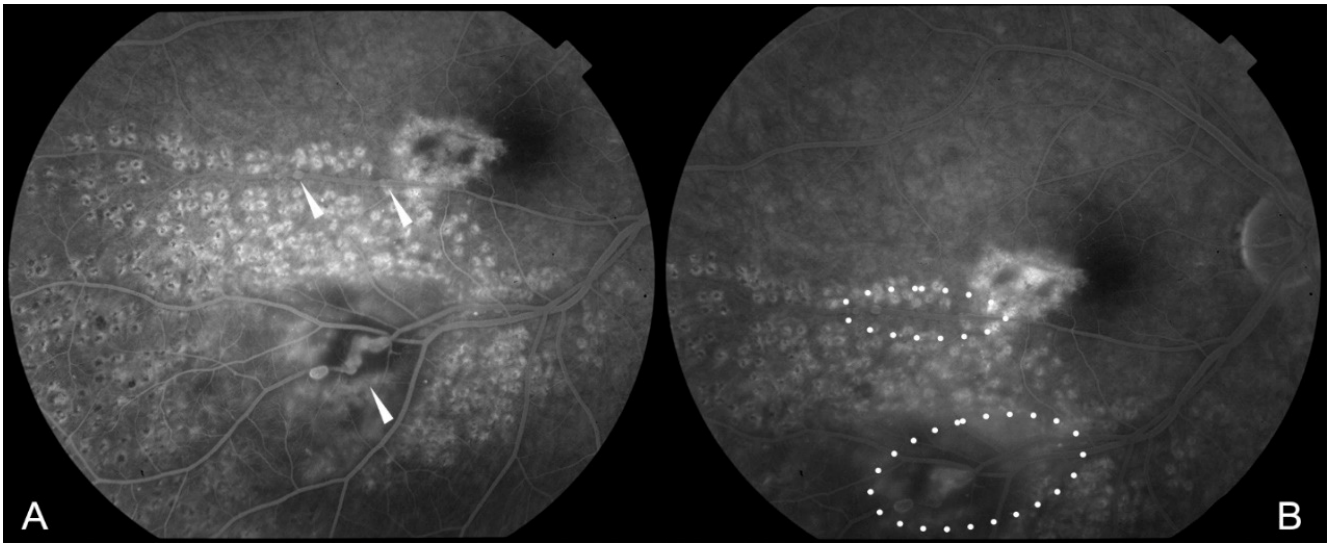

FIG. 6.
A – *FAG: white arrows point to multiple saccular and fusiform aneurysmal dilatations (macroaneurysms) in the inferior temporal branch of the central retinal artery.* ***B.*** *The dotted elliptical line indicates moderate dye extravasation in the projection of the macroaneurysms*

to prevent the development and progression of exudative retinal detachment, as well as secondary neovascular glaucoma and eyeball subatrophy [2, 3, 5].

Today, there are several treatment options available for this disease, but laser coagulation of the retina (zones of nonperfusion) and treatment for vascular changes remains the preferred method. G. Meyer-Schwickerath and K.J. Pesch were the first to propose the use of laser coagulation as a treatment for this pathology in 1960 [3, 4, 9, 10]. The number of laser coagulation stages depends on the severity of the disease and ranges from two to six on average. Recently, there has been a shift in approaches to laser coagulation for Coats' retinitis. Yellow-wavelength lasers (577 nm) are considered to be the most effective as they exhibit maximum absorption by blood hemoglobin and oxyhemoglobin, facilitating direct laser coagulation of vascular malformations [11]. Additionally, due to their low absorption by macular xanthophylls and their central location, yellow-wavelength laser use is preferred, reducing the risk of retinal damage to the central part of the fundus. However, the use of monotherapy with laser coagulation at various wavelengths for Coats' retinitis is restricted to the early stages of the disease (1A, 1B, and 2A, according to the classification system used by I.M. Mosin) and, in most cases, its peripheral location [2, 3, 7, 8]. When there is significant retinal exudation and exudative retinal detachment in the central part, the efficacy of this method is greatly reduced.

In case of central localization of vascular malformations, it is not always feasible to perform laser coagulation to the full extent, as complications after treatment

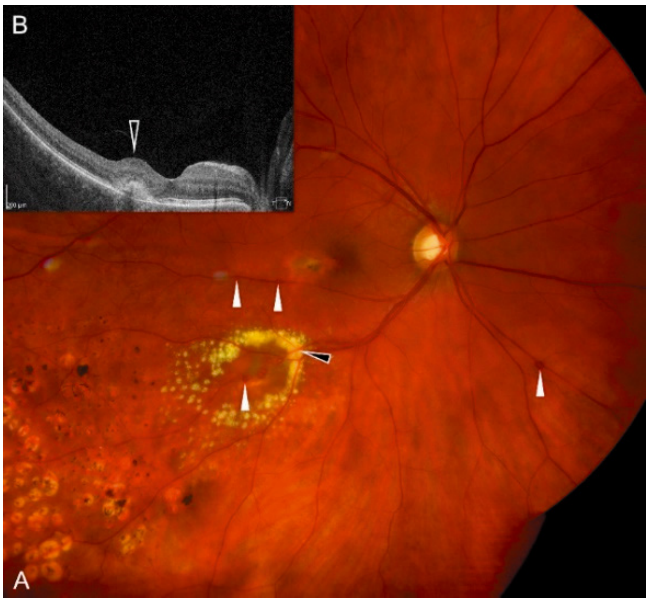

FIG. 7.
A. *– fundus image: white arrows point to retinal arterial macroaneurysms, black arrow with white outline points to hard exudate deposits along the inferotemporal arcade.* ***B.*** *OCT. Horizontal B-scan. Fovealar profile deformation. Juxtafovealar intraretinal lesion of medium reflectivity blocking the underlying retina is indicated by a black arrow with white outline*

may lead to a significant reduction or even loss of visual acuity. Therefore, the efforts to find alternative treatment modalities in order to preserve the patient's visual function as much as possible continue. To date,

vascular theory is considered the predominant theory of Coats' disease pathogenesis. Thickening and hyalinization of blood vessels, as well as loss of endothelial cells from the vascular walls due to the action of "certain" factors, lead to impairment of the blood-retinal barrier and the development of vascular malformations (telangiectasia, micro- and macroaneurysms). These vascular disorders contribute to lipid exudation, retinal ischemia and activation of VEGF [1, 8, 9, 12]. Previous research has demonstrated that intravitreal administration of anti-VEGF drugs is effective for the treatment of retinal arterial macroaneurysms and macular edema of various origins [13].

According to foreign researchers, elevated levels of VEGF have been found in the anterior chamber fluid and vitreous body of patients with Coats' retinitis [10, 12]. Elevated VEGF levels have been associated with retinal ischemia, although the exact role of VEGF in the pathogenesis of Coats' retinitis is still unclear. Considering this data, there has been discussion about the potential use of anti-VEGF medications as a supplementary treatment option (neoadjuvant or adjuvant) in combination with laser therapy [14-17].

On the one hand, analysis of data from foreign and domestic literature has shown the efficacy of anti-VEGF drugs in treating patients with Coats' retinitis [14-18]. However, there is also conflicting data. A group of researchers conducted a retrospective study of cases based on treatment outcomes for Coats' disease (initial stages 1-3A according to Shields' classification), assessing the efficacy by visual acuity and fundus changes. The study analyzed treatment with anti-VEGF monotherapy in 69 eyes and standard laser coagulation treatment in 96 eyes. The results were conflicting. While the use of anti-VEGF as monotherapy (1–5 injections) resulted in subretinal fluid resorption and solid exudate reduction in 33.3 % of cases, active vascular lesions required laser treatment. According to the authors, the use of laser coagulation as monotherapy resulted in an improvement or stabilization of Coats' retinitis in 39 % of early-stage cases, although this was not always accompanied by an increase in visual acuity [19]. Therefore, anti-VEGF therapy can improve the prognosis of the disease, even in the most severe cases of Coats' retinitis. However, it does not lead to a long-term remission or cure for the patient [18, 19]. Laser coagulation of the retina remains the primary treatment method for early-stage Coats' retinitis [2, 16, 19].

Our clinical case demonstrates the benefits of a combined, staged approach to the treatment of Coats' retinitis. A significant increase in exudative activity in the macular region and along the inferior temporal arcade following retinal laser photocoagulation (restricting, macular band) would have prevented the need for further laser treatment without significant complications. Therefore, the use of anti-VEGF drugs as adjuvant therapy is optimal to create favorable conditions for subsequent laser photocoagulation stages. The combined, staged treatment of Coats' retinitis in this patient has stabilized the pathological process and preserved high visual acuity. Therefore, combined treatment with retinal laser photocoagulation and anti-VEGF therapy for Coats' retinitis has shown promising results. Anti-VEGF drugs may be used as adjuvant therapy depending on individual patient presentation. It should also be noted that the course of Coats' retinitis in adult patients is often associated with hypercholesterolemia. Therefore, it is necessary to perform a lipidogram and prescribe appropriate treatment for the identified disorders, which helps to reduce cholesterol excretion [3, 10].

CONCLUSION

Coats' retinitis is a condition that requires constant monitoring and, if necessary, appropriate treatment. The treatment depends on the stage of the disease and is at the discretion of an ophthalmologist. Currently, there is no standardized treatment protocol, and laser photocoagulation is the primary treatment option for Coats' disease. Laser photocoagulation, as a monotherapy, is only feasible for peripheral lesions in the initial stages of Coats' retinitis. Therefore, anti-VEGF drugs can be used as adjuvant therapy for retinal laser photocoagulation.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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PTERYGOPALATINE BLOCK EFFECTIVENESS IN POSTOPERATIVE PERIOD AFTER DONOR CORNEA TRANSPLANTATION

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RESUME

Keratoplasty is a surgical procedure for corneal transplantation, in which a donor graft replaces the patient's damaged cornea. Despite its high efficacy, the procedure carries a risk of postoperative complications (high level of intraocular pressure (IOP) and inflammatory reaction), which contribute to the development of pain syndrome and increase the risk of graft rejection due to the disruption of immune privilege.

The aim. *To evaluate the efficacy of analgesia and the anti-inflammatory effect of pterygopalatine block (PPB) in the early postoperative period in patients after penetrating keratoplasty.*

Material and methods. *The study included 56 patients divided into two groups: Group 1 (n = 28) received PPB with 0.5 % levobupivacaine (4 ml) for 3 days, Group 2 (n = 28) received standard analgesia with NSAIDs (ketoprofen) and intraocular pressure-lowering medications (acetazolamide, timolol). Subjective pain sensations (NRS – numeric rating scale), the presence of discomfort and foreign body sensation in the eye, ocular hypertension, and the level of cytokines (IL-6, IL-8, IL-10) in the patients' tear fluid were assessed on days 1, 3, and 5 after surgery.*

Results. *In Group 1, the mean pain level on the NRS was 1.2 ± 0.6 points (7.14 % of patients), while in Group 2 it was 2.9 ± 1.2 points (21.4 %) ($p \leq 0.05$). On day 1 after surgery, in Group 1, the levels of IL-6 and IL-8 increased by 4.3 and 1.5 times, respectively ($p = 0.002$; $p = 0.001$), whereas in Group 2 they increased by 4.9 and 2.1 times ($p = 0.001$, $p = 0.002$). The concentration of IL-10 in Group 1 increased to 2.61 ± 2.3 ng/ml on day 1 and to 3.08 ± 2.6 ng/ml on day 3 ($p = 0.0011$; $p = 0.0015$), while no significant changes were observed in Group 2. The IL-6/IL-10 and IL-8/IL-10 ratios were significantly lower in Group 1 on day 3 (112.18 ± 78.55) compared to Group 2 (313.96 ± 109.87) ($p = 0.0000$). The correlation between IL-8 and IOP on day 3 was $r = 0.8$ ($p = 0.0000$) in Group 2 and $r = 0.6$ ($p = 0.0049$) in Group 1.*

Conclusion. *After donor cornea transplantation, pterygopalatine block modulates the cytokine profile with a pronounced anti-inflammatory effect, making it an effective component of comprehensive postoperative treatment. It contributes to reduced pain and improved IOP control in patients.*

Keywords: *pterygopalatine block, keratoplasty, interleukins, levobupivacaine*

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ЭФФЕКТИВНОСТЬ КРЫЛОНЁБНОЙ БЛОКАДЫ В ПОСЛЕОПЕРАЦИОННОМ ЛЕЧЕНИИ ПАЦИЕНТОВ ПОСЛЕ ТРАНСПЛАНТАЦИИ ДОНОРСКОЙ РОГОВИЦЫ

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РЕЗЮМЕ

Кератопластика является хирургической операцией по пересадке роговицы, при которой донорский трансплантат заменяет поврежденную роговицу пациента. Несмотря на высокую эффективность, процедура связана с риском послеоперационных осложнений, (высокое внутриглазное давление (ВГД) и воспалительная реакция), способствующих развитию болевого синдрома и повышению риска отторжения трансплантата из-за нарушения иммунных привилегий.

Цель. *Оценить эффективность обезболивания и противовоспалительного действия крылонёбной блокады (КНБ) в раннем послеоперационном периоде у пациентов, перенесших сквозную кератопластику.*

Материал и методы. *В исследование включены 56 пациентов, разделённых на две группы: 1-я группа (n = 28) получала КНБ левобупивакаином 0,5 % (4 мл) в течение 3 дней, 2-я группа (n = 28) – стандартное обезболивание НПВС (кетопрофен) и препараты для снижения внутриглазного давления (ацетазоламид, тимолол). Оценивали субъективные болевые ощущения (цифровая рейтинговая шкала – ЦРШ), наличие дискомфорта и ощущения инородного тела в глазу, уровень ВГД и уровень цитокинов (ИЛ-6, ИЛ-8, ИЛ-10) в слезной жидкости пациентов на 1, 3 и 5 сутки после операции.*

Результаты. *В 1-й группе средняя степень боли по ЦРШ – 1,2 ± 0,6 балла (7,14 % пациентов), во 2-й группе – 2,9 ± 1,2 балла (21,4 %) ($p \leq 0,05$). В 1 сутки после операции в 1-й группе уровни ИЛ-6 и ИЛ-8 выросли в 4,3 и 1,5 раза соответственно ($p = 0,002$; $p = 0,001$), во 2-й группе в 4,9 и 2,1 раза ($p = 0,001$ и $p = 0,002$). Концентрация ИЛ-10 в 1-й группе возросла до 2,61 ± 2,3 нг/мл на 1 сутки и 3,08 ± 2,6 нг/мл на 3 сутки ($p = 0,0011$; $p = 0,0015$), в 2-й группе изменений отмечено не было. Соотношение ИЛ-6/ИЛ-10 и ИЛ-8/ИЛ-10 было значительно ниже в 1-й группе на 3 сутки – 112,18 ± 78,55, по сравнению с результатами во 2-ой группе – 313,96 ± 109,87 ($p = 0,0000$). Корреляция между ИЛ-8 и ВГД на 3 сутки: $r = 0,8$ ($p = 0,0000$) во 2-й группе и $r = 0,6$ ($p = 0,0049$) в 1-й группе.*

Заключение. *После операции по поводу трансплантации донорской роговицы, крылонёбная блокада модулирует цитокиновый профиль с выраженным противовоспалительным эффектом, благодаря чему является эффективным компонентом комплексного послеоперационного лечения пациентов, способствующим уменьшению болевого синдрома и контролю ВГД.*

Ключевые слова: *крылонебная блокада, кератопластика, интерлейкины, левобупивакаин*

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The pterygopalatine ganglion is an important neuroanatomical structure that plays a role in both the autonomic and sensory regulation of facial functions. It contains parasympathetic, nociceptive, and sympathetic fibers. Due to its complex structure, the pterygopalatine ganglion has the ability to affect various neural pathways through the use of a pterygopalatine block (PPB) [1]. Because of its accessibility and flexibility in approach, PPB has been widely used in interventional treatments for headaches and facial pain [2]. Regional anesthesia, including PPB, has a powerful anti-inflammatory effect, partly due to the blocking of sympathetic nerves, which reduces the production of pro-inflammatory mediators [3].

Local anesthetics also contribute to the anti-inflammatory effect by inhibiting the migration and activation of neutrophils, thereby reducing the inflammatory response [4]. Clinical data confirm that regional anesthesia reduces the intensity and duration of postoperative inflammation, decreases the need for opioid analgesics, and improves the recovery period [5]. Postoperative inflammation is accompanied by a complex regulation of pro- and anti-inflammatory mediators, including the key cytokines such as IL-6, IL-8, and IL-10. The levels of IL-6 change depending on the phase and nature of the immune response, reflecting the dynamics of the inflammatory process. IL-8 plays an important role in the initial stage of neutrophil activation and migration, which is responsible for early inflammation. However, its excess is associated with an increased risk of complications [6]. Increased levels of the anti-inflammatory cytokine IL-10 have an immunomodulatory effect, which helps to reduce inflammation and enhance graft survival by promoting the development of tolerogenic cells and inhibiting T-cell activation [7]. This mechanism is particularly significant in corneal transplantation, as the balance between pro-inflammatory and anti-inflammatory mediators significantly influences the surgical outcome [8]. An imbalance in inflammatory processes can result in adverse consequences such as immune-mediated graft rejection and delayed tissue regeneration.

Therefore, the regulation of postoperative inflammation through the use of regional anesthesia and the targeted control of cytokine levels is a promising approach for improving surgical outcomes and patient rehabilitation, as supported by the findings of recent research.

THE AIM OF THE STUDY

To evaluate the efficacy of analgesia and the anti-inflammatory effect of pterygopalatine block (PPB) in the early postoperative period in patients after penetrating keratoplasty.

MATERIALS AND METHODS

A longitudinal, randomized, blinded study was conducted in accordance with the approval of the local ethics committee of the Irkutsk Branch of S.N. Fyodorov Eye Microsurgery Federal State Institution (protocol No. 2, dated January 15, 2024).

The study involved 56 patients who underwent penetrating keratoplasty with donor cornea transplantation. Patients were randomized into two groups:

Group 1 ($n = 28$): postoperative pain relief and IOP control were achieved using a pterygopalatine block with 0.5 % levobupivacaine administered at a dose of 4.0 ml for a period of three days;

Group 2 ($n = 28$): pain relief was achieved using nonsteroidal anti-inflammatory medications (ketoprofen 2.0 mg intramuscularly for pain), and ocular hypertension was managed with acetazolamide 0.5 g once daily and timolol 0.5 % twice daily, according to the standard protocol.

Inclusion criteria: indications for corneal transplantation (penetrating keratoplasty) in cases of corneal opacity following trauma, infections, or severe keratoconus.

Exclusion criteria: history of allergy to local anesthetics, patient unwillingness to participate in the study.

Patients' subjective sensations were evaluated: the degree of pain was assessed using a 10-point numeric rating scale (NRS), with 0 indicating "no pain" and 10 representing the "greatest possible, unbearable, intolerable pain". Discomfort and the sensation of a foreign body in the eye were also recorded. Intraocular pressure (IOP) was measured using the Maklakov method. Cytokine concentrations (IL-6, IL-8, and IL-10) in lacrimal fluid were measured on days 1, 3, and 5 after surgery using an Immunochem-2100 multifunctional microplate photometer with an 8-channel optical reading system. The samples were analyzed using the ELISA method, employing the IL-6-ELISA, IL-8-ELISA, and IL-10-ELISA kits from Vector Best. The measurements were performed in 96-well microplates.

The study was conducted at the Irkutsk Branch of S.N. Fyodorov Eye Microsurgery Federal State Institution from January 16, 2024 to December 20, 2024.

Statistical analysis was conducted using the Statistica 6.0 software. The distribution of the data obtained was tested using the Shapiro – Wilk test. Due to the normal distribution, the data were presented as mean (M) and standard deviation (SD). As a measure of the representativeness of the mean values, the boundaries of the 95% confidence interval (95% CI) were indicated. Student's *t*-test was used to compare the mean values of two groups. For the comparison of three or more groups on a quantitative indicator, whose distribution in each group was normal, one-way analysis of variance was used. Pearson's correlation analysis was used to examine relationships. The critical significance level (p) for the testing of statistical hypotheses was set at 0.05.

RESULTS

The analysis of subjective symptoms is presented in Figure 1. It has been found that in Group 1, with moderate severity, the pain syndrome on the NRC was 1.2 ± 0.6 points in 7.14 % of patients ($n = 2$), while, in Group 2, it was significantly higher – 2.9 ± 1.2 points ($p \leq 0.05$) in 21.4 %

of patients (n = 6). Complaints of discomfort and the sensation of a foreign body in the eye were noted in equal proportions in 6 patients (21.4 %) in Group 1 and in 2 (7.1 %) and 14 (50 %) patients in Group 2, respectively.

The incidence of ocular hypertension on days 2 and 3 after surgery in Group 2 was approximately twice that of Group 1, amounting to 21.4 %, compared to 10.7 % ($p \leq 0.05$) in Group 1. This indicates better IOP control when using PPB.

A comparative analysis of cytokine levels in lacrimal fluid is presented in Figure 2. Following surgery, patients in Group 1 demonstrated an increase in IL-6 and IL-8 levels on the first day (by 4.3- and 1.5-fold, respectively), which were statistically significant (p = 0.002 and p = 0.001, respectively) compared to baseline values. These levels then decreased by the third day (p = 0.003 and p = 0.001 for IL-6 and IL-8, respectively). Patients in Group 2 also demonstrated an initial increase in IL-6 (4.9-fold) and IL-8 (2.1-fold) on the first day, which was also statistically significant (both p = 0.001), but IL-6 levels remained elevated on the third day. Additionally, IL-8 concentrations continued to increase (p = 0.000) at this time.

The concentration of the anti-inflammatory cytokine IL-10 increased significantly in Group 1 on days 1 and 3 after surgery, to 2.61 ± 2.3 ng/ml and 3.08 ± 2.6 ng/ml, respectively (p = 0.0011; p = 0.0015). In contrast, no significant changes in IL-10 levels were observed in Group 2, with a mean value of 2.44 ± 1.7 ng/ml (p = 0.0002). A statistically significant intergroup difference in IL-10 levels was observed on day 3 (p = 0.0002).

An assessment of the IL-6/IL-10 and IL-8/IL-10 antagonist cytokine ratios, as a criterion for the pathophysiological mechanisms of postoperative inflammation and healing, revealed the following concentrations in patients of Group 1 who received pterygopalatine block in their

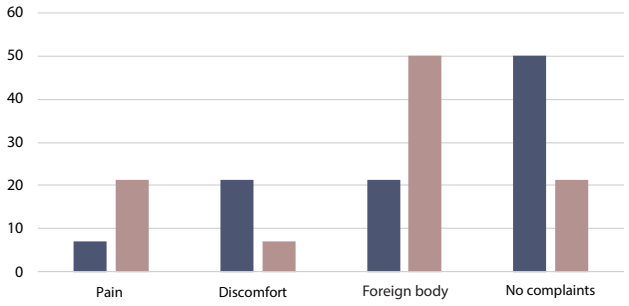


FIG. 1.
Characteristics of subjective sensations in the early postoperative period in groups (%)

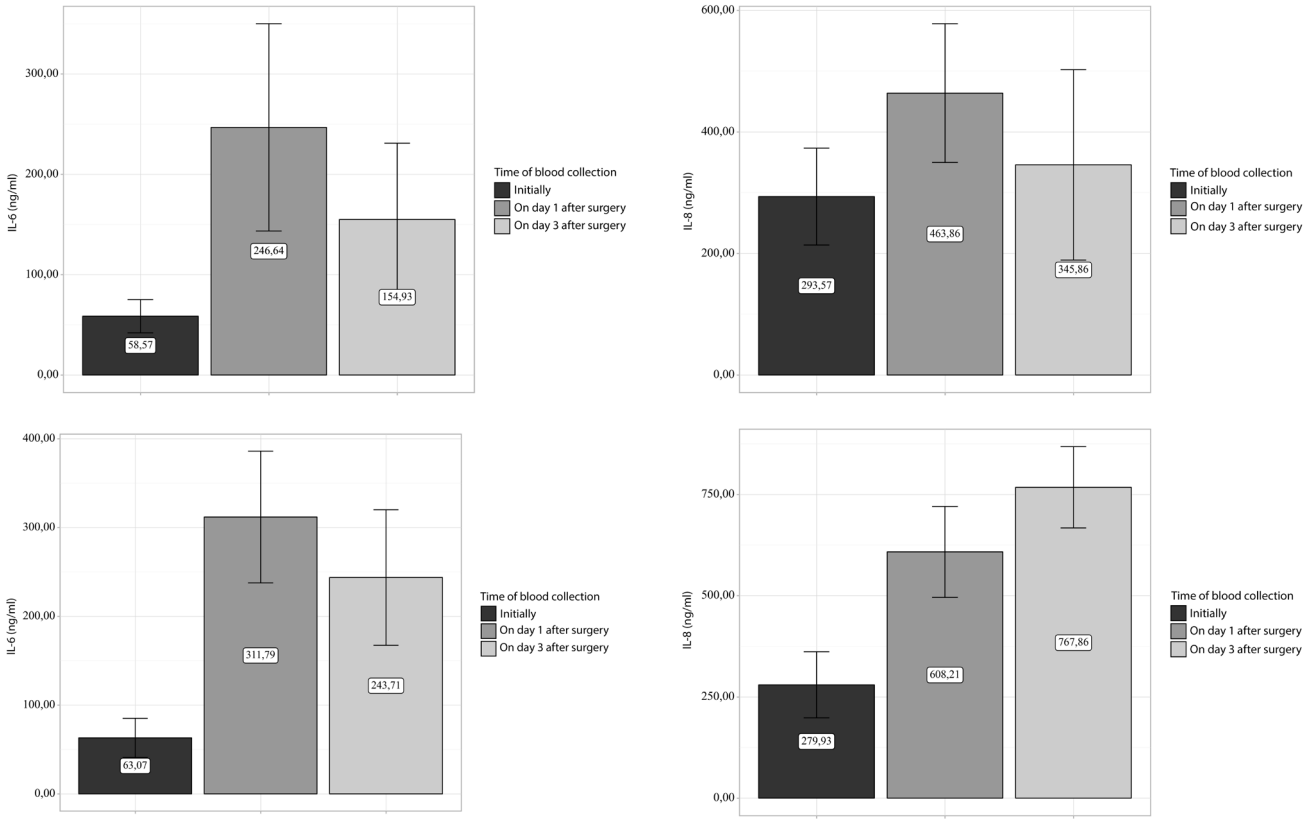


FIG. 2.
Dynamics of changes in IL-6 and IL-8 at the stages of the study in groups (1 – dynamics of changes in IL-6 in patients of the 1st group; 2 – dynamics of changes in IL-8 in patients of the 1st group; 3 – dynamics of changes in IL-6 in patients of the 2nd group; 4 – dynamics of changes in IL-8 in patients of the 2nd group)

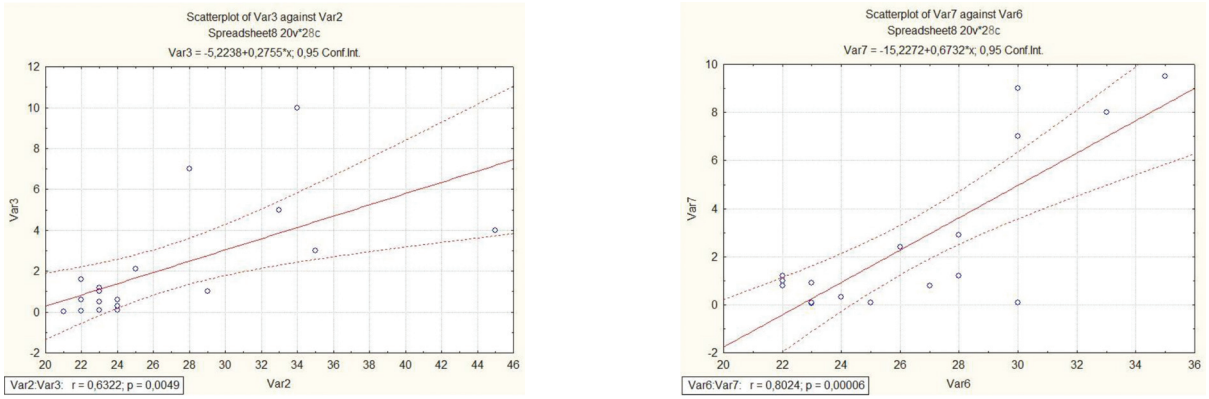
postoperative treatment regimen. On day 3 after surgery, the IL-6/IL-10 and IL-8/IL-10 ratios were significantly lower in Group 1 compared to the values obtained in patients of Group 2 (Table 1). These findings suggest a reduced inflammatory activity in patients of Group 1.

Correlation analysis demonstrated a direct positive association between the levels of IL-8 and IOP on day 3, with r = 0.8 (p = 0.0000) in Group 2 and r = 0.6 (p = 0.0049) in Group 1 (Fig. 3).

DISCUSSION

The pterygopalatine ganglion is an important target for blockade as it is an extracranial structure that is accessible through minimally invasive techniques. The ganglion contains parasympathetic nerve fibers that synapse directly within the ganglion, as well as sensory and sympathetic fibers, which synapse within the ganglion, as well as sensory and sympathetic fibers, which pass through the ganglion without synapsing. This unique structure makes the pterygopalatine ganglion important in the modulation of autonomic and sensory innervation in the facial and ocular regions [9].

Our study demonstrated that the use of PPB in postoperative analgesia after penetrating donor cornea transplantation not only provides effective analgesia, but also has a significant anti-inflammatory effect. PPB reduces the levels of pro-inflammatory cytokines, such as IL-6 and IL-8, in lacrimal fluid while maintaining and increasing the levels of anti-inflammatory cytokine IL-10. This helps to improve the balance between pro- and anti-inflammatory cytokines. These findings are consistent with the previous research and clinical studies that have demonstrated the key roles of IL-6 and IL-8 in the early inflammatory response after surgery, as well as the immunoregulatory function of IL-10 in promoting graft survival [10, 11]. An increase in IL-10 has been shown to contribute to the suppression of pro-inflammatory cytokines and the improvement of postoperative immune balance [12]. In the group without PPB, a significant increase in cytokine imbalance was observed, with a predominance of pro-inflammatory IL-6 and IL-8, which are involved in inflammatory processes and may accompany alloantigen activation, increasing the risk of inflammatory complications. The IL-6/IL-10 ratio has been identified as an important prognostic marker in other medical fields, such as sepsis and cardiac surgery, where a decrease in this ratio is associated with better clinical outcomes [13]. The positive clinical effects of PPB in our study are likely due to the pathogenetic relationship between the levels of interleukins IL-6 and IL-8 and an increase in IOP and the degree of inflammatory response



Group 1 ***Group 2***

FIG. 3.
Correlation between IL-8 and post-op IOP level

TABLE 1

THE RATIO OF IL-6/IL-10 AND IL-8/IL-10 CONCENTRATIONS ON THE 3RD DAY AFTER PENETRATING KERATOPLASTY IN GROUPS

	IL-6/IL-10		IL-8/IL-10		*p*
	Initially	On day 3	Initially	On day 3	
Group 1	29.40 ± 11.44	50.25 ± 18.67	148.28 ± 107.11	112.18 ± 78.55	0.0000
Group 2	31.40 ± 13.67	99.64 ± 32.22	139.36 ± 111.44	313.96 ± 109.87	0.0000

Note. *p* – intergroup difference as determined by the Student's *t*-test.

to surgery. Our findings suggest that a reduction in the activity of the inflammatory response with the use of PPB in the postoperative period occurs through the suppression of its pathogenetic mechanisms due to drug-induced denervation.

Therefore, the results of our study support the potential use of PPB as a viable approach to modulating the postoperative inflammatory response in order to reduce the risk of potential complications, thereby enhancing patient quality of life and increasing the likelihood of successful graft survival.

CONCLUSION

After donor cornea transplantation, pterygopalatine block modulates the cytokine profile with a pronounced anti-inflammatory effect, making it an effective component of comprehensive postoperative treatment. It contributes to reduced pain and improved IOP control in patients.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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CORNEAL ULCER AS THE FIRST MANIFESTATION OF HIV INFECTION: A CLINICAL CASE

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RESUME

Background. *Corneal ulcers are among the severe diseases that are difficult to treat. Most cases of corneal ulcers are caused by infectious etiology in the presence of predisposing risk factors, such as wearing contact lenses, eye injuries, chronic diseases of the accessory apparatus of the eye, dry eye syndrome. Of particular importance at present is the increase in cases of corneal ulcers among HIV-infected patients. HIV leads to thinning of the cornea and the formation of an ulcerative defect, and systemic immunodeficiency contributes to the rapid addition of a secondary infection.*
The aim. *Description of a clinical case of a corneal ulcer with perforation as the first sign of HIV infection.*
Materials and methods. *To assess the clinical case, we used a retrospective analysis of the patient's medical history and the results of laboratory research methods.*
Results. *This clinical example demonstrates the possibility of the occurrence of a corneal ulcer with perforation against the background of immunodeficiency caused by HIV-positive status. The patient came with a corneal ulcer complicated by perforation and fibrinous-plastic iridocyclitis. The localization of the ulcer at the limbus, the absence of loose infiltration of the edges, and high visual functions determined the gentlest surgical tactics in the form of suturing the ulcer defect by applying corneo-limbal sutures without separating the conjunctiva.*
Conclusion. *Timely drug therapy and surgical treatment led to the closure of the ulcer defect and restoration of visual functions. The postoperative course was smooth and had no peculiarities, despite the HIV-positive status of the patient and the lack of therapy for the underlying disease, since a corneal ulcer with perforation was the first manifest sign that forced the patient to seek medical help.*

Keywords: *corneal ulcer, corneal perforation, corneal ulcer etiology, HIV infection, drug treatment, corneal surgery*

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ЯЗВА РОГОВИЦЫ КАК ПЕРВОЕ ПРОЯВЛЕНИЕ ВИЧ-ИНФЕКЦИИ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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РЕЗЮМЕ

Обоснование. *Язвы роговицы относятся к числу тяжелых заболеваний, которые с трудом поддаются лечению. Большинство случаев данной патологии имеют инфекционную этиологию при наличии предрасполагающих факторов риска, таких как ношение контактных линз, травмы глаза, хронические заболевания вспомогательного аппарата глаза, синдром сухого глаза. Особое значение в настоящее время имеет увеличение случаев язвы роговицы среди ВИЧ-инфицированных пациентов. ВИЧ приводит к истончению роговицы и образованию язвенного дефекта, а системный иммунодефицит способствует быстрому присоединению вторичной инфекции.*

Цель. *Описание клинического случая язвы роговицы с перфорацией как первого признака манифестации ВИЧ-инфекции.*

Материалы и методы. *Для оценки клинического случая использовался ретроспективный анализ истории болезни пациентки, результатов лабораторных методов исследования.*

Результаты. *В работе представлен клинический пример, демонстрирующий возможность возникновения язвы роговицы с перфорацией на фоне иммунодефицита, обусловленного ВИЧ-положительным статусом. Пациентка обратилась с язвой роговицы, осложненной перфорацией и фибринозно-пластическим иридоциклитом. Локализация язвы у лимба, отсутствие рыхлой инфильтрации краев, высокие зрительные функции определили максимально щадящую хирургическую тактику в виде ушивания язвенного дефекта путем наложения корнео-лимбальных швов без отсепаровки и покрытия конъюнктивой.*

Заключение. *Своевременная медикаментозная терапия и хирургическое лечение привели к закрытию язвенного дефекта и восстановлению зрительных функций. Послеоперационное течение было гладким и не имело особенностей, несмотря на ВИЧ-позитивный статус пациентки и отсутствие терапии основного заболевания, так как язва роговицы с перфорацией была первым манифестным признаком, заставившим пациентку обратиться за медицинской помощью.*

Ключевые слова: *язва роговицы, перфорация роговицы, этиология язвы роговицы, ВИЧ-инфекция, медикаментозное лечение, хирургия роговицы*

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BACKGROUND

A corneal ulcer is a serious eye condition characterized by damage to the corneal epithelium and stroma. Without adequate treatment, if left untreated, it may lead to vision loss due to purulent complications, such as corneal perforation, or the formation of dense opacity as a result of an inflammatory and destructive process. The factors that contribute to the development of this pathology are diverse. Keratitis often precedes the formation of a corneal ulcer, which may be caused by ocular trauma, inappropriate contact lens use, inflammation of accessory ocular structures, dry eye syndrome, or inability to close the palpebral fissure. These factors facilitate bacterial invasion through a primary superficial epithelial breach into the corneal stroma. The rising incidence of corneal ulcers among HIV-infected patients is of particular concern. Currently, human immunodeficiency virus (HIV) continues to be a significant global public health concern. According to data from the Moscow Regional AIDS Center, the Russian Federation is experiencing a substantial annual increase in the number of individuals infected with HIV. In 2021, there were 851,700 laboratory-confirmed cases of HIV infection in the Russian Federation, and this number has since exceeded 1.5 million as of April 1, 2022. Eye diseases associated with HIV occur in 70–80 % of patients [1]. Anterior segment lesions are present in approximately 50 % of these patients, with infectious corneal pathology accounting for 5 % of cases. Corneal ulcers are significantly more common in HIV-infected patients than in the general population, due to exacerbation of concurrent infectious diseases in the context of immunodeficiency [2]. A thorough understanding of the clinical manifestations of corneal ulcers is essential for the differential diagnosis and management of HIV-infected patients with this condition. The treatment of corneal ulcers in individuals with HIV is a particularly difficult task, as the impaired immune system and concurrent antiretroviral therapy can affect the effectiveness of conservative measures and the outcomes of surgical interventions [3].

THE AIM OF THE STUDY

A case report of a corneal ulcer with perforation as the first sign of HIV infection manifestation.

MATERIALS AND METHODS

A clinical case of a corneal ulcer with perforation in a 47-year-old HIV-infected woman is presented. The patient has given voluntary informed consent for the study. Upon admission, the patient reported decreased vision, pain, redness, and lacrimation of the left eye, as well as joint pain and swelling of the fingers. According to her anamnesis, these symptoms suddenly appeared one month ago, and she had been treated with antibacterial eye drops (levofloxacin 0.5 % (Signicef®)) and anti-inflammatory eye drops (diclofenac 0.1 % (Diclo-F®)). However, she did not consult a doctor during this time. At the time of the examination, the patient's general condition was satisfactory. The visometry results were as follows: OD = 0.6 sph + 0.25 = 1.0 and OS = counting fingers at 10 cm n/c. Biomicroscopic examination of the visual acuity (OS): mixed injection. At the limbus at 14 o'clock, there is an ulcerative lesion with a perforation measuring approximately 2 mm. The iris is inserted into this defect. The anterior chamber is uneven, and the iris is swollen and hyperemic. The relief is blurred. The pupil is of irregular shape, and the reaction to light is slow. Based on the results of the objective examination, the following diagnosis has been made: corneal ulcer with perforation and uveitis in the left eye. Urgent surgical treatment is recommended for the patient. As preoperative preparation, anti-inflammatory and antibacterial therapy has been prescribed (ceftriaxone 1 g once daily intravenously and 1 % tetracycline ointment and picloxidine 0.05 % Vitabact®), which has yielded positive results within 8 hours of administration. The exudate in the area of the pupil has resolved. Immediately prior to surgery, the visual acuity of OS = 0.7. The location of the ulcer near the limbus and the absence of loose infiltration at its edges, as well as the high visual function, determined the need for a gentle surgical approach. This approach involved iris repositioning without iridectomy and applying three 8–0 corneolimbal sutures without conjunctival dissection. At the time of the surgery, the patient's HIV status was not known. Subconjunctival injections of 4 % gentamicin (0.3 ml) and 0.4 % dexamethasone (0.3 ml) were administered, as well as conjunctival instillations of 0.5 % levofloxacin and 1 % tetracycline ointment, were administered. In the postoperative period, the patient was treated with intravenous antibacterial medications: ceftriaxone 1 g once daily, instillations of an antiseptic solution (picloxidine 0.05 % Vitabact® 4 times daily), an anti-inflammatory medication (diclofenac 0.1 % (Diclo-F®) 4 times daily). Additionally, 1 % tetracycline ointment was placed in the conjunctival cavity overnight, and 5 % eye gel containing dexpanthenol (Korneregel®) was applied hourly during the day. The following day after surgery, a positive result for the HIV-1 antibody/antigen p24 was determined using the ELISA method.

RESULTS AND DISCUSSION

During the course of treatment, the patient experienced an improvement in their condition. The inflammation had subsided, as evidenced by the following signs: conjunctival hyperemia, iris calmness, pupil roundness (3.5 mm diameter), light reaction sluggishness, and sutures clean and intact. On day 3 after surgery, a synechia had formed in the area of the sutured ulcer. Phenylephrine 5.0 % and Tropicamide 0.8 % eye drops (Midrimax®) were prescribed twice a day for four days. At the time of discharge, uncorrected VIS OS was

0.5. Biomicroscopic examination (OS) revealed clean and intact sutures, mild conjunctival congestion, clear cornea, and calm iris. The patient was discharged in improved condition with the following recommendations for outpatient treatment: 5 % dexpanthenol gel (Korneregel®), 0.05 % picloxidine drops (Piktorid-SOLO-Pharm®), 0.1 % nepafenac, and human recombinant interferon alpha-2B (Oftalmoferon®). The patient was advised to follow up with the ophthalmologist in the local clinic at regular intervals. The next appointment was scheduled in 10 days. VIS OS = 0.7 is not corrected. Objectively, the OS is calm and a scar is forming at the site of the perforation.

This clinical case demonstrates the observation of a patient infected with HIV who developed an acute corneal ulceration with perforation. The patient presented with signs of fibrinous-plastic iridocyclitis, but no symptoms of endophthalmitis were observed, as confirmed through ophthalmoscopic examination. Examination revealed a unilateral corneal ulcer, with white infiltration and dense edges, located at the superior-outer limbus with a perforation of the cornea. Due to the absence of the characteristic clinical features of a creeping corneal ulcer with undermined edges and purulent discharge, bacterial etiology was ruled out. Positive results in terms of rapid healing of the corneal lesion with standard antibiotic and anti-inflammatory treatment in the postoperative period allowed us to rule out a herpes virus etiology.

In this patient, a differential diagnosis was made with autoimmune inflammatory lesions of the cornea based on the localization of the ulcer at the periphery and the presence of joint syndrome. More than half of cases of peripheral corneal ulcers are associated with systemic autoimmune connective tissue diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and Wegener's granulomatous vasculitis [4, 5]. The clinical features characteristics of peripheral corneal ulcers associated with autoimmune conditions include bilateral lesions, mild infiltration and perifocal edema of the cornea, formation of an oval or crescent-shaped epithelial and stromal defect at a distance of 2–4 mm from the limbus, rapid corneal lysis and perforation, perilimbic arteritis and scleritis, and often accompanying anterior uveitis. The ulcer may present with a peripheral infiltrate extending circumferentially toward the limbus [6, 7]. Most patients with this condition have a known history of autoimmune disease. If there is no such history, a clinical blood test (ESR) should be conducted, followed by consultation with a medical professional to identify any systemic signs of autoimmune activity, as well as specific blood tests for rheumatoid factor, C-reactive protein, anti-neutrophil cytoplasmic antibodies, antinuclear antibodies, and circulating immune complexes. In this patient's case, there were no indications of a systemic autoimmune disorder, and her ESR levels were within the normal range. A consultation was held with a doctor, and the diagnosis of polyosteoarthritis was confirmed.

According to current understanding, in the normally immunologically inactive cornea, activation of lymphocytes and interferons may occur under the influence of both endogenous and exogenous factors, including HIV [8]. This can lead to thinning of the cornea and formation of an ulcerative lesion, with systemic immunodeficiency contributing to the rapid development of a secondary infection and increasing the risk of complications, such as endophthalmitis. In the international literature, there have been reports of cases of spontaneous, sterile thinning of the corneal stroma and silent perforation due to rupture of Descemet's membrane in HIV-positive patients [8, 9]. Therefore, acute occurring corneal ulcers require further evaluation to detect systemic conditions, such as HIV infection. It should be noted that in this patient population, the pathological process is often bilateral and the corneal lesion is typically located in the inferior nasal or inferior temporal quadrant. In the clinical case presented, the lesion was located in the superior temporal quadrant, which contradicts this hypothesis. Therefore, it is possible that immunodeficiency is the cause of corneal thinning and perforation, although the exact mechanism remains unknown.

The patient did not have any objective systemic signs of HIV-associated immunodeficiency, and she had not been taking any medications for the underlying condition. The patient's age and duration of illness were notable. A sudden corneal ulcer in a young patient with no general risk factors for infectious keratitis could be a sign of HIV infection. In such a situation, quick surgical intervention and intensive medical treatment are essential for achieving good results. In this case, careful adaptation of the defect edges during suturing and their proximity to the vascular area of the limbus helped prevent additional conjunctival damage and the formation of severe vascular opacity. This approach was justified due to the position of the defect near the limbus in the upper-lateral quadrant of the cornea and its size up to 4 mm, eliminating the need for a corneal transplantation. Among other surgical options for this clinical situation, amniotic membrane transplantation could be considered. Timely surgical intervention, in combination with systemic and topical drug therapy using antibiotics and anti-inflammatory drugs, resulted in a satisfactory outcome, sealing the corneal defect and restoring the patient's visual function.

CONCLUSION

A perforated corneal ulcer, without any known risk factors, may be the initial manifestation of HIV infection. The treatment is tailored to the individual and depends on the etiology, size, and location of the ulcer. The patient's HIV-positive status and lack of therapy for the underlying condition did not adversely affect the healing of the ulcer in the postoperative period.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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PEDIATRICS

ASSESSMENT OF THE PARAMETERS OF THE FATTY ACID SPECTRUM OF BLOOD SERUM IN RELATION TO HORMONAL STATUS IN OBESE ADOLESCENTS

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RESUME

Rationale. *The development and implementation of new high-tech mass spectrometric diagnostic methods into laboratory practice has determined the possibility of a global analysis of the human lipidome, in particular, for a detailed study of its fatty acid component and assessment of the role of individual free fatty acids (FFA) in the pathogenesis of obesity and associated diseases.*

Objective. *To identify the features of changes in the parameters of the fatty acid spectrum of blood serum and establish their relationship to hormonal status indicators in adolescents with obesity.*

Materials and methods. *A total of 27 adolescents aged 10–18 years with obesity (SDS BMI 2.0-3.9) were examined. The control group consisted of 27 adolescents with normal weight with comparable characteristics by gender and age. SDS BMI was calculated using the WHO Anthroplus calculator. The concentration of hormones and peptides in the blood serum was measured by ELISA. The mobile fatty acid pool of blood serum was assessed by chromatography-mass spectrometry on an Agilent 7000B detector.*

Results. *In adolescents with obesity of 1–3 degrees, elevated levels of insulin and C-peptide, decreased concentration of GLP-2 and fatty acid imbalance (decreased proportion of GLA, DGLA, DPA, DHA, AA and increased content of ALA, OA, POA, BA, MA, PA, MAA), as well as a low risk index for the development of a subintimal inflammatory reaction are recorded in the blood. In the group with obesity, direct and negative correlations were established between the content of individual hormones and fatty acids, which were absent between the corresponding parameters in the group of healthy individuals.*

Conclusion. *The established endocrine-metabolic changes in adolescents with obesity are pathogenetic factors of a complex of compensatory-adaptive reactions accompanying low-intensity inflammation.*

Key words: *adolescents, obesity, fatty acids, insulin, leptin, glucagon-like peptide 2*

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ОЦЕНКА ПАРАМЕТРОВ ЖИРНОКИСЛОТНОГО СПЕКТРА СЫВОРОТКИ КРОВИ ВО ВЗАИМОСВЯЗИ С ПОКАЗАТЕЛЯМИ ГОРМОНАЛЬНОГО СТАТУСА У ПОДРОСТКОВ С ОЖИРЕНИЕМ

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РЕЗЮМЕ

Обоснование. *Развитие и внедрение в лабораторную практику новых высокотехнологичных масс-спектрометрических методов диагностики определило возможность глобального анализа липидома человека, в частности, для детального изучения его жирнокислотной составляющей и оценки роли отдельных свободных жирных кислот (СЖК) в патогенезе ожирения и ассоциированных с ним заболеваний.*

Цель. *Выявить особенности изменений параметров жирнокислотного спектра сыворотки крови и установить их взаимосвязь с показателями гормонального статуса у подростков с ожирением.*

Материалы и методы. *Обследовано 27 подростков в возрасте 10–18 лет с ожирением (SDS ИМТ 2,0–3,9). Группу контроля составили 27 подростков с нормальным весом с сопоставимыми характеристиками по полу и возрасту. Расчет SDS ИМТ проводился с использованием калькулятора ВОЗ «Anthroplus». Концентрацию гормонов и пептидов в сыворотке крови осуществляли методом ИФА. Мобильный жирнокислотный пул сыворотки крови оценивали методом хромато-масс-спектрометрии на детекторе Agilent 7000B.*

Результаты. *У подростков с ожирением 1–3 степеней в крови регистрируются повышенные уровни инсулина и С-пептида, снижение концентрации GLP-2 и жирнокислотный дисбаланс (снижение доли GLA, DGLA, DPA, DHA, AA и повышение содержания ALA, OA, POA, BA, MA, PA, MAA), а также низкий индекс риска развития субинтимальной воспалительной реакции. В группе с ожирением установлены прямые и отрицательные корреляции между содержанием отдельных гормонов и жирных кислот, отсутствующие между соответствующими параметрами в группе здоровых лиц.*

Заключение. *Установленные эндокринно-метаболические изменения у подростков с ожирением являются патогенетическими факторами комплекса компенсаторно-приспособительных реакций, сопровождающих низкоинтенсивное воспаление.*

Ключевые слова: *подростки, ожирение, жирные кислоты, инсулин, лептин, глюкагонподобный пептид 2*

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BACKGROUND

The steady increase in childhood obesity during puberty is a prominent feature of its current epidemiology. The primary causes of excessive body weight include stress-induced overeating, poor nutrition, physical inactivity, hormonal changes during adolescence, and other factors. Obesity during adolescence poses a higher risk than in adulthood, as it can lead to the early onset of a wide range of diseases and pathological conditions. Neurohumoral factors originating from local visceral fat depots are the primary drivers of the systemic and organ-specific disorders that constitute metabolic syndrome [1].

Accurate diagnosis of visceral obesity remains a challenging task. Most current methods, including anthropometric measurements (body mass index, waist circumference, and waist-to-hip ratio) and adipose tissue imaging techniques (ultrasound, magnetic resonance imaging, and computed tomography), lack sufficient accuracy for diagnosing visceral obesity, particularly regarding perivascular fat depots [2]. While these methods serve as effective and accessible screening tools for identifying overweight and obese individuals, they do not always reliably stratify patients into high-risk groups for cardiovascular disease and other complications associated with excess visceral fat accumulation. Furthermore, the growing number of "metabolically healthy" obese individuals underscores the need for standardized identification criteria, as anthropometric indicators alone are insufficient for diagnosis [3].

Recently, there has been a surge of interest in the field of metabolomics, specifically in the area of lipid metabolism, known as lipidomics. The advancement and implementation of novel high-tech mass spectrometry techniques in laboratory settings have made it feasible to conduct a comprehensive, high-resolution analysis of the human lipid profile, particularly its fatty acid component. The analysis of serum free fatty acid (FFA) concentrations has emerged as a promising new biomarker for lipid metabolism, including in the context of obesity [4]. Investigating the mechanisms by which individual FFAs and an imbalanced fatty acid composition contribute to the development of obesity and related metabolic disorders is a crucial area of contemporary research [5]. Alterations in fatty acid profiles, especially when combined with hormonal status parameters, may represent a novel potential biomarker for assessing the risk of metabolic syndrome, cardiovascular disease, rheumatologic conditions, infectious diseases, and other complications associated with visceral obesity. These changes could ultimately form the basis for developing highly accessible, non-invasive laboratory methods for diagnosing and monitoring visceral obesity and its associated conditions.

THE AIM OF THE STUDY

To identify specific changes in the serum fatty acid profile and to establish their correlation with hormonal status in adolescents with obesity.

METHODS

Study design. This single-center, observational, cross-sectional comparative study involved 27 adolescents (16 girls and 11 boys) aged 10 to 18 years, at pubertal stages 2–4 (according to Tanner) with grade 1–3 obesity (body mass index standard deviation score (SDS BMI) within 2.0–3.9). All adolescents were combined into a single (main) group. To assess hormonal status and anthropometric parameters, the participants were divided by sex into two subgroups within the main group. The control group comprised 27 adolescents (17 girls and 10 boys) with normal weight, at pubertal stages 2–4 (according to Tanner) and with statistically comparable age characteristics. The subjects were enrolled in the study using a consecutive sampling approach. Group allocation was performed according to the predefined inclusion and exclusion criteria.

Eligibility criteria. The inclusion criteria for the study were: age 10 to 18 years; a diagnosis of exogenous-constitutional obesity grades 1–3; and written informed consent from the participants or their legal representatives (for participants under the age of 15). The exclusion criteria for the main study group were: age under 10 or over 18 years; absence of a diagnosis of exogenous-constitutional obesity grades 1–3; presence of syndromic or monogenic forms of obesity; diabetes mellitus types 1 or 2; acute or chronic somatic conditions; and diseases requiring the use of antibacterial or hormonal medications. Additionally, individuals with laboratory-confirmed helminthic invasion and those who had taken antibacterial medications in the three months prior to the study were excluded.

The study was conducted at the Children's Clinic of Siberian State Medical University and the Professor Medical Center (Tomsk, Russia), where adolescents with and without obesity were recruited. Healthy school-aged children from the Perspektiva School in Tomsk were also invited to participate.

Study duration. Recruitment for the obesity group took place between September 2023 and October 2024 during patient visits to the healthcare facility.

Materials and methods. The SDS BMI was calculated using the World Health Organization's AnthroPlus software, taking into account the sex, age, and anthropometric measurements (weight and height) of each participant. Height was measured using an MSK-233 vertical stadiometer (accuracy of 0.1 cm), and weight was measured using an electronic scale (accuracy of 0.1 kg).

The study material was venous blood serum, collected once from the cubital vein of each participant under fasting conditions.

Hormone and peptide concentrations in venous serum were measured using enzyme-linked immunosorbent assay (ELISA) on a Uniplan analyzer (Pikon, Russia). Leptin concentration was measured using an Active Human Leptin ELISA Kit (DSL-10-23100, Diagnostic Systems Laboratories Inc., USA). The levels of other hormones and peptides (insulin, C-peptide, glucagon, glucagon-like

peptide 1 and 2, irisin, and resistin) were measured in serum using ELISA reagents from Claudio Clone Corporation (USA).

The mobile fatty acid profile of blood serum was analyzed using validated gas chromatography with mass-selective detection on an Agilent 7000B system (Agilent Technologies Inc., USA) [6]. The results were reported as relative percentages.

Ethical approval. The study was approved by the ethics committee of Siberian State Medical University (protocol No. 8459/2, dated October 28, 2020).

Statistical analysis. Statistical analysis was conducted using standard statistical methods and IBM SPSS Statistics software. The Shapiro-Wilk test was used to test the hypothesis of a normal distribution. For samples with non-normal distributions, the non-parametric Mann – Whitney U-test was used to assess statistical significance between groups. Results are presented as medians and interquartile ranges (Me [Q25; Q75]). Correlations between quantitative variables were determined using Spearman's rank correlation coefficient. Statistical significance was set at $p < 0.05$ for all comparisons.

RESULTS

The characteristics of the study participants, stratified by sex, age, and anthropometric parameters, are presented in Table 1. The median age of subjects in the main group was 14.8 [13.15; 16.15] years, and in the control group, 16.50 [13.45; 17.75] years. The study groups were comparable in terms of sex and age distribution. No statistically significant differences were observed between the parameters of male and female adolescents within each study group.

An analysis of hormone levels in adolescents with obesity revealed increased serum insulin and C-peptide levels, as well as decreased glucagon-like peptide 2 levels, compared to the control group (Table 2). No sex-specific differences in these hormone levels were found within either group; therefore, subsequent analyses of fatty acid profiles were performed on pooled data from both sexes.

In adolescents with grade 1–3 obesity, the serum mobile fatty acid pool was altered relative to controls, characterized by an increase in the relative percentages of saturated (SFA) and monounsaturated (MUFA) fatty acids and a decrease in the proportion of polyunsaturated fatty acids (PUFAs) (Fig. 1).

Detailed analysis of the serum fatty acid profile in obese adolescents revealed an imbalance within the PUFA pool. Specifically, there was a significant decrease in the concentrations of GLA, DGLA, DPA, DHA, and AA, alongside an approximately 1.4-fold increase in the concentration of ALA, compared to controls (Table 3).

An imbalance was also observed within the MUFA pool, reflected by increased levels of OA and POA

TABLE 1

AGE-SEX AND ANTHROPOMETRIC CHARACTERISTICS OF THE EXAMINED ADOLESCENTS IN THE MAIN AND CONTROL GROUPS, ME [Q1; Q3]

Parameters	Control group, *n*=27 Girls, *n*=17 Boys, *n*=10	Main group, *n*=27 Girls, *n*=16 Boys, *n*=11	*p*
Age, years			
All adolescents	16.50 [13.45; 17.75]	14.80 [13.15; 16.15]	0.139
Girls	15.30 [11.75; 16.10]	14.35 [12.00; 15.60]	0.183
Boys	16.30 [13.35; 17.20]	15.50 [14.37; 17.40]	0.122
Weight, kg			
All adolescents	53.30 [49.30; 56.70]	86.80 [65.35; 95.75]	<0.001*
Girls	53.70 [50.10; 56.80]	87.35 [70.35; 96.25]	<0.001*
Boys	54.05 [49.93; 56.08]	90.00 [60.85; 98.10]	<0.001*
Height, cm			
All adolescents	162.00 [156.50; 168.00]	164.00 [154.25; 172.20]	0.395
Girls	159.00 [155.00; 164.00]	162.00 [156.37; 168.50]	0.378
Boys	162.00 [156.50; 168.00]	169.00 [152.00; 174.50]	0.449
SDS BMI, c.u.			
All adolescents	-0.08 [-0.79; 0.50]	2.60 [2.40; 2.95]	<0.001*
Girls	0.27 [-0.21; 0.65]	2.55 [2.40; 2.95]	<0.001*
Boys	-0.80 [-0.70; 0.40]	2.72 [2.51; 2.81]	<0.001*

Note. Me – median, Q1, Q3 – lower and upper quartiles; BMI – body mass index; BMI SDS – body mass index standard deviation score; *p* – significance level for differences between the main and control groups (Mann – Whitney U-test); * – statistically significant differences between groups.

and decreased levels of mid-chain MUFAs in adolescents with obesity compared to their healthy peers (Table 3).

The serum SFA pool was similarly altered in the obesity group, with a significant increase in the proportions of BA, MA, PA, and MAA relative to the control group (Table 3).

Assessment of fatty acid-derived indices revealed a reduction in the AA/EPA ratio, a risk index for subintimal inflammation, in adolescents with obesity compared to those without obesity (Table 3).

Correlation analysis was performed for all parameters. While a number of expected correlations were observed between individual fatty acid levels and hormonal status in both groups, several correlations were identified exclusively in the obese cohort.

In obese adolescents, statistically significant positive correlations were observed between serum levels of adrenic acid (ADA) and resistin (r = 0.584; p = 0.0019; 95% CI [0.262; 0.789]), nervonic acid (NA) and glucagon (r = 0.531; *p* = 0.0045; 95% CI [0.189; 0.758]), and palmitoleic acid (POA) and irisin (r = 0.513; *p* = 0.0018; 95% CI [0.165; 0.747]). Negative correlations were recorded between ADA and irisin (r = –0.520; *p* = 0.0321; 95% CI [-0.751; -0.174]), ALA and resistin (r = –0.544; *p* = 0.0305; 95% CI [-0.765; -0.206]), NA and C-peptide (r = –0.572; *p* = 0.0452; 95% CI [-0.782; -0.245]), and POA and leptin (r = –0.575; *p* = 0.0042; 95% CI [-0.783; -0.249]). These

TABLE 2

SERUM HORMONE CONCENTRATIONS IN OBESE ADOLESCENT CHILDREN WITH NORMAL BODY WEIGHT, ME [Q1; Q3]

Parameters	Control group, *n*=27 Girls, *n*=17 Boys, *n*=10	Main group, *n*=27 Girls, *n*=16 Boys, *n*=11	*p*
Insulin, μU/ml			
All adolescents	8.40 [5.70; 10.55]	22.60 [17.65; 26.25]	0.011*
Girls	8.45 [6.43; 11.10]	23.10 [19.90; 32.03]	0.023*
Boys	7.30 [5.23; 9.58]	21.25 [15.40; 25.80]	0.012*
C-peptide, ng/ml			
All adolescents	2.00 [1.40; 2.40]	2.60 [1.90; 3.10]	0.022*
Girls	2.00 [1.43; 2.38]	2.60 [1.90; 2.80]	0.031*
Boys	2.10 [1.50; 2.40]	2.55 [2.12; 3.52]	0.016*
Glucagon, pg/ml			
All adolescents	188.9 [160.00; 224.70]	170.60 [160.40; 176.00]	0.315
Girls	186.7 [173.80; 234.10]	163.00 [156.65; 193.00]	0.188
Boys	160.0 [152.20; 208.40]	176.60 [168.10; 186.00]	0.240
GLP-1, pg/ml			
All adolescents	24.47 [23.17; 29.37]	22.48 [20.54; 29.47]	0.710
Girls	24.51 [22.62; 29.37]	22.64 [20.27; 29.58]	0.655
Boys	24.47 [23.61; 30.43]	27.43 [20.38; 29.68]	0.789
GLP-2, pg/ml			
All adolescents	506.20 [358.70; 667.00]	114.60 [102.95; 168.80]	<0.001*
Girls	478.00 [295.15; 546.15]	111.65 [103.50; 288.00]	<0.001*
Boys	546.00 [487.45; 684.55]	128.60 [100.12; 235.68]	<0.001*
Irisin, pg/ml			
All adolescents	7.13 [7.13; 7.44]	7.33 [6.98; 7.65]	0.188
Girls	7.13 [7.13; 7.34]	7.30 [7.22; 7.65]	0.270
Boys	7.29 [6.89; 7.44]	7.33 [6.96; 7.49]	0.145
Leptin, ng/ml			
All adolescents	10.00 [7.18; 12.58]	7.84 [3.99; 9.98]	0.083
Girls	10.44 [8.37; 12.91]	6.46 [4.12; 9.38]	0.079
Boys	9.20 [6.68; 11.97]	8.41 [6.78; 10.48]	0.141
Resistin, ng/ml			
All adolescents	12.17 [7.22; 18.49]	14.72 [9.97; 21.03]	0.290
Girls	10.38 [6.92; 18.98]	14.54 [9.44; 21.21]	0.360
Boys	11.51 [7.71; 16.14]	16.53 [12.32; 20.34]	0.494

Note. Me – median, Q1, Q3 – lower and upper quartiles; GLP – glucagon-like peptide; *p* – significance level for differences between groups (Mann – Whitney U-test); * – statistically significant differences between groups.

correlations were not observed in the control group of healthy individuals.

DISCUSSION

Hyperinsulinemia is a well-established pathogenetic factor in obesity, with insulin exerting a pronounced anabolic effect on all types of metabolism. While its primary function is to regulate blood glucose levels, insulin also plays an active role in lipid metabolism. It stimulates lipid synthesis in the liver and adipose tissue, directly induces glucose entry into fat cells, and promotes the hydrolysis of triacylglycerols associated with blood lipoproteins, facilitating fatty acid entry into adipocytes. This process contributes to glycerophosphate formation, leading to increased adipose tissue mass [7]. Furthermore, insulin suppresses cAMP-mediated lipolysis by inhibiting hormone-dependent intracellular lipoprotein lipase [8]. C-peptide, a marker of insulin secretion, varies in response to fluctuations in endogenous insulin levels [9]. Therefore, the elevated C-peptide levels observed in obese adolescents with concurrent hyperinsulinemia were an expected finding.

Conversely, glucagon, a counter-regulatory hormone to insulin, stimulates hepatic glucose release to maintain glucose homeostasis and also promotes fat breakdown in adipose tissue [8]. Glucagon secretion is directly related to blood glucose levels, decreasing as glucose increases. In the present study, no statistically significant differences in glucagon levels were observed between obese and non-obese adolescents, although a downward trend was noted in the obese group.

In obese adolescents with elevated insulin levels, we observed low levels of glucagon-like peptide 2 (GLP-2). GLP-2 is produced by central nervous system neurons and intestinal L-cells and exerts multiple effects, including intestinal trophic actions (mucosal proliferation and improved barrier function), increased mesenteric blood flow, reduced bone loss, and neuroprotection [10]. GLP-2 receptors are present in the gastrointestinal tract, liver, adipose tissue, and central nervous system. While GLP-2 does not affect appetite or food intake in humans, its intestinal trophic action is significant, particularly in the context of obesity. Obesity is associated with impaired intestinal barrier function, leading to increased translocation of pro-inflammatory luminal contents into the bloodstream, which negatively impacts the development of obesity-related conditions. Moreover, GLP-2 has a positive effect on normalizing glucose levels in obese individuals [10]. The reduced GLP-2 levels observed in our overweight cohort may thus contribute to heightened systemic inflammation and, consequently, to the development of complications and comorbidity.

Considering the observed changes in the serum fatty acid profile in conjunction with hormonal alterations, the pattern of reduced total PUFAs and increased SFAs and MUFAs is consistent with the metabolic

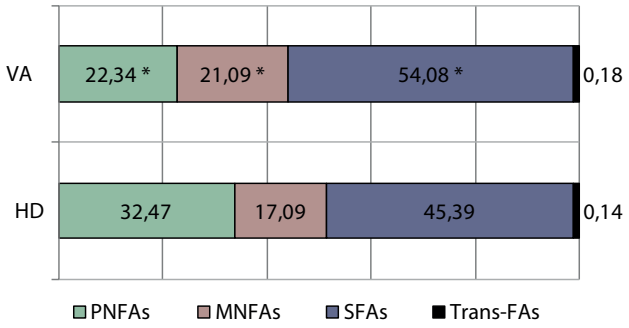

FIG. 1.
*Percentage ratio of pools of polyunsaturated (PN), monounsaturated (MN), saturated fatty acids (SFAs) and their trans-isomers (trans-FAs) in serum in obese adolescents (VA) and normal body weight (HD). Note: * – significance level of differences $p < 0.05$ (Mann – Whitney U test).*

consequences of poor dietary habits, physical inactivity, and stress, which are prevalent in modern adolescents during puberty [11]. This is further supported by the specific fatty acid imbalances identified in the obese group: a reduction in omega-3 (DPA, DHA) and omega-6 (GLA, DGLA, AA) PUFAs, alongside excessive amounts of OA and POA (MUFAs) and BA, MA, PA, and MAA (SFAs). These findings are broadly consistent with existing scientific literature. However, as studies in school-aged children have shown, many children with a normal BMI may exhibit dietary deficiencies similar to those seen in obese children without subsequent weight gain [8]. Notably, our findings indicate that obese adolescents did not exhibit a deficiency in the essential PUFAs (LA, ALA); indeed, ALA concentrations exceeded those in the control group.

Chronic low-grade inflammation, in combination with increased release of fatty acids into the bloodstream and ectopic fat accumulation, is now recognized as a significant factor in the pathogenesis of obesity [12]. Markers of low-grade inflammation include increased levels of certain adipokines (primarily leptin and resistin), as well as elevated concentrations of classic inflammatory markers such as C-reactive protein (CRP) and pro-inflammatory cytokines (IL-6, TNFα, MCP1) [13].

Leptin, primarily produced by adipocytes, serves as a key regulator of body fat mass. As a mediator between adipose tissue and the hypothalamic-pituitary system, it reduces appetite and food intake by signaling to the brain. Numerous studies have shown that blood leptin levels increase with higher body weight, linked to the development of leptin resistance [14]. However, in our study, we did not find an increase in leptin levels in obese adolescents compared to normal-weight controls; in fact, a downward trend was observed. Additionally, a negative correlation was found between leptin and POA levels in the main study group. While this finding may seem counterintuitive regarding leptin's role in appetite and weight regulation,

TABLE 3

FATTY ACID CONTENT AS A PERCENTAGE OF THE TOTAL MOBILE POOL IN THE SERUM OF OBESE ADOLESCENTS WITH NORMAL BODY WEIGHT, ME [Q1; Q3]

Fatty acids in blood serum, %	Control group, *n*=27	Main group, *n*=27	*p*
Polyunsaturated fatty acids			
Alpha-linolenic acid (ALA 18:3n3)	0.18 [0.15; 0.23]	0.26 [0.22; 0.29]	0.029*
Eicosapentaenoic acid (EPA 20:5n3)	0.10 [0.04; 0.14]	0.07 [0.06; 0.08]	0.921
Docosahexaenoic acid (DHA 22:6n3)	1.74 [0.65; 2.21]	1.01 [0.91; 1.25]	0.038*
Docosapentaenoic acid (DPA 22:5n3)	0.40 [0.34; 0.78]	0.22 [0.21; 0.27]	<0.001*
Arachidonic acid (AA 20:4n6)	8.48 [7.81; 9.69]	3.90 [3.58; 4.17]	<0.001*
Gamma-linolenic acid (GLA 18:3n6)	0.22 [0.14; 14.42]	0.11 [0.07; 0.15]	0.017*
Dihomo-gamma-linolenic acid (DGLA 20:3n6)	1.01 [0.89; 1.37]	0.67 [0.50; 0.84]	0.031*
Linoleic acid (LA 18:2n6)	20.40 [16.23; 23.73]	16.50 [15.36; 17.72]	0.107
Adrenic acid (ADA 22:4n6)	0.95 [0.56; 1.28]	1.05 [0.52; 1.48]	0.064
Monounsaturated fatty acids			
Nervonic acid (NA 24:1n9)	1.79 [1.68; 1.99]	1.82 [1.75; 1.94]	0.811
Oleic acid (OA 18:1n9)	14.10 [12.74; 16.41]	17.23 [16.41; 18.72]	0.038*
Erucic acid (ERA 22:1n9)	0.00 [0.00; 0.00]	0.00 [0.00; 0.00]	1.000
Mead acid (20:3n9), %	0.07 [0.04; 0.24]	0.04 [0.03; 0.05]	0.033*
Myristoleic acid (MOA 14:1n5)	0.08 [0.06; 0.09]	0.08 [0.05; 0.10]	0.960
Palmitoleic acid (POA 16:1n7)	0.83 [0.67; 1.02]	1.14 [0.92; 1.32]	0.027*
Saturated fatty acids, including those containing an odd number of carbon atoms			
Arachidic acid (ANA 20:0)	0.35 [0.31; 0.38]	0.37 [0.35; 0.40]	0.097
Behenic acid (BA 22:0)	1.23 [1.14; 1.31]	1.34 [1.24; 1.48]	0.010*
Decanoic acid (DA 10:0)	0.02 [0.01; 0.02]	0.02 [0.02; 0.03]	0.076
Lauric acid (LAA 12:0)	0.04 [0.02; 0.05]	0.07 [0.02; 0.11]	0.371
Lignoceric acid (LCA 24:0)	2.55 [2.14; 2.65]	2.52 [2.37; 2.75]	0.064
Myristic acid (MA 14:0)	0.48 [0.32; 0.78]	0.82 [0.59; 1.06]	0.032*
Palmitic acid (PA 16:0)	24.75 [21.86; 28.12]	31.69 [29.24; 32.52]	<0.001*
Stearic acid (SA 18:0)	14.78 [13.76; 15.25]	16.56 [15.06; 16.98]	0.055

TABLE 3 (*continued*)

Pentadecanoic acid (PDA 15:0)	0.24 [0.19; 0.33]	0.28 [0.23; 0.32]	0.703
Margaric acid (MAA 17:0)	0.33 [0.29; 0.38]	0.44 [0.38; 0.46]	0.008*
Heptadecenoic acid (GDA 17:1n7)	0.07 [0.06; 0.08]	0.08 [0.07; 0.10]	0.710
Heneicosanoic acid (GEA 21:0)	0.02 [0.02; 0.03]	0.01 [0.01; 0.03]	0.512
Tricosanoic acid (TA 23:0)	0.25 [0.21; 0.30]	0.34 [0.26; 0.40]	0.098
	Trans fatty acids		
Linoelaidic acid (LELA 18:2ct)	0.10 [0.08; 0.13]	0.08 [0.06; 0.19]	0.412
Elaidic acid (ELA 18:1n9t)	0.03 [0.03; 0.05]	0.05 [0.05; 0.07]	0.066
	Fatty acid indices		
LA/DGLA	22.05 [18.21; 29.03]	25.34 [21.92; 31.73]	0.112
ω6/ω3	11.98 [10.56; 13.67]	13.98 [11.43; 15.92]	0.295
AA/EPA:(%AA/%EPA)	81.45 [63.12; 168.60]	51.48 [46.81; 65.79]	0.004*

Note. LA/DGLA – omega-6 desaturase activity index; ω6/ω3 – omega-6 to omega-3 fatty acid ratio; AA/EPA:(%AA/%EPA) – index of subintimal inflammatory response (risk of cardiovascular complications/level of body's protective reserve); *p* – significance level for differences between groups (Mann-Whitney U-test); * – statistically significant differences between groups.

an alternative interpretation considers leptin's significant role in the pathogenesis of inflammation and its capacity to regulate immune homeostasis within and beyond adipose tissue.

Leptin's effects influence virtually all cellular components of the immune system. *In vitro*, leptin stimulates the proliferation of circulating human monocytes, enhances the expression of activation markers (CD25, CD38, CD69, CD71, HLA-DR, CD11b, and CD11c), and stimulates neutrophil chemotaxis and oxygen radical release [15]. On eosinophils, leptin promotes the expression of adhesion molecules ICAM-1 and CD18 and induces chemotaxis and secretion of inflammatory cytokines (IL-1β, IL-6). Its effects on basophilic granulocytes include stimulation of migration, degranulation, and pro-inflammatory cytokine synthesis. Low leptin levels have been linked to a shift in basophil and mast cell potential towards anti-inflammatory activity, promoting M2-type macrophage polarization and subsequent IL-10 secretion. Leptin is also implicated in the proliferation, differentiation, and activation of natural killer (NK) cells, enhancing their cytotoxic activity by upregulating IL-2, IL-12, and perforin gene expression. Consequently, leptin plays an active role in the initiation and perpetuation of inflammation.

Regarding POA, this common MUFA plays an important role in metabolism. It is a component of triacylglycerols found in all body tissues and is biosynthesized from PA via stearoyl-CoA desaturase-1. Our study observed elevated concentrations of both PA and POA in obese subjects. While pro-inflammatory effects have been described for PA, consistent with metabolic inflammation in obesity, anti-inflammatory properties have been confirmed for POA. Adding POA to LPS-stimulated macrophage cultures reduced the production of IL-1β, IL-6, and TNFα, decreased expression of NFκB, MyD88, caspase-1, and TLR4 [16]. Furthermore, POA has been shown to enhance adipocyte and hepatocyte sensitivity to insulin and, in combination with oleic acid, to beneficially affect lipid metabolism and reduce inflammation [17]. The inverse correlation between leptin and POA levels established in our study suggests a potential role for POA in mitigating the pro-inflammatory effects of leptin in obese adolescents, possibly by regulating its concentration. This mechanism warrants further investigation, taking into account sex, developmental stage, and, in female participants, menarche status and menstrual cycle phase.

Additional correlations of interest involve the hormone resistin and the fatty acids ALA and ADA. In our study, resistin concentrations in obese adolescents were not significantly different from controls. However, a negative correlation was found between resistin and ALA levels (which were elevated in the study group),

and a positive correlation between resistin and ADA levels.

Originally identified as a molecule involved in insulin resistance, resistin is now recognized as an inflammatory regulator, promoting a pro-inflammatory state both *in vitro* and *in vivo* [18]. Produced by adipocytes, monocytes/macrophages, myocytes, cardiomyocytes, and hepatocytes, resistin influences a wide range of cell types through autocrine, paracrine, and endocrine mechanisms. It increases the reactivity of macrophages, mononuclear leukocytes, and endothelial cells, with NF-κB-mediated secretion of TNFα, IL-6, IL-12, and MCP1 demonstrated in response to recombinant human resistin [18]. Resistin levels positively correlate with common inflammatory biomarkers such as CRP, TNFα, and IL-6 in various diseases, and may reflect disease severity [19]. Thus, resistin is considered a pro-inflammatory hormone.

ALA is an essential PUFA and precursor to other omega-3 PUFAs, although its conversion to EPA is limited, and further conversion to DPA and DHA is minimal (no more than 4–8 %). ALA is generally recognized for its beneficial, anti-inflammatory effects. Studies have shown that ALA treatment can reduce fat accumulation in adipocytes, improve glucose homeostasis, regulate lipid metabolism, and reduce insulin resistance [20]. It reduces TNFα levels and inhibits the expression of nitric oxide synthase, cyclooxygenase-2, and TNFα by inhibiting the NF-κB and MAPK pathways. A novel immunomodulatory role for ALA has recently been identified through the formation of oxylipins with pronounced anti-inflammatory properties [21]. ALA supplementation leads to the formation of oxylipins such as 9-HOTrE and 13-HOTrE, which in murine models significantly reduced reactive oxygen species production and inflammatory cytokine expression (IL-1β, TNFα) while increasing IL-10 secretion by macrophages [21]. In human adipocytes, these oxylipins reduced triacylglycerol accumulation and decreased MCP-1 and TNFα production [22]. Therefore, the increased concentration of ALA in the bloodstream of obese adolescents may represent a compensatory mechanism to help maintain PUFA balance and reduce adipose tissue inflammation. This interpretation is indirectly supported by the negative correlation between resistin levels and ALA concentrations in the context of DPA and DHA deficiency.

ADA is a 22-carbon PUFA widely distributed in the adrenal glands, liver, brain, kidneys, and vascular walls, playing a role in regulating inflammation [23]. Studies have shown that ADA contributes to inflammation in the liver and coronary arteries, as well as triacylglycerol accumulation in fibroblasts [23]. Conversely, ADA can function as an epigenetic regulator of TNFα secretion, increasing its methylation and thereby reducing TNFα-mediated inflammation [24]. The positive correlation between ADA levels and resistin concentrations established in this study suggests a possible role for this fatty acid in regulating hormone levels, potentially facilitating its release into the blood [25]. Additionally, we found a negative correlation between ADA and irisin levels, the latter being within control values in obese adolescents.

Irisin is a thermogenic myokine involved in regulating lipolysis and is also a biomarker for metabolic syndrome in pre-pubertal children [26]. Irisin has been demonstrated to reduce concentrations of pro-inflammatory cytokines (TNFα, IL-1β, MIP1α, MIP1β) and increase anti-inflammatory cytokines in the blood, adipose tissue, endothelial cells, and cardiomyocytes. It reduces LDL and triacylglycerol levels, ameliorates endothelial dysfunction, vascular inflammation, and insulin resistance, and exerts anti-inflammatory effects on the heart, liver, lungs, and intestines [27]. Although we did not observe changes in serum irisin levels in obese adolescents, its active role in reducing the inflammatory response in obesity is suggested by its negative correlation with ADA and its positive correlation with POA.

The negative correlation between NA levels and C-peptide concentrations (a marker of endogenous insulin secretion), coupled with the positive correlation between NA and glucagon, may indicate specific negative effects of insulin/C-peptide on nervous tissue in obese individuals. NA is an omega-9 MUFA crucial for myelin biosynthesis in nerve cells, and its synthesis is a rate-limiting step in myelin sheath lipid homeostasis [28]. An NA-enriched diet has been shown to reduce weight gain, improve memory and learning, and reduce inflammation in mice [29]. While insulin has been associated with neuroprotection, its role remains ambiguous. The correlations identified with NA highlight the need for further study into the mechanisms influencing nervous tissue in obesity.

A comprehensive analysis of changes in the fatty acid spectrum in obese adolescents suggests that many of the observed alterations represent a complex of protective and adaptive responses to obesity and metabolic inflammation. The synthesis pathways for omega-3 and omega-6 PUFAs are similar, both utilizing the same desaturase/elongase enzymes and competing for them. Research indicates that PUFAs from these pathways often exert antagonistic effects, particularly through their eicosanoid derivatives. Generally, EPA-derived eicosanoids have anti-inflammatory or less inflammatory effects compared to those synthesized from AA. Despite sufficient levels of the omega-6 precursor LA, obese adolescents in our study exhibited low levels of GLA, DGLA, and AA. The LA/DGLA ratio (an index of delta-6 desaturase activity), reflecting the conversion of LA to DGLA and endogenous omega-6 synthesis, did not differ significantly from normal values. Meanwhile, EPA concentrations were within normal ranges, suggesting either adequate dietary intake or efficient synthesis from the excess ALA precursor. Eicosanoids synthesized from EPA are likely to exert a more anti-inflammatory effect. The deficiency of other omega-3 fatty acids (DPA and DHA) may be attributed to dietary deficit or reduced synthesis from EPA. For instance, obesity

has been associated with reduced delta-5-desaturase activity, required for DPA production. Furthermore, delta-6-desaturase exhibits a stronger affinity for ALA than for tetracosapentaenoic omega-3 PUFA, a precursor in DHA synthesis [30].

This hypothesis is supported by the lower index of subintimal inflammatory response (AA/EPA ratio) observed in the obese group, which indicates a favorable balance of pro- and anti-inflammatory eicosanoids.

Study limitations. The limitations of this study include its single-center design and relatively small sample size. Additionally, the study did not account for menarche status or menstrual cycle phase in girls, ethnic background, or disease duration in adolescents with obesity.

CONCLUSION

A comprehensive analysis of the observed changes in hormonal levels and blood fatty acid profiles in adolescents with obesity suggests that these alterations represent elements of protective, compensatory, and adaptive responses to low-grade inflammation associated with excessive visceral adipose tissue accumulation. The correlations between specific hormones and fatty acids identified exclusively in the obese cohort warrant further investigation and offer promising avenues for the discovery of novel diagnostic and prognostic biomarkers.

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Conflicts of interest

The authors declare no conflicts of interest.

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PEDIATRICS

PSYCHOEMOTIONAL STATE AND HORMONAL STATUS OF ADOLESCENT GIRLS IN THE POST-COVID PERIOD

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RESUME

Introduction. *Post-COVID syndrome (PCS) in children and adolescents represents a relevant medical and social problem. Adolescent girls may be particularly vulnerable to the development of psychoemotional and endocrine disorders associated with PCS due to hormonal changes during the pubertal period.*

The aims. *To assess the psychoemotional status and hormonal profile in adolescent girls depending on the presence of post-COVID syndrome symptoms, and to establish correlations between psychoemotional indicators and hormone concentrations of the hypothalamic-pituitary-thyroid-adrenal axis in the post-COVID period.*

Materials and methods. *A total of 126 girls aged 11–16 years were examined: 44 with PCS symptoms (main group); 40 without PCS symptoms (comparison group); and 42 conditionally healthy girls (control). The main group was divided into subgroups depending on the time period after COVID-19: 3–5 (n = 11), 6–9 (n = 12), 11–12 (n = 10), and 13–24 months (n = 11). Psychoemotional status was assessed using the SAN (Well-being, Activity, Mood) scale, BDI-1A, and A.M. Prikhozhan's Manifest Anxiety Scale. Concentrations of TSH, free T4, and cortisol were determined by enzyme-linked immunosorbent assay.*

Results. *Girls with PCS symptoms showed more pronounced forms of depressive symptomatology, increased anxiety, and reduced activity and well-being. Elevated levels of TSH and cortisol were observed compared to control groups. The differences persisted throughout the entire post-COVID period with maximum severity at 6–12 months after COVID-19. Correlations were established between the severity of depressive symptoms and TSH concentration (p = 0.002), and between anxiety and cortisol (p = 0.001) in respondents throughout the post-COVID period.*

Conclusion. *The established correlations between psychometric indicators and hormone concentrations indicate the involvement of neuroendocrine mechanisms in the pathogenesis of psychoemotional manifestations of PCS. The results substantiate the need for comprehensive examination of adolescent girls with PCS symptoms for timely diagnosis and correction of disorders.*

Keywords: *COVID-19, Post-COVID syndrome, adolescent girls, psychoemotional status, anxiety, depression, cortisol, TSH, hormonal status, pubertal period*

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ПСИХОЭМОЦИОНАЛЬНОЕ СОСТОЯНИЕ И ГОРМОНАЛЬНЫЙ СТАТУС У ДЕВОЧЕК-ПОДРОСТКОВ В ПОСТКОВИДНОМ ПЕРИОДЕ

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РЕЗЮМЕ

Введение. *Постковидный синдром (ПКС) у детей и подростков представляет актуальную медико-социальную проблему. Девочки-подростки могут быть особенно уязвимы к развитию психоэмоциональных и эндокринных нарушений на фоне ПКС в связи с гормональными перестройками пубертатного периода.*

Цель. *Оценить психоэмоциональное состояние и гормональный статус у девочек-подростков в зависимости от наличия симптомов постковидного синдрома, а также установить взаимосвязь между показателями психоэмоционального состояния и концентрацией гормонов гипофизарно-тиреоидно-надпочечниковой системы в постковидном периоде.*

Материалы и методы. *Обследовано 126 девочек 11–16 лет: 44 с симптомами ПКС (основная группа); 40 без симптомов ПКС (группа сравнения); и 42 условно здоровые девочки (контроль). Основная группа разделена на подгруппы в зависимости от временного периода после COVID-19: 3–5 (n = 11), 6–9 (n = 12), 11–12 (n = 10) и 13–24 месяцев (n = 11). Психоэмоциональное состояние оценивалось с использованием методик САН, BDI-1A и шкалы явной тревожности А.М. Прихожан. Определялись концентрации ТТГ, Т4 св. и кортизола методом иммуноферментного анализа.*

Результаты. *У девочек с симптомами ПКС выявлены более выраженные формы депрессивной симптоматики, повышенная тревожность, сниженная активность и самочувствие. Отмечается повышенный уровень ТТГ и кортизола по сравнению с контрольными группами. Различия сохранялись на протяжении всего постковидного периода с максимальной выраженностью в период 6–12 месяцев после COVID-19. Установлена взаимосвязь между выраженностью депрессивных симптомов и концентрацией ТТГ (p = 0,002), тревожностью и кортизолом (p = 0,001) у респондентов на протяжении всего постковидного периода.*

Заключение. *Установленные корреляции между психометрическими показателями и концентрацией гормонов свидетельствуют о вовлечении нейроэндокринных механизмов в патогенез психоэмоциональных проявлений ПКС. Результаты обосновывают необходимость комплексного обследования девочек-подростков с симптомами ПКС для своевременной диагностики и коррекции нарушений.*

Ключевые слова: *COVID-19, постковидный синдром, девочки-подростки, психоэмоциональное состояние, тревожность, депрессия, кортизол, ТТГ, гормональный статус, пубертатный период*

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INTRODUCTION

The COVID-19 pandemic, caused by a novel coronavirus infection, has significantly impacted the health of people of all ages, including children and adolescents. Clinical experience has shown that the effects of this infection go beyond the acute phase of the disease, and can lead to long-term symptoms, known as "post-COVID syndrome" or "Long COVID-19" [1-3]. According to the World Health Organization, post-COVID syndrome (PCS) in children and adolescents is defined as the presence of persistent or new symptoms that develop 3 months or more after the initial infection with SARS-CoV-2, lasting for at least 2 months and not explained by other diagnoses [4]. Clinical manifestations of this syndrome in children and adolescents include a wide range of symptoms, such as fatigue, sleep disorders, cognitive dysfunction, headaches, anosmia, and psychoemotional disorders [5, 6]. These symptoms may persist for months or even years after COVID-19 infection, making it challenging to resume normal life activities [7, 8].

Modern research indicates a high prevalence of psychosocial and emotional disorders in children and adolescents with PCS [9, 10]. It has been demonstrated that this group of patients experiences increased anxiety, depression, cognitive dysfunction, and behavioral disorders [11, 12]. However, the pathogenic mechanisms underlying these conditions remain poorly understood. Nevertheless, there is speculation about a link between these disorders and the effect of the virus on the central nervous system, as well as dysfunction of the hypothalamic-pituitary-adrenal axis [13, 14]. Oxidative stress is believed to play a significant role in the pathogenesis of PCS, as studies have shown changes in the lipid peroxidation-antioxidant defense system among children and adolescents who have experienced COVID-19 [15, 16]. These alterations may contribute to the development of endocrinological disorders and psychoemotional dysfunction.

Growing evidence suggests that COVID-19 may affect endocrine function, in particular the hypothalamic-pituitary-thyroid and hypothalamic-pituitary-adrenal axes [17, 18]. Reports of subacute thyroiditis and thyroid dysfunction in the post-COVID period in adult patients have been published [19, 20]. Studies of children who have recovered from COVID-19 have also revealed thyroid dysfunction, which can impact growth, development, and metabolic processes in childhood and adolescence [21]. Puberty is a time of significant changes in the endocrine system that can influence the course and severity of the post-COVID syndrome in adolescents. It is of particular interest to study the functional state of the hypothalamic-pituitary-thyroid-adrenal axis in adolescent girls, as this axis plays a crucial role in regulating metabolic processes, stress responses, and the psychoemotional state. Additionally, adolescent girls may be more susceptible to the development of psychoemotional disorders in the post-COVID period compared to boys of a similar age. This could be attributed to both hormonal factors associated with puberty, such as fluctuations in estrogen and progesterone levels that affect neurotransmitter systems, as well as socio-psychological factors such as increased emotional reactivity, coping strategies, and social expectations [2].

Investigating the link between the psychoemotional state and the hypothalamic-pituitary-thyroid-adrenal axis in adolescent girls during the post-COVID period is important for several reasons. Firstly, adolescence represents a critical phase for the development of women's reproductive health, and any disturbances in the endocrine system may have long-term consequences for health. Secondly, hormonal changes are closely associated with the psychoemotional state of adolescents, which may exacerbate the symptoms of post-COVID syndrome. Thirdly, understanding the pathogenic mechanisms underlying the development of disorders in this age group is essential for developing effective strategies for their identification, management, and treatment.

Despite the increasing attention to the issue of post-COVID syndrome in children and adolescents, research into the condition of the thyroid and adrenal glands in this age group remains limited [17, 21]. Virtually no studies have been conducted to assess the psychoemotional state and the functioning of the hypothalamic-pituitary-thyroid-adrenal axis in adolescent girls in the post-COVID period.

Therefore, investigating the psychoemotional state and functioning of the hypothalamic-pituitary-thyroid-adrenal axis in adolescent girls in the post-COVID period presents a significant scientific and practical challenge. The findings from such studies could contribute to a better understanding of the pathogenetic mechanisms underlying the development of PCS in adolescents and could help to optimize medical and psychological treatment for this patient population.

THE AIM OF THE STUDY

To assess the psychoemotional state and hormonal status in adolescent girls based on the presence of post-COVID syndrome symptoms, and to establish correlations between psychoemotional state parameters and hormone concentrations of the hypothalamic-pituitary-thyroid-adrenal axis in the post-COVID period.

MATERIALS AND METHODS

Study design

From November 2021 to May 2025, 126 girls aged 11 to 16 years (mean age 14.84 ± 1.81 years) underwent examination at the clinic of the Scientific Centre for Family Health and Human Reproduction Problems.

At the initial stage of the study, data on the health status of all participants was collected (sex, age, body mass index, COVID-19 PCR test results, details of the acute COVID-19 phase, post-COVID symptoms, and family

history of COVID-19). The presence of post-acute COVID-19 symptoms was determined in accordance with clinical guidelines from the World Health Organization for defining a clinical case of post-COVID-19 condition in children and adolescents (dated February 16, 2023) [4]. To include a participant in the main group with post-COVID symptoms (PCS), they must have experienced one or more of the following: 1) symptoms that developed during or following a COVID-19 infection; 2) symptoms that have persisted for at least two months; 3) symptoms that could not be explained by alternative diagnoses; 4) symptoms that significantly impacted daily activities, such as academic performance, physical activity, and social interactions.

Symptoms of PCS were identified through clinical interviews. The research team, consisting of a pediatrician and psychologist, jointly decided to identify respondents with PCS and include them in the study based on a combination of clinical data, psychological test results, and laboratory parameters.

The comparative group consisted of adolescent girls who experienced COVID-19 within a similar timeframe, but who did not report any symptoms or have clinical manifestations of PCS during a structured interview and psychological assessment.

Based on the data collected, all participants were categorized into three groups:

1. The main group – participants with identified symptoms of PCS (n = 44), consisting of adolescent girls who had COVID-19 between 3 and 24 months before the study and currently experienced health complaints.
2. The comparative group – participants without symptoms of PCS (n = 40), consisting of adolescent girls who had COVID-19 between 3 and 24 months before the study but did not currently experience any health issues.
3. The control group (n = 42), consisting of generally healthy adolescent girls with no history of SARS-CoV-2 infection.

The main group was then divided into four subgroups based on the time since COVID-19 infection:

Subgroup 1.1 (n = 11): 3–5 months after COVID-19 infection.

Subgroup 1.2 (n = 12): 6–9 months after COVID-19 infection.

Subgroup 1.3 (n = 10): 11–12 months after COVID-19 infection.

Subgroup 1.4 (n = 11): 13–24 months after COVID-19 infection.

The second phase assessed the psychoemotional state and hormonal status of adolescent girls in each subgroup.

Eligibility criteria

Inclusion criteria for the study: (1) age 11–16 years (all respondents); (2) a history of laboratory-confirmed mild to moderate COVID-19 (3–24 months before the study) (in the main and comparative groups); (3) presence of symptoms of the post-COVID syndrome (in the main group); (4) absence of symptoms of the post-COVID syndrome (in the comparative group); (5) absence of a positive PCR test for SARS-CoV-2 infection and/or possible COVID-19 symptoms in the medical history (in the control group).

Exclusion criteria for the study: (1) failure to meet the inclusion criteria; (2) the presence of a pituitary microadenoma, hypothalamic dysfunction, obesity, arterial hypertension, or hypogonadism; (3) current or recent (within the past 6 months) use of hormonal medications (thyroid hormone, glucocorticoid hormone); (4) a history of thyroid dysfunction; (5) refusal by the adolescent or their legal representative to participate in the study.

Research methods

Data on the health status of all participants were collected, their psychoemotional state (including well-being, activity, mood, anxiety, and severity of depressive symptoms) was assessed, and serum levels of thyroid-stimulating hormone, free thyroxine, and cortisol were measured.

Clinical history. The following health data were analyzed: sex, age, body mass index (BMI), presence/absence of a positive PCR test for SARS-CoV-2, characteristics of the acute phase of COVID-19, and family history of COVID-19.

The symptoms of PCS were identified through a clinical interview, which included a structured questionnaire for the adolescent girl and her parent/guardian regarding the presence and severity of the following symptoms: fatigue, rapid fatigability; cognitive impairment (memory loss, decreased concentration); sleep disturbances; headaches; mood lability, anxiety; anosmia/dysgeusia; dyspeptic manifestations, and other complaints. To objectify the symptoms, validated psychological methods (WAM, BDI-1A, and the Children's Form of Manifest Anxiety Scale) were used, as well as clinical and laboratory examination data.

The severity of the acute phase of COVID-19 was retrospectively assessed among participants in the main study group in accordance with the Interim Guidelines for the Prevention, Diagnosis, and Treatment of the Novel Coronavirus Infection COVID-19 (Version 17, dated December 14, 2022) [22]. According to these guidelines, mild cases were characterized by symptoms of a respiratory infection, including a low-grade fever (less than 38°C), no shortness of breath, and no evidence of lung damage. In some cases, the only noticeable symptom was loss of smell or taste. Moderate cases were associated with severe fever (a prolonged temperature above 38°C for more than 5 days), shortness of breath, reduced SpO_2, and lung abnormalities typical of viral infection based on computed tomography scans. Treatment for these patients was typically on an outpatient basis [23].

Psychological diagnostics. The following methods were employed to assess the psychoemotional state of adolescent girls: the Beck Depression Inventory (BDI-1A) adapted by N.V. Tarabrina; the "Well-Being. Activity. Mood" (WAM) questionnaire, developed by V.A. Doskin et al.; and the Children's Form of Manifest Anxiety Scale, developed by A.M. Prikhozhan.

Using the Beck Depression Inventory (BDI-1A), developed by A. Beck in 1978 and adapted by N.V. Tarabrina in 2001 [24], the presence of depressive symptoms among adolescent girls was assessed. The scale consists of 13 sets of statements that correspond to various groups of depressive symptoms. Each statement on the scale can be rated from 0 to 3 points, depending on the severity of the symptoms. The overall score ranges from 0 to 9, indicating the absence of depressive symptoms, while scores between 10 and 15 indicate mild depression (or subdepression), scores between 16 and 19 indicate moderate depression, and scores above 20 indicate severe depression.

The "Well-being. Activity. Mood" (WAM) questionnaire, developed in 1973 by V.A. Doskin, N.A. Lavrentieva, V.B. Sharai, and M.P. Miroshnikov [25], consists of 30 pairs of opposing characteristics that the respondent uses to evaluate their state. The respondent marks the number that corresponds to the strength of the particular state. When processing the results, the points obtained are recalculated according to the rule: all positive states always receive high points, and negative states receive low points. The scale is set so that values decrease or increase from 7 to 1 or from 1 to 7, depending on the position of the opposing characteristics in the table. Based on the points obtained, the well-being, activity, and mood levels of the respondent were determined. A score of less than 3.5 points indicates a low level, 3.6-5.5 a moderate level, and over 5.6 a high level of well-being, activity and mood.

To identify anxiety as a relatively stable personality trait among adolescent girls, the Children's Form of Manifest Anxiety Scale was employed [26]. The scale, developed by A.M. Prikhozhan, is based on the adult and child versions of the Taylor Manifest Anxiety Scale (J. Taylor, 1951, 1953; A. Castenada, B.R. McCandless, D.S. Palermo, 1956) and contains 65 items. Analysis of respondents' responses allows for the calculation of "raw" anxiety scores. These "raw" scores are then converted into scale scores (stens) by comparing a subject's data with normative parameters from a group of adolescents of similar age and sex. Based on these resulting scale scores, the severity level of the respondent's anxiety can be determined. Specifically, 1–2 stens indicate a low level of anxiety; 3–6 stens a normal level of anxiety; 7–8 stens for slightly elevated anxiety; 9 stens for high anxiety; and 10 stens for very high anxiety.

Laboratory research methods. Venous blood samples were collected between 8:00 a.m. and 9:00 a.m., on an empty stomach, following generally accepted guidelines. The collection occurred on days 5–9 of the menstrual cycle or during amenorrhea prior to treatment. The blood was then centrifuged at 3,000 RPM for 10 minutes, and the resulting serum was separated and stored in a -80°C freezer until testing. The samples were thawed only once prior to use.

All adolescent girls underwent a hormonal profile assessment. The serum concentrations of thyroid-stimulating hormone (TSH, μIU/ml), free thyroxine (free T4, pmol/l), and cortisol (nmol/l) were measured using enzyme-linked immunosorbent assay (ELISA) with Alkor–Bio test systems (Russia) and the Cobos ELL (USA) enzyme-linked immunosorbent assay system.

Ethical approval

The study was conducted in accordance with the principles outlined in the World Medical Association's Declaration of Helsinki (1964, revised in 2013), and was approved by the Biomedical Ethics Committee of the Scientific Centre for Family Health and Human Reproduction Problems (protocol No. 7, dated October 2, 2020). Parents (or legal representatives) of participants and adolescent girls were informed about the aims, nature, and diagnostic procedures of the study and provided voluntary, informed consent to participate in the research.

Statistical analysis

Sample size calculation principles: no pre-calculated sample size used.

Methods of statistical data analysis: statistical analysis was performed using Statistica 8.0 (StatSoft, Inc., USA). Prior to conducting statistical analysis, the distribution of each variable was assessed using the Shapiro – Wilk test. Quantitative data were described using the arithmetic mean and standard deviation, presented in the format M ± σ. characteristics were presented as absolute counts and event frequencies (percentage of occurrences), and comparisons were made using the Pearson's χ^2 test. Comparisons between independent groups were conducted using the Student's *t*-test. The relationship between variables was assessed using Spearman's correlation coefficient (r), with correlations classified as weak (r = 0.10–0.39), moderate (r = 0.40–0.69), or strong (r = 0.70–1.00). A significance level of $p \leq 0.05$ was used for all statistical tests.

THE RESULTS OF THE STUDY

Analysis of clinical and anamnestic data revealed that the age characteristics of the study participants were comparable across all study groups (Table 1). The mean age of the participants was 14.84 ± 1.81 years, and there were no statistically significant differences in age between the groups ($p = 0.672$). Similarly, analysis of body mass index did not reveal any statistically significant differences between the groups ($p > 0.05$).

A retrospective analysis of the clinical manifestations and severity of COVID-19 during the acute phase of the disease revealed that the majority of participants in the study group (55 %) and in the comparative group (53 %) experienced a moderate course of the disease. A history of a mild COVID-19 infection was observed in 45 % of girls in the study group and 47 % of girls in the comparative group ($p > 0.05$).

Therefore, the study groups were similar in terms of age, body mass index, and the severity of the acute phase of COVID-19.

According to the clinical and anamnestic data obtained, out of the 84 participants who had COVID-19,

40 adolescent girls did not report any health complaints and formed a comparative group without symptoms of post-COVID syndrome (PCS), while 44 participants, who were included in the main group, reported complaints that, according to the clinical guidelines of the World Health Organization for defining a clinical case of post-COVID condition in children and adolescents (dated February 16, 2023), can be classified as manifestations of PCS [4]. The range of post-COVID symptoms among adolescent girls was diverse. Specifically, symptoms of asthenia (weakness, fatigue, rapid fatigability, and decreased resistance to physical activity) were reported by 38 girls (87 %). Cognitive impairment (difficulty concentrating, problems with memory, mental performance and other cognitive issues) was reported by 37 participants (83 %). Mood lability (excitability, tearfulness), irritability, anxiety, or fears (concern for one's health, fear of being alone, or feeling like someone is watching) was reported in 33 participants (76 %), as well as sleep disturbances (difficulties falling asleep, frequent awakenings). Long-term olfactory and gustatory disturbances were reported by 22 individuals (49 %), while dyspeptic symptoms (decreased appetite, abdominal pain, nausea, and in some cases, vomiting) were reported by 14 participants (31 %), and other complaints related to past disease were reported by 5 adolescent girls (12 %). It was observed that the identified symptoms of PCS had a negative impact on the daily activities of the respondents, manifesting themselves through changes in diet, levels of physical and mental activity, behavior, academic performance, and social adjustment.

In addition, subgroups were identified from the main study group based on the duration of PCS symptoms since COVID-19 infection. Specifically, 12 individuals (27 %) reported PCS symptoms between 3–5 months after the disease, 13 individuals (30 %) reported PCS symptoms between 6–9 months after the disease, 8 respondents (18 %) reported PCS symptoms between 11–12 months after the disease, and 11 respondents (25 %) reported PCS symptoms between 13–24 months after COVID-19 diagnosis.

Let us now turn to an analysis of the data collected through the survey. The psychoemotional state parameters for adolescent girls in the post-COVID period are presented in Table 2.

When comparing the parameters of the psychoemotional state between groups of individuals who had experienced COVID-19 and conditionally healthy individuals, the following patterns were observed.

According to the WAM method, the rate of low well-being among patients with PCS symptoms was 27 %, which significantly differed from the prevalence of this parameter among groups without PCS (10 %, $p_{5\text{-}6} = 0.015$) and among conditionally healthy individuals (10 %, $p_{5\text{-}7} = 0.014$). The rate of low activity among respondents with PCS symptoms was recorded in 41 % of cases, which was statistically significantly higher than groups without PCS (20 %, $p_{5\text{-}6} = 0.013$) and among the control group (19 %, $p_{5\text{-}7} = 0.007$). A low emotional state level was observed in 7 % of respondents with PCS symptoms, 3 % of adolescent girls without PCS, and 5 % of conditionally healthy individuals. No statistically significant differences were found between these groups ($p > 0.05$). This may indicate a negative impact of past infection on well-being, including strength, perception of health status, and fatigue, as well as activity, such as mobility and functional tempo, primarily among participants with post-COVID symptoms.

According to the Children's Form of Manifest Anxiety Scale, developed by A.M. Prikhozhan, the frequency of elevated, high, and very high anxiety levels among adolescents with PCS symptoms was 20 %, 5 %, and 16 %, respectively, compared to only elevated (15 %) and high (2 %) anxiety levels among those without PCS symptoms. In the control group, anxiety parameters did not exceed normal values.

TABLE 1

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF ADOLESCENT GIRLS IN THE STUDY GROUPS

Parameter	Study groups						
	With PCS symptoms					Without PCS ($n = 40$)	Control ($n = 42$)
	3-5 months ($n = 12$)	6-9 months ($n = 13$)	11-12 months ($n = 8$)	13-24 months ($n = 11$)	Total ($n = 44$)		
	1	2	3	4	5	6	7
Age, M ± σ	14.8 ± 1.4	14.5 ± 1.7	14.4 ± 1.7	14.2 ± 1.9	14.5 ± 1.6	14.8 ± 1.5	14.2 ± 1.6
BMI (kg/m^2), M ± σ	18.9 ± 1.0	19.8 ± 1.6	19.6 ± 1.0	18.9 ± 1.1	19.3 ± 1.3	19.2 ± 1.1	19.8 ± 1.8
	Severity of COVID-19						
Mild, % (n)	42 ($n = 5$)	54 ($n = 7$)	25 ($n = 2$)	55 ($n = 6$)	45 ($n = 20$)	47 ($n = 19$)	–
Moderate, % (n)	58 ($n = 7$)	46 ($n = 6$)	75 ($n = 6$)	45 ($n = 5$)	55 ($n = 24$)	53 ($n = 21$)	–

Note. PCS – post-COVID syndrome; BMI – body mass index.

TABLE 2

DISTRIBUTION OF ADOLESCENT GIRLS BY LEVEL OF PSYCHOEMOTIONAL STATE IN THE POST-COVID PERIOD (%)

Parameter	Study groups						
	With PCS symptoms					Without PCS (n = 40)	Control (n = 42)
	3-5 months (n = 12)	6-9 months (n = 13)	11-12 months (n = 8)	13-24 months (n = 11)	Total (n = 44)		
	1	2	3	4	5	6	7
Well-being level							
High	17	15	50	27	25	32	40
Moderate	50	46	38	55	48	58	50
Low	33	39	12	18	27	10	10
Reliability of differences	p_{1-2} = 0.790; p_{1-3} = 0.939; p_{1-4} = 0.693; p_{1-6} = 0.141; p_{1-7} = 0.580; p_{2-3} = 0.745; p_{2-4} = 0.864; p_{2-6} = 0.217; p_{2-7} = 0.744; p_{3-4} = 0.664; p_{3-6} = 0.170; p_{3-7} = 0.591; p_{4-6} = 0.350; p_{4-7} = 0.876; **p_{56} = 0.015; p_{57} = 0.014;** p_{6-7} = 0.403						
Activity level							
High	17	8	50	18	20	15	14
Moderate	50	31	25	46	39	65	67
Low	33	61	25	36	41	20	19
Reliability of differences	p_{1-2} = 0.623; p_{1-3} = 0.511; p_{1-4} = 0.908; p_{1-6} = 0.289; p_{1-7} = 0.078; p_{2-3} = 0.252; p_{2-4} = 0.674; p_{2-6} = 0.738; p_{2-7} = 0.260; p_{3-4} = 0.360; p_{3-6} = 0.056; **p_{37} = 0.016;** p_{4-6} = 0.345; p_{4-7} = 0.096; **p_{56} = 0.013; p_{57} = 0.007;** p_{6-7} = 0.197						
Mood level							
High	50	23	50	36	39	42	62
Moderate	42	69	50	55	54	55	33
Low	8	8	–	9	7	3	5
Reliability of differences	p_{1-2} = 0.551; p_{1-3} = 0.908; p_{1-4} = 0.778; p_{1-6} = 0.600; p_{1-7} = 0.786; p_{2-3} = 0.413; p_{2-4} = 0.810; p_{2-6} = 0.812; p_{2-7} = 0.706; p_{3-4} = 0.689; p_{3-6} = 0.524; p_{3-7} = 0.718; p_{4-6} = 0.927; p_{4-7} = 0.933; p_{5-6} = 0.395; p_{5-7} = 0.626; p_{6-7} = 0.784						
Anxiety level							
Low	17	23	–	9	14	8	43
Normal	50	47	38	46	45	75	57
Elevated	25	15	12	27	20	15	–
High	8	–	–	9	5	2	–
Very high	–	15	50	9	16	–	–
Reliability of differences	p_{1-2} = 0.595; p_{1-3} = 0.355; p_{1-4} = 0.850; p_{1-6} = 0.309; **p_{17} = 0.015**; p_{2-3} = 0.768; p_{2-4} = 0.732; p_{2-6} = 0.086; **p_{27} = 0.002**; p_{3-4} = 0.482; **p_{36} = 0.041**; **p_{37} < 0.001**; p_{4-6} = 0.221; **p_{4-7} = 0.009**; **p_{5-6} = 0.006**; **p_{5-7} < 0.001**; p_{6-7} = 0.118						
Severity of depressive symptoms							
Absence	67	39	74	64	59	72	100
Mild	–	8	–	9	5	15	–
Moderate	8	15	13	9	11	5	–
Pronounced	8	23	–	9	11	8	–
Severe	17	15	13	9	14	–	–
Reliability of differences	p_{1-2} = 0.742; p_{1-3} = 0.474; p_{1-4} = 0.285; **p_{1-6} = 0.015**; **p_{1-7} < 0.001**; p_{2-3} = 0.424; p_{2-4} = 0.274; **p_{2-6} = 0.002**; **p_{2-7} < 0.001**; p_{3-4} = 0.898; p_{3-6} = 0.109; **p_{3-7} = 0.013**; p_{4-6} = 0.082; **p_{4-7} = 0.009**; **p_{5-6} = 0.006**; **p_{5-7} = 0.011**; **p_{6-7} < 0.001**						

Note. PCS – post-COVID syndrome; p – significance level for differences between study groups, as determined by Pearson's χ^2 test; here and in Tables 3 and 4, statistically significant values are highlighted in bold.

These differences were statistically significant when comparing the group with PCS symptoms with the group without PCS symptoms ($p_{5-6} = 0.006$) and with the control group ($p_{5-7} < 0.001$).

According to the Beck Depression Inventory (BDI-1A), a small number of participants in the group with PCS symptoms showed mild depressive symptoms (5 %), moderate depressive symptoms (11 %), and severe depressive symptoms (14 %). In the group without PCS, these figures were 15 %, 5 %, 8 %, respectively. No depressive symptoms were found in the control group. The severity of depressive symptoms among adolescent girls with PCS symptoms remains significantly higher than in the group without PCS symptoms ($p_{5-6} = 0.006$) and in conditionally healthy individuals ($p_{5-7} < 0.011$). The difference is statistically significant.

Differences were observed between the group of participants without PCS symptoms and those who were conditionally healthy, with regard to the severity of depressive symptoms only ($p_{6-7} < 0.001$).

Analysis of the dynamics of the psychoemotional state among subgroups of respondents with PCS symptoms has revealed the following patterns.

In the period between 3 and 5 months after the disease, the respondents with PCS symptoms exhibited the following parameters of psychoemotional state: a low level of well-being was observed in 33 % of respondents; low activity levels were recorded in 33 % of respondents; and a low level of mood was registered in 8 % of respondents. Anxiety levels were less pronounced during this period, with elevated levels noted in 25 % and high levels in 8 % of respondents. Statistically significant differences were observed compared to a group of conditionally healthy controls ($p_{1-7} = 0.015$). Depressive symptoms were more pronounced during this time, with moderate and severe symptoms occurring in 8 % and severe symptoms in 17 %, respectively. Significant differences were found compared to the group without PCS symptoms ($p_{1-6} = 0.015$) and conditionally healthy individuals ($p_{1-7} < 0.001$).

By 6–9 months after COVID-19 infection, respondents with PCS symptoms experienced a shift in their psychoemotional profiles. Low levels of well-being were noted in 39 % of respondents. An increase in low activity levels was observed in 61 % of cases. Low mood levels were reported by 8 % of respondents, while a moderate increase in anxiety levels was noted, with elevated levels being reported in 15 % and very high levels being reported by 15 %. Statistically significant differences were identified when compared to a group of conditionally healthy individuals ($p_{2-7} = 0.002$). Depressive symptoms were distributed as follows: mild in 8 %, moderate in 15 %, pronounced in 23 %, and severe in 15 % of respondents. Statistically significant differences persisted when compared to the group without PCS symptoms ($p_{2-6} = 0.002$) and conditionally healthy individuals ($p_{2-7} < 0.001$).

In the period between 11 and 12 months after COVID-19, respondents who had experienced PCS syndrome reported the following changes in their psychoemotional state. A low level of well-being was found in 12 % of the respondents, indicating an improvement trend. A low activity level decreased in 25 % of cases, and significant differences were found compared to a group of conditionally healthy individuals ($p_{3-7} = 0.016$). The level of anxiety continued to increase, with elevated levels reported by 12 % and very high levels by 50 % of respondents. These differences were statistically significant compared to both conditionally healthy individuals ($p_{3-7} < 0.001$) and those without PCS symptoms ($p_{3-6} = 0.041$). Moderate and severe depressive symptoms were reported in 13 % of respondents each, with significant differences compared to the group of conditionally healthy individuals remaining ($p_{3-7} = 0.013$).

In the period between 13 and 24 months after COVID-19, respondents with PCS symptoms showed a partial stabilization of their psychoemotional state parameters. A low level of well-being was observed in 18 % of adolescent girls, while a low level of activity was recorded in 36 % of cases, indicating a slight increase compared to the previous period. Low mood levels were registered in 9 % of respondents with PCS symptoms. Elevated, high, and very high levels of anxiety persisted in 27 %, 9 %, and 9 %, respectively. Statistically significant differences were found between the group with PCS and the group of conditionally healthy individuals ($p_{4-7} = 0.009$). Depressive symptoms exhibited an even distribution, with mild, moderate, pronounced, and severe degrees being reported in 9 % each. Significant differences remained between the individuals with PCS and those without any health issues ($p_{4-7} = 0.009$).

An analysis of the psychoemotional state of adolescent girls who experienced PCS symptoms revealed persistent disturbances throughout the post-COVID period. The severity of depressive symptoms among adolescent girls with PCS was significantly higher than in respondents without PCS or conditionally healthy individuals, and persisted at a statistically significant level throughout the post-COVID period.

Despite the overall downward pattern in poor health outcomes, differences were observed between the non-PCS and control groups throughout the post-COVID period. Similarly, activity parameters showed similar trends, with the most significant impairments occurring between 6 and 9 months after COVID-19.

Therefore, in adolescent girls with PCS symptoms, a deterioration in their psychoemotional state has been observed, mainly during the first 12 months after the disease, which has manifested itself in an increase in the frequency of a low well-being level, decreased activity levels, increased anxiety levels, as well as an increase in depressive symptoms when compared to the control group consisting of individuals without PCS symptoms and conditionally healthy individuals.

Analysis of hormonal status parameters revealed statistically significant differences between the study groups (Table 3). The hypothalamic-pituitary-thyroid axis parameters (TSH and free T4) in adolescent girls remained within reference values regardless of PCS symptoms

or the time since the onset of the disease. However, cortisol levels in adolescent girls with PCS symptoms were on average higher than the reference range (average for the group: 592.00 ± 322.72 nM/l; with a maximum value of 1438.00 nM/l).

When comparing the hormonal status parameters between groups of individuals who had COVID-19 and those who were conditionally healthy, the following patterns emerged. The level of thyroid stimulating hormone (TSH) in the group with PCS symptoms was 2.45 ± 1.32 μIU/ml, significantly different from that in the group without PCS symptoms (1.98 ± 0.75 μIU/ml; $p_{5-6} = 0.008$, $t = 2.012$) and compared to conditionally healthy individuals (1.69 ± 0.62 μIU/ml; $p_{5-7} < 0.003$, $t = 3.407$). The level of free thyroxine (free T4) in the group with PCS symptoms was 14.56 ± 2.68 pM/l and also showed statistically significant differences compared to the group of conditionally healthy individuals ($p_{5-7} = 0.038$, $t = 1.314$). The most significant differences were observed in the level of cortisol concentrations. In the group with PCS symptoms, the parameter reached 592.00 ± 322.72 nM/l, significantly exceeding the values in the comparative groups (454.63 ± 132.44 nM/l; $p_{5-6} < 0.012$, $t = 2.506$) and in conditionally healthy individuals (446.50 ± 110.70 nM/l; $p_{5-7} < 0.001$, $t = 2.770$). At the same time, in 9 adolescent

TABLE 3

INDICATORS OF HORMONAL STATUS OF ADOLESCENT GIRLS IN THE POST-COVID PERIOD (M ± σ)

Study groups			TSH r.r. 0.23 – 3.40 μIU/ml	Free T4 r.r. 10.00 – 23.20 pM/l	Cortisol r.r. 142.00 – 558.00 nM/l
With PCS symptoms	**3-5 months, *n* = 12**	1	2.47 ± 1.45	13.68 ± 2.76	470.67 ± 170.41
	6-9 months, *n* = 13	2	2.90 ± 1.42	14.91 ± 2.76	521.92 ± 308.26
	11-12 months, *n* = 8	3	1.99 ± 1.28	14.40 ± 2.24	876.25 ± 461.39
	13-24 months, *n* = 11	4	2.25 ± 1.04	15.23 ± 2.89	600.45 ± 253.13
	Total, *n* = 44	5	2.45 ± 1.32	14.56 ± 2.68	592.00 ± 322.72
Without PCS, *n* = 40		6	1.98 ± 0.75	14.65 ± 2.28	454.63 ± 132.44
Control, *n* = 42		7	1.69 ± 0.62	13.92 ± 1.72	446.50 ± 110.70
Reliability of differences			$p_{1-2} = 0.837$;	$p_{1-2} = 0.465$;	$p_{1-2} = 0.221$;
			$p_{1-3} = 0.608$;	$p_{1-3} = 0.640$;	**$p_{1-3} < 0.012$;**
			$p_{1-4} = 0.287$;	$p_{1-4} = 0.624$;	$p_{1-4} = 0.172$;
			$p_{1-6} = 0.005$;	$p_{1-6} = 0.572$;	$p_{1-6} = 0.252$;
			$p_{1-7} < 0.011$;	$p_{1-7} = 0.069$;	$p_{1-7} = 0.063$;
			$p_{2-3} = 0.751$;	$p_{2-3} = 0.765$;	**$p_{2-3} = 0.017$;**
			$p_{2-4} = 0.413$;	$p_{2-4} = 0.254$;	$p_{2-4} = 0.853$;
			$p_{2-6} = 0.014$;	$p_{2-6} = 0.525$;	**$p_{2-6} = 0.005$;**
			$p_{2-7} = 0.002$;	$p_{2-7} = 0.724$;	**$p_{2-7} = 0.011$;**
			$p_{3-4} = 0.668$;	$p_{3-4} = 0.307$;	**$p_{3-4} = 0.007$;**
			$p_{3-6} = 0.091$;	$p_{3-6} = 0.902$;	**$p_{3-6} < 0.013$;**
			$p_{3-7} = 0.015$;	$p_{3-7} = 0.330$;	**$p_{3-7} < 0.002$;**
			$p_{4-6} = 0.215$;	$p_{4-6} = 0.208$;	**$p_{4-6} = 0.003$;**
			$p_{4-7} = 0.051$;	**$p_{4-7} = 0.009$;**	**$p_{4-7} < 0.001$;**
			$p_{5-6} = 0.008$;	$p_{5-6} = 0.607$;	**$p_{5-6} < 0.012$;**
			$p_{5-7} < 0.003$;	**$p_{5-7} = 0.038$;**	**$p_{5-7} < 0.001$;**
			$p_{6-7} = 0.800$	$p_{6-7} = 0.074$	$p_{6-7} = 0.449$

Note. PCS – post-COVID syndrome; TSH – thyroid stimulating hormone; free T4 – free thyroxine; r.r. – reference ranges; *p* – significance level for differences between study groups, as determined by Student's *t*-test.

girls (21 %) with PCS symptoms, the serum TSH level exceeded 3.4 μU/ml, with an average value of 4.5 ± 0.8 μU/ml and a maximum value of 6.0 μU/ml, corresponding to subclinical hypothyroidism (elevated TSH level with normal free T4 levels).

Analysis of the dynamics of hormonal parameters in subgroups of respondents with PCS symptoms has revealed the following patterns.

In the period between 3 and 5 months after COVID-19, hormonal parameters remained within the reference ranges: average TSH levels were 2.47 ± 1.45 μIU/ml, free T4 was 13.68 ± 2.76 pM/l, and cortisol was 470.67 ± 170.41 nM/l. However, statistically significant differences compared to groups without PCS symptoms and conditionally healthy individuals were only observed in TSH levels ($p_{1-6} = 0.005$, $t = 1.588$; $p_{1-7} < 0.011$, $t = 2.761$; respectively).

In the period between 6 and 9 months after COVID-19, respondents with PCS symptoms showed a change in their hormonal profile. The TSH level in the blood serum increased to 2.90 ± 1.42 μIU/ml, while free T4 increased to 14.91 ± 2.76 pM/l and cortisol reached 521.92 ± 308.26 nM/l. Significant differences were observed between the groups without PCS symptoms and conditionally healthy individuals in TSH concentrations ($p_{2-6} = 0.014$, $t = 3.032$; $p_{2-7} < 0.002$, $t = 4.379$, respectively) and cortisol levels ($p_{2-6} = 0.005$, $t = 1.115$; $p_{2-7} < 0.011$, $t = 1.350$, respectively).

In the period between 11 and 12 months after COVID-19, respondents with PCS symptoms demonstrated the most significant deviations in their hormonal profiles compared to pre-pandemic levels. Specifically, TSH levels decreased to 1.99 ± 1.28 μIU/ml, while free T4 levels increased to 14.40 ± 2.24 pM/l. Cortisol levels increased sharply to 876.25 ± 461.39 nM/l, indicating statistically significant differences in TSH levels and cortisol levels compared to those in conditionally healthy individuals ($p_{3-7} = 0.015$, $t = 1.011$; $p_{3-7} < 0.002$, $t = 5.468$, respectively). Moreover, among adolescent girls, cortisol levels were statistically significantly higher during this period compared to other subgroups and those without PCS symptoms ($p_{1-3} < 0.012$, $t = -2.803$; $p_{2-3} = 0.017$, $t = -2.119$; $p_{3-4} = 0.007$, $t = 1.676$; $p_{3-6} = 0.013$, $t = 5.007$, respectively).

In the period between 13 and 24 months after COVID-19, respondents with PCS symptoms demonstrated a partial normalization of hormonal profile parameters. Specifically, TSH levels were 2.25 ± 1.04 μIU/ml, free T4 levels were 15.23 ± 2.89 pM/l, and cortisol levels were 600.45 ± 253.13 nM/l. Significant differences with respect to the parameters of conditionally healthy individuals were still observed in terms of TSH and cortisol concentrations in the blood ($p_{4-7} = 0.051$, $t = 2.253$; $p_{4-7} < 0.001$, $t = 3.036$, respectively). Additionally, among adolescent girls, only cortisol levels were statistically significantly higher compared to those of respondents without PCS symptoms ($p_{4-6} < 0.003$, $t = 2.605$).

The hormonal status parameters in adolescent girls without PCS symptoms were slightly higher than in the group of conditionally healthy individuals. However, no significant differences were observed between the two groups ($p > 0.05$).

Statistically significant correlations were observed between psychoemotional state and hypothalamic-pituitary-thyroid-adrenal axis parameters during the post-COVID period (Table 4). It is worth noting that correlation analysis did not reveal any statistically significant relationships between parameters of psychoemotional state and free T4 levels, either in the overall group of girls with PCS or in subgroups based on the time since COVID-19 infection (all $p > 0.05$).

In summary, a strong direct correlation was observed between the severity of depressive symptoms as measured by the Beck scale and TSH levels (r = 0.897, $p = 0.002$), as well as between anxiety levels as assessed by the A.M. Prikhozhan questionnaire and cortisol levels (r = 0.991, $p = 0.001$). A negative correlation was found between parameters of well-being as measured by the WAM method and TSH levels, with higher TSH levels associated with decreased well-being levels (r = -0.798, $p = 0.006$), decreased activity levels (r = -0.898, $p = 0.002$) and decreased mood levels (r = -0.521, $p = 0.015$). Analysis of changes in psychological well-being over time showed the strongest correlations in the period between 6 and 9 months after COVID-19 infection, with increases in TSH associated with worsening well-being, decreased mood, and increased severity of depressive symptoms (r = -0.837, $p = 0.002$; r = -0.305, $p = 0.028$; r = 0.899, $p = 0.002$, respectively). In the 3–5 and 13–24-month periods after COVID-19 infection, there were strong correlations observed between increases in TSH levels and decreases in activity (r = -0.798, $p = 0.006$). Increases in morning cortisol levels were also correlated with increases in anxiety throughout the post-COVID period, with the strongest correlations occurring in the period between 11 and 12 months after infection (r = 0.832, $p < 0.002$). It should be noted that the correlation between anxiety and cortisol levels is a well-known physiological phenomenon that reflects the activation of the hypothalamic-pituitary-adrenal axis during times of stress. However, in the context of the post-COVID syndrome, this correlation takes on particular significance, as elevated cortisol and anxiety levels persist for up to 24 months after infection, potentially indicating dysregulation of stress-response mechanisms in the body in the post-COVID period.

The established correlations between the psychoemotional state and the hormonal status confirm that post-COVID disturbances affect multiple regulatory systems in the body and manifest through interconnected mechanisms. The identified relationships between psychoemotional state parameters (anxiety, depression, and subjective well-being) and concentrations of hormones from the pituitary, thyroid, and adrenal glands indicate the involvement of neuroendocrine regulation in the pathogenesis of the psychoemotional manifestations of PCS in adolescent girls.

DISCUSSION

Most available data on the health status of individuals in the post-COVID period focus on outcomes among previously hospitalized children and adolescents, and do not include patients with a milder course of the infection [8]. Furthermore, the samples often consist of the results of phone interviews with parents or guardians based on pre-designed questionnaires [14]. Our study took into consideration the self-reported complaints of adolescent girls as well as their health data and laboratory and instrumental test results. This enabled us to identify autonomic and psychoemotional disorders associated with PCS in 44 adolescent girls, which caused significant distress in daily life and persisted over a prolonged period after COVID-19 infection. Additionally, there was no correlation between mild to moderate COVID-19 clinical course and the development of PCS symptoms.

The results obtained demonstrate the complex impact of SARS-CoV-2 on the psychoemotional and endocrine systems of adolescent girls in the post-COVID period. The identified psychoemotional disorders in these girls are consistent with international studies showing a high incidence of depressive and anxiety disorders in the post-COVID period. A detailed analysis of their psychoemotional state revealed a predominance of high levels of situational and personal anxiety, as well as lower levels of well-being (strength, self-perception of health, and fatigue) and emotional state [13]. In the study conducted by K.V. Zhmerenetsky et al., children aged 15–17 who had COVID-19 showed lower levels of well-being (strength, self-perception of health, and fatigue) and emotional state (4.1 ± 1.28 and 4.4 ± 1.08 points) compared to those who had not been infected (5.016 ± 1.23 vs. 5.3 ± 1.09) [27].

It should be noted that adolescence is a period characterized by increased susceptibility to stress, owing to active neural development, hormonal changes, and the establishment of psychosocial identity. Furthermore, adolescent girls are more likely to experience psychoemotional difficulties compared to boys, possibly due

TABLE 4

RESULTS OF CORRELATION ANALYSIS OF PSYCHOEMOTIONAL STATE INDICATORS WITH THYROID-STIMULATING HORMONE AND CORTISOL CONCENTRATIONS OF ADOLESCENT GIRLS IN THE POST-COVID PERIOD (SPEARMAN'S CORRELATION COEFFICIENT)

Study groups		Hormone WB	Psychoemotional state parameters				
			WB	Act.	M	Anx.	D
With PCS symptoms	3-5 months (*n* = 12)	TSH	**-0.698 *p* < 0.011**	**-0.897 *p* < 0.002**	-0.343 *p* = 0.275	0.129 *p* = 0.688	**0.695 *p* < 0.013**
		Cortisol	-0.063 *p* = 0.846	0.088 *p* = 0.787	-0.056 *p* = 0.863	**0.688 *p* < 0.011**	0.077 *p* = 0.811
	6-9 months (*n* = 13)	TSH	**-0.837 *p* < 0.002**	**-0.697 *p* < 0.013**	**-0.305 *p* = 0.028**	-0.364 *p* = 0.221	**0.899 *p* < 0.002**
		Cortisol	0.371 *p* = 0.212	0.371 *p* = 0.212	0.069 *p* = 0.823	**0.689 *p* < 0.013**	-0.377 *p* = 0.204
	11-12 months (*n* = 8)	TSH	**-0.676 *p* < 0.014**	**-0.676 *p* < 0.011**	-0.635 *p* = 0.091	-0.013 *p* = 0.976	**0.694 *p* < 0.011**
		Cortisol	-0.122 *p* = 0.774	-0.293 *p* = 0.482	0.120 *p* = 0.778	**0.832 *p* < 0.002**	0.168 *p* = 0.691
	13-24 months (*n* = 11)	TSH	**-0.695 *p* < 0.012**	**-0.798 *p* < 0.006**	-0.534 *p* = 0.090	0.274 *p* = 0.415	**0.698 *p* < 0.013**
		Cortisol	-0.256 *p* = 0.448	-0.246 *p* = 0.466	-0.059 *p* = 0.862	**0.695 *p* < 0.014**	0.219 *p* = 0.518
	Total (*n* = 44)	TSH	**-0.798 *p* < 0.006**	**-0.898 *p* < 0.002**	**-0.521 *p* < 0.015**	-0.035 *p* = 0.821	**0.897 *p* < 0.002**
		Cortisol	0.058 *p* = 0.708	0.038 *p* = 0.808	0.061 *p* = 0.693	**0.991 *p* < 0.001**	-0.043 *p* = 0.780

Note. PCS – post-COVID syndrome; TSH – thyroid stimulating hormone; WB – well-being; Act. – activity; M – mood; Anx. – anxiety; D – symptoms of depression.

to hormonal imbalances, heightened emotional reactivity, and variations in coping mechanisms.

The findings of thyroid function abnormalities in the form of elevated TSH levels with normal free T4 concentrations may be attributed to both the direct cytopathic effect of the virus on the thyroid gland and the indirect effect through the hypothalamic-pituitary axis [28]. Our results are supported by the research conducted by Lazareva et al. [21]. The authors found that in the post-COVID period, TSH secretion levels in children aged 5–17 were doubled (mean 4.9 ± 0.38; max = 7.78 μU/ml) compared to the reference group of healthy children (mean 1.56 ± 0.08 μU/ml) while free T4 remained within reference ranges.

The mechanism of thyroid dysfunction in COVID-19 may be due to several factors. Firstly, direct damage to thyrocytes, as the thyroid gland expresses ACE2 receptors, which serve as the entry point for SARS-CoV-2 [20]. Secondly, a systemic inflammatory response, with an increase in pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β), can disrupt the synthesis and secretion of thyroid hormones [29]. Thirdly, a stress-induced increase in cortisol levels can inhibit the function of the hypothalamic-pituitary-thyroid axis [30].

Elevated cortisol levels in adolescent girls with PCS may reflect a chronic activation of the hypothalamic-pituitary-adrenal axis. This could be due to both direct effects of the virus on adrenal glands and prolonged psychoemotional stress associated with PCS symptoms. Hypercortisolism, in turn, may exacerbate thyroid dysfunction and contribute to the development of psychoemotional disorders.

The established correlations between psychoemotional state and hormonal parameters support the concept of a close interplay between the endocrine and nervous systems. Increased levels of thyroid hormones are linked to the emergence of depressive symptoms, while hypercortisolism contributes to the development of anxiety disorders.

The temporal dynamics of the identified disorders indicate peak severity in the period between 6 and 12 months after COVID-19, followed by a trend towards improvement. However, even up to 13–24 months after the disease, the parameters have not returned to control group levels, indicating the persistent nature of long-term post-COVID-19 complications.

CONCLUSION

Post-COVID syndrome in adolescent girls is characterized by dysfunctions of the psychoemotional state and endocrine system. These changes include thyroid dysfunction (subclinical hypothyroidism) and adrenal dysfunction (hypercortisolism), as well as the development of depressive and anxious symptoms. The correlations between the psychoemotional state and hormonal parameters support the concept of an interaction between the endocrine and nervous systems. Therefore, we recommend actively screening adolescent girls for post-COVID syndrome symptoms three months after infection. If any complaints are reported, a comprehensive clinical, psychological, and hormonal examination is warranted. A multidisciplinary approach involving a pediatrician, psychologist, and endocrinologist is recommended for rehabilitation. It is important to pay particular attention to girls during the 6–12-month period after COVID-19, as psychoemotional and hormonal disturbances reach their peak at this time.

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Conflicts of interest

The authors declare no conflicts of interest.

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PSYCHOLOGY AND PSYCHIATRY

PSYCHOMETRIC PROPERTIES ANALYSIS OF THE HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS) ON A SAMPLE OF RUSSIAN-SPEAKING STUDENTS

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RESUME

Background. *Universal and student-specific stressors can lead to the development of anxiety and depression. The Hospital Anxiety and Depression Scale (HADS) has proven effective in various populations. However, measuring anxiety, depression, and stress in the student population may have its own peculiarities, which create a need for a tailored tool to assess anxiety and depression levels among young people studying in higher education institutions.*
The aim. *Assessment of the psychometric properties, including the factor structure, reliability, and external validity of the HADS in Russian-speaking students.*
Materials and methods. *The sample consisted of 891 students, including 198 males (22 %) and 693 females (78 %), aged 16 to 37 years (mean age is 19.8, median age – 19.0, SD = 2.13).*
Results. *The Cronbach's alpha for the "Anxiety" subscale was 0.73, for the "Depression" subscale it was 0.62, and for the overall questionnaire it was 0.79. Principal Component Analysis confirmed the alignment of the questionnaire's structure with the original two-factor model proposed by the authors. Both the full model and a reduced model (excluding item 6) derived from confirmatory factor analysis demonstrated similar model fit indices. Based on the comparison of principal component and confirmatory analyses, it was decided to exclude item 6 from the questionnaire while retaining item 11 in the second factor.*
Conclusions. *The analysis concluded that the Hospital Anxiety and Depression Scale exhibits satisfactory psychometric properties and can be used for screening emotional distress among students.*

Keywords: *anxiety, depression, psychometrics, Hospital Anxiety and Depression Scale, students*

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АНАЛИЗ ПСИХОМЕТРИЧЕСКИХ СВОЙСТВ ГОСПИТАЛЬНОЙ ШКАЛЫ ТРЕВОГИ И ДЕПРЕССИИ (HADS) НА ВЫБОРКЕ РУССКОЯЗЫЧНЫХ СТУДЕНТОВ

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РЕЗЮМЕ

Обоснование. *Универсальные и специфические для студентов стрессоры могут вести к развитию тревоги и депрессии. «Госпитальная шкала тревоги и депрессии» (HADS) доказала свою эффективность в различных популяциях. Методика измерения тревоги, депрессии и стресса в студенческой популяции может иметь свои особенности, поэтому существует необходимость в получении инструмента для оценки уровней тревоги и депрессии среди молодежи, обучающейся в высших учебных заведениях.*

Цель исследования. *Оценка психометрических свойств, в том числе, факторной структуры, надежности и внешней валидности HADS на русскоязычных студентах.*

Методы. *Дизайн исследования включал однократное прохождение участниками Госпитальной шкалы тревоги и депрессии в онлайн-формате. В исследовании принимали участие студенты российских высших учебных заведений. Данные собирались в течение 1,5 месяцев.*

В выборку вошел 891 студент, из них 198 мужчин (22 %) и 693 женщины (78 %) в возрасте от 16 до 37 лет (средний возраст 19,8 года, медианный возраст 19,0 года, стандартное отклонение 2,13). Факторная структура анализировалась с использованием анализа главных компонент и конфирматорного факторного анализа, надежность оценивалась с помощью коэффициента альфа Кронбаха, которая для субшкалы «Тревога» составила 0,73, для субшкалы «Депрессия» – 0,62, а для общей шкалы – 0,79.

Результаты. *Анализ главных компонент подтвердил соответствие структуры опросника исходной двухфакторной модели, предложенной авторами. Как полная, так и сокращенная модель (с исключением пункта 6), полученные в ходе конфирматорного факторного анализа, показали схожие индексы соответствия модели. По результатам сравнения анализа главных компонент и конфирматорного факторного анализа было принято решение исключить пункт 6 из опросника, оставив пункт 11 во втором факторе.*

Заключение. *Анализ показал, что «Госпитальная шкала тревоги и депрессии» обладает удовлетворительными психометрическими характеристиками и может использоваться для скрининга эмоционального дистресса среди студентов.*

Ключевые слова: *тревога, депрессия, психометрика, «Госпитальная шкала тревоги и депрессии», студенты*

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INTRODUCTION

The Hospital Anxiety and Depression Scale (HADS) was developed in 1983 [1]. The authors designed a self-report mood scale for use in non-psychiatric settings. Due to the requirement for a concise questionnaire, they limited the scale to two main areas: anxiety and depression. This scale consists of 14 items and two subscales (each with 7 items):

I. Depression, which measures the severity of depressive symptoms (normal, subclinical, and clinical depression);

II. Anxiety. The scale reflects the level of anxiety symptoms (from normal to clinical anxiety).

Responses are provided on a 4-point Likert scale. It should be noted that the authors sought to develop a tool for assessing emotional changes in a patient's condition, irrespective of their physical health condition.

The level of depression and anxiety is determined based on the scores obtained: scores between 0 and 7 indicate a normal level, scores between 8 and 10 indicate a subclinical level, and scores of 11 or higher indicate a clinical level of anxiety and depression [1]. The questionnaire has been validated by researchers from various countries [2–4] and is widely used by psychologists to assess the levels of anxiety and depression across different populations [5–8]. It has also been proven to be effective for use with Russian-speaking individuals [9–11].

Limitations of Russian-language adaptation studies include small sample sizes, difficulties in correlating individual items with selected factors based on factor loadings, and a lack of confirmatory factor analysis procedures [9, 10]. This study aims to explore these issues and potential solutions.

Validation in clinical populations. Studies conducted in various Russian clinical settings examined the psychometric properties of the HADS in patients with movement disorders [11]. The study included 100 patients who were undergoing inpatient rehabilitation after a stroke or due to chronic musculoskeletal conditions. The HADS was found to have a tendency to over-diagnose anxiety and depression in comparison with the Hamilton Anxiety Scale and Hamilton Rating Scale for Depression. However, the HADS demonstrated satisfactory internal consistency and discriminant validity. Based on the results of the study, adjusted cutoff values were proposed for the HADS-A (9 points for anxiety) and HADS-D (9 points for depression) to improve the accuracy of screening in this patient population. The modified adaptation of the HADS exhibited high specificity but lower sensitivity, indicating that it is primarily useful as a screening tool to identify patients who may require additional psychological assessment. Another study discusses the validation of the Russian-language adaptation of the HADS among patients with mental disorders and healthy controls [10]. A sample of 283 participants was evaluated, and a factor analysis confirmed the two-factor structure of the scale. The study demonstrated high internal consistency, with the Cronbach's alpha values of 0.90 for the overall scale, 0.86 for anxiety, and 0.84 for depression, confirming the reliability of the instrument. Based on predictive modeling and ROC analysis, optimal cut-off points were proposed for identifying depressive (9 points) and anxious (10 points) symptoms, as well as general symptoms (18 points). These findings support the validity and reliability of the Russian adaptation of HADS and recommend its use in clinical practice for screening for anxiety and depressive disorders.

Validation in student populations. No studies were identified that specifically addressed the adaptation of the Russian HADS for student populations. However, several studies have utilized an existing adaptation of the questionnaire in order to examine student samples. For example, one study conducted among 404 first-year medical students employed the HADS in conjunction with the Zung Self-Rating Anxiety Scale [12]. Another study found that levels of anxiety and depression among students increased during distance learning, potentially impacting their ability to assimilate educational material [13]. Furthermore, a study conducted among first- and sixth-year medical students revealed a high prevalence of anxiety and depression [14]. Subclinical anxiety was detected in 20.68 % of participants, and clinical anxiety in 18.62 %. Subclinical depression was observed in 15.16 % of students, and clinical depression in 7.59 %. These results underscore the need for regular monitoring of the psychoemotional well-being of medical students. Overall, the aforementioned studies support the need to validate and evaluate the psychometric characteristics of the method using student samples.

Psychometric properties of the Russian-language adaptation of the HADS. The psychometric characteristics of the Russian-language adaptation of the HADS demonstrate a level of comparability with other adaptations. One key indicator of reliability is internal consistency, which was assessed using the Cronbach's alpha coefficient. The values typically range from 0.77 to 0.85 for both the anxiety and depression subscales, which is consistent with the results of other studies [15]. Furthermore, factor analysis has confirmed that the Russian adaptation of the HADS retains the original two-dimensional structure with separate components for anxiety and depression. This finding is supported by other research [16]. Additionally, studies have indicated that the commonly used cutoff value of ≥ 8 can be applied to the general population of Russian speakers. However, there is some evidence that suggests the need for slight adjustments depending on demographic or clinical factors [17].

Problems with previous research. Previous studies on the HADS among Russian-speaking populations primarily focused on clinical samples and specific subgroups. It is important to note that the stressors experienced by students which can lead to anxiety and depression development include not only general stressors common to all age groups (such as economic crises, loss of loved ones, and moving to a new residence), but also specific stressors unique to students (such as academic workload, adjusting to university life, interactions with professors,

and peers). Therefore, methods for assessing anxiety, depression, and stress among students may have specific characteristics that require further validation. The current study aims to fill this gap by thoroughly evaluating the psychometric properties of the HADS scale among Russian-speaking student populations.

THE AIM OF THE STUDY

To evaluate the psychometric characteristics, including the factor structure, internal consistency, and external validity, of the HADS among Russian-speaking students. The study aimed to analyze the questionnaire's factor structure, assess its external validity and reliability, and investigate differences across gender, age, years of study, and levels of education.

METHODS

Sample. The initial sample consisted of 1,202 observations. After eliminating missing values, 1,047 observations were retained. Following the exclusion of observations based on reaction times and a Mahalanobis distance test, 908 observations remained. After eliminating implausible ages (< 0) and study years (> 10), as well as uncertain ages, 891 students remained in the sample. The final sample consisted of 891 individuals, of which 198 (22 %) were male and 693 (78 %) were female. The participants' ages ranged from 16 to 37 years, with a mean of 19.8 and a median of 19 years. The standard deviation was 2.13 years. Among the sample, 350 (39 %) were first-year students, 217 (24 %) were second-year students, 189 (21 %) were third-year students, 108 (12 %) were fourth-year students, 19 (2.1 %) were fifth-year students, and 8 (1 %) were sixth-year students; 527 (59 %) of the students were enrolled in bachelor's degree programs, 323 (36 %) in master's programs, 40 (4 %) in specialist programs, and one (0.1 %) was a graduate student; 886 (99 %) of students were studying on a full-time basis, 5 (0.5 %) on a part-time basis; 539 (60 %) of students studied technical specialties (STEM), 288 (32 %) studied humanities, and 64 (7 %) studied natural sciences or other fields; 621 (70 %) of the participants resided in Belgorod and 270 (30 %) in Yekaterinburg. All participants provided informed consent to participate in the study. The project was approved by the Ethics Committee of the Ural Federal University (Protocol No. 4, dated September 20, 2023). Testing was conducted at the end of the second semester of the academic year (May–June).

Questionnaires. The Hospital Anxiety and Depression Scale (HADS), developed in 1983 [1] and validated on a sample of Russian speakers [1, 11], consists of 14 items and 2 subscales (each containing 7 items): depression and anxiety.

Statistical analysis. Statistical analysis was performed using Python 3.11 and R 4.4.1. The nonparametric Mann – Whitney test was used to compare differences in HADS prevalence between gender and age groups. Spearman's correlation coefficient was employed to assess the association between the HADS subscales and the external validity of the instrument. The Cronbach's alpha coefficient was used to evaluate the internal consistency of the HADS and its subscales. Confirmatory factor analysis (CFA) using the DWLS estimator was conducted to examine the factor structure of the HADS.

RESULTS

Principal component analysis

A principal component analysis was conducted to assess preliminarily the number of factors present in the questionnaire. Based on the scree plot, a two-factor model was identified as the most appropriate (Fig. 1).

To analyze the distribution of items across factors, we present the factor loadings are presented in Table 1.

As can be seen from Table 1, items 1–5 and 7 are part of Factor 1, whereas items 8–10 and 12–14 belong to Factor 2. Item 6 does not reach the 0.3 threshold for factor loadings and, therefore, cannot be assigned to either factor. Consequently, it has been decided to exclude this item from the factor analysis. Item 11 has factor loadings that are similar for both factors. Theoretically, this item should belong to Factor 2 (depression scale), but its factor loading is somewhat biased towards Factor 1 (anxiety scale).

Confirmatory factor analysis (CFA)

Confirmatory factor analysis was used to validate and refine the factor structure of the model. The DWLS estimator was employed in the CFA. The two-factor model with correlated factors demonstrated acceptable fit indices (Table 2).

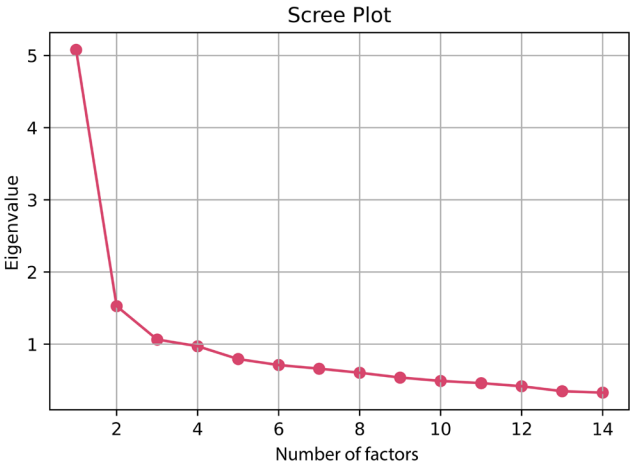

FIG. 1.
Results of principal component analysis for the Hospital anxiety and depression scale (HADS)

For the two-factor model excluding item 6 from the Anxiety scale, there was a slight increase in the RMSEA and SRMR values (indicating a worsening of model fit), but the overall model quality remained within acceptable limits. The TLI and CFI values remained unchanged from the original model. The two-factor model excluding item 6 of the Anxiety scale and 2 items of the Depression scale outperformed the model excluding item 6 of the Anxiety scale across all fit criteria. Compared to the original model, which included all items, this model demonstrated improved TLI and CFI values, but worse RMSEA and SRMR values. Based on these findings, it was decided to proceed with validating the model excluding item 6. Item 11 was assigned to the Anxiety scale.

Descriptive statistics

Next, descriptive statistics were analyzed. General descriptive characteristics are presented in Table 3. Frequency distribution histograms and box plots are presented in Figure 2. The distribution of anxiety, depression, and HADS total scores is skewed towards lower values, which reflects the normative nature of the study population.

Descriptive statistics by gender

Statistically significant gender differences were observed in HADS Anxiety Scale scores. Female participants demonstrated higher scores compared to male participants ($p = 0.020$). No statistically significant differences were observed in the HADS total score or depression scale (Table 4, Fig. 3).

TABLE 1

FACTOR LOADINGS OF HADS ITEMS FOR PCA

№ of the item	Factor 1	Factor 2
1	0.748	0.227
2	0.725	0.192
3	0.775	0.212
4	0.557	0.352
5	0.711	0.196
6	0.151	0.008
7	0.667	0.222
8	0.065	0.592
9	0.063	0.388
10	0.419	0.487
11	0.389	0.378
12	0.190	0.410
13	0.239	0.664
14	0.122	0.500

Note. Initially, items 1–7 were classified as belonging to the Anxiety subscale, and items 8–14 were classified as belonging to the Depression subscale.

TABLE 2

FIE INDICES FOR DIFFERENT VARIANTS OF 2-FACTOR MODELS

Model	TLI	CFI	RMSEA	SRMR
Two-factor model Factor 1: Items 1–7 Factor 2: Items 8–14				
Initial two-factor model (including all items)	0.984	0.987	**0.058** [0.051; 0.065]	0.057
Two-factor model excluding item 6	0.984	0.987	0.062 [0.055; 0.070]	0.059
Two-factor model excluding item 6 and item 9	**0.987**	**0.990**	0.060 [0.052; 0.068]	**0.055**
Two-factor model excluding item 6 and item 11	**0.985**	**0.988**	0.061 [0.053; 0.069]	**0.056**
Two-factor model Factor 1: Items 1–7, 11 Factor 2: Items 8–10, 12–14				
Two-factor model excluding item 6	0.978	0.982	0.073 [0.066; 0.081]	0.067

Descriptive statistics by year of study

Statistically significant differences were observed between students in their first and second years of study (early-year students) and those in their third to sixth years (later-year students). Early-year students exhibited higher scores on the HADS total score, anxiety subscale, and depression subscale (Table 5, Fig. 4).

Descriptive statistics by education level

Statistically significant differences were observed between undergraduate students and other groups of students (specialists, master's students, and doctoral candidates) in terms of the HADS total score and depression scale. Undergraduate students demonstrated higher scores (Table 6, Fig. 5).

Correlations between subscales

Correlations between subscales were calculated. The HADS total score and each of its subscale scores demonstrated statistically significant positive correlations with each other (Table 7).

Internal consistency

An internal consistency analysis was also conducted. The Cronbach's alpha coefficient was 0.73 for the anxiety scale, 0.62 for the depression scale, and 0.79 for the HADS total score.

External validity

External validity was assessed through correlations with the Perceived Stress Scale (PSS) and the Mental Toughness Questionnaire (MTQ) [18]. The Cronbach's alpha coefficient for the MTQ in our sample was 0.77. The correlation between the HADS total score and the PSS total score was 0.72 ($p < 0.001$). The correlation between the HADS anxiety scale and the PSS was 0.73 ($p < 0.001$), and between the HADS depression scale and the PSS was 0.52 ($p < 0.001$). The correlation between the HADS total score and the MTQ was -0.61 ($p < 0.001$), between the HADS anxiety scale and the MTQ was -0.57 ($p < 0.001$), and between the HADS depression scale and the MTQ -0.49 ($p < 0.001$).

DISCUSSION

A preliminary statistical analysis of the data collected from students who completed the Hospital

TABLE 3

GENERAL DESCRIPTIVE STATISTICS FOR THREE SCALES OF HADS

	Mean	Standard deviation	Median	Q1	Q3	Min/max
HADS total score	10.90	6.45	10.0	6.0	15.0	0/35
HADS-A	5.89	3.87	5.0	3.0	8.0	0/18
HADS-D	5.03	3.47	4.0	3.0	7.0	0/18

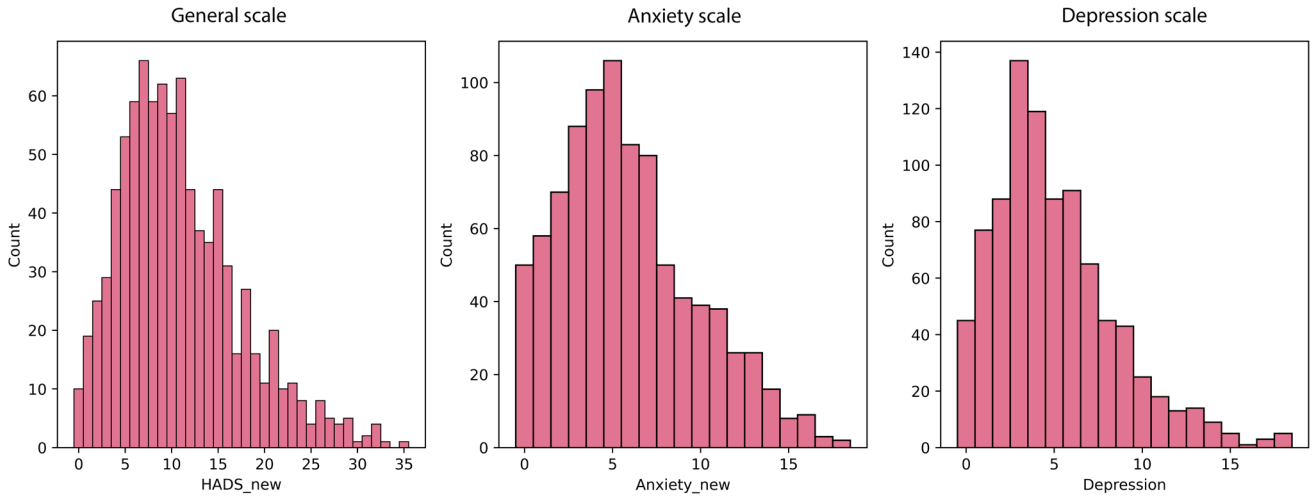

FIG. 2.

Histograms of the distribution of response frequencies for Anxiety, Depression and General scale of HADS. Vertical axis (Count) – frequency of responses; horizontal axis (Anxiety_new, Depression or HADS_new) – sum of scores of the corresponding scale.

Anxiety and Depression Scale questionnaire has allowed us to identify several key statistical indicators and examine the distribution patterns of anxiety and depressive symptoms. The analysis revealed that the anxiety and depression scores tend to be skewed towards lower values, which is consistent with the findings in a normative group [19].

A psychometric analysis of the HADS assessed the reliability, factor structure, and age and gender differences of the test. Cronbach's alpha was 0.73 for the anxiety subscale, 0.62 for the depression subscale, and 0.79 for the total questionnaire. Principal components analysis confirmed the structure of the questionnaire's conformity to the original two-factor model proposed by the authors. Item 6 demonstrated a low factor load, while item 11 was distributed equally across both factors. Confirmatory factor analysis allowed us to evaluate different models: the complete model and the simplified model (excluding item 6) demonstrated comparable fit indices. Based on the comparison of the results from principal components analysis and confirmatory factor analysis, we decided to eliminate item 6 and assign item 11 to factor 2. Therefore, the proposed structure of the questionnaire differs from the theoretical model only by the absence of item 6. A possible explanation for the low factor loadings of item 6 (I cannot sit still; I need to constantly move) may be that difficulties with persistence can be observed not only in cases of anxiety disorders, but also in other conditions (for example, attention deficit hyperactivity disorder and manic episodes).

It should be noted that international adaptations of the HADS have revealed cross-cultural differences in its structure. For example, a 2019 study (pre-COVID-19) using a sample from Poland found that the average anxiety level was 7.19 and depression level was 4.63. In our own sample these levels were 7.44 and 5.24, respectively [20]. In that study, the sixth and ninth items loaded on the "Anxiety" and "Depression" factors, respectively. However, this factor structure was not replicable in other studies using different samples. Another adaptation of the HADS, using an Indonesian sample of 200 individuals aged 18–30 years (including only 8 students), also showed a mixed

TABLE 4

DESCRIPTIVE STATISTICS BY GENDER AND GENDER DIFFERENCES

	Males		Females		Differences (M-F)	*p*-value (Mann–Whitney test)
	M	Sd	M	Sd		
HADS total score	10.79	6.85	10.94	6.33	-0.14	0.41 (67438)
Anxiety	5.41	4.12	6.02	3.78	-0.61	0.02 (62585)
Depression	5.36	3.67	4.94	3.41	0.41	0.24 (73900)

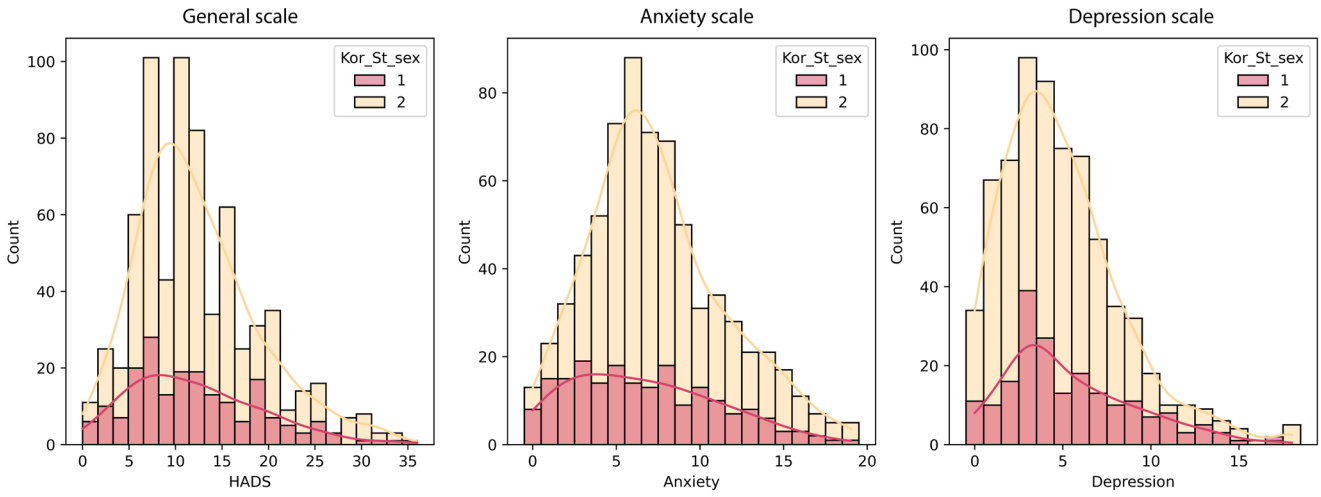

FIG. 3.

Histograms of the distribution of response frequencies for Anxiety, Depression and General scales of HADS by gender (1 – male – red; 2 – female – yellow). Vertical axis (Count) – frequency of responses; horizontal axis (Anxiety, Depression or HADS) - sum of scores of the corresponding scale

structure where the anxiety and depression items were distributed across two factors and does not correspond to the original English version [21]. The Cronbach's alpha coefficients for the anxiety and depression subscales were 0.80 and 0.85, respectively.

Our study revealed significant gender differences in anxiety levels, with women reporting higher average scores than men. This is consistent with previous research on anxiety [22]. Generally, women and girls tend to experience higher levels of anxiety [23], both as a stable personality trait and in specific situations, such as academic anxiety [24]. The prevalence of extreme manifestations associated with anxiety disorders is also higher among women, which can be attributed to biological [25] and social factors. Specifically, in cultures where it is more socially acceptable for women to discuss mental health issues, they are more likely to seek professional help, compared to men, who may provide socially desirable responses in psychological assessments [26].

Statistically significant differences in anxiety and depression levels between early-year students (1st–2nd years of study) and later-year students (3rd–6th years of study) suggest that age and educational level influence these factors. High scores on the HADS among early-year students may be due to their adaptation to a new academic environment, a lack of experience with stress management, and uncertainty about their future. In contrast, decreased anxiety and depression among later-year students can be explained by their development of coping strategies, increased social support, and a clearer understanding of their career prospects. These results are consistent with previous research indicating that anxiety levels are higher among younger students [27, 28].

Statistically significant differences in the HADS total score and depression scale between undergraduates, specialists, master's students, and doctoral candidates reveal significant differences in depression and anxiety levels. These findings highlight the unique challenges faced by undergraduate students. Higher rates of anxiety and depression among undergraduates may be attributed to several factors, including uncertainty about their future career paths, less developed coping strategies, and increased academic workload compared to more experienced students. In contrast, older students typically

TABLE 5

DESCRIPTIVE STATISTICS BY COURSE AND COURSE DIFFERENCES

	Early years of study (1-2)		Later years of study (3-6)		Differences (E-L)	*p*-value (Mann–Whitney test)
	M	Sd	M	Sd		
HADS total score	11.42	6.54	9.10	6.17	1.43	<0.001 (108178)
Anxiety	6.16	3.96	5.41	3.65	0.74	0.005 (105743)
Depression	5.27	3.47	4.58	3.42	0.69	0.001 (105743,5)

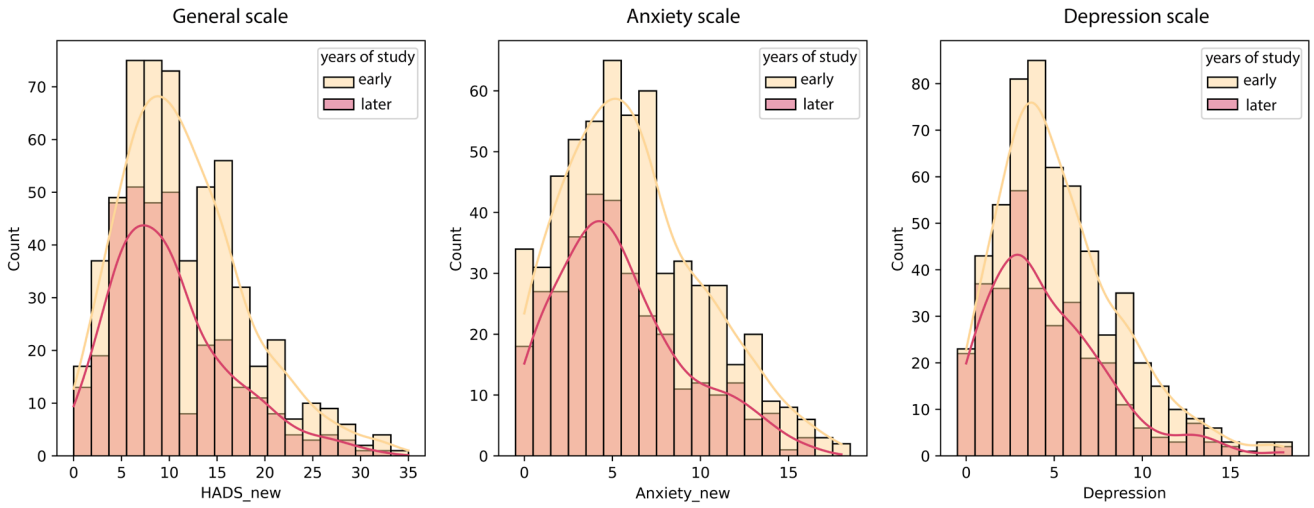

FIG. 4.

Histograms of the distribution of response frequencies for Anxiety, Depression and General scales of HADS by course (junior – yellow; senior – red). Vertical axis (Count) – frequency of responses; horizontal axis (Anxiety_new, Depression or HADS_new) – sum of scores of the corresponding scale

have more defined career goals, better stress management skills, and stronger social support networks. These findings corroborate previous research on the higher prevalence of psychological distress among undergraduates. For instance, N. Bayram and N. Bilgel (2008) reported that undergraduate students were more likely to experience anxiety and depression compared to graduates, likely due to a combination of academic, financial, and social pressures [29]. H.M. Stallman (2010) identified undergraduate students as a high-risk group for mental health issues, emphasizing the need for targeted psychological interventions [30].

External validity analysis using correlations with the PSS and the MTQ confirmed the reliability of the HADS. High positive correlations between the HADS and the PSS (r = 0.72) and between the HADS Anxiety Scale and the PSS (r = 0.73) indicate the sensitivity of the HADS to stress. Negative correlations between the HADS and the MTQ (ranging from -0.48 to -0.61) suggest a link between psychological distress and resilience,

TABLE 6

DESCRIPTIVE STATISTICS BY STAGE OF EDUCATION AND DIFFERENCES BETWEEN STAGES OF EDUCATION

	Bachelor's students		Others		Differences (B-O)	*p*-value (Mann–Whitney test)
	M	Sd	M	Sd		
HADS total score	11.30	6.63	10.34	6.14	0.96	0.036 (107765.5)*
Anxiety	6.06	3.98	5.64	3.69	0.42	0.11 (105730)
Depression	5.24	3.48	4.70	3.42	0.54	0.016 (108915)*

TABLE 7

CORRELATIONS BETWEEN SUBSCALES OF HADS

	HADS total score	HADS-Anxiety	HADS-Depression
HADS total score	1		
HADS-Anxiety	0.81 ($p < 0.001$)	1	
HADS-Depression	0.86 ($p < 0.001$)	0.48 ($p < 0.001$)	1

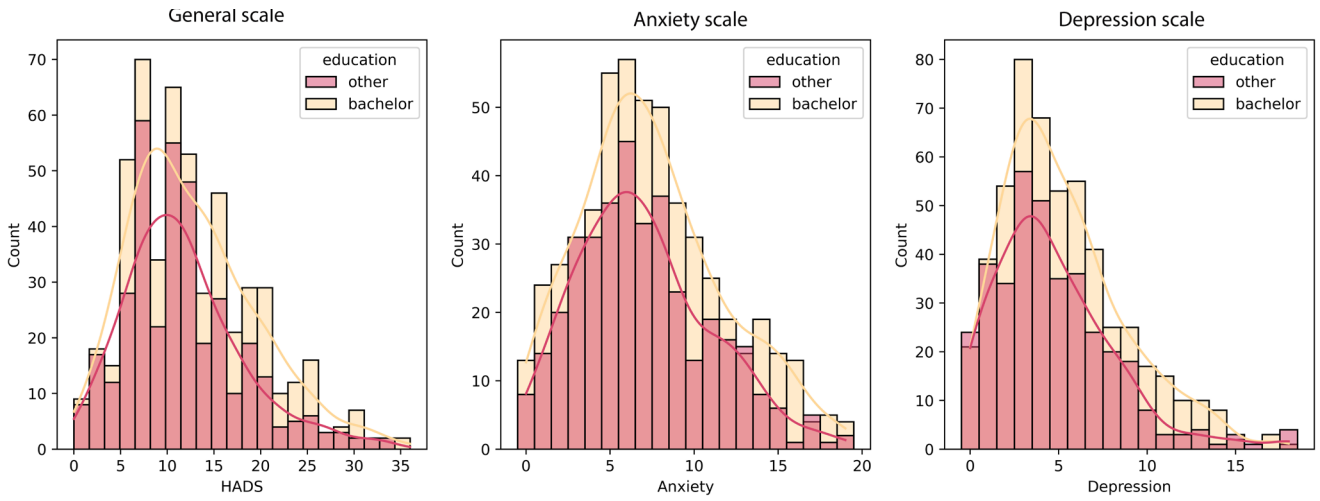

FIG. 5.

Histograms of the distribution of response frequencies for Anxiety, Depression and General scales of HADS by stage of education (bachelor – yellow; other – red). Vertical axis (Count) – frequency of responses; horizontal axis (Anxiety, Depression or HADS) – sum of scores of the corresponding scale

which is associated with stability and the ability to cope with stress. A more pronounced negative correlation with the HADS Anxiety Scale (r = -0.57) suggests that resilience may be more closely related to anxiety than depressive symptoms. These results are consistent with the existing literature on the PSS and the MTQ as measures of stress and resilience. For example, S. Cohen et al. (1983) identified the PSS as a reliable measure of perceived stress that correlates with anxiety and depression [31]. Similarly, P.J. Clough et al. (2002) showed an inverse relationship between the MTQ and psychological distress, highlighting its role in promoting mental well-being [32].

CONCLUSION

The HADS is a reliable and validated instrument for assessing anxiety and depression among young people. This study confirms that the Russian adaptation of the HADS has good reliability and validity, maintaining its utility for screening anxiety and depressive symptoms in students, given its identified factor structure. The exclusion of item 6 from the factor analysis is advantageous, as it enhances the psychometric properties of the scale, including its external validity, as demonstrated by correlations with other established measures of stress and resilience, such as the PSS and MTQ. These findings indicate that the HADS can be used to assess stress-related traits, anxiety, and depression, as well as to detect mental health issues in student populations. Its ease of use and clarity make it a valuable tool for early detection and intervention, as mental health problems are often undetected in this population.

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Conflicts of interest

The authors declare no conflicts of interest.

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ANALYZING THE QUALITY OF LIFE AND EMOTIONAL STATE OF PREGNANT WOMEN

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RESUME

Pregnancy is an important stage in a woman's life, accompanied by significant physiological and psychological changes. During this period, the psychoemotional state of a pregnant woman is influenced by many factors, among which the quality of life and family relationships occupy a special place.

The aim. *To assess the impact of quality of life and family relationships on the psychoemotional state of pregnant women.*

Materials and methods. *The study involved 78 pregnant women who were registered for pregnancy and childbirth at the KSC RAS hospital in Apatity, Murmansk region in 2023–2024 and gave birth at the beginning of December 2024. The average age was 31.3 ± 0.8 years. The control group included 58 non-pregnant women, mean age 32.7 ± 0.6 years. We used the SF-36 questionnaire and the pregnant woman questionnaire developed by the Central Research Institute of Healthcare Organization and Informatization of the Russian Ministry of Health.*

The results. *The results showed that the physical function ($r = 0.48$, $p < 0.05$) has an effect on the pregnant woman's psychological state. Fatigue affects sleep quality ($r = 0.35$, $p < 0.001$) and increases anxiety ($r = 0.43$, $p < 0.001$). Intra-familial relationships ($r = -0.42$ $p < 0.05$) have a significant influence on the emotional background of pregnant women. Support of the partner, harmonious relations in the family contribute to reduce stress and increase the level of psychological comfort. In addition, there is a relationship between psycho-emotional condition and family status ($r = 0.36$, $p < 0.05$), number of children ($r = -0.32$, $p < 0.05$) and average per capita income ($r = -0.31$, $p < 0.05$). The emotional background of the pregnant woman is negatively impacted by complicated obstetric anamnesis, including miscarriages, complicated abortions, infectious and inflammatory diseases during pregnancy, and exacerbation of chronic extragenital diseases.*

Conclusion. *To improve the psychoemotional state of a pregnant woman, full-fledged psychological support is necessary at all stages of pregnancy and childbirth, including consultations and trainings with the development of social support measures and strengthening the institution of the family.*

Keywords: *pregnancy, psychological well-being, quality of life, family relationships*

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ОЦЕНКА КАЧЕСТВА ЖИЗНИ И ПСИХОЭМОЦИОНАЛЬНОГО СОСТОЯНИЯ БЕРЕМЕННОЙ ЖЕНЩИНЫ

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РЕЗЮМЕ

Беременность представляет собой важный этап в жизни женщины, сопровождающийся значительными физиологическими и психологическими изменениями. В этот период на психоэмоциональное состояние беременной оказывают влияние множество факторов, среди которых особое место занимают качество жизни и внутрисемейные отношения.

Цель. *Оценить качество жизни и психоэмоциональное состояние беременных женщин.*

Материалы и методы. *В исследовании приняло участие 78 беременных женщин, вставших на учет по беременности и родам в больницу КНЦ РАН, г. Апатиты Мурманской области в 2023–2024 гг. и родивших на начало декабря 2024 г. Средний возраст составил 31,3 ± 0,8 лет. Контрольную группу составили 58 небеременных женщин, средний возраст 32,7 ± 0,6 лет. Использовали опросник SF-36 и опросник беременной женщины, разработанный Центральным научно-исследовательским институтом организации и информатизации здравоохранения Минздрава России.*

Результаты. *Анализ полученных результатов показал, что в первую очередь на психоэмоциональное состояние беременной оказывает влияние физическое функционирование ($r = 0,48$, $p < 0,05$). Утомляемость влияет на качество сна ($r = 0,35$, $p < 0,001$) и повышает тревожность ($r = 0,43$, $p < 0,001$). Существенное влияние на формировании эмоционального фона беременной оказывают внутрисемейные отношения ($r = -0,42$ $p < 0,05$). Поддержка партнера, гармоничные отношения в семье способствуют снижению стресса и повышению уровня психологического комфорта. Помимо этого, отмечена взаимосвязь между психоэмоциональным состоянием и семейным статусом ($r = 0,36$, $p < 0,05$), количеством детей ($r = -0,32$, $p < 0,05$) и среднедушевым доходом ($r = -0,31$, $p < 0,05$). Также, негативное влияние на эмоциональный фон беременной оказывает осложненный акушерский анамнез (выкидыши, осложненные аборты, инфекционно-воспалительные заболевания во время беременности и обострение хронических экстрагенитальных заболеваний).*

Заключение. *Для улучшения психоэмоционального состояния беременной женщины необходимо полноценное психологическое сопровождение, на всех этапах беременности и родов, включающее в себя так же консультации и тренинги с развитием социальных мер поддержки и укреплением института семьи.*

Ключевые слова: *беременность, психоэмоциональное состояние, качество жизни, внутрисемейные отношения*

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INTRODUCTION

Pregnancy is a significant stage in a woman's life, marked by profound physiological and psychological transformations. During this time, the psychoemotional state of the expecting mother is influenced by numerous factors, with quality of life and familial relationships playing a prominent role [1]. In recent years, there has been a growing focus on the impact of a woman's mental health and emotional state on her reproductive function, pregnancy outcomes, and perinatal health [2, 3]. Typically, many women experience anxiety and stress due to the physiological, psychological, and societal changes associated with pregnancy [4]. Hormonal fluctuations during pregnancy can contribute to emotional instability, including anxiety, depression, nervous tension, and other adverse emotions, which may result in various pathological conditions in the fetus and infant [5, 6]. Antenatal depression and anxiety have been linked to not only influencing birth outcomes, such as preterm birth and low birth weight, but also impacting maternal postnatal mental health and infant development [7].

Various studies have demonstrated that the incidence of perinatal anxiety among pregnant women in different countries is substantial, reaching up to 49 % [8-11].

There is a significant body of evidence regarding the significance of mental well-being during pregnancy. Much of this research has focused on mental health conditions such as depression and anxiety [12, 13].

Factors that influence the quality of life and thus the mental health and psychoemotional state of pregnant women vary and can have both positive and negative impacts [14]. Studies have shown that a low quality of life is linked to an increased risk of anxiety and depression during pregnancy [15].

Social relationships are believed to directly protect mental health or indirectly act as a buffer against stressors [16]. Previous studies have shown that consistent care and support from a partner and family members during pregnancy reduces the risk of depression, anxiety, and other mental health issues [17, 18]. Japanese researchers Ogawa A. et al. found that pregnant women who have husbands experience greater psychoemotional comfort [19]. Partner support and positive family relationships contribute to reduced stress and increased psychological comfort. In contrast, conflicts, emotional distance from a partner, and an unfavorable family environment can exacerbate symptoms of anxiety and depression.

Employment and working conditions during pregnancy can significantly affect the psychoemotional state of expectant mothers [20]. A study conducted in India found that unemployed women experienced lower levels of anxiety and were at a lower risk of depression [21]. Data from developed countries suggests that employment can have a protective effect against stress and depression [22, 23].

Despite a significant amount of research on the quality of life and family relationships of pregnant women, the complex impact of these factors on their psychoemotional state remains an area requiring further investigation. This study seeks to examine the correlation between quality of life, familial relationships, and psychoemotional states among pregnant women. It may also contribute to the development of targeted psychological support interventions for this vulnerable population group.

THE AIM OF THE STUDY

To assess the quality of life and psychoemotional state of pregnant women.

MATERIALS AND METHODS

The study involved 78 pregnant women who were enrolled at the hospital affiliated with the Kola Science Center of the Russian Academy of Sciences between 2023 and 2024 and who gave birth before the beginning of December 2024. The mean age of the participants was 31.3 ± 0.8 years. A control group of 58 non-pregnant women was also included, with the mean age of 32.7 ± 0.6 years. The study was conducted in accordance with the guidelines and regulations for biomedical research ethics outlined in the Helsinki Declaration of the World Medical Association on Ethical Principles for Medical Research (2013). The research was approved by the Ethics Committee of the Biomedical Adaptation Center for Arctic Human Ecology, a branch of the KSC RAS (protocol No. 1/2022, dated March 15, 2022). All participants provided written informed consent for voluntary participation in the study.

The study utilized the SF-36 Health Status Survey, which was translated into Russian and validated by staff from the St. Petersburg Institute of Clinical Pharmacology Research [24]. The questionnaire specifically designed for pregnant women was developed by the Central Research Institute for Healthcare Organization and Information Technology [25].

Statistical analysis was conducted using the STATISTICA 10.0 software (TIBCO Software Inc., USA). The significance of differences between identical parameters in different study groups was compared using non-parametric methods, specifically the Mann–Whitney test for independent samples. A *p*-value of 0.05 was considered statistically significant. The Spearman's correlation coefficient (r-Spearman's) was used to assess the strength and direction of relationships between variables.

THE RESULTS OF THE STUDY

Over a period of two years (2022–2023), a total of 127 pregnant women were examined at the Kola Science

Center hospital of the Russian Academy of Sciences, of which 123 (96.7 %) were registered for pregnancy and 4 (3.3 %) underwent abortions. As of early December 2024, 78 women (66.7 %) have given birth, while 6 (5.1 %) experienced miscarriages during early pregnancy, leaving 33 women (28.2 %) scheduled to give birth in the year 2025.

The average age of the participants in the study was 31.3 ± 0.8 years, ranging from 19 to 44 years. Of these, 44.9 % of the women were primiparas, with an average age of 29.6 ± 4.2 years, ranging from 19 to 36 years. At the time of the study, the pregnant women were between 15 and 33 weeks of pregnancy (second and third trimesters), with a median (Me) of 25 weeks.

All participants were urban residents with a secondary vocational education (25.8 %) or higher education (74.2 %). More than 90 % were in a registered or de facto marriage. Almost all participants reported a positive family environment, free from any form of violence (economic, psychological, physical, and sexual) (97.8 %), and normal living conditions (95.6 %). Among women, 55.6 % reported nicotine addiction in their partners' fathers, and 2.2 % reported alcohol abuse. A total of 73.1 % stated that they did not have any bad habits, and 17.9 % quit smoking during their pregnancy (Table 1).

An analysis of the attitudes of husbands and partners towards pregnant women and their unborn children has revealed that 76.9 % of women reported a positive attitude towards themselves and 88.5 % towards their unborn child. However, one woman reported a negative attitude towards herself and her child, in addition to her partner's intention to leave her. Additionally, approximately 30 % of pregnant women reported a change in their employers' attitude towards them after they informed them of their pregnancy (Table 2).

Analysis of the quality of life among pregnant and non-pregnant women, using the SF-36 questionnaire, revealed significant differences between the two groups on individual parameters (Table 3).

Specifically, significant differences were observed in the following physical health parameters:

1. Physical functioning (PF, U = 98.0; $p < 0.04$), which measures the degree of limitations in performing various physical activities, including self-care, mobility, climbing stairs, and lifting heavy objects;

2. Role functioning (RP, U = 85.0; $p < 0.025$), which reflects the impact of physical fitness on the ability to perform everyday social and work-related responsibilities.

Differences in mental health parameters were observed between the compared groups for the following variables:

1. Role functioning related to emotional state (RE, U = 85.0; $p < 0.025$), which reflects the extent to which daily activities (including work-related responsibilities) are limited due to emotional difficulties, as manifested by decreased productivity, increased time spent, and reduced quality of work;

2. Mental health (MH, U = 77.0; $p < 0.013$), which encompasses aspects of the affective sphere such as anxiety levels, presence of depressive symptoms, and overall emotional state.

An analysis of the physical condition of pregnant women based on the results of the "Pregnant Women's Questionnaire" [25] revealed that only 44.4 % were able to maintain their work capacity; most women experienced a reduction in performance or a lack of desire to work. Nearly all pregnant women reported feelings of fatigue: 44.9 % after prolonged exertion, and 31.1 % after significant physical activity. Approximately 70 % experienced shortness of breath while climbing 3–4 flights of stairs, and 11.1 % experienced it during any activity. No more than 13.4 % reported frequent headaches (Fig. 1).

An analysis of psychoemotional states of pregnant women revealed that 64 % reported sleep disturbances, with 2 % experiencing nightmares. Approximately 51 % rated their mood as variable, and 66 % described themselves as easily upset and tearful. A minority of 14 % expressed unreasonable anxiety, while 5 % expressed concerns about their ability to provide for their child and family. Only 42 % did not report any fears, while the remaining 58 % expressed at least one form of anxiety, including fear of childbirth (for first-time mothers), worry about the health of their child, concern about their appearance, and fear of job loss (Fig. 2).

Spearman's correlation analysis revealed a significant association between physical functioning and psychoemotional state parameters ($r = 0.48$, $p < 0.05$). In particular, the psychoemotional state measures showed a relationship with physical functioning, particularly sleep disturbances ($r = 0.35$, $p < 0.001$) and anxiety ($r = -0.34$, $p < 0.001$). Additionally, individual psychoemotional state parameters correlated with fatigue and shortness of breath (Fig. 3).

In addition, a correlation was observed between the psychoemotional state and the "Attitude towards the mother and the unborn child" block ($r = -0.42$, $p < 0.05$). Anxiety was influenced by the following factors: "the attitude of relatives from the mother's and father's sides towards the pregnant woman and her unborn child" ($r = -0.49$, $p < 0.05$ and $r = -0.36$, $p < 0.05$, respectively), as well as "the attitude of the management at work towards the pregnant employee" ($r = -0.48$, $p < 0.05$) (Fig. 3).

Among other assessment criteria, the following relationships were noted: marital status and anxiety ($r = 0.36$, $p < 0.05$); fears, sleep disturbances, and the number of children ($r = -0.42$, $p < 0.05$ and $r = -0.32$, $p < 0.05$, respectively); and per capita income and anxiety ($r = -0.31$, $p < 0.05$).

Among women registered for pregnancy at the Kola Scientific Center of the Russian Academy of Sciences, 28.2 % had a history of complications in previous pregnancies (miscarriages, stillbirths, or complicated abortions) (Table 4). In addition, 11.5 % had chronic gynecological conditions such as endometritis or oophoritis in their medical history. During pregnancy, 9.0 % of women reported experiencing acute infectious

TABLE 1

SOCIAL FUNCTIONING AND LIVING CONDITIONS OF PREGNANT WOMEN, %

Parameters	*n*=78	%
Age, years		
<25	10	12.8
25–30	19	24.4
31–35	25	32.1
36–40	24	30.8
Marital status		
Married	62	79.5
De facto marriage	10	12.8
Visiting partner	0	0.0
Single, living with relatives	0	0.0
Single, living alone (without support)	6	7.7
Maternal employment status		
Homemaker (before and during pregnancy)	14	17.9
Stopped working during pregnancy	30	38.5
Continued working during pregnancy	34	43.6
Family composition		
No children	35	44.9
Has one or two children	36	46.2
Has three or more children	7	9.0
Has a child with a disability	0	0.0
Per capita monthly family income, based on municipal data for 2024		
Below the subsistence minimum (25,390 RUB)	0	0.0
25,390 to 30,000 RUB	24	30.8
31,000 to 40,000 RUB	21	28.2
More than 41,000 RUB	33	42.3
Housing conditions		
Standard living conditions	45	57.7
No separate bedroom for the couple	3	3.8
Substandard housing (lacking amenities, damp, or cold)	0	0.0
Family environment		
Positive	70	89.7
Conflictual situation	8	10.3
Father's characteristics:		
Smoker	49	62.8
Drinks alcohol	8	10.3
Unemployed (has a disability)	0	0.0
Drug user	0	0.0
Maternal substance use		
None	57	73.1
Former smoker (quit before pregnancy)	14	17.9
Currently smoking during pregnancy	7	9.0
Consumes alcohol (e.g., vodka, beer) at least once every two weeks	0	0.0
Consumes alcohol more than once every two weeks / Uses narcotic substances	0	0.0

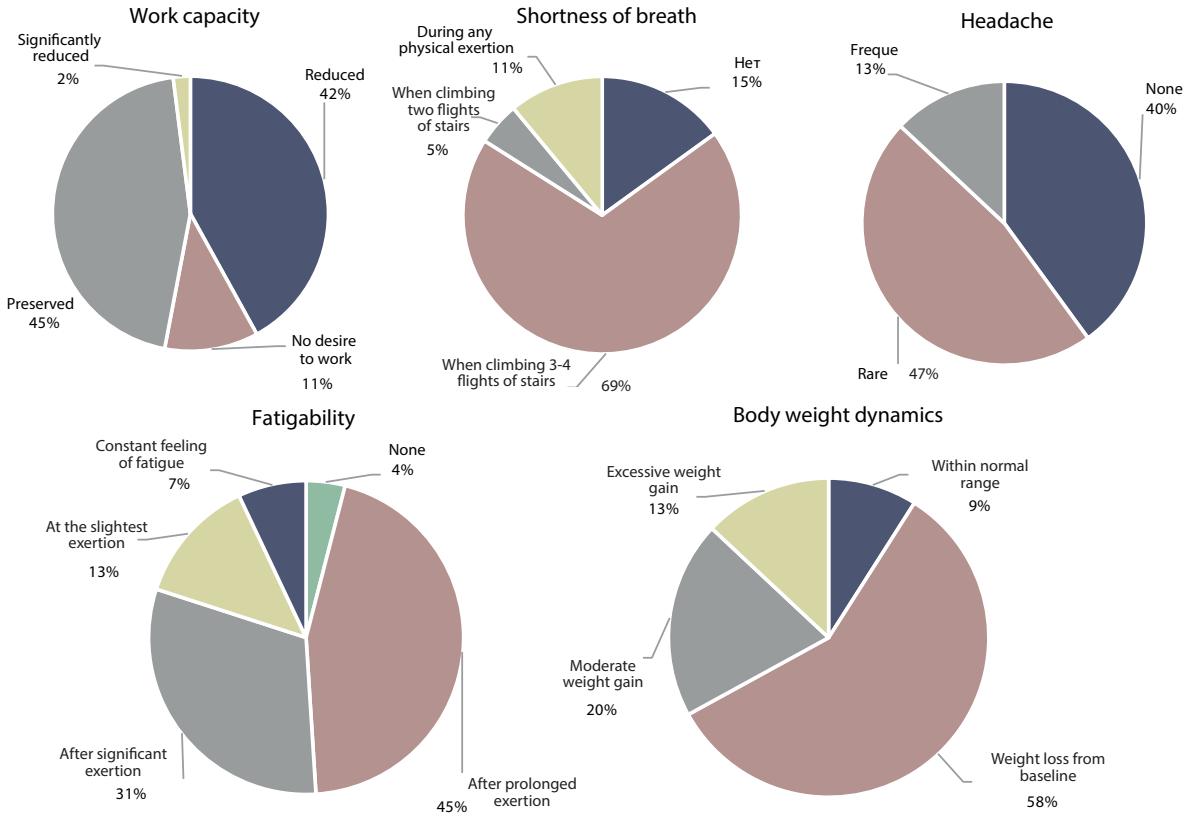

FIG. 1.
Assessment of the physical condition of pregnant women

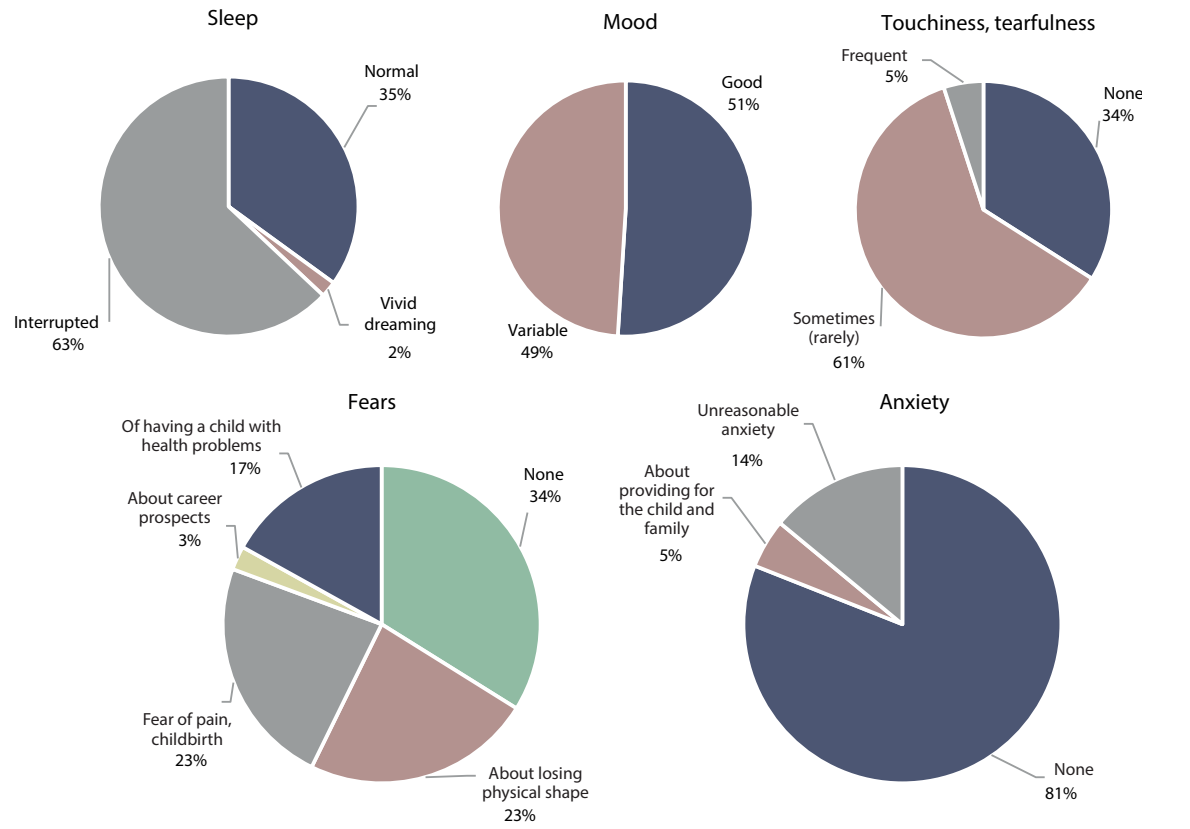

FIG. 2.
Assessment of the psychoemotional state of pregnant women

or inflammatory conditions (ARIs or bronchitis). Approximately 40 % had extragenital pathologies (EGPs), with hypertension and gastritis being the most common conditions. Complications during pregnancy occurred in 52.6 % of cases, including edema, polyhydramnios (excess amniotic fluid), threatened miscarriage (associated with bleeding), high blood pressure, and first-trimester toxicosis.

A correlation analysis between the "morbidity of pregnant women" block and the psychoemotional state revealed a relationship between anxiety and miscarriages complicated by abortion ($r = 0.42$, $p < 0.006$); infectious and inflammatory illnesses (ARI) during pregnancy ($r = 0.32$, $p < 0.05$) and exacerbation of chronic extragenital diseases ($r = 0.42$, $p < 0.05$).

DISCUSSION

Factors influencing the quality of life (QoL) of pregnant women are diverse and can have both positive and negative effects. As an integrated measure, QoL provides an effective and informative method for assessing the overall health of a population and specific subgroups.

According to available data, one of the main factors positively influencing the QoL of pregnant women is support from a spouse and relatives [26]. Negative factors include physical symptoms [27, 28], as well as depression, anxiety, and fatigue [29]. These factors reflect the levels of physical, mental, and social adjustment of the pregnant woman and can be considered emotional and behavioral characteristics of high-risk pregnancies. They can also be used to measure the level of adaptation and assess individual behavior.

According to the literature, physical activity in pregnant women may be restricted by their health condition. In their study, Litvinova A.A. et al. [29] showed that among pregnant women, the "Physical Functioning" (PF) score was rather low, at 43.78 ± 2.3, compared to a control group score of 74.15 ± 4.8. In our study, we identified differences between pregnant women and a control group in two components of the "Physical Functioning": PF was 63.1 ± 3.4 for pregnant women versus 89.3 ± 2.9 for the control, and "Role Functioning" RP was 63.2 ± 2.8 for pregnant women and 85.8 ± 3.1 for the control.

The course of pregnancy may be indirectly influenced by a number of factors, including the mother's psychological state (psychosomatic condition), living conditions, and family relationships [25]. An analysis of the data collected revealed that housing conditions may influence the incidence of infectious and inflammatory illnesses (ARI) during pregnancy ($r = 0.66$, $p < 0.035$).

TABLE 2

THE ATTITUDE OF OTHERS TOWARDS THE MOTHER AND THE UNBORN CHILD, %

Parameters	*n*=78	%
Father's attitude towards the unborn child		
Positive	69	88.5
Indifferent	8	10.3
Fearful	0	0.0
Negative	1	1.3
Insists on termination of pregnancy	0	0.0
Father's attitude towards the mother of his unborn child		
Attentive	60	76.9
Absent due to work	3	3.8
Provides no support	4	5.1
Constantly dissatisfied	10	12.8
Leaves the mother of his unborn child	1	1.3
Attitude of maternal relatives towards the expectant mother and her unborn child		
Positive	60	76.9
Overprotective	1	1.3
Overly critical and opinionated	16	20.5
Worried about additional burdens	1	1.3
Unwilling to have the child in the home	0	0.0
Attitude of paternal relatives towards the expectant mother and her unborn child		
Positive	62	79.5
Overprotective	12	15.4
Overly critical and opinionated	1	1.3
Worried about additional burdens	3	3.8
Unwilling to have the child in the home	0	0.0
Management's attitude towards the pregnant employee		
Positive	52	66.7
Increased fault-finding	19	24.4
No transfer to light-duty work	6	7.6
Reduced payments	1	1.3
Termination of employment	0	0.0

CONCLUSIONS

Therefore, an analysis of the findings suggests that physical functioning, which plays a significant role and has a negative impact on emotional well-being, predominantly influences the psychoemotional state of pregnant women. A decrease in psychoemotional state primarily results from increased fatigue, which manifests itself in reduced physical activity in daily life and an overall deterioration in health, leading to sleep disturbances, the development of anxiety and depressive disorders, and heightened anxiety.

The family environment, particularly that of a woman's parents and extended family, as well as the attitude of her employer, significantly influence her psychoemotional state during pregnancy. Family relationships are critical in shaping a pregnant woman's emotional state. The support of a partner and harmonious family relationships can reduce stress and promote psychological well-being, while conflicts, emotional distance from a partner, and an unfavorable family environment can exacerbate anxiety and depression. Marital status, the number of children in the family, and per capita income all have an impact on a woman's experience of pregnancy. A family's financial stability is directly linked to the quality of a pregnant woman's life. Low income can limit access to healthcare, healthy nutrition, and adequate living conditions, increasing stress and negatively impacting her psychological well-being.

An analysis of the "morbidity of pregnant women" block revealed that the most significant negative impact on their psychoemotional state (specifically, anxiety and fear) was exerted by a complicated obstetric history, including miscarriages and complications from abortions ($r = 0.42$, $p < 0.006$). Additionally, infectious and inflammatory diseases during pregnancy (ARI) ($r = 0.32$, $p < 0.05$), as well as exacerbations of chronic extragenital conditions ($r = 0.42$, $p < 0.05$), also had a significant impact on the women's mental health.

To improve the psychoemotional state of pregnant women, it is essential to provide comprehensive medical support throughout all stages of pregnancy and childbirth. This includes psychological counseling and support programs, as well as the development of measures to strengthen social support for women and the institution of family.

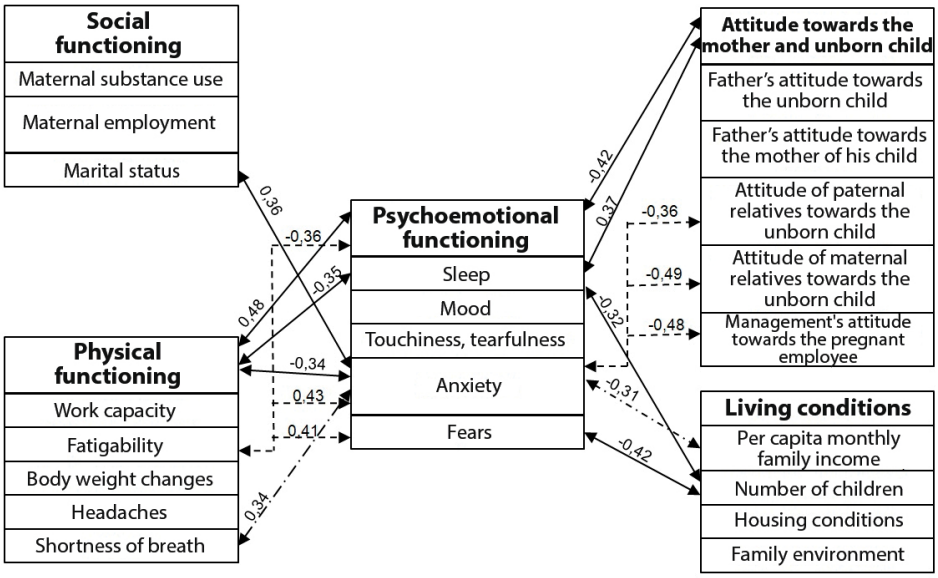

FIG. 3.
The relationship between the quality of life and the psychological state of a pregnant woman

TABLE 3

AVERAGE VALUES OF SF-36 TEST SCALES BY GROUPS

Parameters		Pregnant women (*n*=78)	Control group (*n*=58)
Physical health component scales	PF	89.3*	61.3
	RP	85.8*	63.2
	BP	78.9	76.4
	GH	67.4	62.9
Mental health component scales	VT	81.1	78.1
	SF	82.1	80.7
	RE	87.4*	64.1
	MH	65.7*	47.3

Note. Significance level * $p < 0.05$; Mann–Whitney test.

TABLE 4

FACTORS COMPLICATING THE COURSE OF PREGNANCY, %

Parameters	*n*=78	%
Complicated obstetric history:	22	28.2
miscarriages	15	19.2
recurrent pregnancy loss	3	3.8
complicated abortions	4	5.1
Chronic gynecological inflammatory diseases:	9	11.5
endometritis	6	7.7
oophoritis	3	3.8
Infectious and inflammatory diseases during pregnancy:	7	9.0
acute infectious and inflammatory diseases (ARVI and bronchitis)	5	6.4
exacerbation of chronic inflammatory diseases during pregnancy	2	2.6
Chronic extragenital diseases (EGD):		
anemia, hypertension, gastritis, asthma	31	39.7
exacerbation of EGD during pregnancy	19	24.4
Pregnancy complications:	41	52.6
edema and polyhydramnios	34	43.6
threatened miscarriage (bleeding)	27	34.6
high blood pressure (>140 mmHg)	24	30.8
first-trimester toxicosis	17	21.8
injuries, surgeries during pregnancy	0	0.0

Conflicts of interest

The authors declare no conflicts of interest.

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PHARMACOLOGY AND PHARMACY

ETHNOPHARMACOLOGICAL CHARACTERISTICS OF PIPER BETLE FROM INDONESIAN-ASIAN REGION AND PROSPECTS OF ITS USE IN BIOMEDICAL PURPOSES

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RESUME

Rationale. *Piper betle of the family of Piperaceae, (P. betle) is a liana growing in the tropics of the Indonesian-Asian region, has long been actively used in folk medicine as a source of remedies for a variety of health problems. At the same time, the methods and purposes of using P. betle in folk medicine vary from region to region, and the effectiveness of its impact on human remains fully underestimated.*
The aim of the study. *To systematize and analyze modern literature data on the pharmacological potential of the medicinal plant Piper betle, growing in the countries of Madagascar, India, Bali and China of the Indonesian-Asian region.*
Materials and methods. *The search and analysis of data were carried out in international and regional databases (PubMed, Scopus, Web of Science, Science Direct, and Google Scholar) for the period from 1996 to 2025.*
Results. *The analysis of scientific literature data showed that the target fragment of metabolome (TFM) of Peper betle is characterized by a complex composition of biologically active compounds (BAS), which varies significantly from region to region. BAS of the TFM of this plant are responsible for various types of pharmacological activity, which justifies its use in traditional medicine and growing interest to the medical scientific community. It was found that within the range of P. betle growth, the chemical composition of TFM varies in terms of the content of alkaloids, terpenes, phenolic compounds, including flavonoids and volatile components.*
Conclusion. *P. betle is a promising object for further research in the field of phytopharmacology and reproductive medicine. Obviously, in-depth preclinical and clinical studies are needed to confirm the identified effects based on literature sources. At the same time, the collected literature data can contribute to future research in the field of pharmacology in order to create new promising drugs.*

Keywords: *Piper betle, ethnobotany, phytochemistry, chemical composition, biological activity, traditional medicine*

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ЭТНОФАРМАКОЛОГИЧЕСКИЕ ХАРАКТЕРИСТИКИ *PIPER BETLE* ИЗ ИНДОНЕЗИЙСКО-АЗИАТСКОГО РЕГИОНА И ПЕРСПЕКТИВЫ ЕГО ИСПОЛЬЗОВАНИЯ В БИОМЕДИЦИНСКИХ ЦЕЛЯХ

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РЕЗЮМЕ

Обоснование. *Piper betle семейства перечных Piperaceae, (P. betle) — лиана, произрастающая в тропиках Индонезийско-Азиатского региона, издавна активно используется в народной медицине в качестве источника средств для решения самых различных проблем со здоровьем. Вместе с тем, способы и цели использования P. betle в народной медицине различаются от региона к региону, а эффективность его воздействия на человека остается недооцененной в полной мере.*

Цель исследования. *Систематизировать и проанализировать современные литературные данные о фармакологическом потенциале лекарственного растения Piper betle, произрастающего в странах Индонезийско-Азиатского региона: Мадагаскар, Индия, Бали и Китай.*

Материалы и методы. *Поиск и анализ данных проводился в международных и региональных базах данных (PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar) за период с 1996 по 2025 гг.*

Результаты. *В ходе анализа научных литературных данных было показано, что целевой фрагмент метаболома (ЦМФ) Peper betle характеризуется сложным составом биологически активных веществ (БАВ), который существенно варьирует от региона к региону. БАВ ЦФМ этого растения отвечают за различные виды фармакологической активности, что оправдывает его применение в традиционной медицине и вызывает растущий интерес со стороны медицинского научного сообщества. Установлено, что в пределах ареала произрастания P. betle отличается вариабельностью химического состава ЦФМ по содержанию алкалоидов, терпенов, фенольных соединений, в том числе флавоноидов и летучих компонентов.*

Заключение. *P. betle представляет собой перспективный объект для дальнейших исследований в области фитофармакологии и репродуктивной медицины. Очевидно, для подтверждения выявленных эффектов на основе литературных источников необходимы углубленные доклинические и клинические исследования. Вместе с тем, собранные литературные данные могут способствовать проведению будущих исследований в области фармакологии с целью создания новых перспективных лекарственных средств.*

Ключевые слова: *Piper betle, этноботаника, фитохимия, химический состав, биологическая активность, традиционная медицина*

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INTRODUCTION

The emergence of substantial evidence supporting the successful therapeutic use of *Piper betle (P. betle)* in the central and eastern regions of Malaysia has recently sparked significant scientific and practical interest in the plant [1]. In the wild, this species is primarily distributed across South and Southeast Asia, including India, Sri Lanka, Bangladesh, Malaysia, Indonesia, Myanmar, the Philippines, and parts of China. It is also found on Pacific islands such as Fiji, Micronesia, and the Solomon Islands [2]. Furthermore, it is widely cultivated for commercial purposes in India, Thailand, Sri Lanka, Taiwan, and many other tropical regions of South and Southeast Asia, Africa, and Madagascar, where it serves as both a food product and a source of raw material for the pharmaceutical industry.

P. betle is notable for being referred to as the "green gold of India," as an estimated 20 million people depend on this plant for their livelihood through the cultivation, processing, and trade of its leaves [3]. *P. betle* leaves are deeply embedded in the culture of the Hindu people, where they are widely used in various social, cultural, and religious ceremonies. Since ancient times, *P. betle* has been utilized in numerous traditional medical systems, including Indian Ayurvedic medicine, Traditional Chinese Medicine, and the folk medicine of the West Indies and Latin America. In Ayurveda, the juice extracted from the leaves is used, often as an auxiliary component in combination with other medicinal plants [4]. In traditional medicine, *P. betle* leaves are employed to treat a variety of ailments, such as colds, bronchial asthma, coughs, stomach pain, rheumatism, and inflammatory conditions including boils, halitosis, constipation, conjunctivitis, oral diseases, abscesses, wounds, and cuts [5].

Recently, particular interest has been drawn to the biological activity of the chemical compounds found in medicinal plants, which belong to diverse classes such as alkaloids, various glycosides, phenolic compounds (including flavonoids and tannins), terpenes, and oligosaccharides [6]. The broad spectrum of chemical compounds in *P. betle*, including chavicol, chavibetol, hydroxychavicol, eugenol, estragole, methyleugenol, hydroxycatechin, α-pinene, caryophyllene, β-pinene, 1,8-cineole, among others, is largely determined by specific growth conditions, soil type, and the geographical characteristics of the plant's habitat. In this review, we have analyzed information on the target metabolome fragments (TMFs) of *P. betle* growing in different parts of the Indonesian–Asian region and evaluated data on its pharmacological activity, which establishes it as one of the most important representatives of the region's ethnomedicine. At the same time, considering the vast untapped potential for the practical use of *P. betle* as a medicinal agent, we have focused on a comprehensive examination of current research pertaining to its application in maintaining human health.

Maintaining reproductive health in both women and men is a critically important component of overall human health, as fertility and hormonal balance disorders are becoming increasingly prevalent among the reproductive-age population in many countries. The traditional use of *P. betle* by the peoples of various regions to enhance sexual activity and fertility suggests its potential role in supporting reproductive health. Given that the biologically active compounds (BACs) of *P. betle*, characterized by their multifunctional action, can influence both inflammatory and hormonal processes directly involved in the regulation of reproductive function, systematizing this modern scientific data will allow for an assessment of the plant's possible role in regulating human and animal reproductive function.

Thus, this article presents a review of recent research on the biological activity of various morphological parts of *P. betle* from four different areas of the Indonesian–Asian region, describing the cause-and-effect relationship between the traditional use of this plant by the inhabitants of these regions and the potential improvement of their health.

THE AIM OF THE STUDY

To systematize and analyze current literature data on the pharmacological potential of the medicinal plant *Piper betle* growing in Madagascar, India, Bali, and China within the Indonesian–Asian region.

MATERIALS AND METHODS

The literature search and data analysis were conducted using international and regional databases (PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar) for the period from 1996 to 2025.

RESULTS

Growth conditions of *P. betle* in the wild and under cultivation

P. betle grows in tropical and subtropical climate regions. The plant thrives at a consistent temperature range of 15 to 30 °C and under relatively high air humidity [7]. Temperatures below 10 °C can threaten its growth and, ultimately, its survival. Thus, the plant's natural distribution range is limited by its thermal and water requirements. Since *P. betle* requires diffused light rather than direct sunlight for active growth, it prefers the understory of tropical forests, beneath the canopy of tall trees. Prolonged exposure to sunlight can lead to water and heat stress, negatively affecting plant development [7]. For optimal growth, the plant requires well-drained soil rich in organic matter. A soil pH in the range of 5.5 to 6.5 is considered

optimal [8]. Conditions that deviate from these norms can lead to nutritional problems and a decline in plant health.

The optimal conditions for cultivating *P. betle* are highlands, particularly with fertile sandy, sandy-clay, or sandy-loam soils that have a good drainage system and a pH range of 5.6–8.2. Consequently, saline and alkaline soils, where waterlogging is an issue, are unsuitable. The plant requires approximately 2,250–4,750 mm of rainfall, relative humidity of 40–80 %, and a temperature range of 15–40 °C, all of which are considered suitable. Under cultivation, regular, abundant watering every 3–4 days is necessary; however, it is crucial to avoid waterlogging. Regular misting with water is beneficial for increasing ambient humidity [7]. On farms, *P. betle* is propagated by stem cuttings, with the necessary support for the vine to grow vertically. One year after planting the cutting, the leaves can already be harvested as raw material for practical use, and harvesting from a single plant can continue for several years [9].

Biologically active compounds of the target metabolome fragment of *Piper betle* from different regions

Piper betle, known as "pan" in Hindi, holds significant importance in both the cultural life and medicine of India. It is widely cultivated and consumed throughout the country, playing an important role in various religious ceremonies. Numerous studies have demonstrated the extensive phytochemical diversity of *P. betle*, which is influenced by the climatic conditions of its growing region, including soil composition, air humidity, and rainfall. The content of biologically active compounds (BACs) also depends on the harvest time of the betel leaves in a given region, the species diversity of other plants growing in the betel pepper's habitat, and the type of agrochemical practices in the region [10]. Interestingly, the composition of *P. betle* from the Indian region includes compounds from the phenol and terpene classes. Terpenoids and their derivatives are particularly prevalent, including cadinene, 1,8-cineole, chavicol, chavibetol, safrole, camphene, limonene, caryophyllene, pinene, carvacrol, allylpyrocatechol, and eugenol [11]. Aqueous and methanolic extracts of *P. betle* from the Indian region have been found to contain alkaloids, flavonoids, tannins, steroids, glycosides, saponins, and terpenoids [12]. Extracts of *P. betle* leaves from Sri Lanka have been shown to contain the sesquiterpenes cadinene and caryophyllene, as well as safrole (52.7 %), eugenyl acetate (5.8 %), allylpyrocatechol diacetate (15.4 %), and eugenol (6.4 %) [13]. The predominant chemical constituents of *P. betle* in the Indian region include hydroxychavicol, known for its antibacterial and antioxidant properties, piperitenone, and chavibetol acetate (a phenolic compound), which exhibit significant antimicrobial and antifungal activity against 10 gram-positive and 12 gram-negative strains, as well as a fungal strain, *Candida tropicalis* [14].

P. betle is a medicinal plant valued in Asia and used as an important source of biologically active chemical compounds such as hydroxychavicol, flavonoids, eugenol, chavibetol, and naturally occurring nitrogenous compounds. The authors of one publication assert that various bioactive compounds, including tannins, flavonoids (quercetin), eugenol, hydroxychavicol, and chavibetol, possess antibacterial, antifungal (against *Aspergillus niger* and *Candida albicans*), antioxidant, antidiabetic, and anticancer properties [15]. The antimicrobial activity of phenolic compounds such as hydroxychavicol and eugenol has been studied against a range of microorganisms, including gram-negative *Escherichia coli* and *Pseudomonas aeruginosa*, gram-positive *Staphylococcus aureus*, and *Candida albicans* [16]. The presence of volatile compounds, among which limonene, linalool, and methylchavicol are of greatest interest, accounts for the characteristic aroma of *P. betle* [17]. Flavonoids, including quercetin and kaempferol, have demonstrated pronounced antioxidant and anti-inflammatory properties [18]. In addition to the aforementioned classes of compounds, *P. betle* from the Asian region also contains terpenes and amino acids [19].

The use of *P. betle* since ancient times has formed the basis of many cultural and medical traditions in various regions of the island of Bali. Balinese *P. betle* is characterized by a high content of phenolic compounds and essential oils, particularly safrole, chavibetol, and eugenol, as well as flavonoids, tannins, and hydroxychavicol. Due to this composition, *P. betle* extracts from Bali exhibit pronounced antioxidant activity, manifested in their ability to neutralize free radicals, prevent oxidative cell damage, and reduce oxidative stress levels. This is particularly important for protecting reproductive cells and other biological structures from damage [20]. The phenolic compounds, including hydroxychavicol and eugenol, abundant in *P. betle* in Bali, demonstrate strong antibacterial activity against specific pathogens, inhibiting the growth of both gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* bacteria and disrupting biofilm formation [21]. Volatile compounds, especially limonene, linalool, and methylchavicol, contribute to the characteristic aroma of Balinese *P. betle* [22].

Extracts of *P. betle* leaves growing in the southern regions of China possess a complex phytochemical composition, including bioactive compounds such as *hydroxychavicol, eugenol, chavibetol, flavonoids* (e.g., *quercetin* and *apigenin*), and tannins. *Hydroxychavicol* and *eugenol* exhibit pronounced *in vitro* antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*, as well as antioxidant activity, confirmed by DPPH (*2,2-diphenyl-1-picrylhydrazyl*) and ABTS (*2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid*)) assays. These phenolic compounds are also abundant in Chinese *P. betle* [23]. Volatile compounds, with linalool and β-caryophyllene as the major constituents

identified in Chinese studies, impart the characteristic aroma to Chinese *P. betle* [24]. Flavonoids such as quercetin and kaempferol have been detected in Chinese *P. betle*, and their antioxidant and anti-inflammatory potential has been extensively studied [25].

Biological activity of compounds derived from *Piper betle*

P. betle, a plant widely used in traditional Asian medicine, possesses an impressive diversity of biological properties that have been the subject of extensive research. Phenolic compounds such as hydroxychavicol and eugenol exhibit significant antioxidant activity, neutralizing free radicals and protecting cells from oxidative damage [26].

The target metabolome fragment (TMF) of *P. betle* has demonstrated pronounced antimicrobial properties, as confirmed by a number of studies. It has been established that compounds such as hydroxychavicol are responsible for these properties, exhibiting antibacterial (against *Staphylococcus aureus* and *Escherichia coli*) [27] and fungicidal activity [28]. Hydroxychavicol, eugenol, allylpyrocatechol, carvacrol, and methyleugenol, all constituents of *P. betle*, have demonstrated antifungal activity against various fungal species [27, 21, 16]. In two studies published in 2023, the pronounced antimicrobial activity of *P. betle* leaf extracts against pathogenic bacterial strains was confirmed. For instance, a study conducted by Lao R.C.C. et al. showed that an ethanolic extract of *P. betle* leaves is active against the *Staphylococcus aureus ATCC 29213* strain and is capable of disrupting the biofilms it produces [29]. Jantorn P. et al. demonstrated that *P. betle* leaf extract is effective against clinical isolates of *Staphylococcus pseudintermedius*, including both methicillin-sensitive (MSSP) and methicillin-resistant (MRSP) strains, highlighting the potential of *P. betle* as a natural antimicrobial agent [30].

P. betle leaves possess antiparasitic properties and also inhibit the growth and viability of protozoa (*Giardia intestinalis*) [31]. Some studies have shown that compounds such as *hydroxychavicol* may have beneficial effects in cancer treatment [32]. It has been shown that *P. betle* leaves have a stimulating effect on the central nervous system, associated with stimulant, euphoric, and cognitive properties, making it a compound of interest for neuropharmacological research [5].

Hydroxychavicol, abundantly present in *P. betle* L., has been studied for its anti-inflammatory potential. It acts by inhibiting the production of inflammatory mediators, suggesting its potential application in the treatment of inflammatory diseases [33].

A number of human studies have investigated the effects of *P. betle* TMF compounds on sperm function. A study [34] showed that regular consumption of this plant may have a negative impact on sperm quality. In a study of spermatogenesis in male Wistar rats, administration of the extract at doses of 200, 400, and 800 mg/kg body weight for 30 days reduced sperm count, concentration, motility, and normal morphology. When studying the effect of the extract on the estrous cycle in female rats, a change in the duration of the cycle was observed, suggesting an influence of *P. betle* on the regularity of the reproductive cycle [35]. Furthermore, these studies have shown that components of the plant's TMF can interfere with normal sperm production, affect testicular function and sperm quality, and may potentially disrupt ovarian function and oocyte maturation, consequently affecting the estrous/menstrual cycle. It is important to note that the impact of *P. betle* on reproductive health may vary depending on the dose, frequency, and duration of use.

Animal studies have also investigated the potential effect of *P. betle* TMF on blood glucose levels. A study published in 2025 [36] showed that *P. betle* extracts can reduce blood glucose levels in diabetic rats, indicating its potential use in the treatment of type 2 diabetes.

A comparison of scientific data on the key bioactive compounds of the *P. betle* TMF growing in different regions and studies of their biological activity is presented in Table 1.

Prospects for research on *Piper betle* for the development of reproductive health products

Extracts obtained from *P. betle* possess antioxidant properties due to the presence of hydroxychavicol and eugenol, suggesting a potential role in protecting reproductive cells from oxidative damage [50]. Studies indicate that the complex of bioactive compounds in the *P. betle* TMF exhibits anti-inflammatory properties, which may help reduce inflammation in the organs of the reproductive system. Some researchers suggest that these effects may be attributed to compounds such as eugenol [1]. Certain compounds of the *P. betle* TMF have demonstrated a modulating effect on sex hormones, such as estradiol and progesterone. This could potentially have a positive impact on the hormonal regulation associated with reproductive health [51].

Extracts from *P. betle* have shown antimicrobial activity against various bacterial strains (*Staphylococcus aureus, Escherichia coli*) and fungi (*Trichophyton rubrum, T. mentagrophytes, Microsporum gypseum, Epidermophyton floccosum*, and *Candida albicans*), which is important for the prevention of sexually transmitted infections that affect reproductive health [52, 53]. Individual studies indicate that extracts from *P. betle* possess antitumor activity *in vitro*, particularly in the context of reproductive organ cancers [54].

Despite the need for further research, an analysis of published scientific data suggests that the bioactive compounds of the *P. betle* TMF may have a beneficial effect on libido and sexual function, which could indirectly contribute to reproductive health [55].

CONCLUSION

P. betle is a plant of cultural, nutritional, and medicinal significance in countries where it grows wild

TABLE 1

COMPARATIVE DATA FROM STUDIES OF THE CHEMICAL COMPOSITION AND BIOLOGICAL ACTIVITY OF *P. BETLE* IN THE INDONESIAN-ASIAN REGION

Geographical range	Key BACs of the TMF isolated from *P. betle* leaves	The described biological and pharmacological properties of BACs
Indian region	Eugenol [37, 38]	Anticariogenic, antiprotozoal [37] Antioxidant [38, 39, 40] Anti-inflammatory [39, 41]
		Antifungal, antioxidant [37]
	Hydroxychavicol [42] Allylpyrocatechol [37] Chavicol [43]	
Asian region	Allylpyrocatechol diacetate [44]	Antidiabetic [44]
	Chavibetol acetate [44]	Antinociceptive [44] Antimicrobial [44] Insecticidal [44] Antioxidant [44] Gastroprotective [44] Antidiabetic [44]
	3-Fluoro-2-propynenitrile [45] Tris(trifluoromethyl)phosphine [45]	Antimicrobial [45]
	Coniferyl aldehyde [7]	Anti-inflammatory [46]
Bali and the Indonesian region	Eugenol [47]	Antifungal [47]
	Hydroxychavicol [48]	Anti-inflammatory [48] Antioxidant [48]
China	Eugenol [41]	Antibacterial [41] Antioxidant [41]
	Lignans: Licarin A [49]	Antipruritic [49]

or is cultivated for practical use. Its success as an agricultural crop largely depends on specific environmental conditions, and a thorough understanding of the plant's biological characteristics is crucial for its sustainable cultivation and conservation within its natural range.

The complex mixture of BACs within the *P. betle* TMF is responsible for various types of pharmacological activity, which justifies its use in traditional medicine and has generated growing interest from the medical research community. Across its geographical range, *P. betle* exhibits variability in the chemical composition of its TMF in terms of the presence and content of alkaloids, phenolic compounds (including flavonoids), and volatile components. These compounds confer unique properties upon the plant, making it a vital component of traditional medicine in the countries where it grows.

It is important to note that the chemical composition of the *Piper betle* TMF can vary depending on various factors, such as the diversity of plant species in the surrounding tropical biocenosis, climatic conditions, and the geographical region of growth. This adaptive variability underscores the importance of conducting targeted studies to determine the chemical composition of the plant in each specific region.

At the same time, the impact of traditional remedies derived from this plant on human health improvement remains a poorly understood topic with respect to the safe use of ethnomedicine, an issue that warrants serious attention in future research. Consequently, further studies are clearly needed to investigate the molecular biological activity underlying the pharmacological characteristics of the chemical components of the medicinal plant *P. betle*. Furthermore, clinical trials are required to elucidate the full spectrum of pharmacological effects of drugs developed from *P. betle* plant material.

P. betle exhibits a wide range of biological activities associated with its TMF: from antimicrobial properties to anti-inflammatory, antioxidant, central nervous system-stimulating, and antiparasitic effects, and even prospects in cancer therapy. This diversity of biological properties makes *P. betle* an intriguing subject for research and a valuable resource in both traditional and modern medicine. Current research is underway to explore the potential of *P. betle* as a source of anti-inflammatory, antimicrobial, antidiabetic, and anticancer agents. However, it should be noted that most of these experiments are in the early stages, and further research is required to confirm and clarify their potential benefits for humans.

Despite the abundance of scientific publications, most research on the effects of *P. betle* on human reproductive health remains at the preclinical level. Some animal studies have demonstrated a positive effect of *P. betle* bioactive compounds on oogenesis, cycle regularity, and sperm quality; however, the data obtained require more rigorous clinical confirmation. Given the traditional use of this plant by various peoples of the Indonesian–Asian region as an aphrodisiac, and the presence of active compounds that potentially influence hormone regulation and inflammatory processes, *P. betle* represents a promising subject for further research on supporting human reproductive health.

Conflicts of interest

The authors declare no conflicts of interest.

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PHTHISIOLOGY

TUBERCULOSIS IS NOT AN OBSTACLE TO KIDNEY TRANSPLANTATION

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RESUME

Background. *Monitoring patients with chronic kidney disease during preparation for kidney transplantation, in the immediate postoperative period and then over the years is a unique opportunity to verify the effectiveness of anti-tuberculosis therapy.*
The aim. *To analyse the results of long-term observation of patients with chronic kidney disease stage 5 (CKD stage 5), who received a course of anti-tuberculosis therapy before kidney transplantation.*
Materials and methods. *The analysis of the results of long-term observation of 7 patients with CKD stage 5 who had tuberculosis (TB) while receiving renal replacement therapy (RRT) using the method of programmed hemodialysis and continued observation by a phthisiatrician at the stages of preparation for kidney transplantation and for a year after, was carried out.*
Results. *At the time of tuberculosis diagnosis, the observed multicomorbid patients had been on programmed hemodialysis for an average of 2.9 years. Anti-tuberculosis therapy was administered according to individualized regimens. The average waiting period for kidney transplantation for these patients was 3.6 years. Kidney transplantation was performed successfully in all 7 observed patients, after that all patients received three-component immunosuppressive therapy (tacrolimus, mycophenolate mofetil, methylprednisolone). Control examination to exclude reactivation of tuberculosis was carried out once every 6 months on a planned basis or upon complaints. The average follow-up period for recipients was 3.9 years. Reactivation of tuberculosis after kidney transplantation was recorded in only one patient. Thus, in 6/7 (85.7 %) patients with CKD with tuberculosis infection, kidney transplantation and administration of immunosuppressive therapy were performed without reactivation of tuberculosis.*
Conclusions. *The long-term absence of tuberculosis reactivation in the majority of patients (85.7 %) against the background of not only renal failure, but also immunosuppressive therapy after kidney transplantation was achieved through an individual approach to the treatment and management of each patient with CKD and interdisciplinary interaction of doctors.*

Key words: *tuberculosis, chronic kidney disease, hemodialysis, kidney transplantation antituberculosis therapy*

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ТУБЕРКУЛЕЗ – НЕ ПРЕГРАДА ДЛЯ ТРАНСПЛАНТАЦИИ ПОЧКИ

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РЕЗЮМЕ

Обоснование. *Наблюдение за больными хронической болезнью почек в процессе подготовки к пересадке почки, в ближайшем послеоперационном периоде и далее в течение лет, является уникальной возможностью убедиться в эффективности противотуберкулезной терапии.*
Цель исследования. *Провести анализ длительного наблюдения за больными хронической болезнью почек (ХБП 5 ст.), прошедших курс противотуберкулезной терапии перед трансплантацией почки.*
Методы. *Проведен анализ результатов длительного наблюдения 7 больных хронической ХБП 5ст., перенесших туберкулез (ТБ) во время получения заместительной почечной терапии (ЗПТ) методом программного гемодиализа и продолживших наблюдение у фтизиатра на этапах подготовки к трансплантации почки и в течение года после проведения пересадки почки.*
Результаты. *На момент диагностики туберкулеза наблюдаемые мультиморбидные больные находились на программном гемодиализе в среднем 2,9 лет. Противотуберкулезная терапия проводилась по индивидуализированным режимам. Срок ожидания трансплантации почки для данных больных в среднем составил 3,6 лет. Трансплантация почки была выполнена всем 7 наблюдаемым больным успешно, после трансплантации почки все больные получали трехкомпонентную иммуносупрессивную терапию (такролимус, микофенолата мофетил, метилпреднизолон). Контрольное обследование для исключения реактивации туберкулеза проводилось 1 раз в 6 месяцев в плановом порядке или по жалобам. Срок наблюдения за реципиентами почечного трансплантата в среднем составил 3,9 лет. Реактивация туберкулеза после пересадки почки была зафиксирована лишь у одного больного. Таким образом, у 6/7 (85,7 %) больных ХБП с туберкулезной инфекцией трансплантация почки и назначение иммуносупрессивной терапии выполнены без реактивации туберкулеза.*
Заключение. *Многолетнее отсутствие реактивации туберкулеза у большинства больных (85,7 %) на фоне не только почечной недостаточности, но и иммуносупрессивной терапии после трансплантации почки достигнуто за счет индивидуального подхода к лечению и ведению каждого больного ХБП и междисциплинарного взаимодействия врачей.*

Ключевые слова: *туберкулез, хроническая болезнь почек, гемодиализ, трансплантация почки, противотуберкулезная терапия*

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BACKGROUND

Infectious processes represent the most formidable potential complications following organ transplantation, particularly in the context of immunosuppressive therapy [1]. Among these, tuberculosis (TB) is one of the most severe, as its reactivation can occur at any stage, both before and after transplantation [2]. The presence of active TB infection is defined as an absolute contraindication to kidney transplant surgery, while the presence of latent TB infection or residual post-TB changes necessitates a course of chemoprophylaxis [1]. The higher incidence of tuberculosis in patients with stage 5 chronic kidney disease (CKD) in the post-transplant period compared to the general population (2,700 cases per 100,000 people) is evidently associated with the use of prolonged immunosuppressive therapy (methylprednisolone, mycophenolate mofetil or mycophenolic acid, tacrolimus/extended-release tacrolimus). From the moment of TB diagnosis, mycophenolate mofetil/mycophenolic acid is discontinued, and patients receive dual-component immunosuppressive therapy [3]. According to WHO clinical guidelines on tuberculosis preventive treatment (TPT), patients with stage 5 CKD receiving renal replacement therapy (RRT) and awaiting kidney transplantation are indicated for a course of TB chemoprophylaxis. The recommended regimens include the use of isoniazid, rifampicin, and their various combinations, with variations in dosages and duration of administration [4]. However, in real-world clinical practice, prescribing these medications is often not feasible [5].

However, a review of published studies on the outcomes of tuberculosis chemoprophylaxis in patients with stage 5 CKD reveals that methods for monitoring the effectiveness of such preventive therapy courses in patients on hemodialysis are rarely described; in most cases, this objective was not included in the study design [6, 7, 8, 9]. The available data are primarily focused on the application of standard chemoprophylaxis regimens [10, 11]. Furthermore, no data are available on the effectiveness of individualized courses of anti-tuberculosis therapy based on long-term follow-up observations.

THE AIM OF THE STUDY

To analyze the long-term follow-up results of patients with stage 5 CKD treated with anti-tuberculosis therapy for tuberculosis infection.

MATERIALS AND METHODS

The study included 7 patients with stage 5 chronic kidney disease (CKD) receiving renal replacement therapy (RRT) via maintenance hemodialysis. These patients were under the observation of the Central Tuberculosis Research Institute (CTRI) from 2016 to 2024 and had received a course of anti-tuberculosis therapy for tuberculosis infection. Specialists at the CTRI monitored tuberculosis infection activity both before and after kidney transplantation. The study group consisted of 4 women and 3 men. Patient ages ranged from 35 to 50 years, with a mean age of 39.86 years (SD = 6.09). In all patients, a diagnosis of tuberculosis was first established at the CTRI based on the results of a comprehensive examination. A patient-centered approach to treatment strategy was applied to the patients included in the study. This approach was based on a careful assessment to determine the optimal risk/benefit ratio when prescribing anti-tuberculosis medications, as well as joint monitoring by relevant specialists (e.g., nephrologist, cardiologist). Follow-up examinations by a phthisiatrician, including analysis of chest CT results (incorporating expert radiological interpretation), were conducted once every 6 months.

The study project was approved by the Ethics Committee of the Central Tuberculosis Research Institute (CTRI) (Protocol No. 1/2 dated March 31, 2015), in strict adherence to the principles of the World Medical Association's Declaration of Helsinki (1964, as revised in 2013), as well as the norms and regulations of clinical practice in the Russian Federation (Order of the Ministry of Health of the Russian Federation No. 200n dated April 1, 2016). The study was conducted after obtaining informed consent from all participants.

RESULTS

At the stage of analyzing the clinical and anamnestic data of the observed patients, the underlying causes of chronic kidney disease were determined. It was found that in 5 out of 7 individuals, the etiology of chronic kidney disease was chronic glomerulonephritis (histologically verified); in one patient, it was diabetic nephropathy; and in another patient, the nature of CKD was unknown.

The duration of renal replacement therapy (RRT) at the time of referral to a phthisiatrician among the observed patients ranged from 2 months to 11 years, with a mean of 2.886 years (SD = 3.736). None of the patients were receiving immunosuppressive therapy at the time of tuberculosis infection diagnosis. All patients had 2 or more comorbidities in addition to kidney disease and its complications. Comorbidities observed in the study patients included: hepatitis C (in 3 patients), aseptic necrosis of the femoral head, nonspecific osteomyelitis of the mandible, chronic erosive gastritis, and others.

An analysis of the initial clinical forms of tuberculosis diagnosed in the observed patients during the renal replacement therapy period was performed (Table 1).

As shown in Table 1, the majority of patients (5/7 individuals; 71.4 %) were followed up with residual pulmonary changes after tuberculosis, while two patients

had an active tuberculosis process. According to the activity of the tuberculous process, the observed patients with stage 5 CKD undergoing renal replacement therapy received anti-tuberculosis treatment as follows: 5 patients received a prophylactic course, and 3 patients received a full course of anti-tuberculosis chemotherapy.

The observed patients did not exhibit bacterial excretion. *Mycobacterium tuberculosis* was identified in only one patient with infiltrative pulmonary tuberculosis, based on the results of a bronchoalveolar lavage fluid culture, which revealed multidrug resistance (MDR). In the other CKD patients, *M. tuberculosis* was not detected; therefore, in accordance with clinical guidelines, treatment for drug-sensitive tuberculosis was indicated. However, considering a number of factors (including comorbidities and ongoing therapy for complications of renal failure), the standard regimens for tuberculosis chemotherapy and chemoprophylaxis were not applicable to the observed patients. In most cases, anti-tuberculosis treatment was administered according to individualized regimens.

An analysis of the actual versus recommended anti-tuberculosis treatment (ATT) regimens in patients with stage 5 CKD is presented in Table 2.

As shown in Table 2, among patients receiving a course of tuberculosis chemoprophylaxis (CP), only one patient received a standard regimen (a combination of H and E daily for 3 months), while the remaining CKD patients received individualized regimens. Patients with active tuberculosis undergoing renal replacement therapy also received individualized anti-tuberculosis treatment regimens, both in cases of identified MDR *M. tuberculosis* and when following a drug-sensitive tuberculosis regimen.

TABLE 1

CLINICAL FORMS OF TUBERCULOSIS IN PATIENTS INCLUDED IN THE STUDY

Clinical forms of tuberculosis	Number of patients
Residual pulmonary changes after tuberculosis	5
Focal pulmonary tuberculosis	1
Infiltrative pulmonary tuberculosis	1

The duration of preventive treatment in most cases was 2 months, using a combination of two anti-tuberculosis medications.

The treatment duration for infiltrative pulmonary tuberculosis with MDR *Mycobacterium tuberculosis* (MTB) was 12 months, while the duration of treatment for a patient with focal pulmonary tuberculosis following a drug-sensitive TB regimen was 8 months.

An analysis of the reasons for such individualization of anti-tuberculosis treatment in the observed patients was performed (Table 3).

As shown in Table 3, 5 out of 6 patients for whom rifampicin was indicated had contraindications to this drug: either at baseline (hepatic impairment, in one patient combined with adverse drug interactions with antifungal agents) or identified upon initial drug administration (hematotoxic reactions) – 3 out of 6 patients. Contraindications to isoniazid use in the form

TABLE 2

ANALYSIS OF ACTUAL AND RECOMMENDED ANTI-TB TREATMENT REGIMENS IN CKD STAGE 5 PATIENTS

Anti-tuberculosis treatment regimen	Recommended ATT regimen	Actual ATT regimen
Preventive (*n* = 5)	H 6–9 months daily R, H 3 months daily H, E 3 months daily H, P 3 months once weekly H, P 1 month daily H, Z 3 months daily	R, E 2 months daily E, Mfx 2 months daily H, E 2 months daily H, E 3 months daily Z, E 2 months daily
Full course (*n* = 3)	H, R, Z, E/S (*n* = 1) 6–7 months Bq, Lzd, Fq, Cs\Ter, E\Z\Cm (*n* = 1) 12 months (for limited disease)	H, Z, E 8 months daily Bq, Imp, Z, Mfx, Ter 12 months

Notes. H – isoniazid, R – rifampicin, Z – pyrazinamide, E – ethambutol, S – streptomycin, P – rifapentine, Mfx – moxifloxacin, Bq – bedaquiline, Lzd – linezolid, Fq – fluoroquinolones, Cs – cycloserine, Ter – terizidone, Cm – capreomycin.

TABLE 3

ANALYSIS OF THE REASONS FOR INDIVIDUALIZATION OF ANTI-TUBERCULOSIS THERAPY REGIMENS IN CKD 5 STAGE PATIENTS

Recommended drug	Reasons for prescribing individualized anti-tuberculosis treatment regimens		Number of patients with contraindications to the drug
	Condition	Number of cases	
isoniazid	psychopathy	1	*n* = 3
	heart failure	3	
pyrazinamide	drug intolerance	1	*n* = 4
	liver dysfunction	2	
	adverse drug interactions (anti-gout medications)	1	
rifampicin	adverse drug interactions (anti-fungal agents)	1	*n* = 5
	liver dysfunction	2	
	hematotoxic reactions	3	
linezolid	polyneuropathy	1	*n* = 1

of decompensated heart failure were present; in one female patient, this was combined with a psychiatric disorder. Four out of seven patients for whom pyrazinamide was recommended in the treatment regimen had contraindications to this drug, mainly at baseline – hepatic impairment and concomitant use of anti-gout medications; and one patient developed drug intolerance identified after the initial dose. One patient with MDR-TB was indicated for linezolid according to clinical guidelines; however, due to severe polyneuropathy, the use of this drug was not possible.

After completing ATT, all 7 patients with stage 5 CKD awaited kidney transplantation for varying periods, ranging from 2 months to 15.5 years. The mean waiting time for transplantation was 3.63 years (SEM = 2.09, SD = 5.54, median = 1.2 years). Kidney transplantation was successfully performed in all 7 observed patients: 6 patients received a deceased donor kidney, and 1 patient received a kidney from their mother. Following kidney transplantation, all patients received triple immunosuppressive therapy (tacrolimus, mycophenolate mofetil, methylprednisolone). The follow-up period after kidney transplant surgery ranged from 1 to 6.5 years (mean = 3.85 years, SD = 2.23).

All patients were followed up by a nephrologist and concurrently by a phthisiatrician. Follow-up examinations to rule out tuberculosis reactivation were performed routinely every 6 months or upon presentation of complaints. Tuberculosis reactivation after kidney transplantation was recorded in only one patient: this patient was diagnosed with tuberculous lymphadenitis 13 months after receiving an allograft from their mother. This patient received anti-tuberculosis therapy according to an individualized regimen and underwent lymphadenectomy. Graft function remained satisfactory, and the patient continued follow-up. Thus, in 6 out of 7 patients with stage 5 CKD and tuberculosis infection, kidney transplantation and the initiation of immunosuppressive therapy were accomplished without tuberculosis reactivation.

A clinical case from practice serves as a clear example of the profile of this category of patients with stage 5 CKD and tuberculosis infection, both before and after kidney transplantation.

Patient K., born in 1976 (44 years old at the time of referral), was referred to the CTRI by a nephrologist to determine eligibility for kidney transplantation.

Life history. The patient is a resident of the Moscow region. Family history and allergy history are unremarkable.

Phthisiatric history. The patient had previously been followed up at a tuberculosis clinic at her place of residence in 2006; however, the medical records have not been preserved, and the patient herself does not recall receiving any anti-tuberculosis medications. No documented contact with a tuberculosis patient has

been identified. She underwent annual chest X-rays, which revealed no pathology.

Medical history. The onset of kidney disease occurred in November 2019, when the patient developed lower extremity edema and elevated blood pressure. A medical examination at an outpatient clinic revealed the presence of proteinuria. The patient was hospitalized and was diagnosed with stage 5 CKD. On November 20, 2019, an arteriovenous fistula (AVF) was created. Renal replacement therapy via maintenance hemodialysis was initiated on June 29, 2020. However, the patient tolerated the procedures poorly, experiencing elevated blood pressure during sessions and weight loss down to 39 kg.

In October 2020, a complication in the form of an AVF thrombosis was identified, and hemodialysis was continued using a central venous catheter. The patient was consistently receiving antiplatelet and antihypertensive therapy (losartan, bisoprolol, amlodipine), Mircera® as an erythropoiesis-stimulating agent, and alfacalcidol as a regulator of calcium and phosphorus metabolism.

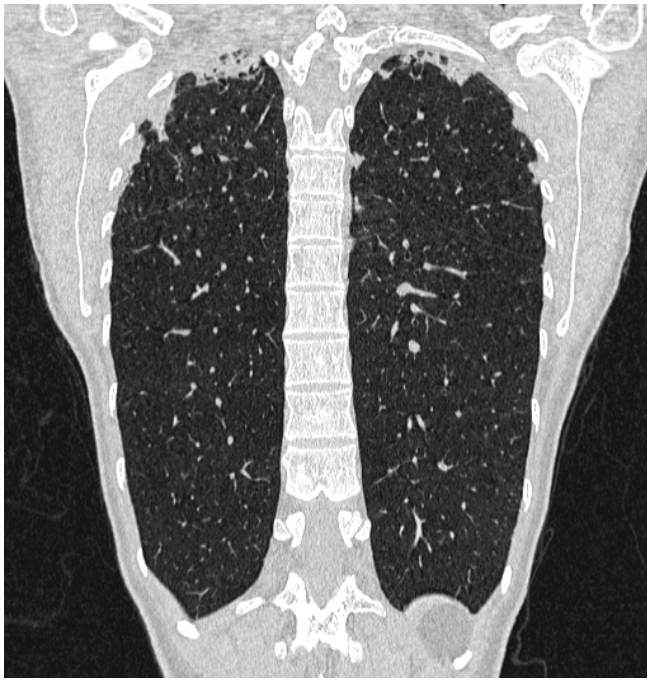
Considering the patient's medical history, recommendations from a nephrologist, and the ongoing COVID-19 pandemic, the patient underwent a chest CT scan on September 26, 2020. The scan was performed independently in preparation for a planned kidney transplantation. The scan revealed focal fibrotic changes in the upper lobes of the lungs.

On December 15, 2020, the patient presented to the consultative department of the Center for Diagnosis and Rehabilitation of Respiratory Diseases at the CTRI with complaints of general weakness and blood pressure fluctuations. At the time of examination, there were signs of anemia and malnutrition: the skin and visible mucous membranes were pale, and the patient had a significant body weight deficit (weight is 39 kg, BMI 14.7). There was no edema present. Auscultation revealed vesicular breathing without wheezing. Heart sounds were clear and rhythmic with a regular rhythm. The heart rate was 100 bpm, and blood pressure was 100/80 mmHg. The abdomen was soft and non-tender. Bowel movements occurred once a day with formed brown stools. The patient was receiving renal replacement therapy through maintenance hemodialysis three times a week for 3 hours via a central venous catheter.

An analysis of the patient's clinical and laboratory records revealed the following: a significant body weight deficit, signs of asthenia, a history of venous thrombosis, difficulty tolerating hemodialysis treatments, and moderate anemia, with a hemoglobin level reduced to 68 g/L. A borderline leukocyte count of 4.9×10^9/L (reference range $4.8–9.0\times10^9$/L) was also noted.

Chest CT findings from December 15, 2020: apical superimpositions extending along the dorsal regions to the interlobar fissure, appearing as areas of consolidation with a partially preserved air bronchogram; a single subpleural nodule in segment S9 of the left lung measuring up to 6 mm. The lumens of the upper lobe bronchi are unevenly dilated (Figure).

The results of the immunological skin tests (Diaskintest and Mantoux test with 2 TU PPD-L) showed complete anergy, as the reaction to both tests was negative and limited to the injection site.



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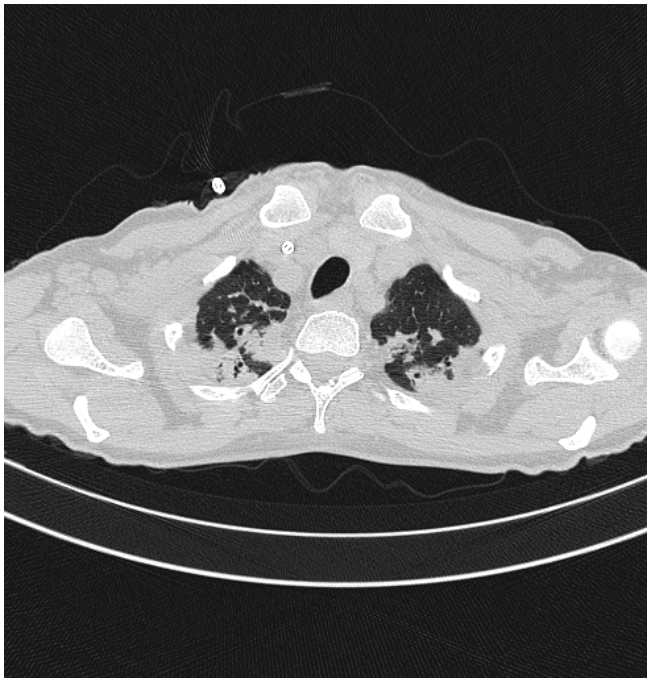

B

FIG. 1.
Data of the CT-scan chest of patient K. at the time of admission: A – in the coronal projection, B – in the axial projection

Functional assessment findings: the pulmonary ventilatory function was within normal limits. However, the ECG analysis conducted on January 12, 2021, showed: sinus rhythm with a heart rate of 80 bpm, a normal electrical axis of the heart, an incomplete right bundle branch block, and signs of left ventricular hypertrophy.

To clarify the activity of pulmonary changes and verify the diagnosis, a bronchoscopy with bronchoalveolar lavage (BAL) was performed on January 14, 2021. Cytological and comprehensive microbiological analysis of the BAL fluid was conducted. Examination of the tracheobronchial tree revealed endoscopic signs of diffuse, bilateral, and deforming atrophic bronchitis. Analysis of the BAL fluid for *M. tuberculosis* revealed no acid-fast bacilli (AFB) and no *M. tuberculosis* DNA. The BAL cytogram revealed a predominance of alveolar macrophages (89 %), neutrophils (3 %), and lymphocytes (8 %); atypical cells and AFB were not observed during cytological examination.

BAL fluid culture using the BACTEC MGIT 960 liquid culture system did not show any growth of *Mycobacterium tuberculosis* complex. Based on the examination results, the following diagnosis was established: residual post-tuberculosis pulmonary changes in the form of fibrous pleuroapical superimpositions and dense pulmonary nodules; chronic deforming atrophic bronchitis in remission; bronchiectasis of the upper lung lobes; MBT (-); stage 5 CKD due to tubulointerstitial nephritis; maintenance hemodialysis since June 29, 2020; moderate secondary anemia; stage 3 secondary arterial hypertension with a cardiovascular complication risk of 4; left ventricular hypertrophy; CHF class 2 according to NYHA classification, FC 2; AVF thrombosis on October 25, 2020, and central venous catheter implantation on October 27, 2020, as well as severe body weight deficit.

The patient was recommended to undergo a course of chemoprophylaxis to prevent tuberculosis reactivation. According to the clinical guidelines, isoniazid and rifampin/rifampicin should be the first-line drugs of choice.

However, due to the presence of heart failure and malnutrition, the isoniazid administration was not advisable. Additionally, considering drug interactions (rifampicin reduces the activity of beta-blockers and calcium channel blockers), as well as the high risk of hematotoxic reactions with concurrent rifampicin and isoniazid administration, given the patient's baseline blood count abnormalities, an individualized chemoprophylaxis regimen was required.

After excluding pathology of the optic nerve and retina through an ophthalmological examination, the patient was prescribed a combination of 1000 mg pyrazinamide and 400 mg ethambutol daily. The medications were taken daily for two months on dialysis days, after the hemodialysis procedure. Clinical and laboratory tolerance to the anti-tuberculosis drugs was satisfactory (the patient underwent regular examinations at the dialysis center and outpatient clinic).

Following the completion of the two-month preventive anti-TB therapy course, a medical team approved kidney transplantation. Approximately two months after finishing the chemoprophylaxis regimen, in spring 2021, the patient received a deceased donor kidney allotransplantation.

Subsequently, the patient received triple immunosuppressive therapy (Advagraf, mycophenolate mofetil, methylprednisolone) and was regularly monitored by a phthisiatrician. Over a three-year period, no signs of tuberculosis reactivation were observed. Moreover, the patient reported an improvement in their overall well-being, an increase in exercise tolerance, a gain of 10 kg in weight, normalization of hemoglobin levels, and a significant improvement in quality of life.

DISCUSSION

The problem of tuberculosis among candidates for organ transplantation, particularly kidney transplantation, has been widely recognized. This condition is a common cause of renal graft loss and/or death of the kidney recipient themselves. Over the years, researchers in the Russian Federation and other countries have investigated the characteristics of tuberculosis in kidney transplant recipients and sought to determine the optimal strategy for tuberculosis treatment. In 1999, Indian researchers, followed by Russian specialists, attempted to develop anti-tuberculosis treatment (ATT) regimens that did not include rifampicin due to potential drug interactions with cyclosporine A and everolimus. Alternatives to rifampicin such as ofloxacin and prothionamide were suggested. However, high mortality rates continued to persist, and treatment success was achieved only in short-term follow-up studies. All authors emphasized the importance of early detection of tuberculosis and the timely initiation of appropriate treatment [12-15].

Undoubtedly, addressing the challenge of managing anti-tuberculosis treatment for patients with stage 5 CKD before and after kidney transplantation is beyond the expertise of a single medical specialty. Rather, it requires continuous collaboration among professionals from various fields, primarily including phthisiatricians, nephrologists, gastroenterologists, internal medicine specialists, and transplant surgeons. Currently, most research focuses on short-term studies covering either the preparation period for kidney transplantation or the initial year following surgery. This publication differs significantly in that it presents the results of a long-term follow-up study of patients with stage 5 CKD that encompasses both the pre-transplant phase and the postoperative period. Prolonged follow-up periods allow specialists from various fields to validate the clinical strategy chosen: phthisiatricians can attest to the high effectiveness of anti-tuberculosis therapy, based not only on the lack of tuberculosis recurrence over many years, but also in the context of ongoing

immunosuppressive therapy; nephrologists and transplant surgeons can assess treatment efficacy, including the viability of kidney transplantation, administration of immunosuppressive therapy, and significant improvement in the quality of life of CKD patients who have survived tuberculosis.

CONCLUSION

Patients with chronic kidney disease who are receiving renal replacement therapy and have tuberculosis infection represent a complex and multimorbid group of patients that requires long-term follow-up and continuous interdisciplinary collaboration between various specialists.

The high effectiveness of an individualized approach to the treatment and management for each CKD patient has been demonstrated by the fact that the majority of these patients have had no reactivation of TB over the long term, not only during renal failure but also during the period of immunosuppressive therapy after transplantation.

Our results from the treatment and management of CKD patients with tuberculosis infection before and after kidney transplantation show that tuberculosis infection is not a barrier to kidney transplantation, but rather a factor that unites the efforts of medical professionals from different specialties.

Conflicts of interest

The authors declare no conflicts of interest.

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SURGERY

APPLICATION OF MEMBRANE-PROTECTANT IN THE PROCESS OF INCREASING THE VIABILITY OF AUTOLOGOUS FAT GRAFT

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RESUME

Background. *Autologous adipose tissue transplantation is becoming increasingly popular in reconstructive surgery, but the main unsolved problem at the moment is the high percentage of partial volume loss due to autograft resorption.*
The aim. *Evaluation of the viability of adipocytes under incubation in solutions of different biochemical compositions, and clinical testing of the effectiveness of an optimized fat graft.*
Materials and methods. *The comparative spectral analysis of the content of ions (mainly oxygen) in the cytoplasm of fat cells grown from solution samples on a solid substrate using a scanning electron microscope in low vacuum was performed. The composition in 3 samples that spent 6 h in artificial solutions was investigated. The EDAX TEAM program was used to analyze the energy dispersive X-ray spectroscopy data.*
Results. *Statistical and morphological analysis of the obtained results revealed differences in the composition of viable cells in the studied samples, varying up to 50 %. The most effective was the solution with dimethyloxobutylphosphonyldimethylate, which demonstrated an optimal level of oxygen ion content (O), as well as pronounced integrity of the cell membrane compared to other samples during electron microscopy and histological examination.*
Conclusion. *One of the key factors is the medication support of the autograft during the initial stages of engraftment after transplantation. By measuring the ionic content of the intracellular matrix, we were able to examine in vitro the effect of solutions of different substances to achieve this goal. For autograft preservation, the best option is a solution with a membrane protector dimethyloxobutylphosphonyldimethylate for its ability to preserve cell homeostasis.*

Keywords: *reconstructive surgery, ionic composition, electron microscopy, hypoxia, lipofilling*

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ПРИМЕНЕНИЕ МЕМБРАНОПРОТЕКТОРОВ В ПРОЦЕССЕ ПОВЫШЕНИЯ ЖИЗНЕСПОСОБНОСТИ АУТОЛОГИЧНОГО ЖИРОВОГО ТРАНСПЛАНТАТА

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РЕЗЮМЕ

Обоснование. *Трансплантация аутологичной жировой ткани становится все более популярна в реконструктивной хирургии, однако основной нерешенной проблемой на текущий момент является высокий процент частичной потери объема из-за резорбции аутотрансплантата.*

Цель исследования. *Оценка жизнеспособности адипоцитов в условиях инкубации в растворах различного биохимического состава и клиническая апробация эффективности оптимизированного жирового трансплантата.*

Методы. *Производился сравнительный спектральный анализ содержания ионов (преимущественно кислорода) в цитоплазме жировых клеток, высаженных из образцов растворов на твердую подложку при помощи растрового электронного микроскопа в низком вакууме. Исследовался состав в 3 образцах, которые провели 6 часов в искусственных растворах. Для анализа данных энергодисперсионной рентгеновской спектроскопии использовалась программа EDAX TEAM.*

Результаты. *Статистический и морфологический анализ полученных результатов выявил различия в составе жизнеспособных клеток в исследуемых образцах, варьирующиеся в пределах до 50 %. Наиболее эффективным оказался раствор с диметилоксобутилфосфонилдиметилатом, продемонстрировавший оптимальный уровень содержания ионов кислорода (O), а также выраженную целостность клеточной мембраны по сравнению с другими образцами в ходе проведения электронной микроскопии, а также гистологического исследования.*

Заключение. *Одним из ключевых факторов является медикаментозная поддержка жировой ткани на начальных этапах приживления после трансплантации. Путем измерения содержания ионов во внутриклеточном матриксе мы смогли рассмотреть в лабораторных условиях влияние растворов различных веществ для достижения данной цели. Для сохранения аутотрансплантата лучшим вариантом является раствор с мембранопротектором диметилоксобутилфосфонилдиметилата по способности сохранения гомеостаза клетки.*

Ключевые слова: *реконструктивная хирургия, ионный состав, электронная микроскопия, гипоксия, липофилинг*

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BACKGROUND

Autologous fat grafting is becoming increasingly popular, with statistics indicating a 10 % annual rise in the number of lipofilling procedures in Russia [1]. In addition to aesthetic corrections, this tissue is increasingly being used in various reconstructive techniques, particularly as an alternative to synthetic implants or volume-enhancing agents (e.g., those based on hyaluronic acid) [2, 3, 4], or in combination with implants for enhanced results [5].

Special attention is given to the use of autologous fat grafts for closing deep soft tissue defects. This method is preferred for chronic non-healing wounds with a bone bed, offering advantages such as ease of application and good aesthetic results following subsequent dermoplasty [6].

Consequently, we can observe the increasing popularity of adipose tissue utilization. Unfortunately, as with any method, lipofilling has its own drawbacks. The key complications of lipofilling include ischemia, hypoxia, and necrosis of the transplanted fat tissue. These conditions develop due to insufficient neoangiogenesis and limited diffusion of oxygen and nutrients to the graft. Impaired microcirculation leads to a cascade of ischemic changes, manifested by progressive cellular hypoxia and adipocyte death. In clinical practice, this results in partial graft resorption, the formation of cystic cavities, and foci of fat necrosis, which significantly reduces the predictability and stability of the outcome. Resorption of fat tissue after transplantation can sometimes reach 80 % [7]. Currently, research is being conducted to increase cell viability by incorporating autologous mesenchymal stem cells or treating the lipoaspirate with radiofrequency helium plasma [8, 9].

Therefore, this study explored solutions that improve graft cell survival. Establishing an optimal microenvironment is essential to enhance the antioxidant effect, accelerate engraftment, shorten revascularization time, and improve cell membrane stability through cytoprotective properties.

This requires an understanding of the nutritional mechanisms of fat tissue after transplantation, including the sources of substances and the pathways for their delivery to cellular structures.

Initially, it was believed that the transplanted tissue rapidly revascularizes through the formation of vascular anastomoses between the capillaries of the fat graft and the vascular network of the recipient site [10]. That is, survival was determined by their revascularization and the provision of adequate blood supply from the recipient site's vascular network. It has been shown that only the superficial layer of the lipograft, approximately 300 μm thick, is accessible to microcirculation from the recipient site's capillaries, with subsequent blood flow restoration through neoangiogenesis. In this regard, small fat conglomerates show better survival than large volumetric areas of transplanted tissue introduced into the recipient site as a single mass without uniform distribution [11]. According to genetic studies, free fat grafts undergo metabolic reprogramming towards the glycolytic pathway [12]. The shift from aerobic energy metabolism to glycolysis allows cells to survive under oxygen-deficient conditions. As a result of glycolytic glucose utilization, 2 ATP molecules are formed, instead of 36 as in the aerobic pathway. With insufficient blood supply, this leads to rapid depletion of the cells' own energy stores. Also, under oxygen deficiency, the conversion of lactate to pyruvate is interrupted, leading to lactate accumulation and the subsequent development of local tissue acidosis [13].

Optimizing the graft microenvironment through the use of specialized solutions that ensure cellular homeostasis and metabolic activity (antioxidants (glutathione, mannitol), membrane protectors (dimethyloxobutylphosphonyldimethylate) [14], energy metabolism substrates (adenosine and others) is a key approach to preventing or compensatorily correcting these pathological mechanisms.

THE AIM OF THE STUDY

A comprehensive assessment of adipocyte viability under incubation in solutions of various biochemical compositions and clinical testing of the effectiveness of an optimized fat graft in soft tissue defect reconstruction.

MATERIALS AND METHODS

Within the framework of this study, a quantitative analysis of the intracellular ionic composition, particularly the concentration of oxygen and other elements, in adipose tissue cell cytoplasm exposed to various storage media was conducted. Adipose tissue was obtained from 3 patients (female, aged 30–35 years, without chronic diseases) undergoing elective upper blepharoplasty for aesthetic purposes and used as biological material. All samples were collected under sterile conditions and not subjected to any additional processing. Upon collection, the material was divided into three equal-volume and equal-mass portions (Samples 1–3), each exposed to a different storage medium for analysis.

Characteristics of experimental groups:

Sample 1 (control): Stored in a standard injection solution without any additional ionic supplements. This sample was used as a control medium with minimal ionic exposure.

Sample 2: Incubated in 0.9 % sodium chloride solution (saline), which is the most commonly used medium in clinical practice.

Sample 3: Placed in a 15 % dimethyloxobutylphosphonyldimethylate solution, which has potential antioxidant and membrane-stabilizing properties.

All samples were stored at a temperature of +22 ± 1 °C for a strictly fixed period of 6 hours.

After the completion of the specified period, each specimen was analyzed using low-vacuum scanning electron microscopy (LVSEM). For quantitative analysis of the ionic composition, energy-dispersive X-ray spectrometry (EDX) analysis was employed, utilizing EDAX TEAM™ software. Through the quantitative elemental analysis conducted by energy-dispersive X-ray spectroscopy (EDX), using the eZAF algorithm (ZAF-correction), verification was carried out for the presence of specific peaks in the spectral graph, which may indicate an increase in the concentration of additional ions that were not included in the scope of this study.

Quantitative data are presented as the mean (M) ± the standard error of the mean (SEM), as well as the median (Me) and the interquartile range (Q1–Q3). The normality of distribution was tested using the Shapiro – Wilk test. For comparisons, the Student's *t*-test or Mann – Whitney U-test was used (depending on the distribution). If more than two groups were analyzed, analysis of variance (ANOVA) with Tukey's post hoc test was applied. Differences were considered statistically significant at $p < 0.05$.

Measurements were performed on representative areas of the cytoplasm with a diameter of 25 micrometers. Repeated scans ($n = 3$ per sample) were used to determine the mean values of key ions, including oxygen, sodium, potassium, and chlorine. The obtained data were compared to identify changes in ionic profiles depending on the storage medium composition.

A total of 103 foreign and domestic literature sources indexed in RSCI, PubMed, Scopus, and SSCI were analyzed for this study. Of these, 22 sources were specifically used for the article, with 18 published within the past 5 years.

Prior to the study, informed consent was obtained from the patient regarding the use of their data in the form of photographs and publication of the clinical case. The patient was informed about possible risks and complications associated with the study, and a clinical study was conducted.

RESULTS AND DISCUSSION

The primary aim of the study was to assess the impact of the chemical composition of the medium on the maintenance of the intracellular ionic composition, which can serve as an indicator of cellular viability in transplanted adipose tissue and may change significantly during their storage, processing, and transplantation [15, 16]. Oxygen levels can serve as a diagnostic marker when assessing cell viability [17, 18], which can be explored using electron microscopy in conjunction with spectral analysis of adipocytes.

In each specimen, visually intact cells were selected (Fig. 1):

Cell surface contours: The cell has a regular round or oval shape, the contour is clear, without ruptures, folds, or deformation.

Cell membrane: Smooth or with a uniform, fine-grained structure, without any defects such as cracks, pores, or areas of damage.

Plasmolysis/damage artifacts: no signs of wrinkled and collapsed cells, or membrane "blurring" or fragmentation, are observed.

Surface uniformity: intact cells exhibit a homogeneous surface.

In the photo, the following features can be observed:

1. Substrate fibers (cellulose);
2. Connective tissue remnants;
3. Solution droplets;
4. Adipocyte.

Visual analysis by electron microscopy was used as a method to assess morphology [19, 20]. The results showed that Sample 3, which had been incubated for 6 hours in a solution containing dimethyloxobutylphosphonyldimethylate, demonstrated the best preservation of cellular structure (Fig. 1C). Scanning electron microscopy examination revealed uniformity and integrity of cell surface contours, as well as the absence of significant signs of plasmolysis and membrane damage, which may indicate a membrane-stabilizing effect of the solution component.

In contrast, Samples 1 and 2, which were stored in an injection solution and 0.9 % sodium chloride solution (saline), respectively, showed focal changes in the cell membrane morphology, with localized areas of deformation and irregularities in the perimeter. These changes may indicate a decrease in the structural integrity of cell membranes under conditions without the specific membrane protective properties presumably possessed by dimethyloxobutylphosphonyldimethylate.

Subsequently, the study conducted a quantitative analysis of ion content (Fig. 2) and a spectral analysis (Table) of the samples. The obtained data allowed for a comparison of the effects of different solutions on the level of adipocyte ionic homeostasis and the identification of a preferred medium for short-term storage of adipose tissue for transplantation purposes.

Analysis of the spectral composition of the cellular environment revealed a significant increase in the oxygen ion concentration in Samples 2 and 3 compared to Sample 1 (control). This increase in O concentration, according to EDX data, may reflect increased metabolic activity or improved tissue respiration conditions as a result of exposure to the components of the studied solutions, particularly physiological saline (NaCl) and dimethyloxobutylphosphonyldimethylate. However, simultaneously, there was an increase in the sodium ion concentration, especially in the NaCl solution. This finding requires particular attention, as sodium is the main extracellular cation and its intracellular accumulation may serve as a marker of impaired ionic homeostasis. An excessive Na^+ influx into the cell can lead to an osmotic imbalance, destabilization of membrane potential, and activation of pathways associated with cellular dysfunction and death [21, 22, 23]. This emphasizes the importance of choosing a medium that

ensures both membrane stability and a physiologically balanced ionic environment for preserving the viability of transplanted cells.

During the study, while searching for ion "peaks" that are not included in the studied structure and may potentially affect viability, we only observed the presence of phosphorus ions in the sample containing dimethyloxobutylphosphonyldimethylate. This occurrence is due to the specific composition of the preparation.

In the context of a clinical study (approved by the Local Ethics Committee of the Russian Biotechnological University, Moscow, Volokolamskoye Shosse, 11, Protocol No. 9/4-6 dated April 28, 2025), we performed an additional autologous adipose tissue graft transplantation to verify the laboratory results (Fig. 3).

A soft tissue defect measuring 5 × 3 cm, with exposed muscle fibers and moderate signs of inflammation is present. There is peripheral edema and skin hyperemia, as well as the presence of fibrin. The general blood parameters are within the range of a moderate inflammatory response.

Treatment course: After surgical debridement of the wound, a fat graft was harvested from the anterior abdominal wall region, following the standard lipoaspiration technique using an infiltration solution (0.9 % NaCl with lidocaine and epinephrine). The extracted lipoaspirate was divided into two equal portions: one portion was washed three times with standard isotonic solution and the other with a solution containing 15 % dimethyloxobutylphosphonyldimethylate.

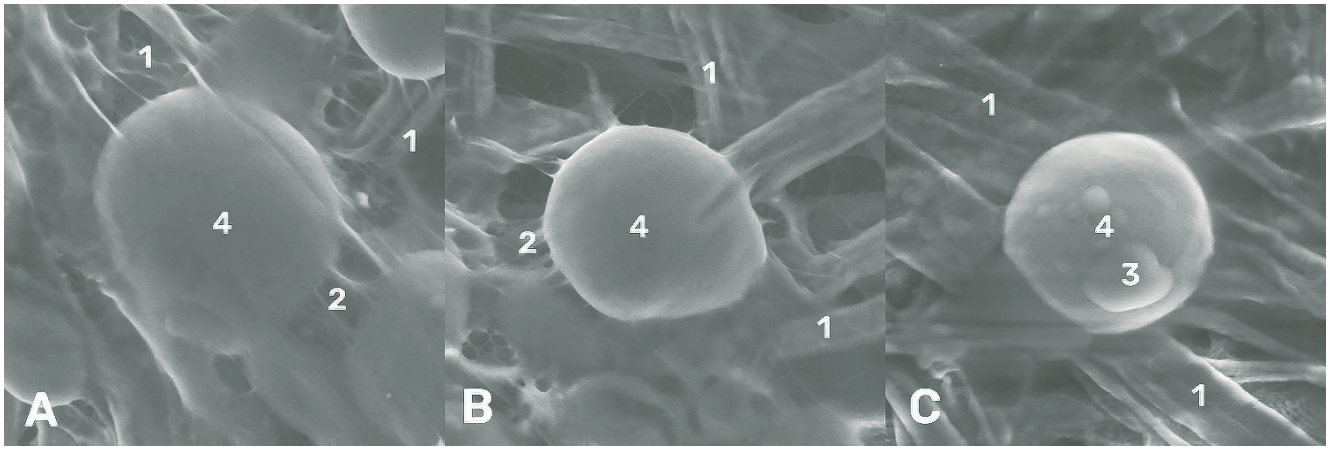


FIG. 1.
Study of adipocytes by electron microscopy (A – solution for injection, B – 0.9 % NaCl, C – 15 % Dimethyloxobutylphosphonyldimethylate)

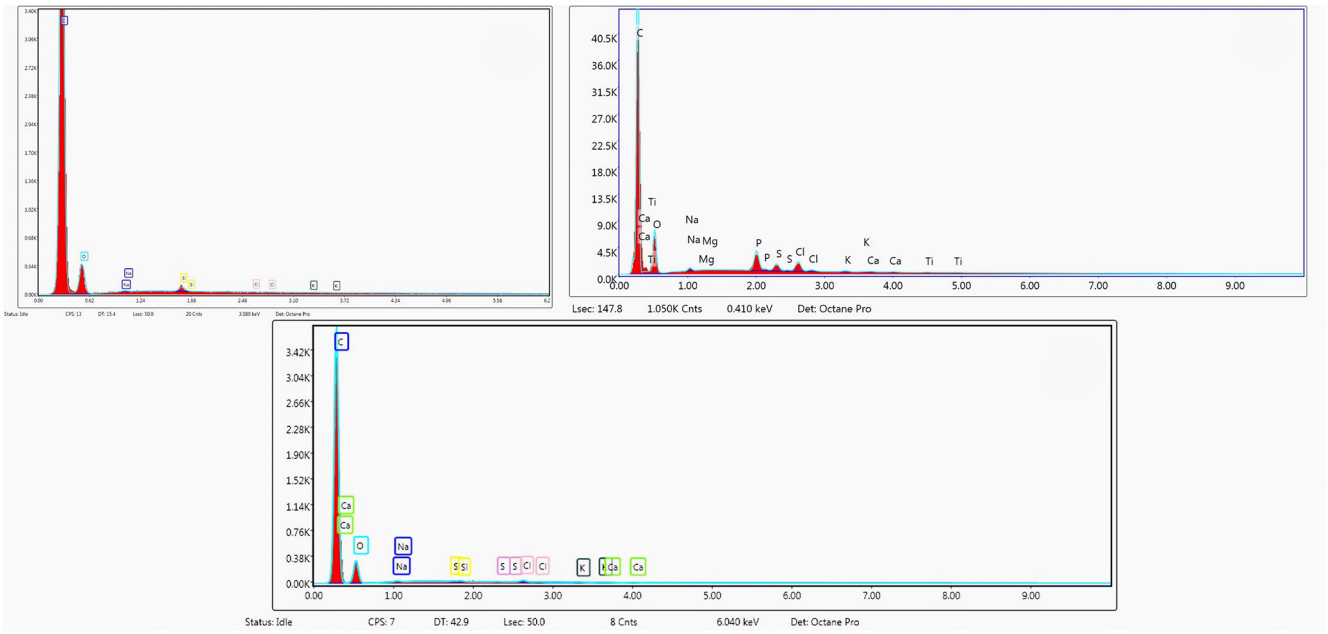


FIG. 2.
eZAF Smart Quant Results. (A – injectable solution, B – 15 % dimethyloxobutylphosphonyldimethylate, C – 0.9 % NaCl)

Subsequently, these solutions were mixed in a 1:10 ratio (1 part of the solution to 10 parts of washed lipoaspirate and added to the samples that had been previously washed with the same solution. After preparation, the fat grafts were placed throughout the entire depth of the defect, and both areas were covered with mesh aseptic dressings using Voskopran wound coverings, followed by application of a vacuum therapy (VAC) system to enhance graft viability and create a controlled healing environment.

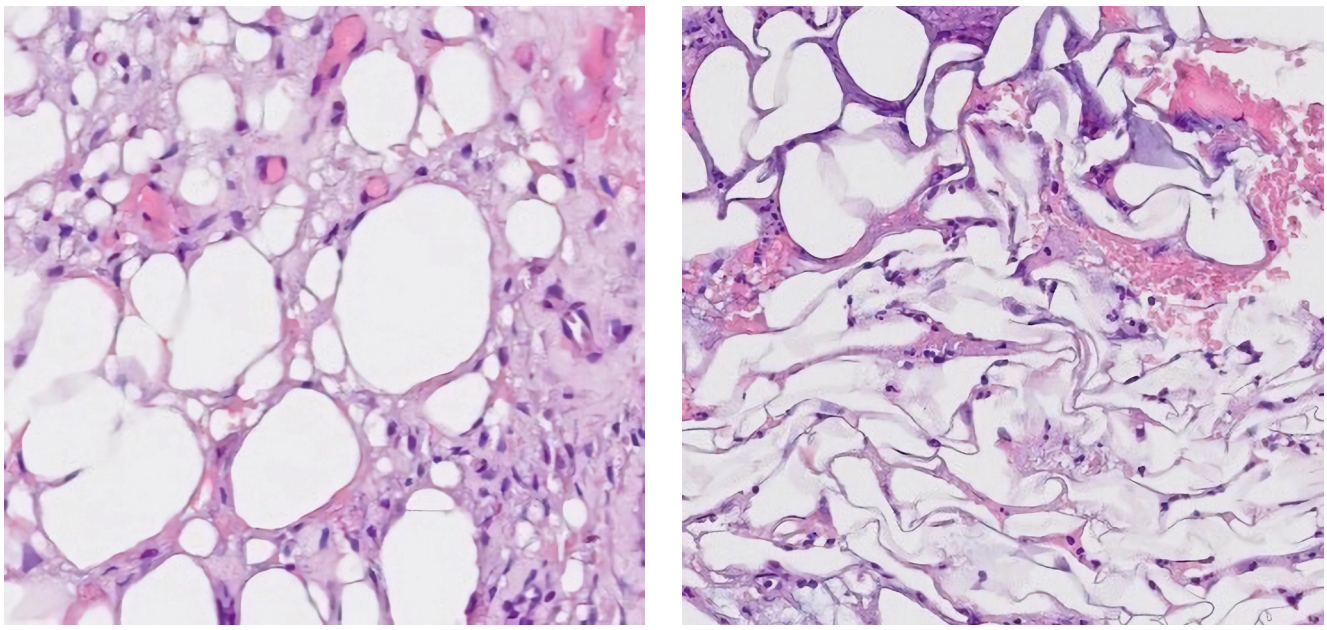
On day 5, a dressing change was performed, followed by a visual assessment of the condition of the graft and the healing process. Tissue samples were also taken for histological examination (Fig. 3).

The histological analysis revealed the presence of mature adipocytes with preserved morphological structure in the area treated with Dimephosphon. In the control group (0.9 % NaCl), there was fragmentation of cellular structures and signs of partial membrane destruction.

TABLE

QUANTITATIVE ION CONTENT (SUM SPECTRUM)

Element	Sample	Repeats (*n* = 3)	M ± m	Me (Q1–Q3)
C	1	83.9; 84.7; 85.2	84.60±0.38	84.70 (83.90–85.20)
C	2	79.1; 80.2; 81.0	80.10±0.48	80.20 (79.10–81.00)
C	3	75.5; 76.4; 77.5	76.47±0.59	76.40 (75.50–77.50)
O	1	14.3; 14.9; 15.4	14.87±0.33	14.90 (14.30–15.40)
O	2	18.5; 19.2; 20.0	19.23±0.37	19.20 (18.50–20.00)
O	3	21.8; 22.5; 23.0	22.43±0.33	22.50 (21.80–23.00)
Na	1	0.10; 0.13; 0.16	0.13±0.03	0.13 (0.10–0.16)
Na	2	0.22; 0.28; 0.34	0.28±0.06	0.28 (0.22–0.34)
Na	3	0.15; 0.19; 0.23	0.19±0.04	0.19 (0.15–0.23)
S	1	0.08; 0.11; 0.16	0.12±0.04	0.11 (0.08–0.16)
S	2	0.02; 0.05; 0.08	0.05±0.02	0.05 (0.02–0.08)
S	3	0.45; 0.55; 0.65	0.55±0.10	0.55 (0.45–0.65)
Cl	1	0.01; 0.03; 0.05	0.03±0.02	0.03 (0.01–0.05)
Cl	2	0.15; 0.24; 0.32	0.24±0.09	0.24 (0.15–0.32)
Cl	3	0.18; 0.21; 0.25	0.21±0.04	0.21 (0.18–0.25)
K	1	0.02; 0.04; 0.06	0.04±0.02	0.04 (0.02–0.06)
K	2	0.05; 0.07; 0.09	0.07±0.02	0.07 (0.05–0.09)
K	3	0.10; 0.16; 0.18	0.15±0.04	0.16 (0.10–0.18)
Ca	1	0.04; 0.05; 0.06	0.05±0.01	0.05 (0.04–0.06)
Ca	2	0.04; 0.05; 0.06	0.05±0.02	0.05 (0.03–0.08)
Ca	3	0.07; 0.10; 0.11	0.09±0.02	0.10 (0.07–0.11)



A B

FIG. 3.
Histological examination. Hematoxylin and eosin staining. Magnification x20. (A – lipoaspirate treated with 15 % dimethyloxobutylphosphonyldimethylate, B – lipoaspirate treated with 0.9 % NaCl)

CONCLUSION

In addition to the technical aspects of adipose tissue transplantation, such as injection volume, anatomical characteristics of the recipient area, and high injection pressure, a key factor in the success of the procedure is the preparation of the autologous graft. This study investigated the effect of various processing methods of harvested tissue on the viability of adipocytes.

Sample 3 showed the most favorable results after being incubated in a solution containing dimethyloxobutylphosphonyldimethylate. This was evident from both the high level of oxygen saturation and the preserved cellular membrane integrity. Sample 2 showed satisfactory oxygenation parameters, but it had elevated intracellular sodium and chloride concentrations and decreased membrane stability when maintained in isotonic sodium chloride (NaCl) solution.

Histological analysis confirmed the benefit of using a specialized solution. In the group treated with dimethyloxobutylphosphonyldimethylate, mature adipocytes with an intact morphological structure and minimal signs of liponecrosis were predominant. In contrast, in the NaCl group, there was significant cell fragmentation and extensive areas of necrosis, indicating reduced graft viability.

The obtained data confirm the positive effect of specialized solutions on adipocyte viability, and emphasize the need for further research into various compositions, including clinical assessment of a solution containing dimethyloxobutylphosphonyldimethylate as a potential membrane-stabilizing agent.

Conflicts of interest
The authors declare no conflicts of interest.

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EXPERIMENTAL RESEARCHES

QUANTIFICATION OF BACKGROUND EXPRESSION OF INTERFERON BETA IN CELL CULTURE OF SIBERIAN BAT (*MYOTIS SIBIRICUS*)

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RESUME

Background. *The study of the immune response of these mammals to viral infections is necessary to reveal the fundamental mechanisms of the circulation of zoonotic infections in nature. There is a hypothesis about the constantly "on" activity of the interferon pathway proteins, developed evolutionarily in bats to counteract viral infections. We assessed the expression of interferon beta as a marker of the innate immune system in kidney cells of the Siberian bat (Myotis sibiricus, Kastschenko, 1905) MdbK3-14.*
The aim. *Evaluation of the background level of interferon beta (IFN-β) gene expression in bat cells as a marker of the activity of the mammalian innate immune system.*
Materials and methods. *MdbK3-14 cells were grown in 24-well plates. Cell monolayers were detached with trypsin solution and total RNA was isolated. The concentration of mRNA of IFN-β gene transcripts and reference genes beta actin (ACTB) and succinate dehydrogenase subunit A (SDHA) was determined by one-step multiplex RT-qPCR and confirmed by RT-dPCR.*
Results. *Specific primers with a probe for detecting mRNA of the IFN-β gene in bat cells were designed. The detection of SDHA and IFN-β gene transcripts was stable both in RT-qPCR (CV = 0.5 % and CV = 0.2 %, respectively) and in RT-dPCR (CV = 0.8 % and CV = 1.4 %, respectively). In addition, stable detection of ACTB mRNA was achieved using RT-dPCR (CV = 0.8 %), but the average variability value for actin using RT-qPCR exceeded the permissible value (CV = 3.6 % with an acceptable CV ≤ 2 %). The results of quantitative determination in RT-qPCR and RT-dPCR correlated with each other. The expression levels of IFN-β in MdbK3-14 cells averaged 0.97 ± 0.15 relative units in RT-qPCR and 0.13 ± 0.05 relative units in RT-dPCR.*
Conclusions. *In the absence of immune stimulation, background expression of IFN-β occurs in the M. sibiricus kidney cell line.*

Key words: *Myotis sibiricus, cell lines, expression, mRNA, SDHA, ACTB, IFN-β, housekeeping genes, quantitative RT-PCR, digital PCR*

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КОЛИЧЕСТВЕННОЕ ОПРЕДЕЛЕНИЕ ФОНОВОЙ ЭКСПРЕССИИ ИНТЕРФЕРОНА БЕТА В КУЛЬТУРЕ КЛЕТОК СИБИРСКОЙ НОЧНИЦЫ (*MYOTIS SIBIRICUS*)

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РЕЗЮМЕ

Обоснование. *Рукокрылые являются хозяевами и переносчиками широкого спектра зоонозов. Исследование иммунного ответа этих млекопитающих на вирусные инфекции необходимо для раскрытия фундаментальных механизмов циркуляции зоонозных инфекций в природе. Существует гипотеза о постоянно «включенной» активности белков интерферонового пути у рукокрылых для противодействия вирусным инфекциям. В этом исследовании мы оценили уровень активности системы врожденного иммунитета в клеточной линии почки сибирской ночницы (Myotis sibiricus, Kastschenko, 1905) MdbK3-14, взяв в качестве маркера экспрессию интерферона бета.*

Цель исследования. *Оценить фоновый уровень экспрессии гена интерферона бета (IFN-β) в неинфицированных клетках Myotis sibiricus.*

Методы. *Культуру клеток MdbK3-14 выращивали в 24-луночных планшетах. Монослои клеток открепляли раствором трипсина и выделяли суммарную РНК. Концентрацию мРНК транскриптов гена IFN-β и референтных генов бета-актина (ACTB) и субъединицы A сукцинатдегидрогеназного комплекса (SDHA) определяли с помощью одностадийной мультиплексной ОТ-рвПЦР и подтверждали с помощью ОТ-цПЦР.*

Результаты. *Разработаны специфичные праймеры с зондом для детекции мРНК гена IFN-β в клетках рукокрылых. Выявлена стабильная детекция транскриптов генов SDHA и IFN-β как в ОТ-рвПЦР (CV = 0,5 % и CV = 0,2 % соответственно), так и в ОТ-цПЦР (CV = 0,8 % и CV = 1,4 % соответственно). Детекция мРНК ACTB в ОТ-цПЦР также проходила равномерно во всех образцах (CV = 0,8 %), однако в ОТ-рвПЦР выявлена некоторая нестабильность для бета-актина (CV = 3,6 %). Результаты количественного определения в ОТ-рвПЦР и ОТ-цПЦР коррелировали между собой. Установлено, что уровень экспрессии IFN-β в клетках MdbK3-14 сопоставим (в ОТ-рвПЦР в среднем 0,97 ± 0,15 отн.ед.) или несколько ниже (в ОТ-цПЦР в среднем 0,13 ± 0,05 отн.ед.), чем экспрессия белков домашнего хозяйства ACTB и SDHA.*

Заключение. *При отсутствии иммунной стимуляции в клетках почки M. sibiricus наблюдается фоновая экспрессия IFN-β.*

Ключевые слова: *Myotis sibiricus, клеточные линии, экспрессия, мРНК, SDHA, ACTB, IFN-β, гены «домашнего хозяйства», количественная ОТ-ПЦР, цифровая ОТ-ПЦР*

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BACKGROUND

Bats are hosts and vectors of a diverse range of zoonotic infections [1]. Studying the immune response of these mammals to viral infections is essential to uncover the underlying mechanisms of zoonotic pathogen circulation in nature and to assist in understanding the emergence of novel human diseases. The first line of defense in mammals is the innate immune system, composed of various cells and molecules that recognize and eliminate pathogens of viral and bacterial origin, thereby protecting the organism from the development of immunopathological processes.

A key component in the activation of the innate immune response is interferon beta (IFN-β). This cytokine is part of the type I interferon family, which is induced directly in response to viral infection [2]. The expression and antiviral activity of *IFN*-β have been described in kidney cells of the Chinese bat, *Myotis davidii*, after infection with Sendai virus, a member of the *Paramyxoviridae* family [3]. It has been established that virus-induced *IFN*-β gene expression is higher in bat cells than in cells from murid rodents [4]. Type I interferons (IFN-α/β) are thought to play a role in the high tolerance of bats to zoonotic viruses [5]. There is a hypothesis that bats have a constitutively active interferon system [6]. It is possible that novel viruses entering the body of bats do not cause immunopathological responses due to the evolutionary development of the constant activity of interferon pathway proteins. This feature may be characteristic of all bat species. However, this area of research remains under-investigated. For instance, foreign researchers have demonstrated that IFN-α is expressed constitutively in all organs of healthy individuals from the Australian black flying fox (*Pteropus alecto*) and the Malayan short-nosed fruit bat (*Cynopterus brachyotis*). IFN-β, on the other hand, was found to be barely detectable in these species [7]. However, both of these bat species are members of the *Pteropodidae* family, suborder Megachiroptera (flying foxes). In contrast, other researchers have identified basal levels of IFN-β and type I IFN subtypes in kidney cells of *Myotis daubentonii*, a species belonging to the suborder Microchiroptera (vesper bats) [5]. Furthermore, in contrast to the findings from fruit bats, the researchers did not identify any specific IFN-α subtypes or unusually high levels of basal IFN expression in *Myotis daubentonii* cells. This suggests a clear distinction between the interferon systems of bats (Microchiroptera) and flying foxes (Megachiroptera). This finding clearly warrants further research into each group of bats.

Previously, we established a continuous cell line, MdbK3-14, derived from the kidney of the Siberian bat (*Myotis sibiricus*, Kastschenko, 1905). This species is widespread and abundant in nature. We found that the replication of flaviviruses, particularly tick-borne encephalitis virus (TBEV), in this cell line, is reduced compared to other cell lines derived from reservoir (Korean field mouse) and laboratory (pig) hosts of the virus [8]. This was demonstrated by impaired virus entry into MdbK3-14 cells, decreased efficiency of RNA replication and production of infectious viruses, delayed viral replication kinetics, and lower final titers of infectious viruses [9]. Additionally, compared to cells derived from laboratory and reservoir hosts, the MdbK3-14 cell culture was less susceptible to TBEV infection. The virus did not cause a cytopathic effect and cell death was not observed as a result of TBEV infection [10]. To investigate the mechanisms of cellular resistance to viral infection, we assessed the basal level of the innate immune response in uninfected MdbK3-14 cells.

This study aimed to evaluate the basal expression level of the *IFN*-β gene, encoding interferon beta, in Siberian bat cells as a marker of innate immune system activity.

The primary method for the quantitative analysis of gene expression profiles was reverse transcription quantitative polymerase chain reaction (RT-qPCR). The genes encoding beta-actin (*ACTB*) and succinate dehydrogenase complex subunit A (*SDHA*) were selected as references. Beta-actin is a crucial protein for cell motility, structure, and integrity in eukaryotic cells [11], while succinate dehydrogenase complex subunit A is an integral part of the protein complex located in the mitochondrial membrane and involved in the Krebs cycle and respiratory chain [12]. The selection of these genes was based on their critical role in maintaining cell viability, which ensures the stability of their expression under various external conditions. The methodology for assessing the expression of *ACTB* and *SDHA* has been previously validated in rodent and artiodactyl cell cultures [13], suggesting that it can be applied to bat cells as well. In addition to the previously described methods, we utilized reverse transcription digital polymerase chain reaction (RT-dPCR) as a further method for quantifying the mRNA concentrations of both the target and reference genes. While RT-dPCR allows for absolute quantification of the target fragment concentration in each sample, it is also advisable to normalize the results using reference genes [14], since the samples may be affected by other factors, such as the reverse transcription process.

MATERIALS AND METHODS

Primer design

A primer-probe set was designed for the detection of bat interferon beta (*IFN-β*) mRNA from *Myotis* species based on sequence data published in the GenBank database under accession numbers XM_005853023 and XM_036329120. Sequence alignment was performed using BioEdit 7.0.5.3 software, incorporating the integrated CLUSTAL W algorithm. Manual adjustment was then performed. The OligoCalc web-based tool was also used for oligonucleotide sequence design. The specificity of the primers and probes was verified through BLAST searches and by PCR, with amplicons visualized on an agarose gel. The design, structure, and validation

of primers and probes for reference genes *ACTB* and *SDHA* have been published previously [13].

Cell culture

The continuous adherent cell line, MdbK3-14, was derived from the kidney tissue of *Myotis sibiricus* (Kastschenko, 1905) and was established in the Laboratory of Transmissible Infections at the Scientific Centre for Family Health and Human Reproduction Problems [9]. A cell stock of passage 64 was used for this study. The cell culture was maintained in RPMI1640 medium, supplemented with antibiotics and 10 % fetal bovine serum (FBS) from HyClone (Thermo Scientific, UK).

The study was approved by the Biomedical Ethics Committee of the Scientific Centre for Family Health and Human Reproduction Problems (Protocol No. 2 dated February 18, 2020).

Cell preparation

A cell monolayer with a confluence of 90–100 % was detached from a flask using trypsin supplemented with 0.5 mM EDTA (T/E). Cells were then resuspended in growth medium (RPMI1640 supplemented with L-glutamine, penicillin (100 U/mL), streptomycin (100 µg/mL), and 10 % FBS), and the cell concentration was determined using a Goryaev hemocytometer. The resulting cell suspension was adjusted to a concentration of 1×10^5 cells/mL and seeded into 24-well plates, with 1 mL of suspension per well. The plates with cells were incubated for 16–18 hours at 37 °C under 5 % CO_2. Subsequently, the growth medium was removed and replaced with 1 mL of maintenance medium (RPMI1640 with L-glutamine, antibiotics, and 2 % FBS) per well. After 24 hours of incubation, the maintenance medium was removed and the cells were washed three times with serum-free medium. They were then detached using 0.25 mL of T/E. Finally, 0.25 mL of maintenance medium was added to each well to resuspend the cells, which were transferred to 1.5 mL Eppendorf tubes. Cells were pelleted by centrifugation using an Eppendorf MiniSpin centrifuge at 13,400 rpm for 5 min at +4 °C. The cells were then resuspended in 1 mL of sterile phosphate-buffered saline (PBS, pH 7.4). The cell concentration was determined and aliquots containing 5×10^4 cells per sample were transferred to cryovials. The cells were again pelleted using centrifugation at +4 °C, and the supernatant was removed, leaving only the cell pellet. This pellet was then stored at -70 degrees C and used for RNA isolation immediately. All steps involving cell sample collection took place on ice to ensure optimal conditions.

RNA isolation

To assess the expression of the *SDHA, ACTB*, and *IFN*-β genes in MdbK3-14 cells, RNA samples were isolated using the HiPure Total RNA Kit (Magen Biotechnology, Guangzhou) and the RNAse Free DNAse I Set (Magen Biotechnology, Guangzhou) according to the manufacturer's protocol. The purified RNA sample volume was 100 µL. The quality of RNA purification from genomic DNA was assessed by performing an additional PCR without RT reaction using primers specific for the target genes. The RNA preparations that did not show specific fluorescence in RT-quantitative PCR (RT-qPCR) and did not contain the target fragment after standard PCR were considered suitable for further analysis. Negative control RNA samples were included in each experiment.

One-step RT-PCR

One-step multiplex RT-qPCR and RT-dPCR assays were performed using the Luna Universal Probe One-Step RT-qPCR reagent kit (New England Biolabs, USA), following the manufacturer's protocol. The reaction volume was 30 µL. The reaction mix contained two specific primers at a final concentration of 400 nM each, a corresponding probe at 200 nM, and 3 µL of RNA template. The thermal cycling conditions for both RT-qPCR and RT-dPCR were as follows: reverse transcription at 55 °C for 10 min, reverse transcriptase inactivation at 95 °C for 1 min, followed by 45 cycles of PCR. Each cycle consisted of 10 s at 95°C, annealing at a gene-specific temperature (Ta°C) for 1 s; and 20 s at 60 °C. Fluorescence acquisition was performed during the 60 °C step of each cycle using the FAM, ROX, and Cy5 channels. The quantification cycle (Cq) for RT-qPCR was defined as the first cycle in which the fluorescence signal intensity exceeded ten standard deviations above the background fluorescence. Fluorescence from cycles 1 to 10 was considered background. Data analysis for RT-qPCR was performed using Bio-Rad CFX Manager v3.1 software (Bio-Rad Laboratories Inc., USA).

RT-dPCR was performed using the SCI Digital S500 automated digital PCR system (TurtleBiotech, China) according to the manufacturer's protocol. This platform partitions the sample into more than 20,000 independent, uniformly sized microdroplets within the microcavities (wells) of a digital PCR chip using an automated system device. Following reaction completion, the fluorescent signal from each microdroplet is detected and enumerated. The concentration of specific RNA molecules in the original sample was determined based on the Poisson distribution principle using SCI Digital v1.0.0.0P1.7 software (TurtleBiotech, China).

Assessment of PCR linearity and efficiency

For each RNA sample, a series of three 10-fold serial dilutions (10^{-2} to 10^{-5}) was prepared in RNase-free water.

For the RT-qPCR assay, the mean Cq value and standard deviation were calculated for each dilution. A standard curve was generated using the mean Cq values. RT-qPCR efficiency (*E*) was calculated using the formula {10^(-1/k) – 1} × 100, where k is the slope of the standard curve, and expressed as a percentage. Reaction efficiency was considered acceptable within the range of 90 % ≤ *E* ≤ 110 %.

To assess RT-dPCR linearity, the expected RNA concentrations of the dilutions were compared with the observed values. The RNA concentration in the 1×10^{-2} dilution was considered the starting concentration. Expected RNA concentrations for the 1×10^{-3} and 1×10^{-4} dilutions were calculated by dividing the starting concentration by 10 and 100, respectively. For each dilution, the mean concentration obtained by RT-dPCR was calculated and used as the observed concentration, along with its standard deviation.

Assessment of RT-qPCR and RT-dPCR repeatability

Intra-assay repeatability was determined as the coefficient of variation (CV, %) and expressed as $\log_{10}$ concentration. For RT-qPCR, the CV was calculated from three independent replicates of each RNA dilution performed within a single assay on the same day using the same instrument. For RT-dPCR, the CV was determined from two independent replicates of each RNA dilution.

Statistical analysis

RT-PCR linearity was assessed using regression analysis of the calibration curves. The relationship between Cq and the sample dilution factor for RT-qPCR, and between the observed and expected RNA concentrations for RT-dPCR, were considered linear when the coefficient of determination (R^2) was > 0.8. To assess data variability, the standard deviation of the mean values was determined. Outlier Cq values for RNA were excluded using the quartile method [15]. The Pearson correlation coefficient (*r*) was used to identify correlations between RNA concentrations obtained by RT-dPCR and Cq values obtained by RT-qPCR. Relative *IFN-β* expression from RT-qPCR results was calculated using the ΔΔCq method and normalized to the *SDHA* and *ACTB* reference genes. Normalized *IFN-β* expression from RT-dPCR results was calculated as the ratio of *IFN-β* mRNA concentration to the geometric mean of the reference gene concentrations. Calculations were performed using MS Office Excel 2003, MaxStat Lite v.3.06, and CFX Manager software.

RESULTS AND DISCUSSION

PCR specificity

The selected primer pairs for the *ACTB, SDHA*, and *IFN*-β genes demonstrated high specificity, producing amplicons of the expected size and no additional or non-specific bands at an annealing temperature of 55 °C (Fig. 1). The identical PCR conditions for all genes allowed for multiplexing of the reaction, thereby enhancing the comparability of the data obtained.

RT-qPCR analysis revealed a clearly defined sigmoidal shape of the amplification curves for the target mRNAs of the studied genes, with negligible background fluorescence. In all plots, the fluorescence curves for the 10-fold serial RNA dilutions ranging from 10^{-2} to 10^{-4} crossed the threshold line at approximately 3-cycle intervals, corresponding to a 10-fold dilution of the samples. Samples with a 10^{-5} dilution for the *ACTB* and *SDHA* genes were identified as outliers based on the quartile test and were excluded from further analysis. No increase in fluorescence signal was observed in the negative control samples, indicating the absence of DNA contamination and confirming the specificity of *ACTB, SDHA*, and *IFN*-β mRNA detection in bat cells. The overall dynamic range of the assay was 10,000:1.

PCR linearity and efficiency

The coefficient of determination (R^2) for linearity in RT-qPCR exceeded 0.99 for all calibration curves (Fig. 2). This indicates that across all assay variants, the relationship between Cq and target RNA concentration conforms to a linear regression model and provides a good fit to the observed data. The mean RT-qPCR efficiency values fell within the optimal range of 90 % to 110 % inclusive [16, 17] and were 105 % (*ACTB*), 92 % (*SDHA*), and 101 % (*IFN*-β), with calibration curve slopes of 3.22, 3.53, and 3.31, respectively.

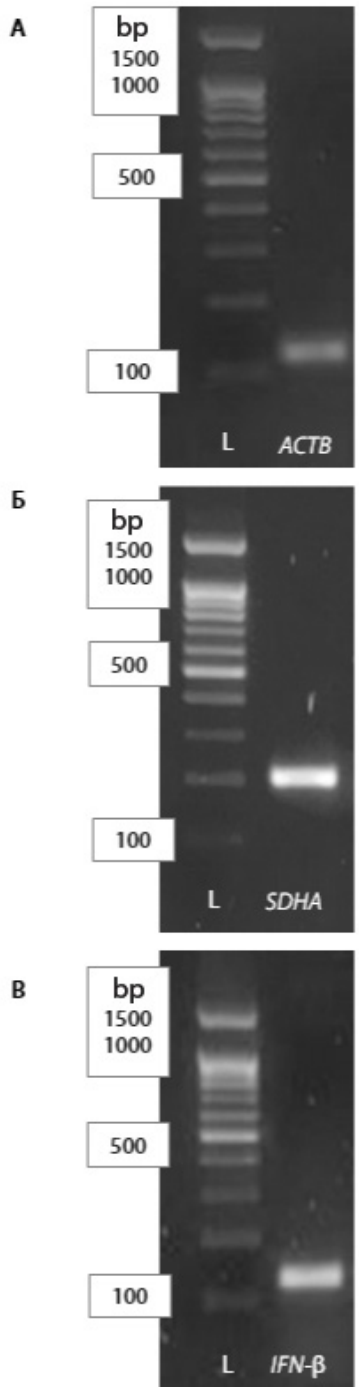

FIG. 1.
Specificity of PCR for fragments of ACTB, SDHA and IFN-β mRNA transcripts of bats at an annealing temperature of 55°C. A – ACTB gene, expected fragment length 120 bp; Б – SDHA gene, expected fragment length 209 bp; B – IFN-β gene, expected fragment length 119 bp. L – DNA size ladder, the bands of 100, 500, 1000 and 1500 base pairs are labeled aside of the gel

In RT-dPCR, at high template loads (1:100 dilution), the distribution of positive wells across the chip surface was uneven, with an evident depletion towards the right edge of the image. Visually, this artifact occupied approximately 10–20 % of the chip capacity (Fig. 3, row "1 × 10^{-2}"). As a similar pattern was observed in the second RT-dPCR replicate (image available upon request), it is unlikely that this phenomenon is due to a defect in a single chip. Further investigation and optimization of the SCI Digital S500 system are required to elucidate the nature and potential consequences of this uneven distribution of positive signals when processing high (up to saturating) mRNA concentrations. At RNA template dilutions of 1:1000 and 1:10,000, the distribution of positive wells on the chip was random and uniform (Fig. 3, rows "1 × 10^{-3}" and "1 × 10^{-4}"), allowing for further analysis.

In a series of 10-fold dilutions of total RNA, it is theoretically expected that the concentration of the target mRNA should also change 10-fold with each dilution. To assess the reliability of RT-dPCR quantification using the SCI Digital S500 system, expected mRNA concentrations were calculated based on the 1:100 dilution as the reference point. A regression analysis was then performed to evaluate the agreement between the observed and expected mRNA concentrations. The observed data for all target genes demonstrated a strong linear correlation with the expected values ($R^2 > 0.98$, Fig. 4), indicating a good fit to the linear model. These findings suggest that, despite the uneven signal distribution observed at high template concentrations, the data obtained accurately reflects the true mRNA concentration and is suitable for evaluating *IFN*-β expression.

Repeatability of RT-qPCR and RT-dPCR assays

The coefficients of variation for intra-assay reproducibility of *SDHA, ACTB*, and *IFN*-β quantification are presented in Table 1.

In Siberian bat MdbK3-14 cells, *IFN*-β mRNA detection was more stable with RT-qPCR than with RT-dPCR (CV = 0.2 % vs. CV = 1.4 %), although both CV values fell within the optimal range (CV ≤ 2 %). RT-qPCR demonstrated higher sensitivity for *IFN*-β mRNA detection, as it consistently detected mRNA at a 10^{-5} dilution (Cq = 39.9 and CV = 0.3 %). In contrast, RT-qPCR consistently yielded negative results under identical conditions (Table 1). Due to the fact that both the reaction mixtures and RNA preparations were identical in the two assays, it is apparent that optimization of the experimental conditions is necessary, taking into consideration the specific characteristics of the dPCR platform.

The stability of *SDHA* gene transcript detection between RT-dPCR and RT-qPCR was comparable (CV = 0.8 % and CV = 0.5 %, respectively), falling within the acceptable range for intra-assay variability.

ACTB mRNA detection by RT-dPCR was uniform across all samples (CV = 0.8 %), with little deviation from the mean quantitative value. In contrast,

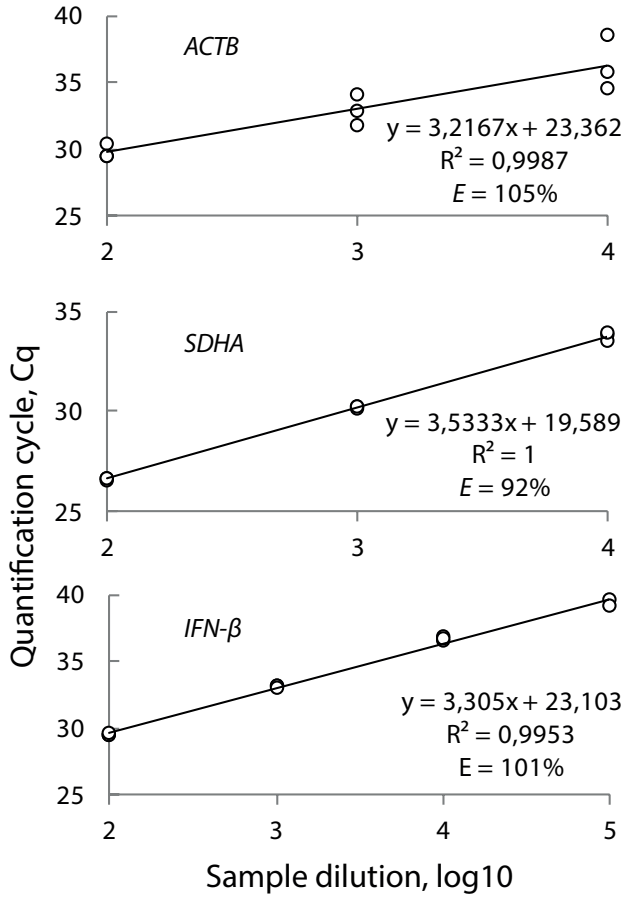

FIG. 2.
Evaluation of the linearity (R^2) and efficiency (E) of RT-qPCR targeting bat genes for beta-actin (ACTB), succinate dehydrogenase subunit A (SDHA) and interferon beta (IFN-β). Error bars indicate standard deviations of three replicates of RT-qPCR

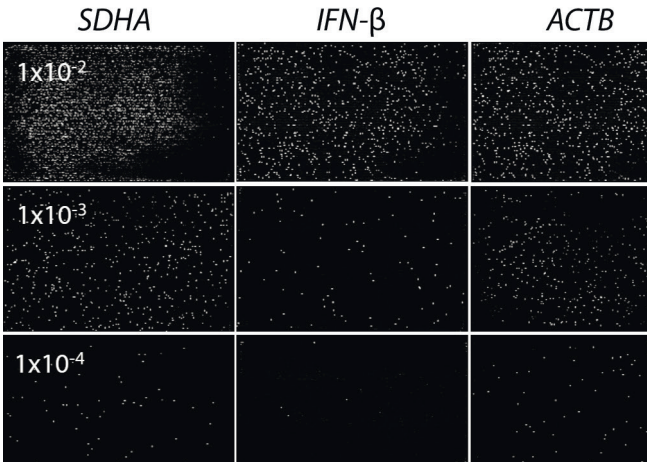

FIG. 3.
Positive droplets distribution in the chips «1x10^{-2}», «1x10^{-3}» and «1x10^{-4}» with triplex RT-dPCR reactions in the FAM (for detection of SDHA transcripts), ROX (IFN-β), and Cy5 (ACTB) fluorescence channels. The RNA template dilution in each chip was 1:100, 1:1000, and 1:10000, respectively. White dots indicate a positive PCR-amplification signal in the corresponding channel

some instability in beta-actin detection was observed with RT-qPCR (CV = 3.6 %). It is generally accepted that for accurate quantitative PCR results, intra-assay reproducibility should correspond to CV values of ≤ 2 % [17]. A CV value exceeding this acceptable threshold indicates higher data variability within the studied sample set. In the case of *ACTB*, this may be attributed to technical in the RT-qPCR process. This suggests the need to optimize the RT-qPCR conditions in order to improve the stability of *ACTB* mRNA detection throughout the experiment, by automating as many manual procedures as possible, such as the preparation of RNA sample dilutions and the pipetting of samples into the PCR mixture. This is expected to reduce the variability in the quantitative data obtained.

Agreement analysis of RT-qPCR and RT-dPCR results

Pearson correlation analysis revealed a strong negative correlation between Cq values obtained from RT-qPCR and mRNA concentrations measured by RT-dPCR for all genes under study (Fig. 5). Therefore, the quantitative mRNA concentrations derived from RT-qPCR and RT-dPCR assays are consistent with each other, and an inverse linear relationship exists between them, such that an increase in mRNA molecule concentration measured by RT-dPCR corresponds to a decrease in Cq value calculated by RT-qPCR.

Assessment of basal IFN-β expression in the MdbK3-14 cell line

The results obtained suggest that there is a continuous basal expression of interferon beta in the MdbK3-14 cell line (Fig. 6). When measured by RT-dPCR, the expression level was approximately 10-fold lower than that of housekeeping genes (mean 0.13 ± 0.05 relative units). However, when measured by RT-qPCR, the *IFN*-β expression was comparable to the expression of reference genes (0.97 ± 0.15 relative units).

The observed differences in the relative levels of *IFN*-β expression can be attributed to two factors. Firstly, the values obtained for *IFN*-β expression by RT-dPCR may be slightly underestimated due to technical limitations. Specifically, the uneven distribution of positive wells on the chip (Fig. 3) can significantly affect the accuracy of mRNA quantification. Secondly, the high variability in *IFN*-β expression levels measured by RT-qPCR results in a wide range of values, ranging from 0.4 to 1.6 relative units (Fig. 6). Considering both factors, it can be hypothesized that the actual basal level of *IFN*-β expression lies within the range of 0.2–1 relative units.

TABLE 1

REPEATABILITY OF RT-qPCR AND RT-dPCR ASSAYS FOR mRNA OF *ACTB*, *SDHA* AND *IFN*-β GENES IN MdbK3-14 CELL LINE

Gene	RNA dilution	RT-dPCR, mRNA transcripts, log10 copies/μL			RT-qPCR, Cq		
		log10 copies/μL	SD	CV, %	Mean*Cq	SD	CV, %
IFN-β	10^{-2}	2.8	1.5	0.8	30.2	0.1	0.1
	10^{-3}	1.6	0.8	1.2	34.1	0.1	0.1
	10^{-4}	0.5	0	1.5	37.1	0.6	0.3
	10^{-5}	0	0	0	39.9	0.6	0.3
	Mean intra-assay reproducibility for *IFN-β* detection, %: 1.4				Mean intra-assay reproducibility for *IFN-β* detection, %: 0.2		
SDHA	10^{-2}	3.5	1.8	0.3	26.7	0.02	0.1
	10^{-3}	2.6	1.5	0.8	30.2	0.05	0.2
	10^{-4}	1.6	0.8	1.3	33.7	0.23	0.7
	Mean intra-assay reproducibility for *SDHA* detection, %: 0.8				Mean intra-assay reproducibility for *SDHA* detection, %: 0.5		
ACTB	10^{-2}	3.4	2.4	1	29.9	0.51	1.7
	10^{-3}	2.6	1.1	0.5	32.9	1.11	3.4
	10^{-4}	1.6	0.7	1	36.3	2.03	5.6
	Mean intra-assay reproducibility for *ACTB* detection, %: 0.8				Mean intra-assay reproducibility for *ACTB* detection, %: 3.6		

Note. * – Mean Cq (*n* = 4 intra-assay replicates).

Overall, the basal level of IFN-β expression is comparable to or slightly lower than that of housekeeping genes, such as beta-actin and the succinate dehydrogenase complex subunit A. This finding may indicate a potential role for interferon beta in maintaining the viability of *M. sibiricus* kidney cells, or it could suggest continuous activation of the innate immune response in the Siberian bat.

Therefore, the linearity, sensitivity, and reproducibility parameters of RT-qPCR and RT-dPCR suggest that a reliable assessment of the innate immune response necessitates enhancing the sensitivity of RT-dPCR for *IFN*-β and improving the reproducibility of RT-qPCR for *ACTB*. The quantification of *SDHA* mRNA is consistent across both RT-PCR methods and does not require optimization.

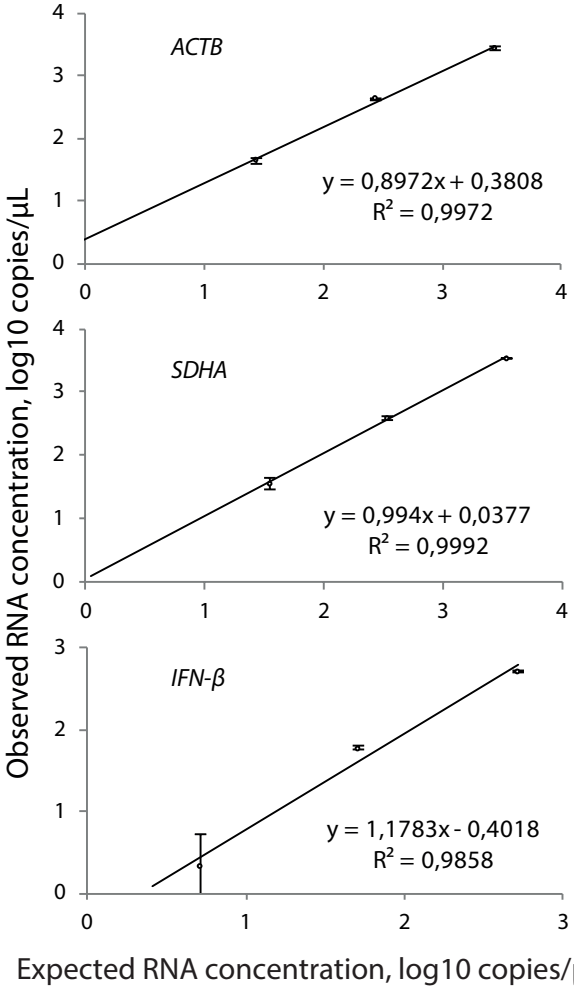

FIG. 4.
The linearity (R^2) of the RT-dPCR was evaluated using linear regression model of observed changes in mRNA concentrations in comparison to the changes in estimated expected concentrations. RNA concentrations were expressed in log10. Error bars represent the standard deviation of two RT-dPCR replicates

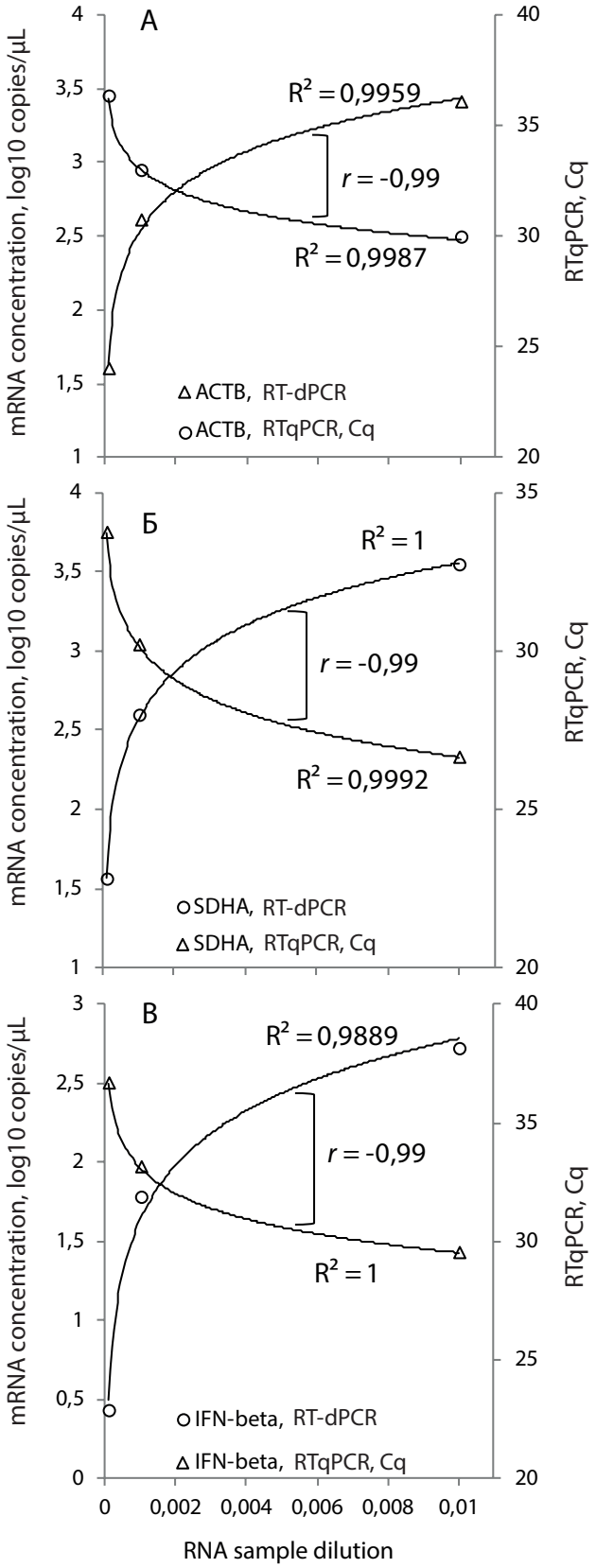

FIG. 5.
There are strong negative correlation between mean Cq values and mRNA transcripts targeting bat genes. A –beta-actin (ACTB), Б – succinate dehydrogenase subunit A (SDHA), B – interferon beta (IFN-β). Solid lines reflect the logarithmic trend model; R^2 reflects the goodness of fit of logarithmic model; r – Pearson`s correlation coefficient between two datasets (brackets)

It has previously been demonstrated that the results obtained through RT-dPCR are comparable to those obtained through RT-qPCR, with dPCR exhibiting higher sensitivity in estimating RNA concentration [18], detecting trace amounts of template in the sample. In this study, RT-dPCR analysis allowed for the quantitative detection of hepatitis B virus (HBV) RNA in serum samples as low as 10^2 copies/mL. Furthermore, it has been shown that RT-dPCR improves the interpretation of Cq values obtained through RT-qPCR in SARS-CoV-2 diagnostics, making it a useful complementary method for enhancing the accuracy and reliability of RNA quantification. This can also help improve the interpretation of RT-PCR results [19]. Our findings align with published data and we believe RT-dPCR to be a valuable tool for gene expression studies. It is particularly promising for investigating small differences in target gene expression levels. However, certain factors such as the high cost of reagents and consumables (e.g. microfluidic chips), the relatively lengthy and labor-intensive process of setting up and running the dPCR, and the need for additional optimization and validation of the RT-PCR protocol for a specific dPCR platform can complicate the analysis of large numbers of samples. It should be noted that establishing a reliable RT-dPCR procedure requires the use of at least three synthetic positive RNA controls with known concentrations, representing high (10,000–10,000,000 copies per reaction), medium (100–10,000 copies), and low (1–100 copies) target fragment loads. RT-dPCR results can only be considered trustworthy if the measured RNA concentrations within each range correspond to the expected values. This complexity becomes particularly significant when multiple targets and reference genes are analyzed, along with a comprehensive set of control assays in subsequent routine RT-dPCR experiments. This implies the inclusion of a negative control sample (without template) in each RT-dPCR run to monitor for contamination during RNA purification, reaction mixture preparation, and chip loading. Additionally, one positive control sample containing a known concentration of each target should be included to confirm reaction efficiency. Furthermore, it is advisable to include an internal RNA control with a known concentration in each reaction to assess RT-PCR efficiency and detect inhibitors in test RNA samples. At the current stage of technology development, RT-qPCR remains the preferred method for large-scale screening studies, while RT-dPCR can be used as a complementary confirmatory technique.

CONCLUSION

The study, which employed two independent methods (quantitative RT-PCR and digital RT-PCR), demonstrated that there is uninduced basal expression of interferon beta in the Siberian bat kidney cell line. The expression levels are comparable to, or slightly lower than, those of housekeeping proteins such as beta-actin and succinate dehydrogenase complex subunit A.

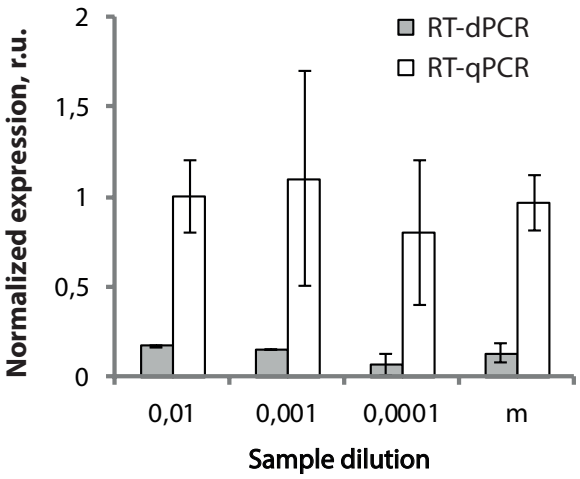

FIG. 6.
Relative normalized expression of IFN-β in the MdbK3-14 cell line. Error bars represent the standard deviation of the mean values; m – the mean expression level of IFN-β in three dilutions of RNA samples. Expression values are normalized to the reference genes ACTB and SDHA and are shown relative to the zero expression level

The developed primer-probe sets are suitable for the detection of *ACTB, SDHA*, and *IFN*-β mRNA in bat cells. Both RT-qPCR and RT-dPCR approaches used in this study demonstrated comparable linearity and yielded similar results statistically. While RT-qPCR requires more optimization to reduce technical errors and variability in mRNA quantification, it has a faster processing time and is more cost-effective than RT-dPCR.

This study was conducted using the equipment of the Core Facility "Center for Development of Advanced Personalized Health Technologies", Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk.

Conflicts of interest

The authors declare no conflicts of interest.

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EPIDEMIOLOGY

MORBIDITY STATUS FOR SELECTED VACCINE-PREVENTABLE INFECTIONS IN THE IRKUTSK REGION IN DIFFERENT PERIODS OF VACCINE PREVENTION

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RESUME

Background. *The success of vaccination prevention at the present stage is undeniable. However, the epidemiological features of individual infections dictate the need of optimizing this preventive measure. This study is devoted to the epidemiological analysis of measles and whooping cough morbidity as infections with proven epidemiological effectiveness of the conducted vaccination, but at the same time, characterized by an increase in the incidence rate over the past years. Chickenpox and meningococcal infection are nosological forms, despite the continuing epidemiological, social and economic significance, characterized by a selective approach to vaccination of the population.*
The aim. *Study intensity of the epidemic process of infections with different vaccination strategies using the example of whooping cough, measles, chickenpox, meningococcal infection to justify the optimization of vaccination prevention tactics in the region.*
Materials and methods. *A retrospective epidemiological analysis of the incidence of whooping cough, measles, chickenpox, and meningococcal infection was conducted using previously published data and reporting forms from the Office of Rospotrebnadzor for the period 1955–2023 in the Irkutsk region.*
Results. *The introduction of mass vaccination against whooping cough and measles in the National Immunization Schedule has contributed to a decrease in morbidity. The period 2014–2023 in the region was characterized by an uneven distribution of indicators with an upward trend for these infections (Tgrow. was 15.1 and 18.7 %, respectively). It has been shown that against the background of a selective vaccination strategy against meningococcal infection and chickenpox, a decrease in morbidity is observed until 2021. At the same time, direct correlations are observed between the number of vaccinated and morbidity levels ($\rho = 0.952$, $\rho = 0.842$ at $p < 0.05$, respectively).*
Conclusion. *The obtained results of the study are necessary for optimization of the existing vaccination prevention program in the region. The introduction of revaccination of children, adolescents and adults against whooping cough, cohort vaccination of children against chickenpox and meningococcal infection will reduce the burden of infections with different vaccination strategies at the level of the subject of the Russian Federation.*

Key words: *vaccine-preventable diseases, regional calendar of preventive vaccinations, epidemiological analysis, morbidity status, vaccination prevention, vaccination strategy*

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СОСТОЯНИЕ ЗАБОЛЕВАЕМОСТИ ПО ОТДЕДЬНЫМ ВАКЦИНОУПРАВЛЯЕМЫМ ИНФЕКЦИЯМ В ИРКУТСКОЙ ОБЛАСТИ В РАЗНЫЕ ПЕРИОДЫ ВАКЦИНОПРОФИЛАКТИКИ

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РЕЗЮМЕ

Обоснование. *Успехи вакцинопрофилактики на современном этапе неоспоримы. Однако эпидемиологические особенности отдельных инфекций диктуют необходимость оптимизации этого профилактического мероприятия. Данное исследование посвящено эпидемиологическому анализу заболеваемости корью и коклюшем, как инфекциям с доказанной эпидемиологической эффективностью проводимой вакцинопрофилактики, но при этом, характеризуется ростом уровня заболеваемости на протяжении последних лет. Ветряная оспа и менингококковая инфекция – нозологические формы, несмотря на сохраняющуюся эпидемиологическую, социальную и экономическую значимость, характеризуются селективным подходом к вакцинации населения.*

Цель исследования. *Изучение интенсивности эпидемического процесса инфекций с разными стратегиями вакцинации на примере коклюша, кори, ветряной оспы, менингококковой инфекции для обоснования оптимизации тактики вакцинопрофилактики в регионе.*

Материалы и методы. *Ретроспективный эпидемиологический анализ заболеваемости коклюшем, корью, ветряной оспой, менингококковой инфекцией проведен по ранее опубликованным данным и отчетным формам Управления Роспотребнадзора по Иркутской области за период 1955–2023 гг.*

Результаты. *Внедрение массовой вакцинации против коклюша и кори в Национальный календарь профилактических прививок способствовало снижению заболеваемости. Период 2014–2023 гг. в регионе характеризовался неравномерным распределением показателей с тенденцией к росту по данным инфекциям (Тпр. составил 15,1 и 18,7 % соответственно). Показано, что на фоне селективной стратегии вакцинации против менингококковой инфекции и ветряной оспы отмечается снижение заболеваемости до 2021 г. При этом между числом привитых и уровнями заболеваемости прослеживаются прямые корреляционные зависимости ($\rho = 0,952$, $\rho = 0,842$ при $p < 0,05$ соответственно).*

Заключение. *Полученные результаты исследования необходимы для оптимизации имеющейся программы вакцинопрофилактики в регионе. Внедрение ревакцинации детей, подростков и взрослых против коклюша, когортной вакцинации детей против ветряной оспы и менингококковой инфекции позволят снизить бремя инфекций с разными стратегиями вакцинации на уровне субъекта Российской Федерации.*

Ключевые слова: *вакциноуправляемые инфекции, региональный календарь профилактических прививок, эпидемиологический анализ, состояние заболеваемости, вакцинопрофилактика, стратегия вакцинации*

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INTRODUCTION

At the present stage, vaccinal prevention is a priority component of public health protection and ensuring the sanitary and epidemiological well-being of the population. For certain infections, it represents the only effective measure for preventing the occurrence of infectious diseases, reducing their incidence, and achieving elimination. Within the territory of the Russian Federation (RF), vaccinal prevention has evolved from the first domestic list of recommended inoculations, "On the timing of preventive inoculations for children", developed in 1958, to the immunization schedule granted "National" status in 2001, with its subsequent gradual expansion to include infections against which the state guarantees protection [1].

Thanks to the successful implementation of vaccinal prevention programs, sustainable epidemiological well-being has been achieved for a number of infections, including diphtheria, rubella, viral hepatitis B, and tetanus [2].

Currently, in accordance with Order of the Ministry of Health of Russia No. 1122n dated December 6, 2021 (as amended in 2023) "On the approval of the national calendar of preventive immunizations, preventive immunizations according to epidemic indications, and the procedure for conducting preventive immunizations", routine vaccination of children and adults is carried out. Furthermore, for certain categories of citizens, vaccination according to epidemic indications is provided for a fairly large number of infectious diseases. In addition, by Decree of the Government of the Russian Federation No. 2390-r dated September 18, 2020, the Strategy for the Development of Immunoprophylaxis of Infectious Diseases for the period up to 2035 was approved, which envisions a phased expansion of the National Calendar of Preventive Immunizations (NCPI).

A number of constituent entities, taking into account the specific features of the epidemiology of infectious diseases, are actively developing and implementing regional preventive immunization schedules into practice. This measure allows for additional vaccination of the population against infections for which vaccination is not currently included in the NCPI or is carried out according to epidemic indications [3-6]. The development of regional vaccination programs aligns with the key goals of the Strategy for the Development of Immunoprophylaxis in the Russian Federation [7].

In the territory of the Irkutsk Region, as in the Russian Federation as a whole, diphtheria, tetanus, mumps, and rubella have not been registered for a number of years, and the number of cases of acute hepatitis B is registered at a sporadic level [8]. Furthermore, the region has accumulated considerable successful experience with vaccination according to epidemic indications [9, 10].

Despite the fact that the epidemiological situation regarding vaccine-preventable infections in the region has been favorable for a number of years, there is an objective need for additional study of morbidity and optimization of vaccinal prevention for infections with universal and selective vaccination strategies.

THE AIM OF THE STUDY

To study the intensity of the epidemic process of infections with different vaccination strategies using the examples of pertussis, measles, varicella, and meningococcal infection, in order to substantiate the optimization of vaccinal prevention tactics in the region.

MATERIALS AND METHODS

The study was conducted with the approval of the Ethics Committee of the Irkutsk State Medical University (Protocol No. 1 dated March 7, 2022). A retrospective epidemiological analysis of morbidity covering more than 60 years was performed. The dynamics of measles and pertussis incidence in the total population of the region were reconstructed for the period 1955–2023; the dynamics of varicella and meningococcal infection incidence were reconstructed for the period 1980–2023, based on previously published data [11] and current data from official medical statistics. A more detailed analysis of morbidity for the studied infections was conducted for the total population and children in different age groups in 2014–2023, according to data from federal state statistical observation (Form 2 "Information on infectious and parasitic diseases"). Vaccination volumes against varicella and meningococcal infection from 2014 to 2023 are presented according to data from federal state statistical observation (Form 5 "Information on preventive immunizations").

Morbidity rates in different age groups were studied over the last 10 years (2014–2023), for which the following periods were identified: 2014–2019 (the period before the spread of COVID-19); 2020–2022 (the period of COVID-19 spread); and 2023 (the last year of analysis). For measles, this analysis was conducted for the period from 2011 to 2023 (10 years of observation), as no cases of measles were registered in the region in 2014, 2021, and 2022.

Descriptive epidemiological methods were applied to identify patterns in the long-term dynamics of morbidity for the studied infections and the distribution of morbidity by age group. Time series analysis (calculation of intensive and extensive rates, average annual growth/decline rates (Tgr./Tdecl.), Spearman correlation coefficients, regression equations), and graphical representation of data were performed using Microsoft Office Excel 2011. Confidence intervals with a significance level of 95% (95% CI) were calculated to assess the statistical significance of differences in relative indicators.

RESULTS

Following the introduction of mass pertussis vaccination in the Russian Federation in 1957, a widespread decline in incidence was noted [12]. In the Irkutsk Region, within 10 years of vaccine use, the incidence rate decreased 10-fold, from 450 per 100,000 to 41.5 per 100,000. Over the subsequent 50 years, the long-term average annual rate (LAAR) remained at 8.2 [6.0÷10.4] per 100,000 (Tdecl. = -2.2 %, regression coefficient = -3.5). However, the period 2014–2023 was characterized by an uneven distribution of incidence rates, with levels varying from 0.79 [0.49÷1.1] to 3.4 [1.8÷5.0] per 100,000, showing an upward trend (regression coefficient = 1.8, Tgr. = 15.1 %). In 2023, a record number of pertussis cases was registered – 834 cases, with a rate of 36.2 [33.5÷38.9] per 100,000 in the total population and 136.9 [129.5÷144.3] per 100,000 among children under 17 years of age (Fig. 1). These changes occurred against the backdrop of achieving regulated indicators of preventive immunization coverage among children — 97.0–98.0 % and higher [8].

In the age structure of the cases, children under 17 years predominated, with their proportion ranging from 90.2 % to 93.3 % in different years. The proportion of individuals aged 18 years and older varied slightly, from 6.7 % to 9.8 %. Among children of different age groups, those under 2 years and aged 7–14 years prevailed, accounting for 33.1 % [29.4÷36.8] and 37.1 % [29.8÷44.4] of cases, respectively.

The dynamics of measles incidence in the total population also showed a pronounced downward trend over the study period, with a regression coefficient of -19.0 (Fig. 2). The measles elimination period (since 2001) was characterized by the registration of sporadic cases in various years, with the maximum number of cases recorded in 2023 – 59 cases, corresponding to a rate of 2.5 [2.0÷3.0] per 100,000 population. The average annual growth rate for 2014–2023 was 18.7 %. Coverage rates for preventive immunization among children and adults were maintained at regulated levels of 98.0 % and above [8].

Children under 17 years of age predominated in the case structure, with their proportion ranging from 56.4 % to 62.7 %. An exception was the period 2020–2022, during which measles cases were registered only in 2020 and exclusively among adults (2 cases, with a rate of 0.1 per 100,000 population).

The incidence rate of meningococcal infection (MI) over the observation period showed a steady downward trend, with rates ranging from 7.6 [6.4÷8.8] to 0.42 [0.22÷0.62] per 100,000 population (Fig. 3). Since 2020, only generalized forms of MI (GFMI) have been subject to official registration in statistical reporting forms for infectious diseases; therefore, the dynamics of GFMI incidence for the period 2014–2023 are presented in more detail. The long-term average annual incidence rate of GFMI in the total population was 0.4 [0.25÷0.55] per 100,000, with annual rates varying from 0.13 [0.03÷0.23] to 0.87 [0.57÷1.17] per 100,000.

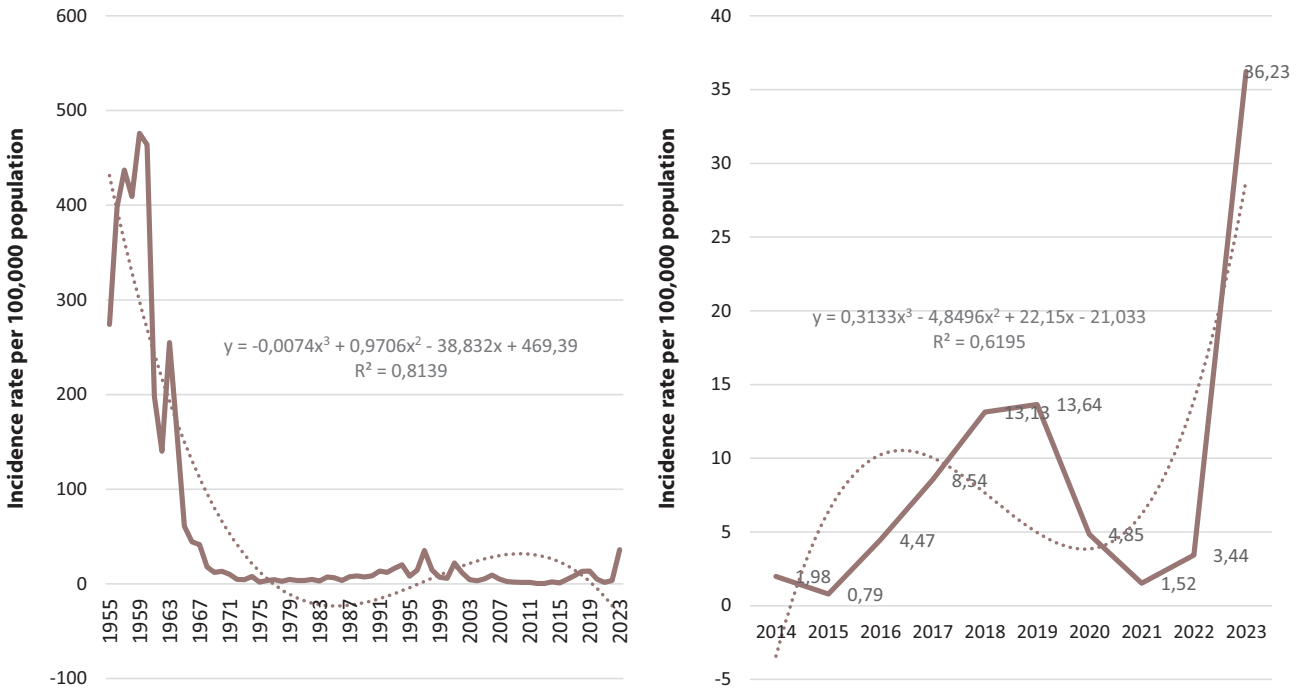

FIG. 1.
Long-term dynamics of whooping cough incidence in the total population of the Irkutsk region for the period from 1955 to 2023 (left) and for the period from 2014 to 2023 (right)

The period 2020–2022 was characterized by a marked decrease in rates, similar to most airborne infections; however, in 2023, the incidence rate increased by 2.3 times. In the age structure of cases, children under 17 years predominated, accounting for 79.0 %.

Despite the relatively low incidence rates of MI and GFMI, the case fatality rate remained quite high. The average case fatality rate over the observation period was 21.4 %, ranging annually from 10.0 % to 42.5 %.

These changes in morbidity and mortality occurred against the backdrop of selective vaccination of the population based on epidemic indications. The period 2014–2023 was characterized by a statistically significant 2.9-fold decrease in the incidence rate ($p < 0.05$). However, a direct correlation was observed between the number of vaccinated individuals and the incidence rate of MI and GFMI (0.952, $p < 0.05$).

The incidence rate of varicella over the observation period remained consistently high, with a long-term average annual rate of 573.2 [563.6–582.8] per 100,000 population. The long-term dynamics of incidence were characterized by alternating periods of increase

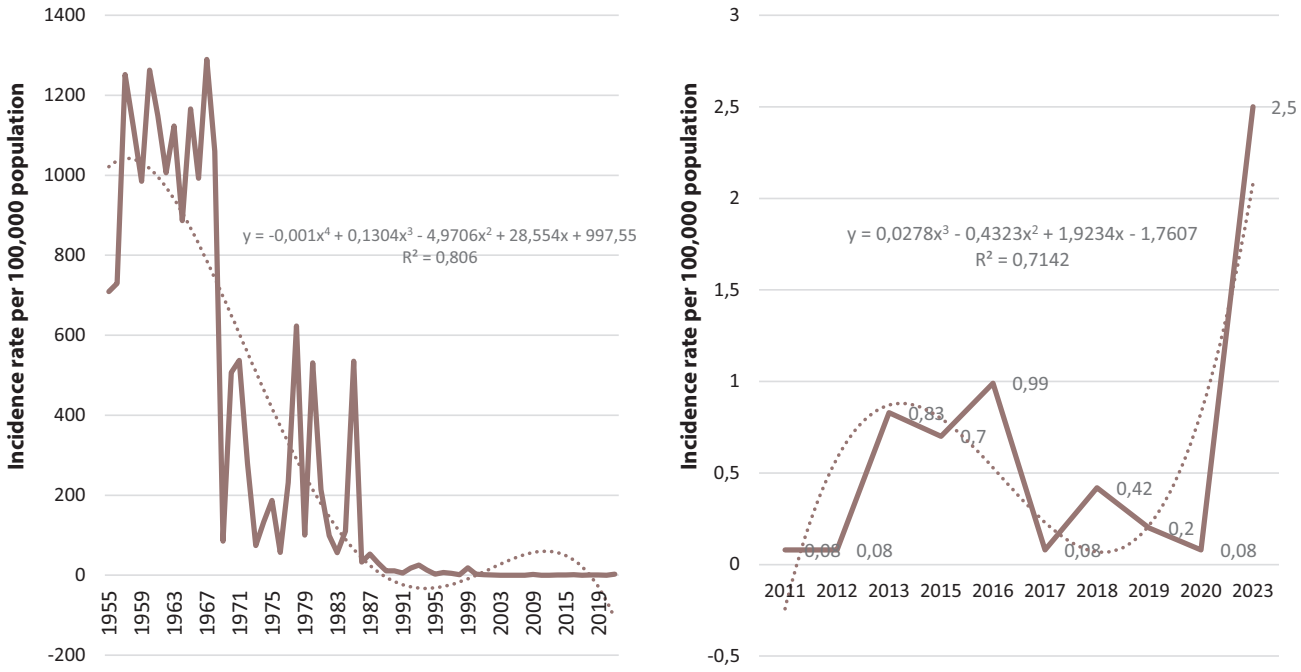

FIG. 2.
Long-term dynamics of measles incidence in the total population of the Irkutsk region for the period from 1955 to 2023 (left) and for the period from 2011 to 2023 (right)

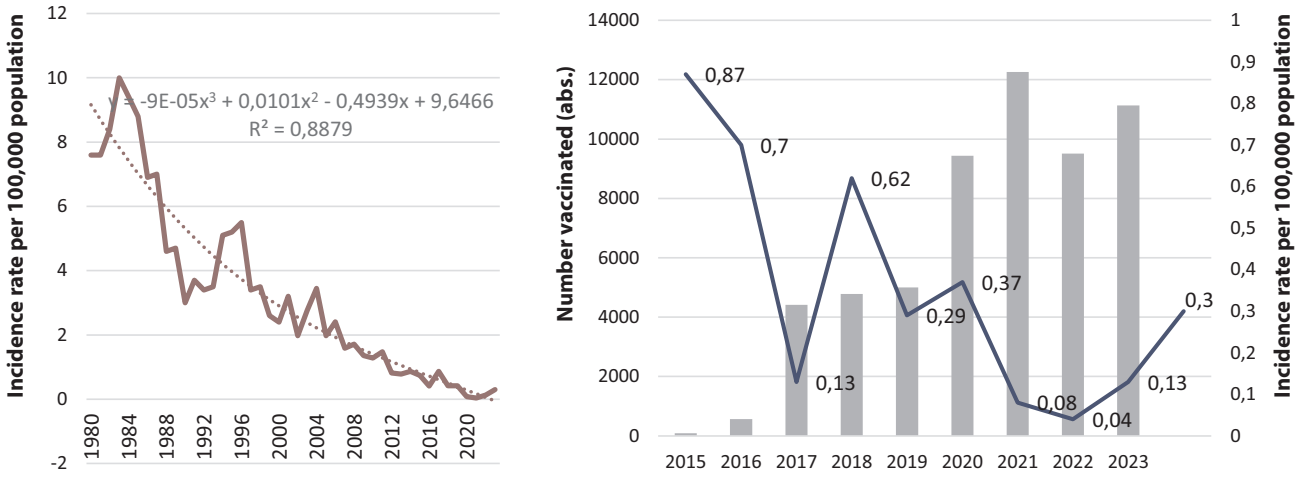

FIG. 3.
Long-term dynamics of meningococcal infection incidence in the total population of the Irkutsk region for the period from 1980 to 2019 (period 2020–2023 dynamics of GFMI incidence) on the left and dynamics of generalized meningococcal infection incidence and the number of vaccinated for the period from 2014 to 2023 (on the right)

and decrease. For instance, the period 1982–1998 was marked by a pronounced decline in incidence (regression coefficient = -40.8, Tdecl. = -2.8 %) (Fig. 4). Subsequently, an increase in rates was observed (regression coefficient = 21.9, Tgr. = 2.7 %). Starting from 2013, another decline in the incidence rate was recorded (regression coefficient = -44.3, Tdecl. = -2.8 %). This decline occurred alongside the implementation of selective vaccination of the population within the framework of the preventive immunization schedule for epidemic indications (primarily contacts in epidemic foci and military conscripts). Vaccination volumes in the region increased annually, with the total number of vaccinated individuals exceeding 22,000 people, including over 13,000 children. At the same time, a direct correlation was observed between the number of vaccinated individuals and the varicella incidence rate (0.842, $p < 0.05$).

The period 2020–2022 was characterized by a statistically significant decline in the incidence rates of the studied infections (Table 1). Thus, the incidence of pertussis among children under 17 years decreased by 2.3 times, and among adults, by 1.5 times. In 2023, an increase in incidence was registered, by 11.2 times and 10.7 times in the respective groups. During 2014–2019, measles incidence was recorded at levels of 0.9 and 0.2 per 100,000 in children and adults, respectively; in 2020–2022, only sporadic cases among adults were registered. In 2023, the incidence rates in the compared groups were 6.5 and 1.2 per 100,000, respectively. The incidence of GFMI in 2023 returned to the average annual level of 2014–2019. The epidemiological situation for varicella was similar to that of pertussis: a sharp decline in 2020–2022, followed by an increase in 2023, which was not statistically different from the levels observed in 2014–2019.

Analysis of morbidity across different observation periods and age groups of the population showed that the highest incidence rates for pertussis, measles, and GFMI were recorded among children, with the primary risk groups being children under 1 year and those aged 1–2 years. For varicella, the highest rates were observed in children aged 3–6 years. Notably, in 2023, the greatest increase in varicella incidence (a 1.7-fold rise) occurred among children aged 7–17 years (Table 1).

DISCUSSION

Infectious diseases remain one of the most significant challenges to public health worldwide. The history of combating "contagious diseases (plagues, pestilences)" spans several centuries [13]. At the present stage, the effective implementation of vaccinal prevention programs can preserve achieved successes and ensure the maintenance of the sanitary and epidemiological well-being of the population. Global practice has shown that a decline in population coverage with preventive immunizations is immediately followed by an increase in the incidence of vaccine-preventable infections, escalating into large outbreaks and epidemics [14-16].

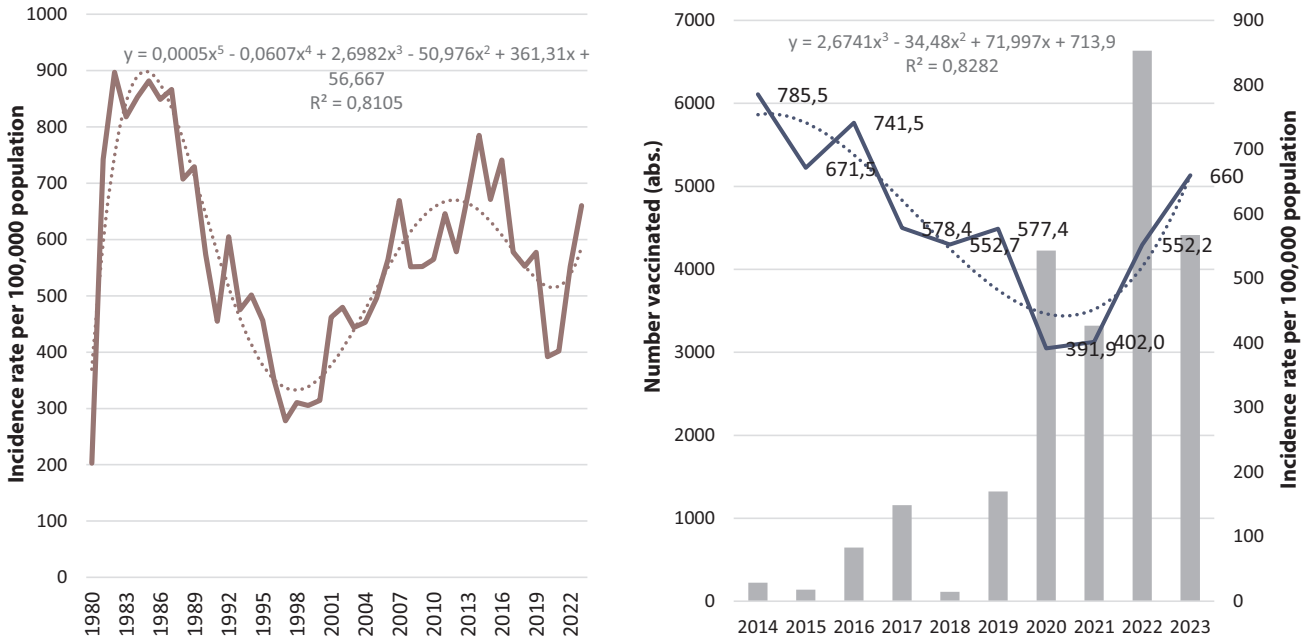

FIG. 4.
Long-term dynamics of chickenpox incidence in the total population of the Irkutsk region for the period from 1980 to 2023 (left); dynamics of chickenpox incidence and the number of vaccinated for the period from 2014 to 2023 (right)

TABLE 1

INCIDENCE OF WHOOPING COUGH, MEASLES, CHICKENPOX AND GENERALIZED FORMS OF MENINGOCOCCAL INFECTION AMONG DIFFERENT AGE GROUPS OF THE POPULATION (PER 100 THOUSAND OF THE CORRESPONDING GROUP)

Period	2014–2019				2020–2022				2023			
Age / Disease	Pertussis	Measles	GFMI	Varicella	Pertussis	Measles	GFMI	Varicella	Pertussis	Measles	GFMI	Varicella
Under 1 year	67.4 [63.7÷71.1]	8.5 [7.2÷9.8]	9.5 [8.1÷10.9]	1241.0 [1225.4÷1256.7]	31.5 [28.9÷34.0]	Not registered	3.8 [2.9÷4.7]	896.8 [888.5÷910.1]	596.4 [585.5÷607.3]	36.8 [34.1÷39.5]	12.5 [10.9÷14.1]	1397.1 [1380.5÷1413.7]
1–2 years	36.0 [33.3÷38.7]	2.0 [1.4÷2.6]	6.6 [5.5÷7.7]	2855.7 [2832.2÷2879.2]	26.0 [23.7÷28.3]	Not registered	Not registered	2217.0 [2196.2÷2237.8]	163.5 [157.8÷169.2]	13.3 [11.7÷14.9]	1.9 [1.3÷2.5]	3632.1 [3605.7÷3658.5]
3–6 years	23.4 [21.2÷25.6]	1.6 [1.0÷2.2]	1.2 [0.7÷1.7]	6315.0 [6280.6÷6349.4]	16.7 [14.9÷18.5]	Not registered	Not registered	4376.1 [4347.2÷4405.0]	66.6 [62.9÷70.3]	6.4 [5.3÷7.5]	0.8 [0.4÷1.2]	6256.5 [6222.3÷6290.7]
7–17 years	25.1 [22.9÷27.3]	0.3 [0.06÷0.5]	0.04 [0÷0.13]	1056.1 [1041.7÷1070.6]	6.4 [5.3÷7.5]	Not registered	0.03 [0÷0.1]	727.6 [715.6÷739.6]	126.4 [121.4÷131.4]	3.6 [2.8÷4.5]	Not registered	1255.9 [1240.2÷1271.6]
0–17 years	28.3 [25.9÷30.7]	0.9 [0.5÷1.3]	1.9 [1.3÷2.5]	2634.3 [2611.7÷2656.9]	12.2 [10.6÷13.8]	Not registered	0.2 [0÷0.4]	1758.1 [1739.5÷1776.7]	137.0 [131.8÷142.2]	6.5 [5.4÷7.6]	0.9 [0.5÷1.3]	2580.3 [2557.9÷2602.7]
18 years and older	0.6 [0.3÷1.0]	0.2 [0÷0.4]	0,1 [0÷0.24]	51.7 [48.5÷54.9]	0.4 [0.1÷0.7]	0.1 [0÷0.2]	0.1 [0÷0.2]	29.3 [26.9÷31.7]	4.3 [3.4÷5.2]	1.2 [0.7÷1.7]	0.1 [0÷0.2]	46.9 [43.8÷49.9]

In the Irkutsk Region, the incidence of infectious (contagious) diseases remained at a high level for a number of years [11, 17].

In the territory of the Russian Federation, against the background of implementing mass vaccination programs, epidemiological well-being has been achieved for infections controllable by specific preventive measures [2]. The results of this study also confirm this. A manifold decrease, by dozens of times, in diseases such as measles and pertussis over a period of more than 50 years testifies to the need to maintain high levels of vaccination coverage in the population [15, 18, 19]. However, the last 10–15 years are characterized by somewhat different trends and manifestations of the epidemic process for this group of infections: an uneven distribution of incidence rates over time and among different age groups of the population [12, 18-20]. Thus, in 2023, a record number of pertussis cases was registered both in the Russian Federation and in the Irkutsk Region. Objective reasons for this phenomenon included the introduction of new diagnostic methods, leading to the detection of mild, atypical forms [2, 8]. The incidence rate in the region exceeded that of the Russian Federation [8]. Despite routine vaccination among children, pertussis remains a relevant "under-controlled" infection [12], with fatal cases being registered [2]. This necessitates a change in approaches to the organization of vaccinal prevention, including among children aged 3–6 years, adolescents, and adults [19, 20].

The measles elimination period was characterized by sporadic cases registered everywhere [16, 18]. In the Irkutsk Region, the annual number of cases among children and adults varied from 2 to 24, with a maximum in 2023 (59 cases). In accordance with the execution of Decree No. 1 of the Chief State Sanitary Physician of the Russian Federation dated February 8, 2023, "On conducting catch-up immunization against measles in the territory of the Russian Federation", over 80 thousand people were vaccinated [8]. Thus, special attention must be directed towards timely vaccination of children and adults within the framework of the NCPI. To achieve the goals of the Immunization Agenda 2030 (IA2030), it is necessary to maintain population coverage with preventive immunizations and consider the results of serological monitoring assessing the level of population immunity.

Meningococcal infection occupies a special place among aerosol anthroponoses, retaining its status as a deadly and difficult-to-control infectious disease [21, 22]. In the region, despite sporadic cases, the case fatality rate remains high (21.4 %).

Varicella is a widespread infectious disease. In terms of the magnitude of economic damage, it has been leading for a number of years, second only to acute upper respiratory tract infections [2, 6]. The results of this study demonstrate a persistently high incidence rate in the population (573.2 and 2366.1 per 100,000 for the total population and children under 17 years, respectively).

Vaccination carried out according to epidemic indications is undoubtedly effective in epidemic foci and among certain categories of citizens. However, the practice of selective immunization does not significantly affect overall incidence rates. The results of this study regarding MI and varicella clearly confirm this: direct correlations are observed between the number of vaccinated individuals and incidence rates. The priority direction for the prevention of these infections remains routine vaccination of children. Studies by domestic and foreign researchers [6, 23-25] have demonstrated the effectiveness, including economic effectiveness, of this measure.

Against the background of the spread of the new coronavirus infection COVID-19, a decrease in the incidence of a number of nosological forms was registered, including for the group of airborne infections. This was primarily associated with the isolation of the population and the anti-epidemic measures implemented against COVID-19 [2]. Furthermore, according to temporary WHO recommendations dated March 26, 2020, it was recommended to temporarily suspend mass vaccination campaigns due to the increased risk of infection spread in the population [26]. These measures contributed to the accumulation of non-immune and thus highly susceptible individuals in the population, consequently leading to a registered increase in 2023 in the number of infections controllable by specific preventive measures among different population groups [2, 8, 14, 19, 21, 23].

CONCLUSION

The obtained results of the study can be used to optimize the existing vaccinal prevention program in the region. Thus, despite routine vaccination against pertussis and measles, there is an objective need to introduce booster vaccination against pertussis for children, adolescents, and adults, as well as for adult risk groups, in accordance with the methodological guidelines "Vaccination of the Adult Population". It is advisable to monitor documented vaccination coverage among the adult population, particularly vaccination and revaccination against measles among decreed groups and other contingents (students of higher and secondary educational institutions, migrants, etc.). The introduction of cohort vaccination of young children against varicella and meningococcal infection will significantly reduce the burden of these infections at the level of the constituent entity of the Russian Federation.

Conflicts of interest

The authors declare no conflicts of interest.

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HISTORY OF MEDICINE AND ANNIVERSARIES

VIKTOR S. RUKAVISHNIKOV
(August 6, 1949 – October 23, 2025)

On October 23, 2025, Viktor S. Rukavishnikov, Scientific Director of the East-Siberian Institute of Medical and Ecological Research, Corresponding Member of the Russian Academy of Sciences (since 2004), and a distinguished scientist in the fields of hygiene, occupational health, and human ecology, passed away.

Viktor S. Rukavishnikov dedicated over 50 years of his life to science. He linked his entire career with the Institute, progressing through every stage of professional advancement. In 1992, he became its director and led the institution for a quarter of a century. For a number of years, he served as the Deputy Chairman of the East-Siberian Scientific Center (ESSC) of the Siberian Branch of the Russian Academy of Medical Sciences and effectively acted as its chairman from 2001 to 2011. He made a significant contribution to the establishment and development of the ESSC and its divisions. He also served as an Assistant to a Deputy of the State Duma of the Federal Assembly of the Russian Federation and was a member of the State Duma's Ecology Council.

Under Dr. Rukavishnikov's leadership, a comprehensive series of scientific studies was successfully carried out across the Irkutsk region. These studies formed the basis for developing public health preservation and improvement strategies. His broad erudition and creative potential ensured the successful implementation of interdisciplinary projects dedicated to exploring the Asian North and the Baikal region. He made an invaluable contribution to substantiating new forms of occupational diseases resulting from chronic exposure to cyanide compounds in workers at gold extraction plants, and to developing a classification for previously unstudied visual impairments caused by chronic mercury intoxication. Dr. Rukavishnikov developed the theory of «sensory conflict» in the pathogenesis of diseases caused by physical factors in the working environment. Thanks to his efforts, Russia saw the first development and approval of a classification and criteria for identifying environmentally determined health disorders, a framework that continues to underpin research into environmentally related diseases.

His name is associated with pioneering research into the acute and long-term consequences of exposure to complex toxic substances in firefighters, the development of a conceptual model for the formation of toxic encephalopathies, and the substantiation and implementation of new methodological foundations for the safety of nanocomposites.

At his initiative and with his active participation, collaborative research was conducted with scientific institutions in the United States, Belarus, Armenia, and Mongolia. Key findings from his work in occupational health have been translated into the Mongolian language.

Viktor S. Rukavishnikov devoted considerable attention to training the next generation of scientists. Under his supervision, 13 Candidate of Sciences (PhD) and 9 Doctor of Sciences (DSc) dissertations were completed. He was the author of over 20 inventions, 400 scientific publications, and 14 monographs. He was also a co-author of the national guidelines: Occupational Respiratory Diseases (2015); Occupational Pathology (2014, 2024); and the monograph Ophthalmomercurialism (2016).

Dr. Rukavishnikov was a member of the Presidium of the Irkutsk Branch of the Siberian Branch of the Russian Academy of Sciences (SB RAS), a member of the SB RAS Scientific Council for Lake Baikal Issues, Vice President

of the All-Russian Association of Occupational Health Physicians and Specialists, a member of the Occupational Pathology Commission of the Ministry of Health of the Russian Federation, and Chairman of Dissertation Councils specializing in hygiene and occupational health. For many years, he served on the editorial boards of the journals Occupational Medicine and Industrial Ecology, Siberian Scientific Medical Journal, and Medicine in Kuzbass.

His work in organizing collaborative research between his institute and other SB RAS institutions was recognized with the V.A. Koptyug Commemorative Jubilee Medal from the SB RAS. His international collaborative efforts were acknowledged with the Golden Badge of Mongolia, the "Badge of Best Employee of Social Security and Labour Sector".

Dr. Rukavishnikov was the first laureate in Russia to receive the award named after Academician N.F. Izmerov in the category "For Personal Contribution to the Development of Occupational Medicine in Russia". He was a five-time laureate of the regional competition in science and technology, was awarded the "For Services to the Irkutsk Region" Distinguished Service Badge, received a Certificate of Honor from the Governor of the Irkutsk Region, and was awarded the Commemorative Medal "For Services to the City of Angarsk". By decision of the City Duma, he was named an Honorary Citizen of Angarsk. He held the title of Honorary Professor at the Academician N.F. Izmerov Research Institute of Occupational Health, the All-Russian Research Institute of Railway Hygiene of Rospotrebnadzor, and the Irkutsk Scientific Center of Surgery and Traumatology.

Dr. Rukavishnikov's professional achievements were recognized with numerous state and public awards: the Order of Friendship; medals of the Order "For Merit to the Fatherland", I and II degree; the "For Labor Valor" medal; the "350th Anniversary of Buryatia's Incorporation into Russia" medal; the "Honorary Health Worker" badge; the Honorary Badge of the Republic of Buryatia; a medal from the International Charitable Foundation "Patrons of the Century"; and badges commemorating the "75 Years of Irkutsk Region" and "80 Years of Irkutsk Region". He held the honorary titles "Honored Veteran of the SB RAS", "Honored Scientist of the SB RAS", and was awarded the "Golden Sigma" badge and the title "Honored Worker of Science and High Technologies of the Russian Federation".

All who worked with Viktor Stepanovich will remember him as a talented organizer, leader, mentor, and scientist of immense erudition. He was a demanding yet deeply committed individual who contributed immensely to the development of the Institute and the ESSC SB RAS. He never stood still; he constantly moved forward, confirming, challenging, and proposing his own vision for solving problems, always astonishing those around him with his inexhaustible energy, tirelessness, and optimism.

The members of the Russian Academy of Sciences and the staff of the East-Siberian Institute of Medical and Ecological Research mourn the passing of Viktor S. Rukavishnikov and extend their sincere condolences to his family and friends.

The bright memory of Viktor S. Rukavishnikov will forever remain in the hearts of his colleagues and students.

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