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ПАТОФИЗИОЛОГИЯ — МЕДИЦИНЕ

Обзор

И.А. Баранов, Н.В. Тивирикин, А.В. Деревянко, Д.П. Гладин, Е.С. Зубарева, Н.С. Козлова, М.Э. Лозовская
Микробиота легких при туберкулезе — практическое значение (обзор литературы) 7

Оригинальные статьи

Л.А. Автайкина, А.В. Буданова, Д.Д. Борискин, Д.В. Пузакова, Е.В. Арсентьева, Т.И. Власова
Половые особенности когнитивного и эмоционального статуса, мозгового кровотока при разных уровнях академического стресса 23

Е.В. Белянина, А.А. Овсепян, М.С. Аксенова, Ю.В. Ишкова, Ю.С. Арилина, В.Н. Гаранова, Н.В. Бельская, М.В. Лыков
Применение лазерной допплеровской флоуметрии для исследования тканевого кровотока на модели каррагинан-индуцированного отека у мышей 32

А.Р. Искалиева, А.Л. Семенов, З.В. Пачулия, В.В. Криштоп, Р.И. Глушаков
Влияние гипо- и гипертиреоза на морфологию почек при экспериментальной гиперплазии предстательной железы у крыс 39

Обзор

А.А. Сериков, А.К. Иорданишвили
Профилактика осложнений окклюзионной сплинт-терапии . . . 48

ИННОВАЦИОННАЯ ФАРМАКОЛОГИЯ

Обзор

Р.В. Кораблев, А.Г. Васильев, С.С. Пюрвеев, Т.В. Брус, А.Ю. Пырх, А.Е. Куртукова, Ю.Р. Рыжов, Ю.А. Таминкина, З.К. Эмиргаев
Создание продуктов на основе внеклеточных везикул из мезенхимальных стволовых клеток 54

Оригинальная статья

Н.С. Деданишвили, С.С. Пюрвеев, А.А. Лебедев, А.Г. Васильев, А.В. Васильева, М.А. Пахомова, П.Д. Шабанов
Патофизиологическая роль системы глюкагоноподобного пептида-1 в регуляции стресс-индуцированных нарушений импульсивного и компульсивного поведения у крыс 67

НОВЫЕ ТЕХНОЛОГИИ В МЕДИЦИНЕ

Оригинальная статья

Н.Ю. Кипятков, С.А. Лытаев, Н.В. Скребцова, В.В. Гайворонская, К.А. Бельская
Количественный анализ электроэнцефалографии у амбулаторных пациентов с психосоматическими проявлениями после COVID-19 77

CONTENTS

PATHOPHYSIOLOGY — MEDICINE

Review

I.A. Baranov, N.V. Tivirikin, A.V. Derevyanko, D.P. Gladin, E.S. Zubareva N.S. Kozlova, M.E. Lozovskaya
Lung microbiota in tuberculosis — practical significance (literature review) 7

Original articles

L.A. Avtaykina, A.V. Budanova, D.D. Boriskin, D.V. Puzakova, E.V. Arsentieva, T.I. Vlasova
Gender characteristics of cognitive and emotional status, cerebral blood flow at different levels of academic stress 23

E.V. Belyanina, A.A. Ovsepyan, M.S. Aksenova, Yu.V. Ishkova, Yu.S. Arilina, V.N. Garanova, N.V. Belskaya, M.V. Lykov
Laser Doppler flowmetry for stuying tissue blood flow in a model of carrageenan-induced edema in mice 32

A.R. Iskalieva, A.L. Semenov, Z.V. Pachuliya, V.V. Krishtop, R.I. Glushakov
Effect of hypo- and hyperthyroidism on kidney morphology in experimental prostate hyperplasia in rats 39

Review

A.A. Serikov, A.K. Iordanishvili
Occlusive splint therapy complication prevention 48

INNOVATIVE PHARMACOLOGY

Review

R.V. Korablev, A.G. Vasiliev, S.S. Pyurveev, T.V. Brus, A.Yu. Pyrkh, A.E. Kurtukova, Yu.R. Ryzhov, Yu.A. Taminkina, Z.K. Emirgaev
Constructing products based on extracellular vesicles obtained from mesenchymal stem cells 54

Original article

N.S. Dedanishvili, S.S. Pyurveev, A.A. Lebedev, A.G. Vasiliev, A.V. Vasilieva, M.A. Pakhomova, P.D. Shabanov
Pathophysiological role of the glucagon-like peptide-1 system in the regulation of stress-induced impairments of impulsive and compulsive behavior in rats 67

NEW TECHNOLOGIES IN MEDICINE

Original article

N.Yu. Kipyatkov, S.A. Lytaev, N.V. Skrebtsova, V.V. Gaivoronskaia, K.A. Belskaya
Quantitative electroencephalography analysis data in outpatient patients with psychosomatic manifestations following COVID-19 77

Обзор и описание клинического случая

А.А. Кучай, А.Н. Липин, К.Л. Козлов, Н.Н. Груздев
Эндоваскулярная реваскуляризация при окклюзии бедренно-подколенной артерии 91

ЭКОЛОГИЧЕСКАЯ МЕДИЦИНА

Обзор

В.О. Еркудов, В.В. Гайворонская, Н.В. Скребцова, С.С. Рогозин
Проблема ожирения и избытка массы тела во Вьетнаме. Часть 3. (Литературный обзор исследований во Вьетнаме) 104

РЕДКИЕ ВОПРОСЫ БИОМЕДИЦИНЫ

Лекция

Д.Н. Стрелков, Е.Ю. Калинина, Е.В. Щербакова, А.М. Федюк, А.А. Севрук, А.Д. Крамаренко, К.И. Лазарева, А.В. Коган, Л.М. Стрелкова
Современные представления об анатомии добавочных ребер шейного отдела позвоночного столба 118

ИЗ ИСТОРИИ МЕДИЦИНЫ

Персоналии

А.Н. Зубрицкий
Леонид Иосифович Смирнов — выдающийся советский ученый-нейроморфолог 128

Review and description of a clinical case

A.A. Kuchay, A.N. Lipin, K.L. Kozlov, N.N. Gruzdev
Endovascular revascularization in case of femoropopliteal artery occlusion 91

ENVIRONMENTAL MEDICINE

Review

V.O. Erkudov, V.V. Gaivoronskaya, N.V. Screbtsova, S.S. Rogozin
The problem of obesity and overweight in Vietnam. Part 3. (Literature review of research in Vietnam) 104

RARE QUESTIONS IN BIOMEDICINE

Lecture

D.N. Strelkov, E.Yu. Kalinina, E.V. Shcherbakova, A.M. Fedyuk, A.A. Sevruk, A.D. Kramarenko, K.I. Lazareva, A.V. Kogan, L.M. Strelkova
Contemporary concepts of the vertebral column additional cervical ribs anatomy 118

HISTORY OF MEDICINE

Personalities

A.N. Zubritsky
Leonid Iosifovich Smirnov — outstanding soviet scientist-neuromorphologist 128

Review

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Lung microbiota in tuberculosis — practical significance (literature review)

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Abstract. Tuberculosis remains one of the leading causes of death from infectious diseases worldwide. To date, some progress has been made in the fight against this serious disease, but problems such as the multidrug resistance of *Mycobacterium tuberculosis* and tuberculosis/HIV coinfection are of serious concern. A significant discovery was the discovery of microbiota in the distal parts of the respiratory tract — respiratory bronchioles and alveoli, which, as it turned out, plays an important role in maintaining local immunity and protecting against pathogens. It has been established that in healthy people this locus is dominated by commensals, for example *Prevotella*, whereas in tuberculosis dysbiosis develops: species diversity decreases and the number of opportunistic microorganisms (*Streptococcus, Neisseria*) increases. This specific microbiota profile can serve as a diagnostic and prognostic marker, helping to detect the disease at an early stage and predict the risk of developing drug resistance of *Mycobacterium tuberculosis*. At the same time, tuberculosis therapy restores the normal composition of the lung microbiota, but at the same time promotes the growth of antibiotic resistance among opportunistic bacteria. A promising area is the management of the lung microbiota. The development of inhaled probiotics opens up new opportunities for tuberculosis prevention and improved treatment effectiveness, especially in complex cases of multidrug resistance of *Mycobacterium tuberculosis*. Thus, the study of the lung microbiota marks the transition to personalized approaches in the fight against tuberculosis.

Keywords: tuberculosis, lung microbiota, bronchoalveolar lavage, pathobionts, tuberculosis therapy, 16S ribosomal RNA gene sequencing, shotgun complete genome sequencing, new generation metagenomic sequencing, inhaled probiotics, horizontal gene transfer

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Микробиота легких при туберкулезе — практическое значение (обзор литературы)

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Резюме. Туберкулез остается одной из ведущих причин смертности от инфекционных заболеваний во всем мире. На сегодняшний день достигнут определенный прогресс в борьбе с этим тяжелым заболеванием, но такие проблемы, как множественная лекарственная устойчивость микобактерий туберкулеза и коинфекции туберкулез/ВИЧ, вызывают серьезную обеспокоенность. Значимым открытием стало обнаружение микробиоты в дистальных отделах дыхательного тракта — респираторных бронхиолах и альвеолах, которая, как выяснилось, играет важную роль в поддержании местного иммунитета и защите от патогенов. У здоровых людей в этом локусе доминируют комменсалы, например *Prevotella*, тогда как при туберкулезе развивается дисбиоз: снижается видовое разнообразие и увеличивается численность условно-патогенных микроорганизмов (*Streptococcus, Neisseria*). Этот специфический профиль микробиоты может служить диагностическим и прогностическим маркером, помогая выявлять болезнь на ранней стадии и прогнозировать риск развития лекарственной устойчивости микобактерий туберкулеза. Противотуберкулезная терапия при этом восстанавливает нормальный состав микробиоты легких, но одновременно способствует росту антибиотикорезистентности среди условно-патогенных бактерий. Перспективным направлением является управление микробиотой легких. Разработка ингаляционных пробиотиков открывает новые возможности для профилактики туберкулеза и повышения эффективности лечения, особенно в сложных случаях множественной лекарственной устойчивости микобактерий туберкулеза. Таким образом, изучение микробиоты легких знаменует переход к персонализированным подходам в борьбе с туберкулезом.

Ключевые слова: туберкулез, микробиота легких, бронхоальвеолярный лаваж, патобионты, противотуберкулезная терапия, секвенирование гена 16S рибосомальной РНК, секвенирование полного генома методом дробовика, метагеномное секвенирование нового поколения, ингаляционные пробиотики, горизонтальный перенос генов

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

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INTRODUCTION

Despite significant progress made by the global community in the fight against tuberculosis (TB), the disease remains a pressing concern. It is still a source of anxiety for scientists, clinicians, and public health officials.

According to the 2024 Global Tuberculosis Report published by the World Health Organization (WHO), in 2023 TB once again became the leading cause of death among all infectious diseases, displacing COVID-19 (CoronaVIrus Disease 2019), which had dominated in the previous three years [1]. The COVID-19 pandemic severely damaged the health care systems of many countries and became one of several factors preventing humanity from achieving the WHO's 2025 TB elimination targets [2].

Thanks to significant efforts by the Russian healthcare system, Russia joined the ranks of 13 countries that managed to reduce TB deaths by 50% or more between 2015 and 2023. In 2021, the WHO removed Russia from the list of countries with a high TB burden. However, our country still remains on the so-called Global TB Watchlist [1, 3]. This is primarily due to problems with TB caused by multidrug-resistant (MDR-TB) strains of the *Mycobacterium tuberculosis* complex (MTB) and co-infection caused by MTB and the human immunodeficiency virus (TB/HIV) in the Russian Federation [3, 4].

Currently, the Russian Federation is also seeing a sustained positive trend in the TB epidemic among children [5], but sporadic cases of late-stage TB diagnosis in this population group mean that physicians of all specialties must remain vigilant regarding this infection.

Thus, measures for the prevention, diagnosis, and treatment of TB require constant improvement. Since TB is the result of a complex interaction between MTB and the host's immune system [6], which is significantly modulated by the pulmonary microbiota [7], a detailed study of the latter is of particular relevance.

NORMAL LUNG MICROBIOTA

Previously, the respiratory bronchioles and alveoli were considered completely sterile [8]. However, it is now known that all sections of the respiratory tract in a healthy person, including the lower respiratory tract, are colonized by various commensal microorganisms: bacteria, viruses, fungi [9], and, according to the latest data, even archaea [10] .

It is believed that the microbiota of the lower respiratory tract (LRT) is exclusively transient. Nevertheless, its composition in conditionally healthy individuals remains relatively constant due to a dynamic equilibrium between the influx of microorganisms, the upper respiratory tract (URT) and the host's immune response [11, 12]. Researchers have figuratively named this model "Yin and Yang" [13], as the optimal qualitative and quantitative composition of the microbiota (eubiosis) arises from the dynamic interplay of various forces.

It should be noted that the URT system consists of the nasal cavity, nasopharynx, and oropharynx, while the LRT includes the larynx, trachea, bronchi, bronchioles, and alveoli [14].

The LRT microbiota in a healthy individual is primarily composed of phyla such as *Pseudomonadota* (Proteobacteria), *Bacillota* (Firmicutes), and *Bacteroidota* (Bacteroides), which together account for about 90% of the bacteria inhabiting this area [15] At the genus level, the following taxa predominate: *Veillonella*, *Prevotella*, *Sphingomonas*, *Pseudomonas*, *Acinetobacter, Fusobacterium, Megasphaera, Staphylococcus, and Streptococcus [16].*

It is important to note that the microbiota of the LRT has been studied mainly by molecular genetic methods. Traditional culture-based methods almost never yield results [17]. Detection of DNA fragments does not allow us to determine whether they originate from a living or a dead bacterial cell. Therefore, it is extremely difficult to establish which microorganisms are resident and which are transient in the LRT.

The nasal cavity is colonized by *Corynebacterium, Propionibacterium, Staphylococcus spp., Moraxella, Pseudomonadota (Proteobacteria),* and *Fusobacterium [14]. Corynebacterium* and *Staphylococcus* dominate the nasopharynx [18]. The oropharynx is inhabited by *Streptococcus, Haemophilus, Neisseria, Prevotella, Veillonella,* and *Leptotrichia* [14].

The microbiota of the URT is richer than in the LRT in both quantitative and qualitative terms. However, their composition largely correlates due to the direct connection between these two sites [19]. In addition, the upper respiratory tract represents an ecological niche for important pathobionts: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus (S. aureus)*. These are symbiotic microorganisms, however, they can cause disease under certain conditions [20].

Viruses found in the respiratory tract include families such as *Picornaviridae, Paramyxoviridae, Orthomyxoviridae, Coronaviridae, Adenoviridae, Parvoviridae, Herpesviridae, Anelloviridae, Papillo-*

maviridae, Polyomaviridae, and numerous bacteriophages [21].

Fungi are predominantly represented by the genera *Aspergillus, Cladosporium, Eurotium, Penicillium,* and several others [22].

Archaea in the respiratory tract include such types as *Euryarchaeota (e.g., Methanobrevibacter smithii* as a result of microaspiration from the gastrointestinal tract), *Thaumarchaeota* (representatives of the skin and upper respiratory tract microbiota) and *Woesearchaeota*, which are specific to the lower respiratory tract. Their role in a healthy organism and in pathological conditions has not yet been sufficiently studied [23].

Some representatives of the normal human respiratory tract microbiota are shown in the diagram (Fig. 1).

The beneficial role of the respiratory tract microbiota is extremely diverse. In particular, it ensures the formation of a balanced immune response, preventing the development of excessive inflammation when exposed to harmless antigens [24] . It also inhibits the proliferation of pathogenic microorganisms by competing with them [25]; enhances antiviral immunity [26]; prevents the development of lung cancer [27]; and, through the production of various bioactive substances, participates in forming the “gut-lung axis” [28].

A disruption in the qualitative and quantitative composition of the respiratory tract microbiota, or dysbiosis, can lead to impairment of the aforementioned protective functions and declined resistance to both specific [29] and nonspecific respiratory infections [24, 30].

Factors leading to respiratory tract dysbiosis include smoking, air pollution, immunodeficiency states (including HIV/AIDS), infectious and non-infectious respiratory diseases, the use of antibacterial drugs, medical interventions (mechanical ventilation, bronchoscopy, etc.), as well as an imbalance in the gut microbiota and diseases of other organs and systems [11, 31, 32]. Figure 2 illustrates the functions of the lung microbiota as well as factors leading to its imbalance.

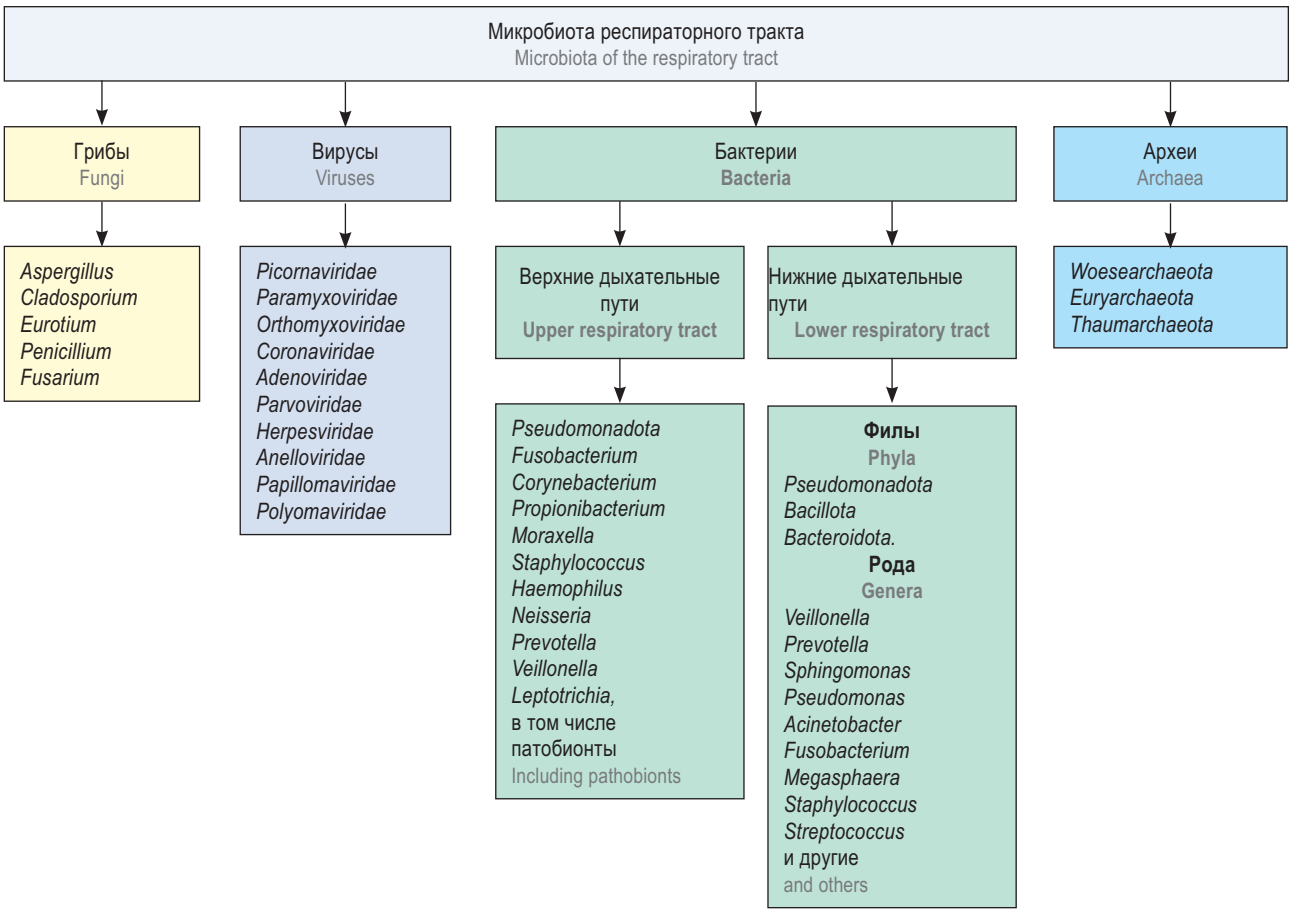


Fig. 1. **Microbiota of the respiratory tract (the figure is prepared by the authors of this article)**

Рис. 1. Микробиота респираторного тракта (рисунок авторов данной статьи)

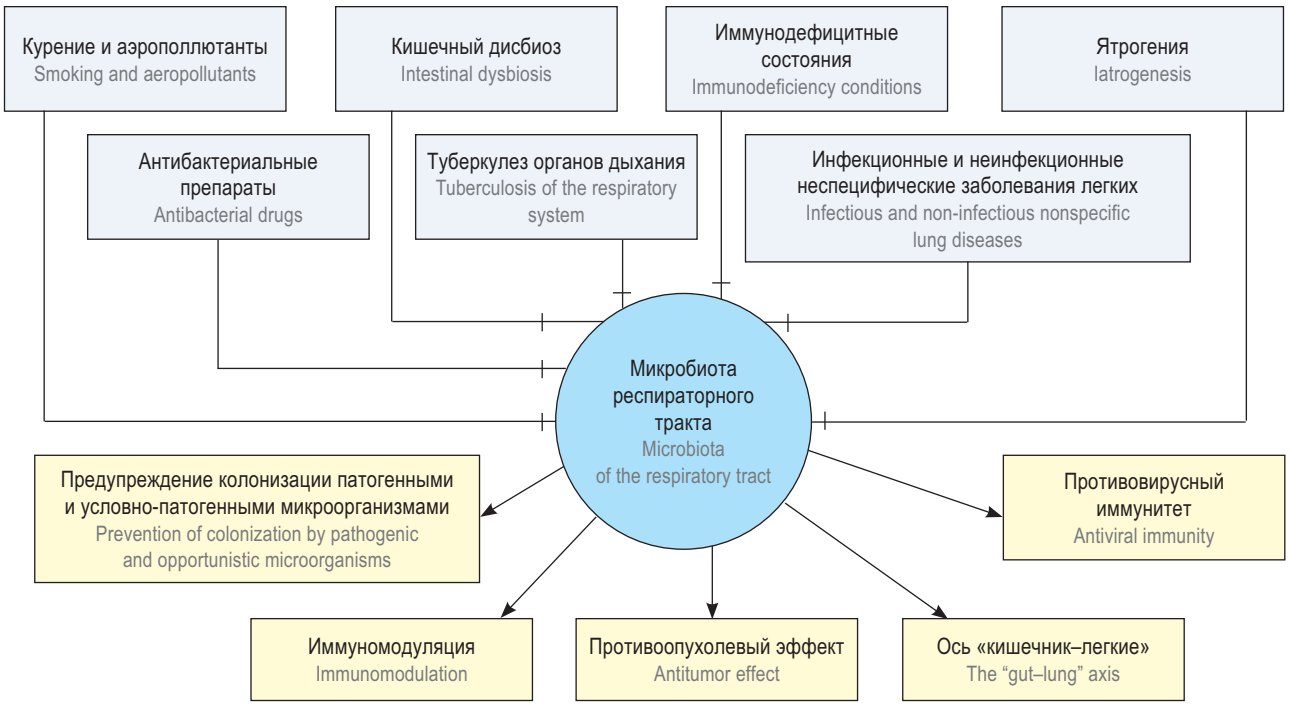


Fig. 2. **The functions of the lung microbiota and the factors leading to its imbalance (the figure is prepared by the authors of this article)**

Рис. 2. Функции микробиоты легких и факторы, приводящие к ее дисбалансу (рисунок авторов данной статьи)

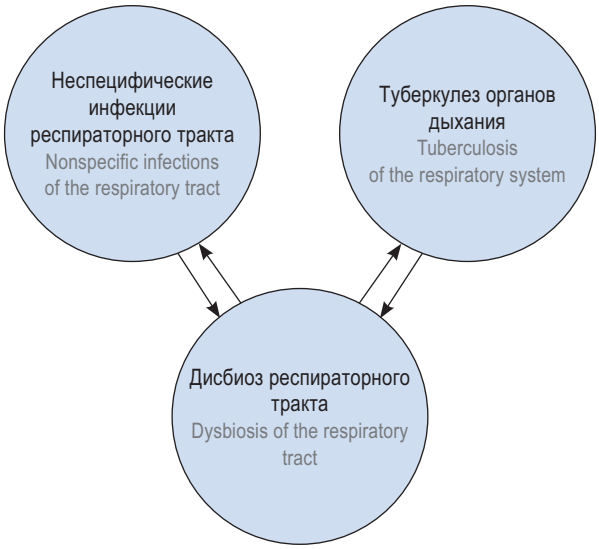


Fig. 3. **A schematic diagram of the relationship between dysbiosis, pulmonary tuberculosis and nonspecific infection (the figure is prepared by the authors of this article)**

Рис. 3. Принципиальная схема взаимосвязи дисбиоза респираторного тракта, туберкулеза легких и неспецифической инфекции (рисунок авторов данной статьи)

Thus, a bidirectional relationship or vicious cycle is formed. Both TB and nonspecific lung infections can lead to local dysbiosis, which increases susceptibility to these diseases [33]. Fig. 3 presents a schematic diagram of the relationship between respiratory tract dysbiosis, pulmonary TB, and nonspecific infection.

Tuberculosis Impact on Lung Microbiome

In 2022, Chinese researchers conducted a large-scale study examining the lung microbiome profile in patients with TB [34]. Bronchoalveolar lavage fluid samples were collected to study the lung microbiota, which is more informative than sputum analysis, as sputum collection inevitably introduces microorganisms from the nasopharynx and oral cavity into sample [15]. The qualitative and quantitative composition of the microbiota was determined using metagenomic next-generation sequencing (mNGS).

Samples obtained from healthy individuals in the control group contained higher levels of *Prevotella melaninogenica (P. melaninogenica)* and *Ralstonia pickettii (R. pickettii)*, while samples from patients with untreated TB contained *S. aureus* and *Neisseria* spp. [34]. These results are partially consistent with data from a 2019 meta-analysis, according to which Streptococcus and Neisseria were more common in TB patients (35.01 and 27.1% of the total, respectively), while *Prevotella* was more common in healthy individuals from the control group (36.9%) [35]. The same study reported that *Veillonella*, *Rothia, Leuconostoc,* and

Lactobacillus were detected only in TB patients and found in 7, 8, 4, 3, 2, and 1.8% of patients, respectively. In addition, the genera *Gammaproteobacteria, Haemophilus,* and *Actinobacillus* were found only in healthy individuals from the control group [35]. Differences in the composition of the lung microbiota at the genus level between TB patients and healthy individuals from the control group are shown in Fig. 4 [34].

It is worth noting that the proportion of MBT in TB patients, according to some data, accounts for only about 0.06% of the total number of all bacteria detected in sputum analysis [36].

Whether TB or respiratory tract dysbiosis is the primary factor remains uncertain. However, MBT appear to significantly influence the lung microenvironment, thereby promoting proliferation of certain microorganisms and suppressing others [34].

Additionally, according to the literature, the microbiota identified in TB patients' sputum via 16S rRNA gene sequencing may vary significantly at the genus level depending on resistance or susceptibility of MTB to various drugs (Fig. 5) [36]. Thus, it has been established that *Delftia* can serve as a potential diagnostic marker for identifying patients with TB caused by MTB resistant to rifampicin; *Kingella* and *Chlamydophila* — to isoniazid; and Bordetella — to rifampicin and isoniazid (in patients with MDR to the pathogen) [36].

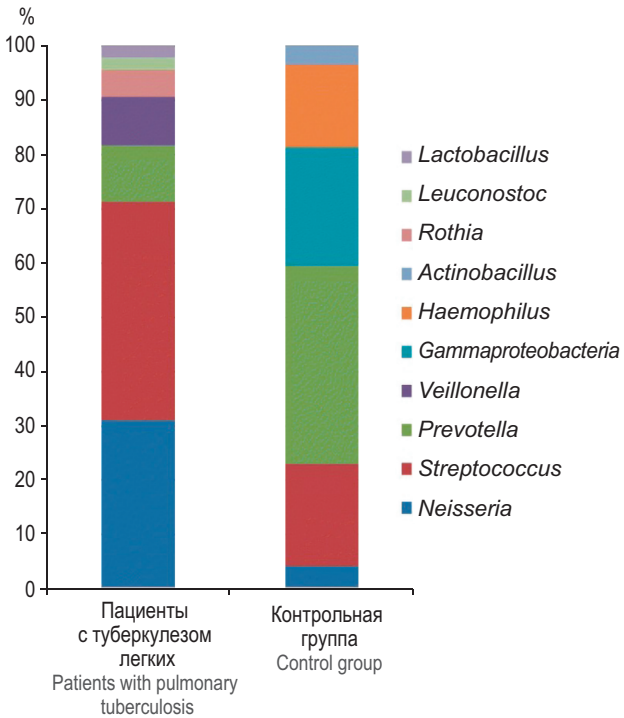


Fig. 4. The composition of the lung microbiota at the genus level in patients with tuberculosis and in healthy people (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/e984/6347808/ff898c63225f/12879_2019_3712_Fig3_HTML.jpg)

Рис. 4. Состав микробиоты легких на уровне рода у пациентов с туберкулезом и у здоровых людей (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/e984/6347808/ff898c63225f/12879_2019_3712_Fig3_HTML.jpg)

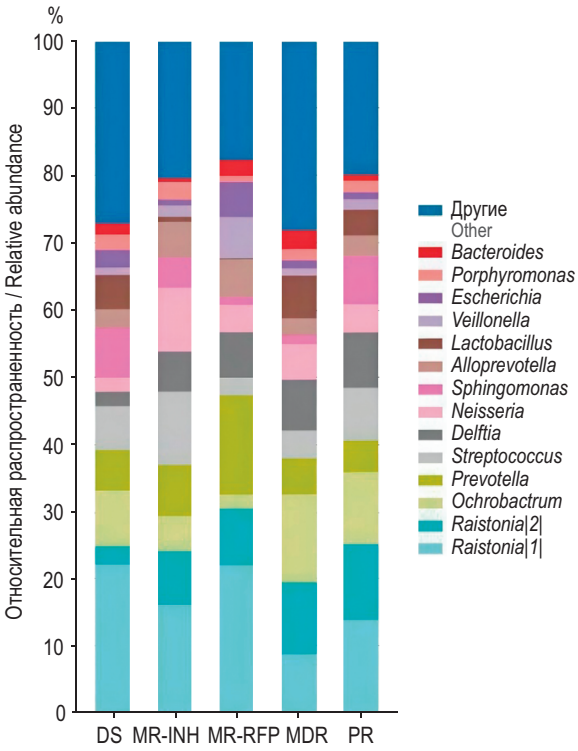


Fig. 5. Composition of the upper respiratory tract microbiota at the genus level in patients with tuberculosis caused by Mycobacterium tuberculosis with different sensitivity profiles to anti-tuberculosis drugs. Relative abundance — prevalence of microorganisms of different species; DS — drug-sensitive tuberculosis; MR-INH — monoresistance isoniazid; MR-RFP — monoresistance rifampicin; MDR — multidrug resistance; PR — polyresistance (this is resistance to two first-line anti-tuberculosis drugs and more, while maintaining sensitivity to at least isoniazid and rifampicin simultaneously) (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/ca0b/8040397/f0e6c4a78ba9/ijmsv18p1935g003.jpg)

Рис. 5. Состав микробиоты верхних дыхательных путей на уровне рода у пациентов с туберкулезом, вызванным микобактериями туберкулеза с различными профилями чувствительности к противотуберкулезным препаратам. Относительная распространенность — распространенность микроорганизмов разных видов; DS — лекарственно-чувствительный туберкулез; MR-INH — монорезистентность к изониазиду; MR-RFP — монорезистентность к рифампицину; MDR — множественная лекарственная устойчивость; PR — полирезистентность (это устойчивость к двум противотуберкулезным препаратам первого ряда и более при сохранении чувствительности как минимум к изониазиду и рифампицину одновременно) (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/ca0b/8040397/f0e6c4a78ba9/ijmsv18p1935g003.jpg)

ANTITUBERCULOSIS THERAPY AND LUNG MICROBIOME

The lung microbiome is significantly influenced by antituberculosis therapy (ATT) [34, 37]. All patients included in the study had drug-sensitive TB and received treatment according to the following regimen: 2 months of HRZE (isoniazid, rifampicin, pyrazinamide, and ethambutol) and 4 months of HR (isoniazid and rifampicin). The microbial composition of healthy individuals, TB patients receiving ATT during the study, and patients who had recently completed a course of chemotherapy (clinically cured with bacteriological confirmation) was similar. However, there was a marked difference in the taxonomic profile of the microbiota among those patients with pulmonary TB who were not receiving treatment during the study. It was noted that the opportunistic pathogen *S. aureus* was significantly more prevalent in the group of patients with untreated TB, while the relative abundance of *R. pickettii and P. melaninogenica,* conversely, was much lower [34]. It has been reported that *R. pickettii* is capable of converting ethionamide into its active form, and a decrease in its abundance in patients with TB may negatively affect treatment outcomes [38]. According to some data, bacteria of the genus *Prevotella* play a positive role in maintaining lung function and controlling inflammation. Accordingly, a decrease in the abundance of *P. melaninogenica* may be associated with impaired lung function and an excessive inflammatory response [39].

Overall, microbial diversity in patients with untreated TB was significantly lower than in other groups. Thus, ATT rapidly restored normal microbial composition in this study, contrary to expectations [34]. Apparently, this is due to the strong local effect of MBT on the microecology of the lower respiratory tract. There are studies both confirming [40] and refuting this observation [37].

At the same time, ATT undoubtedly has negative consequences as well. Of the four drugs prescribed to patients in the study, rifampicin is a broad-spectrum antibiotic and may lead to the development of antibiotic resistance, including in opportunistic pathogens [34]. Other broad-spectrum antibiotics used in various TB treatment regimens include rifabutin and rifapentine; fluoroquinolones (levofloxacin, moxifloxacin, sparfloxacin); aminoglycosides (kanamycin, amikacin, capreomycin); carbapenems (the combination drug imipenem + cilastatin and meropenem); and the semi-synthetic penicillin antibiotic in combination with a beta-lactamase inhibitor—amoxicillin + clavulanic acid [3]. It has been demonstrated that ATT increases

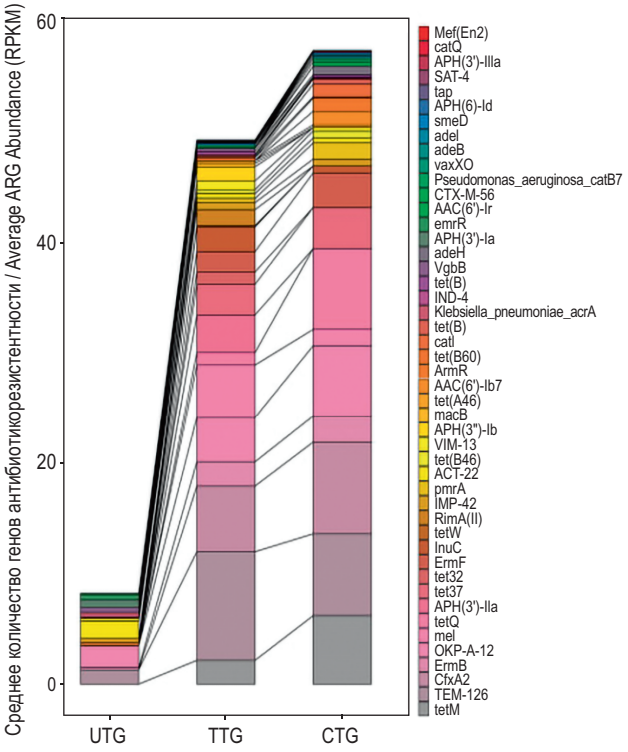


Fig. 6. **The abundance of different lung microbiota resistance genes in different observation groups. Average ARG Abundance — average number of antibiotic resistance genes; UTG — the untreated pulmonary TB group; TTG — the treated pulmonary TB group; CTG — the cured pulmonary TB group (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/3411/8865484/d7e5b5637cde/spectrum.01901-21-f005.jpg)**

Рис. 6. Количество различных генов резистентности микробиоты легких в разных группах наблюдения. UTG — пациенты с туберкулезом, не получавшие лечения; TTG — пациенты с туберкулезом в процессе лечения; CTG — пациенты, излеченные от туберкулеза легких в недавнем прошлом (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/3411/8865484/d7e5b5637cde/spectrum.01901-21-f005.jpg)

the diversity and number of genes responsible for antimicrobial resistance across an entire microbial community. This raises concerns regarding the potential development of nonspecific respiratory infections in patients caused by antibiotic-resistant strains of pathobionts during or after ATT. A histogram showing the number of different resistance genes in the pulmonary microbiota across different observation groups is presented in Fig. 6 [34].

It should be noted that nonspecific lung infections complicating the course of TB are often caused not by the patient's own pathobionts, but by hospital-acquired strains of microorganisms circulating within hospitals with antibiotic resistance profiles specific to them [41]. This is particularly relevant during prolonged

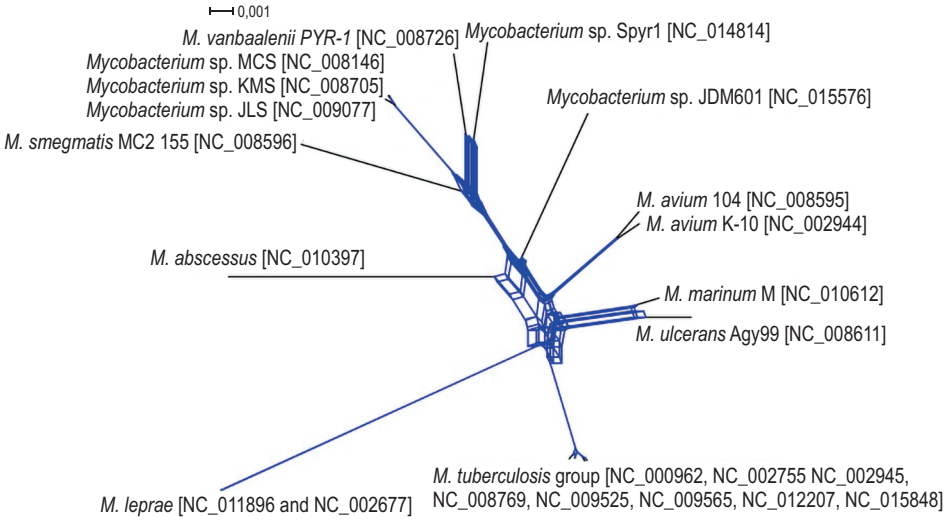


Fig. 7. **A reticulate network showing the events of the exchange of conserved genes between different Mycobacteria (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/d4f0/4331801/b230cfc44751/1471-2148-15-S1-S2-4.jpg)**

Рис. 7. Сетчатая структура, демонстрирующая события обмена консервативными генами между различными микобактериями (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/d4f0/4331801/b230cfc44751/1471-2148-15-S1-S2-4.jpg)

hospitalization of patients with tuberculosis, as well as during their stay in intensive care units, especially when mechanical ventilation is used, which is not uncommon among patients with TB/HIV coinfection, whose immune systems are, moreover, severely compromised [42–44].

In addition, horizontal gene transfer must be mentioned in this context. This process occurs when a microorganism transfers genetic material to another microorganism that is not its descendant via various mobile genetic elements (plasmids, transposons, integrons) [45]. Thanks to this mechanism, resistance determinants can rapidly spread among pathogens causing nosocomial infections, including those belonging to the so-called ESKAPE group, which poses a significant problem for both individual hospitals and healthcare systems worldwide [46].

However, it is encouraging that horizontal gene transfer is not possible between *M. tuberculosis* and pathogens of nonspecific infections. Currently, the evolution of *M. tuberculosis*, including the acquisition of drug resistance, is entirely driven by spontaneous mutations, genomic recombination, gene duplication, and selective pressure [47]. Nevertheless, pathogenicity clusters have been identified in the *M. tuberculosis* genome. They may have been acquired by the microorganism from external sources during its phylogeny and account for its high virulence. Furthermore, other mycobacteria, such as *Mycobacterium avium* and *Mycobacterium marinum*, are currently actively exchanging mobile genetic elements both with each other and with taxonomically distant microorganisms. Thus, we cannot exclude the possibility that, sooner or later in the future, conditionally pathogenic mycobacteria will evolve from pathogens of predominantly opportunistic infections into pathogens that are no less dangerous than MTB [47]. It is particularly important to take this fact into account given the increasing frequency of mycobacterial infections not only among individuals with HIV infection but also among the immunocompetent population [48]. Figure 7 presents a network diagram illustrating the exchange of conserved genes among various mycobacteria [47].

DIAGNOSTIC SIGNIFICANCE OF ASSESSING LUNG MICROBIOME IN ASSOCIATION WITH TUBERCULOSIS

Therefore, assessing the lung microbiome appears to be an important diagnostic tool for pulmonologists and other specialists. Patients with TB have a unique lung microbiome profile, and its determination can help verify TB in early stages, conduct differential diagnosis between TB and lung cancer, as well as other pathologies, and predict the severity of TB, the likelihood of a secondary nonspecific infection, and the development of drug resistance in a specific patient [34–36, 49]. Furthermore, since respiratory tract dysbiosis is one of the risk factors for developing TB, modifying a microbal composition could help to prevent TB [50, 51].

Currently, three main molecular genetic methods are used to study the microbiota. Each of these methods has its own advantages and disadvantages: 16S rRNA gene sequencing [52], whole-genome

Table 1

Comparison of some molecular genetic methods of microbiota research

Таблица 1

Сравнение некоторых молекулярно-генетических методов исследования микробиоты

Характеристика Characteristic	Секвенирование гена 16S рибосомальной РНК 16S ribosomal RNA Gene Sequencing [52]	Секвенирование полного генома методом дробовика Shotgun Whole-Genome Sequencing [53]	Метагеномное секвенирование нового поколения Next-generation metagenomic sequencing (mNGS) [54]
Объект секвенирования Sequencing facility	Один ген (16S рибосомальной РНК) A single gene (16S ribosomal RNA)	Весь геном одной изолированной бактерии The entire genome of a single, isolated bacterium	Вся ДНК/РНК из образца (бактерии, археи, вирусы, грибы) All DNA/RNA from a sample (bacteria, archaea, viruses, fungi)
Принцип метода The principle of the method	Амплификация и секвенирование консервативного гена с вариабельными регионами для идентификации таксонов Amplification and sequencing of a conserved gene with variable regions to identify taxa	Случайная фрагментация всей ДНК бактерии, секвенирование фрагментов и «сборка» полного генома Random fragmentation of the entire bacterial DNA, sequencing fragments and “assembling” the complete genome	Секвенирование всей ДНК/РНК, извлеченной из образца среды, с последующей сборкой и таксономическим/функциональным анализом Sequencing of all DNA/RNA extracted from a medium sample, followed by assembly and taxonomic/functional analysis
Разрешающая способность Resolution capacity	Уровень рода, реже вида Genus-level, rarely species-level	Уровень штамма, возможно определение генов вирулентности и резистентности Strain level, possible determination of virulence and resistance genes	Уровень вида, иногда штамма. Дает представление о функциональном потенциале сообщества Species-level, sometimes strain-level. Functional potential of the community
Количественная оценка Quantitative assessment	Относительная численность микроорганизмов в микробном сообществе (доля в сообществе) Relative abundance (proportion within the community)	Невозможна (метод используют для чистой культуры) Not applicable (the method is used for pure culture)	Относительная и абсолютная численность микроорганизмов (при использовании методов калибровки) Relative and absolute abundance of microorganisms (when using calibration methods)
Основное применение Main application	Оценка таксономического профиля сообщества, альфа- и бета-разнообразия Taxonomic profile of a community, alpha- and beta-diversity	Детальное изучение конкретного микроорганизма: геномика, вирулентность, эволюция Detailed study of a specific microorganism: genomics, virulence, evolution	Полная картина сообщества: таксоны и гены вирулентности, резистентности и т.д. (то есть функциональный потенциал) The full picture of the community: taxa and genes of virulence, resistance, etc. (i.e. functional potential)
Преимущества метода Advantages of the method	Низкая стоимость, стандартизированный метод, наличие больших баз данных Low cost, standardized method, availability of large databases	«Золотой стандарт» для изучения индивидуальных геномов, высокая разрешающая способность The “gold standard” for studying individual genomes, high resolution	Наиболее полная информация без необходимости культивирования The most complete information without the need for cultivation
Недостатки метода Disadvantages of the method	Низкое разрешение, не дает представления о функциональном потенциале сообщества, ПЦР-амплификация вносит искажения, не применяется для изучения вирусов и грибов Low resolution, does not provide an idea of the functional potential of the community, PCR amplification introduces distortions, and is not used to study viruses and fungi	Требует выделения и культивирования чистой культуры (трудоемкость) Requires isolation and cultivation of pure culture (labor intensity)	Высокая стоимость, сложный анализ, требует больших вычислительных мощностей High cost, complex analysis, requires a lot of computing power

Note: PCR — polymerase chain reaction.
Примечание: ПЦР — полимеразная цепная реакция.

The table is prepared by the authors
Таблица составлена авторами

shotgun sequencing [53], and mNGS [54]. A comparison of these methods for sequencing the microbiota's genetic material is presented in Table 1.

All methods have their own unique capabilities and limitations, making them complementary tools in the modern microbiologist's arsenal.

As mentioned above, the upper respiratory tract is colonized by a much greater variety of microorganisms than the lower respiratory tract. Therefore, certain aspects of sampling from the latter deserve special mention. To avoid unwanted contamination, the following techniques are used: rinsing the mouth before the procedure, refraining from aspiration during bronchoscope insertion until it enters the trachea, and the use of protected sampling methods [55]. These methods include protected bronchoalveolar lavage, in which a sterile protected catheter is passed through the working channel of the bronchoscope, after which sterile saline is introduced and aspirated from the distal airways, and protected brush biopsy (protected brush biopsy), which involves keeping the brush within a special sheath before and after obtaining material from the area of interest [55]. Performing these procedures can be associated with significant difficulties and requires specific training for endoscopists. Figure 8 shows a photograph from the endoscope camera depicting bronchoalveolar lavage fluid in the bronchial lumen, which, when properly obtained, should have a foamy look.

When studying the microbiota of the lower respiratory tract, it is essential to examine control samples, namely flushing fluid from a working channel, uninoculated sterile saline solution, and throat swabs, which undergo the same analysis as main samples [56]. Then, using bioinformatics methods, a "subtraction" is performed: the number of counts of all microbial taxa detected in the additional controls is subtracted from the corresponding counts obtained from the main samples, which allows to exclude contaminants from the final analysis [55, 56].

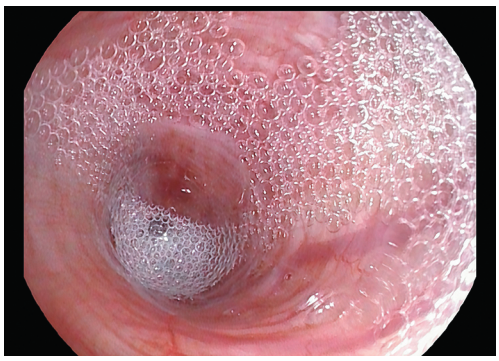


Fig. 8. **A photograph of foamy bronchoalveolar lavage fluid in the bronchial lumen, taken using an endoscope camera (from the personal archive of A.V. Derevyanko)**

Рис. 8. Фотография пенистой бронхоальвеолярной лаважной жидкости в просвете бронха, сделанная при помощи камеры эндоскопа (из личного архива А.В. Деревянко)

INHALED PROBIOTICS IN TREATMENT AND PREVENTION OF LUNG DISEASES

As described above, the normal lung microbiota performs a large number of beneficial functions [24–28]. In this regard, it is proposed to use special probiotics for inhalation to treat and prevent various infectious and non-infectious lung diseases [49, 50].

There are a number of challenges in developing probiotics that can be delivered to the lungs by means of inhalation. Particles with a diameter of 1–5 μm are considered ideal for accumulating in the lungs. Larger particles are cleared retrograde via mucociliary clearance, while smaller ones are cleared with exhaled air [57]. Therefore, to ensure the required particle size, drug delivery systems such as microcapsules, microspheres, liposomes, and niosomes (similar to liposomes but containing synthetic nonionic surfactants) are preferred [51].

Careful selection of a device is also necessary to ensure effective delivery of probiotics into the lungs. Nebulizers with vibrating mesh technology and "soft mist" inhalers (respirators) are best suited for this task [58]. One limitation is that the preparation must be soluble in water or in a mixture of water and ethanol to prevent filter clogging [59]. Another option is the use of dried powdered probiotics via dry powder inhalers. Lactose is used as a carrier in approximately 90% of dry powder inhalers that are currently available on the market. Consequently, the drug under development must remain stable and effective in the presence of lactose [51].

Already today, there are proposals to use an inhaled biotherapeutic preparation based on lactobacilli for treating bronchopulmonary dysplasia in preterm newborns and chronic obstructive pulmonary disease. It has demonstrated its efficacy in various experimental models in vitro and *in vivo* [60]. There are proposals to consider lung microbiota transplantation by analogy with gut microbiota transplantation [61].

Inhaled probiotics will be undoubtedly useful for treating and preventing infectious lung diseases [50, 51], including TB. The use of such preparations is

particularly promising in treating TB caused by drug-resistant mycobacteria or complicated by a nonspecific infection, as well as for the rapid normalization of the lung microbiota in convalescents. This area is highly interesting for future scientific research.

The lung microbiota is a highly active participant in maintaining respiratory homeostasis. By shaping local immunity and providing colonization resistance, it acts as a key factor in defense against respiratory pathogens, including *M. tuberculosis* [24, 25, 33, 34].

As studies have shown, tuberculosis infection has a profound effect on lung microbial communities, leading to characteristic dysbiosis. Specifically, this involves a decrease in biodiversity, a reduction in commensals such as *Prevotella*, and an increase in the abundance of pathobionts [34, 35]. This specific profile has significant diagnostic and prognostic potential and opens up prospects for developing non-invasive methods for detecting TB in cases that are difficult to diagnose, assessing the risk of drug resistance, and predicting disease progression. It is important to note that modern anti-tuberculosis chemotherapy may partly restore normal lung microbiota composition but simultaneously induces the selective growth of antibiotic-resistant strains among opportunistic pathogens [34, 40, 62].

In this regard, modulating the lung microbiota appears to be an extremely promising strategy in combating TB. The development of inhaled probiotics and methods for correcting pulmonary dysbiosis could become a new tool for improving treatment efficacy, especially in cases of drug-resistant TB, as well as for preventing the disease in at-risk populations, including children [50, 51, 60, 61].

Thus, an in-depth study of the microecology of the respiratory tract opens new horizons for phthisiology, heralding a transition to more personalized and effective approaches in the diagnosis, treatment, and prevention of one of the oldest and most socially significant infections in human history.

ADDITIONAL INFORMATION

Author contribution. I.A. Baranov — review concept, writing the final text of the article; N.V. Tivirikin — writing and editing the test, developing infographics; A.V. Derevyanko — editing the text, providing photo materials; D.P. Gladin, M.E. Lozovskaya — management, editing the text; E.S. Zubareva, N.S. Kozlova — writing and editing the text.

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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Gender characteristics of cognitive and emotional status, cerebral blood flow at different levels of academic stress

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Abstract. ***Introduction.*** A progressive trend in the field of healthcare and education is a personalized approach, which determines the urgency of searching for individual risk factors for the development of asthenic syndrome in young people in order to create an optimized educational trajectory and measures to prevent asthenic syndrome. ***The aim of the study.*** To evaluate the relationship between individual psychophysiological characteristics, variations in cerebral blood flow and risk factors for asthenic syndrome, taking into account gender, and to compare the effectiveness of options for preventing asthenic syndrome. ***Materials and methods.*** The study involved 147 students divided into two groups based on gender. The students were tested in three stages under different conditions of basic workload and stress levels through a specially designed and standardized online questionnaire. The assessment of the personal characteristics of cerebral circulation was carried out using the rheoencephalography technique. Cognitive training games and transcranial micropolarization were used for stimulation. ***Results.*** Men have more pronounced reserves of cognitive functions, they demonstrate a more stable state to the basic level of stress and intellectual load, however, with increasing psychocognitive load, they experience a marked increase in asthenia, which may indicate limited compensatory resources under prolonged exposure to stress factors. Women, on the contrary, have a higher predisposition to asthenic manifestations against the background of a basic level of stress, however, with an increase in the intensity of stress, they demonstrate better adaptation and less variability in their emotional state. ***Conclusions.*** The results of the study indicate that gender differences have an impact on psychophysiological characteristics under different intellectual and stress loads. The data obtained can be used to develop individual educational trajectories, while creating mobile applications to optimize daily routines in order to increase the effectiveness of the educational process and prevent the development of asthenic syndrome.

Keywords: asthenic syndrome, educational process, cognitive functions, compensatory abilities, young people

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Половые особенности когнитивного и эмоционального статуса, мозгового кровотока при разных уровнях академического стресса

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Резюме. ***Введение.*** Прогрессивной тенденцией в сфере здравоохранения и образования является персонифицированный подход, что обусловливает актуальность поиска индивидуальных факторов риска развития астенического синдрома у лиц молодого возраста с целью создания оптимизированной образовательной траектории и мероприятий по профилактике астенического синдрома. ***Цель исследования*** — оценить взаимосвязь индивидуальных психофизиологических особенностей, вариаций мозгового кровотока и факторов риска развития астенического синдрома с учетом половой принадлежности, сравнить эффективность вариантов профилактики астенического синдрома. ***Материалы и методы.*** В исследовании приняли участие 147 студентов, разделенных на две группы по половому признаку. Студенты прошли тестирование, проведенное в три этапа в разных условиях базовой нагрузки и уровня стресса посредством специально разработанного и стандартизированного онлайн-анкетирования. Личностные особенности мозгового кровообращения оценивали с помощью методики реоэнцефалографии. Для стимуляции использовали игры на тренировку когнитивных функций и транскраниальную микрополяризацию. ***Результаты.*** У мужчин отмечены более выраженные резервы когнитивных функций, они демонстрируют более устойчивое состояние к базовому уровню стресса и интеллектуальной нагрузки, однако при возрастании психокогнитивной нагрузки у них наблюдается выраженный рост показателей астении, что может указывать на ограниченные возможности компенсаторных ресурсов при длительном воздействии стресс-факторов. У женщин, напротив, отмечена более высокая предрасположенность к астеническим проявлениям на фоне базового уровня нагрузки, однако при увеличении интенсивности стрессового воздействия они демонстрируют лучшую адаптацию и меньшую вариабельность эмоционального состояния. ***Выводы.*** Результаты исследования свидетельствуют, что гендерные различия влияют на психофизиологические характеристики при различной интеллектуальной и стрессовой нагрузке. Полученные данные могут использоваться при разработке индивидуальных образовательных траекторий, создании мобильных приложений для оптимизации распорядка дня с целью повышения результативности образовательного процесса и профилактики развития астенического синдрома.

Ключевые слова: астенический синдром, образовательный процесс, когнитивные функции, компенсаторные возможности, лица молодого возраста

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

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INTRODUCTION

Recent years have seen a growing trend across all spheres of life to adopt a personalized approach. The aim is to tailor products and services as closely as possible to people's needs and capabilities [1–4]. Educational policy also emphasizes creating personalized learning paths for each student, taking into account their individual characteristics [2–4]. Knowledge of individual characteristics of cognitive status and emotional balance, as well as variations in cerebral blood flow, can contribute to creating a system of learning that is both highly effective and physiologically sound. This can significantly improve the effectiveness of educational processes and help prevent functional disorders in many organs and systems [1, 5].

One such disorder associated with prolonged or intense psychological and emotional stress is asthenic syndrome [6–8]. This is a borderline condition between health and illness, which clinically manifests as an energy deficit and an inability to maintain functional activity as before (a phenomenon of intolerance to habitual activities) [9–11].

Thus, identifying the interrelationship between risk factors for the asthenic syndrome, indicators of emotional balance, and cognitive status in young adults is relevant from the perspective of creating an individualized educational trajectory [12–14]. The use of an optimal method to address the aforementioned characteristics is equally important for enhancing learning progress in young individuals and preventing asthenic syndrome [15, 16].

AIM

To assess the relationship between individual psychophysiological indicators, cerebral blood flow characteristics, and risk factors for the development of asthenic syndrome, taking gender into account, as well as to compare the effectiveness of methods for preventing asthenia.тении.

MATERIALS AND METHODS

147 third-year students from the Medical Institute of N.P. Ogarev Moscow State University participated in the study; they were divided into two groups based on gender: Group 1 (n=111) consisted of women, and Group 2 (n=36) consisted of men. Both groups were similar in age. The mean age in Group 1 was 19.36±0.13 years, and in Group 2, 18.94±0.13 years. The study included generally healthy participants who reported no complaints. They subjectively considered themselves healthy, did not take medication on a regular basis, and had no chronic somatic diseases according to their medical records. Individuals who had suffered from acute respiratory viral infections within the past month were excluded from the study.

Students underwent testing conducted in three stages under different conditions of baseline workload and stress levels (Stage 1—mid-semester; Stage 2 — during exam period; and Stage 3 — before and after stimulation) using a specially developed and standardized online questionnaire. In the first stage, rheoencephalography (REG) with functional tests (REO-Spectrum, NeuroSoft LLC) was performed for all respondents; a repeat examination was conducted after stimulation in the third stage. The correction methods used included the "Neurostim" transcranial micropolarization stimulator (NeuroSoft LLC) and games designed to train memory and attention. Sixty students were selected for stimulation and divided into four groups based on the intervention method: Group 1 (n_1=15 participants)—dual stimulation (combined use of the transcranial micropolarization technique and neurostimulation games), Group 2 (n_2=15 participants)—control group; Group 3 (n_3=15 participants)—transcranial micropolarization in single mode; Group 4 (n_4=15 participants)—memory and attention training games in single mode.

The online tests "Number Memory" and "Image Memory" were used to determine the level of short-term memory. The "Proofreading Test" (letter version) was used to assess attention characteristics. Indicators of emotional balance were examined using the eight-factor Spielberger Personality Questionnaire. Features of higher nervous activity (HNA) were assessed using Y. Streliau's methodology. Indicators of asthenia were studied using the subjective asthenia assessment scale (MFI-20). Personality-related features of cerebral blood flow were assessed using the REG methodology (REO-spectrum, NeuroSoft LLC) with functional testing. The obtained data were analyzed by medical statistical methods (normality of distribution test, parametric t-test, nonparametric U-test, χ^2 — for assessing the distribution of relative values, r — correlation coefficient; descriptive statistics with the calculation of means and confidence intervals). Differences were considered statistically significant at a probability of a correct prediction of more than 95% ($p < 0.05$).

RESULTS

An analysis of the gender-specific characteristics of the higher nervous activity revealed a predominance of the "Strength of Excitation Processes" and "Mobility of Nervous Processes" in Group 2. The values of

these indicators at the first stage were 62.32±2.49 and 84.15±3.16 conventional units, respectively (p <0.05). During the second stage, which involved a period of intense physical exertion and stress, a predominance of these indicators was also observed in the group of men, with a slight decrease in both groups.

Assessment of short-term memory revealed the following patterns: in both the first and second stages, the indicator was higher in the first group (women) during the first stage, accounting for 85.99±1.41%, and 89.96±1.03% in the second stage. Dynamic changes during the exam period under intense intellectual load were characterized by a slight increase in this indicator in both groups. in Group 1, it amounted to 4.41%, and in Group 2, 4.69% (p <0.05).

The following patterns were identified when evaluating attention measures. The greatest increase during the second stage of the study, specifically during the exam period, was observed across all indicators in Group 2 (men), whereas during the first stage, these indicators were approximately the same in both groups.

Thus, the attention speed score during the first stage of the study in Group 1 (women) was 4.07±0.10 conventional units; in Group 2 (men) — 4.05±0.15 conventional units, and at the second stage — 4.94±0.61 and 10.15±3.75 CUs, respectively. This indicator increased by 17.61% in the women's group and by 60.10% in the men's group (p <0.05). The task accuracy index was calculated using three methods, and in all cases, its values in the first stage of the study were higher in the second group (men). They amounted to 0.73±0.02; 0.69±0.02; and 0.90±0.10 conventional units, respectively. Dynamic changes during the exam period compared to the baseline cognitive load period showed the greatest increase in indicators in the men's group, with minor changes in all three measurements in the women's group. Changes in the men's group were 21.27, 24.50, and 4.85%, respectively (p <0.05).

The assessment of the "Mental Work Capacity" and "Mental Productivity Coefficient" indicators revealed similar patterns. At the first stage, their values were higher in men, amounting to 2.66±0.18 and 875.02±54.44 conventional units, respectively. During the exam period, the maximum increase was also observed in this group (66.16 and 7.41%), whereas women showed the smallest increase (p < 0.05).

When assessing the indicators "Attention Concentration" and "Sustained Attention," the highest values were found in women — 67.36±1.57 and 146.63±18.05 conventional units, respectively. However, in the second stage of the study, a slight decrease in these indicators was observed in the group of women and a significant increase in the group of men (10.63 and 22.79%, respectively; p <0.05).

An analysis of the "Visual Memory Capacity" and "Information Processing Speed" measures demonstrated that during the first stage, under a baseline load, their values were approximately the same in both groups: Group 1 (women) — 724.15±13.76 and 2.2±0.05 conventional units; Group 2 (men) — 725.31±25.21 and 2.25±0.08 conventional units. During the second stage of the study, which took place during the exam period, Group 2 showed an increase in these indicators by 16.12 and 48.04%, while Group 1 showed a slight decrease (p <0.05). The dynamics of some indicators are shown in Fig. 1.

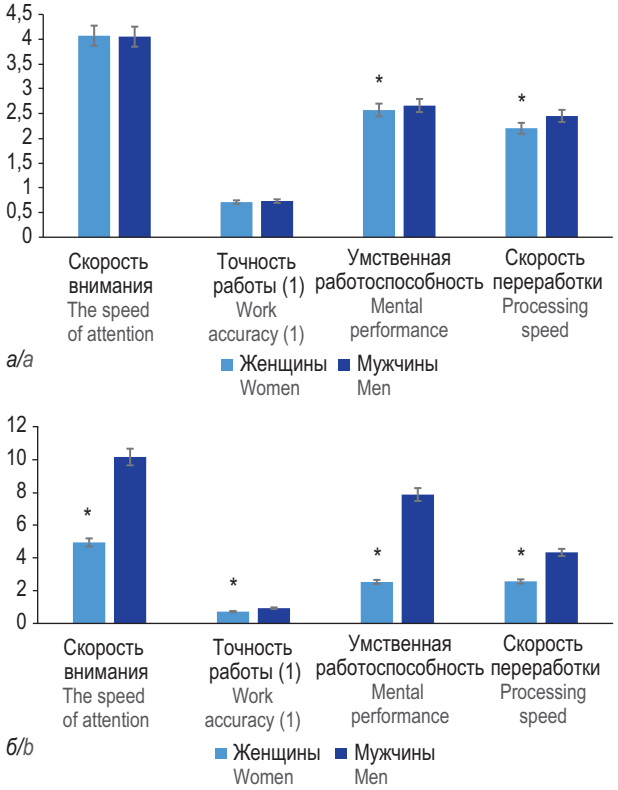


Fig. 1. **Sexual characteristics and dynamic changes in some indicators of attention in young people: a — attention indicators at the 1st stage of the study; b — attention indicators at the 2nd stage of the study. * — reliability of intergroup differences at p <0.05; 1 — determination of the indicator according to the first calculation option (figure by the authors of this article)**

Рис. 1. Половые особенности и динамические изменения некоторых показателей внимания у лиц молодого возраста: а — показатели внимания на 1-м этапе исследования; б — показатели внимания на 2-м этапе исследования. * — достоверность межгрупповых отличий при p <0,05; 1 — определение показателя по первому варианту расчета (рисунок авторов данной статьи)

Thus, a study of gender differences in cognitive functions and the effects of various levels of intellectual load revealed that short-term memory scores were higher among women, while attention scores were higher among men. Maximum dynamic changes in these indicators under the influence of intense cognitive loads were observed in the group of men, indicating a greater reserve of their cognitive capacity [17].

The study of asthenia indicators revealed the following patterns. At the first stage of the study, under a baseline level of psychoemotional stress, the maximum values for all indicators under study were observed in the group of women: "General Asthenia" — 12.93±0.76 conventional units, "Physical Asthenia" — 10.83±0.65 CUs, "Psychological Asthenia" — 11.06±0.78 CUs, "Reduced Activity" — 12.73±0.90 CUs, and "Decreased Motivation" — 10.34±0.75 CUs ($p < 0.05$). However, during the second stage of the study, which took place during the exam period under the influence of intense stress, the greatest increase in these scores was observed in men: "General Asthenia" — 22.32%, "Physical Asthenia" — 19.17%, "Mental Asthenia" — 39.58%, "Reduced Activity" — 37.75%, and "Decreased Motivation" — 30.25%. The dynamics and relationship between gender and asthenia indicators are presented in Fig. 2.

Consequently, the greatest influence of intellectual workload and stress factors on asthenia indicators was observed in men, despite initially higher values in women, indicating that men adapt to stressors less effectively [18].

When studying the influence of psychological and cognitive load and gender on students' emotional balance, the following patterns were identified regarding indicators of reactive states . In the first stage, the "Interest" indicator was highest in men, reaching 24.79±0.88 units, whereas the "Aggression," "Anxiety," and "Depression" indicators were highest in women, amounting to 11.84±0.35; 17.32±0.58 and 14.01±0.47 CUs, respectively ($p < 0.05$). During the second stage of the study, influenced by stress, an increase in the "Aggression," "Anxiety," and "Depression" scores was observed in both groups. Women's scores increased by 7.94, 14.04, and 6.23%, respectively, while men's scores increased by 2.92%, 10.72, and 11.40%, respectively. The "Interest" score increased by 7.15% in men and decreased slightly in women during the second stage ($p < 0.05$).

With regard to personality characteristics of emotional balance, such as "Curiosity," "Aggressiveness," "Anxiety," and "Depression," no statistically significant

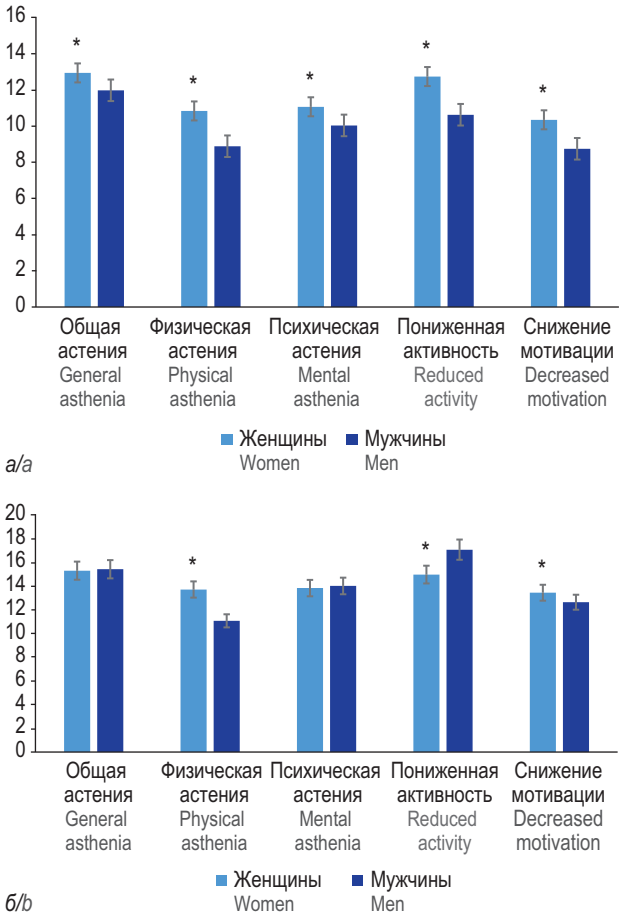


Fig. 2. **Sexual characteristics and dynamic changes in asthenia indicators in young people: a — indicators of asthenia at the 1st stage of the study; b — indicators of asthenia at the 2nd stage of the study.* — reliability of intergroup differences at $p < 0.05$ (figure by the authors of this article)**

Рис. 2. Половые особенности и динамические изменения показателей астении у лиц молодого возраста: а — показатели астении на 1-м этапе исследования; б — показатели астении на 2-м этапе исследования. * — достоверность межгрупповых отличий при $p < 0,05$ (рисунок авторов данной статьи)

changes were observed under stress. The increase during the exam period was less than 1% for all indicators in both groups.

Thus, the greatest impact on emotional balance, stress levels, and cognitive load was observed in women, while their personality traits remained virtually unchanged under the influence of these factors [19].

In the third stage, 60 participants were divided into groups based on the stimulation method. Changes in cognitive functions were characterized by the following features. The greatest increase in the short-term memory score was observed in the first (dual

stimulation) and fourth (neurostimulation games) groups, it amounted to 10.07 and 11.11%, respectively. The minimum increase was observed in the second group (control), amounting to 3.53% . There were no statistically significant differences in attention indicators between the groups using stimulation. However, a slight decrease was observed in the control group. For example, the “Attention Concentration” measure decreased by 16.04%, the “Visual Memory Capacity” measure by 12.17%, and the “Information Processing Speed” by 7.02% ($p < 0.05$).

When investigating the effect of various stimulation options on students’ emotional balance, no statistically significant differences were found between the stimulation options and their impact on reactive states and personality characteristics. Changes identical to the dynamics of emotional balance were observed with regard to indicators of asthenia.

When conducting REG at Stage 1 under a baseline level of psychological and cognitive load, no statistically significant correlation was found with indicators of cognitive functions and emotional balance. The effect of gender was determined for the “Venous Outflow Index” indicator, since its value was lower in men than in women,. Moreover, this difference increased during functional tests: the mean value of indicators for all leads during resting recordings was 0.61±0.03 CUs in men and 0.67±0.01 CUs in women . When recording REG during head rotation to the left he mean value of indicators was 0.58±0.02 and 0.64±0.01 CUs, respectively; during head rotation to the right — 0.61±0.02 and 0.64±0.01 CUs, respectively; during the orthostatic test — 0.57±0.03 and 0.62±0.03 CUs, respectively ($p < 0.05$). The data are presented in Fig. 3.

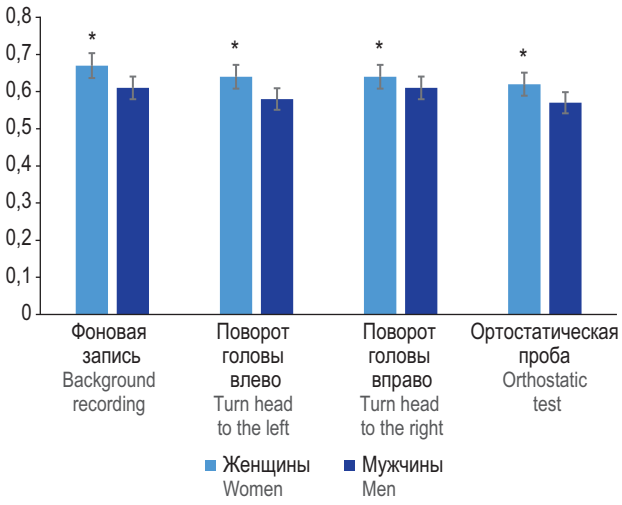


Fig. 3. **Sexual characteristics of cerebral blood flow (Venous outflow index) at 1st stage. * — reliability of intergroup differences at $p < 0.05$ (figure by the authors of this article)**

Рис. 3. Половые особенности показателей мозгового кровотока (индекс венозного оттока) на 1-м этапе. * — достоверность межгрупповых отличий при $p < 0,05$ (рисунок авторов данной статьи)

A repeat REG recording during the third stage of the study, following stimulation, also demonstrated the absence of a statistically significant correlation with indicators of cognitive function, emotional balance, and the type of stimulation used. During this stage, all groups showed a slight increase in large and medium vessel tone and a minor increase in the “Venous Outflow Index” [20].

DISCUSSION

This study revealed the following patterns. Men exhibited more pronounced cognitive reserves, as evidenced by the greatest increase in short-term memory and attention scores during the phase of intense intellectual exertion. At the same time, men demonstrate greater resilience to baseline levels of stress and cognitive load, indicating greater stability of adaptive mechanisms under standard conditions. However, as psychocognitive load increases, they exhibit a marked rise in asthenia indicators, which may indicate limited compensatory resources under prolonged exposure to stressors. In addition, men typically exhibit lower values of the rheoencephalographic parameter “venous outflow index” in all leads, both at rest and during functional tests, reflecting characteristics of cerebral blood flow that may influence the dynamics of cognitive processes.

By contrast, women show a higher predisposition to asthenic manifestations under baseline stress levels; however, as the intensity of the stressor increases, they demonstrate better adaptation and less variability in their emotional state. The greatest influence of emotional stress is manifested in changes in reactive states while personality characteristics remain stable. These data indicate greater flexibility and adaptability of emotional-cognitive mechanisms in women when activity conditions change.

CONCLUSIONS

1. The study of short-term memory, attention, and emotional balance revealed greater cognitive reserves and less lability in reactive states among men.

2. Gender features of cognitive status and emotional balance in young adults are associated with adaptive characteristics under varying degrees of intellectual and stress load. Greater adaptation to increased stress levels was observed in women, and more adequate adaptation to baseline stress was observed in men.

3. Individual differences in cerebral blood flow had no discernible effect on cognitive functions, emotional balance, or indicators of asthenia.

4. Compared to other neurostimulation methods, dual stimulation and monocorrection using games had the greatest effect on cognitive functions.

Thus, the obtained data can serve as a basis for further research aimed at optimizing approaches to maintain cognitive and emotional health. These approaches should take gender-specific characteristics into account. They should also guide individual educational pathways tailored to students' gender characteristics and the development of mobile applications to optimize daily routines for efficient time management, improving the effectiveness of learning, and preventing the development of asthenic syndrome and other functional disorders [21–23]

ADDITIONAL INFORMATION

Author contribution. L.A. Avtaykina — development of the study concept, writing the original text; A.V. Budanova — collection of data, participation in the analysis and writing of the text; D.D. Boriskin — conducting the experimental study; D.V. Puzakova — performing the statistical analysis; E.V. Arsentyeva — scientific and technical editing; T.I. Vlasova — development of the study model, evaluation of intermediate and final results.

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

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Л.А. Автайкина — разработка концепции исследования, написание исходного текста; А.В. Буданова — сбор материала, участие в осуществлении анализа и написания текста; Д.Д. Борискин — проведение экспериментального исследования; Д.В. Пузакова — выполнение статистического анализа; Е.В. Арсентьева — научное и техническое редактирование; Т.И. Власова — построение модели исследования, оценка промежуточных и окончательных результатов.

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

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

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

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Laser Doppler flowmetry for studying tissue blood flow in a model of carrageenan-induced edema in mice

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Abstract. ***Introduction.*** Carrageenan-induced edema is the most common *in vivo* model for evaluating the therapeutic efficacy of anti-inflammatory drugs. The pathogenesis of carrageenan-induced edema is based on acute exudative inflammation, in which microcirculation disorders play an important role. The study of the pathogenesis of microcirculation is of great interest, both diagnostic and prognostic, in assessing the functional status of the organism. One of the promising and successfully applied diagnostic methods for studying tissue blood flow is laser Doppler flowmetry, which makes it possible to assess changes in microcirculatory processes. ***The aim*** is to evaluate tissue blood flow in mice using the laser Doppler flowmetry method in comparison with plethysmometry parameters in the carrageenan-induced edema model to study the efficacy and pharmacodynamics of biomedical cellular products and pharmaceutical substances in preclinical practice. ***Materials and methods.*** 40 mice (20 males and 20 females) of the BALB/c line aged 8–10 weeks were used in the study. During the experiment, carrageenan-induced edema was modeled, laser Doppler flowmetry and plethysmometry were performed in the area of the left hind limb of the experimental animal. According to the results of the conducted research, the following tasks were performed: 1) assessment of tissue perfusion in mice in the area of plantar aponeurosis in dynamics; 2) plethysmometry in dynamics (assessment of the severity of edema in animals by changes in the volume of the animal's paw); 3) comparison of plethysmometry and laser Doppler flowmetry. It was found that the degree of blood flow restoration and the severity of edema correlate with each other (the correlation coefficient is 96%). ***Conclusions.*** The use of laser Doppler flowmetry in the carrageenan-induced edema model in mice makes it possible to assess the state of microcirculation *in vivo* and dynamically. The method is characterized by accuracy and high sensitivity, which makes it possible to determine changes in blood microcirculation in the early stages, including before the "visual" manifestation of edema. At the same time, there is a high correlation between the data obtained using laser Doppler flowmetry and plethysmometer. In the future, this method can be widely used in preclinical practice to evaluate the therapeutic efficacy and pharmacodynamics of drugs under development that affect regional blood circulation and microcirculation.

Keywords: carrageenan-induced edema, laser Doppler flowmetry, LDF, biological test system

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Применение лазерной допплеровской флоуметрии для исследования тканевого кровотока на модели каррагинан-индуцированного отека у мышей

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Резюме*. Введение.* Каррагинан-индуцированный отек — наиболее распространенная модель *in vivo* для оценки терапевтической эффективности противовоспалительных лекарственных препаратов. В основе патогенеза каррагинан-индуцированного отека лежит острое экссудативное воспаление, в котором важную роль играет нарушение микроциркуляции. Изучение патогенеза микроциркуляции представляет большой интерес, как диагностический, так и прогностический, при оценке функционального статуса организма. Одним из перспективных и успешно применяемых диагностических методов исследования тканевого кровотока является лазерная допплеровская флоуметрия, которая позволяет оценить изменения микроциркуляторных процессов. ***Цель*** — провести оценку тканевого кровотока в динамике у мышей методом лазерной допплеровской флоуметрии в сопоставлении с показателями плетизмометрии в модели каррагинан-индуцированного отека для изучения эффективности и фармакодинамики биомедицинских клеточных продуктов и фармацевтических субстанций в доклинической практике. ***Материалы и методы.*** В работе использовали 40 мышей (20 самцов и 20 самок) линии BALB/c в возрасте 8–10 недель. В процессе эксперимента моделировали каррагинан-индуцированный отек, проводили лазерную допплеровскую флоуметрию и плетизмометрию в области левой задней конечности экспериментального животного. По результатам исследования выполнены: 1) оценка тканевой перфузии у мышей в области подошвенного апоневроза в динамике; 2) плетизмометрия в динамике (оценка степени выраженности отека у животных по изменению объема лапы животного); 3) сопоставление показателей плетизмометрии и лазерной допплеровской флоуметрии. Установлено, что степень восстановления кровотока и выраженность отека коррелируют между собой (коэффициент корреляции составляет 96%). ***Выводы.*** Лазерная допплеровская флоуметрия в модели каррагинан-индуцированого отека у мышей позволяет прижизненно и в динамике оценить состояние микроциркуляции. Метод отличается точностью и высокой чувствительностью, с его помощью можно определить изменения микроциркуляции кровотока на ранних этапах, до «визуального» проявления отека. Наблюдается высокая корреляция между данными, полученными при использовании лазерной допплеровской флоуметрии и плетизмометра. В перспективе данный метод может быть широко применен в доклинической практике для оценки терапевтической эффективности и фармакодинамики разрабатываемых препаратов, влияющих на регионарное кровообращение и микроциркуляцию.

Ключевые слова: каррагинан-индуцированный отек, лазерная допплеровская флоуметрия, ЛДФ, биологическая тест-система

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INTRODUCTION

The microcirculatory bed is a trophic component of bloodstream circulation. It indirectly reflects tissue viability, as well as an ability to regenerate, perform immune functions, and carry out many other physiological functions that are essential for healthy tissues. Impaired tissue perfusion indicates more than just damage to a specific organ or tissue. It often results from systemic processes that lead to serious consequences. Understanding how microcirculation is affected by inflammation is important in preclinical research for evaluating the therapeutic efficacy of anti-inflammatory drugs [1–5].

One of the most common models of in vivo inflammation is carrageenan-induced edema. The pathogenesis of carrageenan-induced edema is characterized by acute exudative inflammation. Microcirculation disorders, accompanied by exudation and cell emigration, are considered one of its key components. Laser Doppler flowmetry (LDF) serves as a concise method for diagnosing microcirculatory disorders and has been attracting sustained interest from researchers worldwide for more than a decade [5, 6].

This method has been successfully used to study tissue microcirculation in humans; however, it is not currently widely applied in animals [2, 4, 7, 8].

Thus, LDF remains a promising area of research in preclinical practice.

AIM

The aim of the research was to evaluate dynamic tissue blood flow in mice using LDF in comparison with plethysmography parameters in a carrageenan-induced edema model. Thus, the study aimed to investigate the efficacy and pharmacodynamics of biomedical cell products and pharmaceutical substances in preclinical practice.

MATERIALS AND METHODS

Animals. The experiment involved 40 BALB/c mice (20 males and 20 females) aged 8–10 weeks, SPF-grade, obtained from the “Laboratory Animal Breeding Facility” of the Branch of the M.M. Shemyakin and Yu.A. Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences, Pushchino town. Animal housing, care, and experimental procedures were conducted in accordance with international European bioethical standards, Russian ethical standards for the housing and handling of laboratory animals, and the norms and rules specified in the “Animal Use Policy of JSC ‘GENERIUM’.”

Study design. Two groups of animals were established: Group 1 (n=20: 10 females and 10 males) was used to model carrageenan-induced edema; Group 2 (n=20: 10 females and 10 males) was used to model carrageenan-induced edema + intramuscular administration of diclofenac, 25 mg/mL (Hemofarm, Serbia), administered as a single dose one minute after the induction of carrageenan-induced edema, at a dose of 3 mg/kg.

The experiment consisted of three stages: *Stage I* — induction of carrageenan-induced edema; *Stage II* — LDF; *Stage III* — assessment of the severity of edema in animals by plethysmography based on changes in paw volume.

Stage I. Modelling carrageenan-induced edema

When modeling carrageenan-induced edema, a 1% carrageenan solution (λ Carrageenan plant mycopolysaccharide (SIGMA-ALORICH/LOT:1408463V)) was administered subplantarly once into the animal’s left hind limb beneath the plantar aponeurosis in a volume of 25 μL (Fig. 1, a). The 1% carrageenan solution was prepared according to the method described by E. Phyllis et al. [9].



а/a *б/b*

Fig. 1. **Modeling of carrageenan-induced edema and assessment of microcirculation by laser Doppler flowmetry method: *a* — administration of 1% carrageenan solution (3 and 4 — plantar tubercules); *b* — laser Doppler flowmetry (photo by the authors)**

Рис. 1. Моделирование каррагинан-индуцированного отека и оценка микроциркуляции методом лазерной допплеровской флоуметрии: *а* — введение 1% раствора каррагинана (1 и 4 — подошвенные бугорки); *б* — лазерная допплеровская флоуметрия (фото авторов)

Stage II. Laser Doppler Flowmetry

Tissue perfusion was measured on the animal's left hind limb in the region of the plantar aponeurosis [10].

LDF was performed using a TSD145 laser Doppler sensor (BIOPAC Systems Inc., USA) and AcqKnowledge® 4 software.

For each time point, measurements were taken three times within one minute for each animal, and the average value of three measurements was recorded (Fig. 1, b).

Layout of the laser Doppler flowmetry recording setup

1. "0" time point — before administration of the 1% carrageenan solution.

2. "5 minutes," "10 minutes," "15 minutes," "30 minutes," "1 h," and "3 h" time points - 5, 10, 15, and 30 minutes, 1 hour, and 3 hours after administration of the 1% carrageenan solution.

The "0" measurement was performed on the hind limbs of animals in all experimental groups. No statistically significant differences were found between the left and right hind limbs. Subsequent LDF recordings were performed on the left hind limb. When analyzing the LDF trace, capillary blood flow was calculated to characterize the integrity of microcirculation at all time points of tissue perfusion recording relative to the baseline ("0" point).

Stage III. Assessment of edema severity in animals using a plethysmograph based on changes in paw volume

The severity of edema in animals was assessed using a plethysmograph (Ugo Basile Biological Research Apparatus, Italy) based on changes in the volume of the animal's left hind limb, according to the method described by C.J. Marris [11].

The paw volume was measured three times at each time point for each animal, and the average of the three measurements was calculated.

Scheme for assessing the severity of edema

1. "0" time point — before administration of the 1% carrageenan solution.

2. "1 h" and "3 h" time points — 1 and 3 hours after administration of the 1% carrageenan solution.

Limb volume at the "0" time point was assessed in the hind limbs of animals in all experimental groups. No statistically significant differences were found between the left and right hind limbs. Subsequent volume assessments were performed on the left hind limb.

After measuring limb volume, the edema index (EI) was calculated using the formula:

$$EI = 100 \cdot (V_t - V_0) / V_0,$$

where V_0, mL — paw volume before administration of *the* 1% carrageenan solution; V_T, mL — the volume of the paw 1 hour and 3 hours after the administration of a 1% carrageenan solution.

Statistical analysis of the results. The data obtained were tested for normality of distribution. Statistical analysis included calculation of the mean and standard deviation. To compare the values, the parametric test (Student's t-test) was used, since the sample corresponded to a normal distribution. Differences were considered statistically significant at $p < 0.05$. Statistical analysis of the data was performed using the IBM SPSS Statistics software package (version 23, IBM Corp., USA).

RESULTS AND DISCUSSION

The results of tissue perfusion in the plantar aponeurosis region of mice in a carrageenan-induced edema model, showed a statistically significant decrease in microcirculation at all measurement time points after the administration of a 1% carrageenan solution relative to the "0" time point in all animal groups. After carrageenan injection, all animal groups showed a 10–12% preservation of microcirculation by the 5th minute, which is typical for the stage of transient vasospasm. By the 10th minute, a marked increase in capillary blood flow (arterial hyperemia) was recorded in mice, with microcirculation preserved at 56% relative to the "0" point. At the 15th minute, a state of venous hyperemia was observed, with microcirculation preserved at 30% of baseline. When modeling carrageenan-induced edema based on LDF parameters at the "5 minutes," "10 minutes," and "15 minutes" time points, no statistically significant differences were detected within the experimental groups. At the "30 minutes," "1 h," and "3 h," when microcirculation parameters were recorded, a statistically significant improvement in blood flow was observed in animals in the second experimental group compared to the first group. At the "30-minute" time point, blood flow was preserved at 25% in the first group and at 36% in the second group. At the "1 h" and "3 h" time points, the level of microcirculation in the first group was 20% and 15%, respectively, and in the second group, 45% and 55%, respectively (Fig. 2).

According to plethysmography data, 1st group demonstarted increased edema in the experimental limb at 1–3 h time point which ammounted to 46–51% compared to "0" baseline. The peak swelling was observed at 3 h (51%). The degree of edema in Group 2 at 1–3 hours was 36–25% of the normal value (the peak degree of edema was recorded at 1 hour — 36%) (Fig. 3).

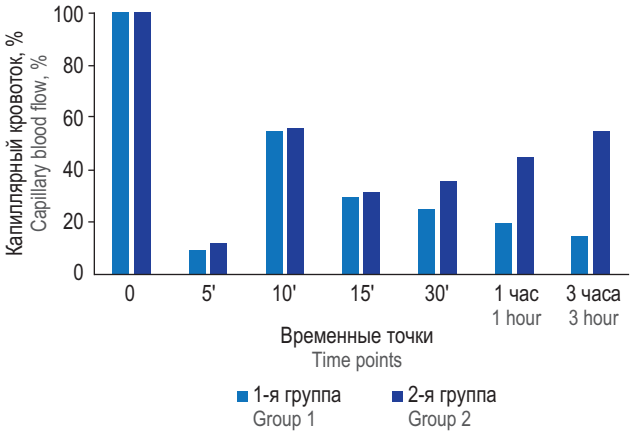


Fig. 2. **Dynamics of changes in capillary blood flow (according to laser Doppler flowmetry data), %. Group 1 — 1% carrageenan solution; Group 2 — 1% solution of carrageenan + Diclofenac, 3 mg/kg (figure by the authors of this article)**

Рис. 2. Динамика изменения капиллярного кровотока (по данным лазерной допплеровской флоуметрии), %. 1-я группа — 1% раствор каррагинана; 2-я группа — 1% раствор каррагинана + диклофенак в дозе 3 мг/кг (рисунок авторов данной статьи)

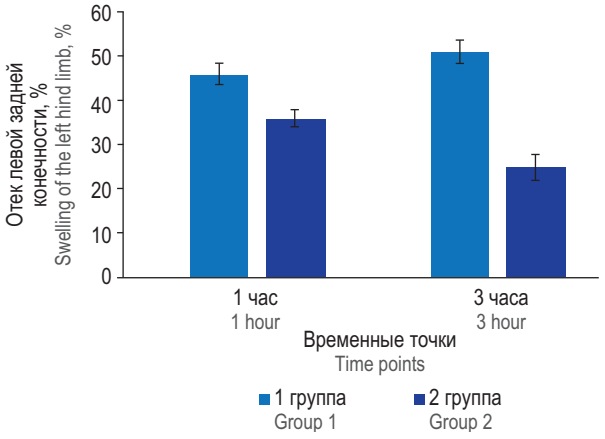


Fig. 3. **The severity of edema of the left hind limb (by volume; according to plethysmography), %. Group 1 — 1% carrageenan solution; Group 2 — 1% solution of carrageenan + Diclofenac, 3 mg/kg (figure by the authors of this article)**

Рис. 3. Степень выраженности отека левой задней конечности (по объему; по данным плетизмографии), %. 1-я группа — 1% раствор каррагинана; 2-я группа — 1% раствор каррагинана + диклофенак в дозе 3 мг/кг (рисунок авторов данной статьи)

Correlation analysis revealed that the degree of blood flow recovery and the severity of edema correlate with each other (correlation coefficient — 96%).

According to published research on carrageenan-induced edema, maximum paw edema in mice following carrageenan induction was observed after 3–5 hours and amounted to 41% of the initial paw volume, as measured by the plethysmographic method [9]. The plethysmography method is widely used and is highly accurate. However, it does not allow to assess microcirculation in this model, although this is the primary criterion for evaluating the anti-inflammatory properties of drugs in a number of studies. In addition to plethysmography, the severity of edema is assessed using the paw amputation method. However, this method yields data from a single animal at only one point, and it is technically difficult to apply to mice [12]. Currently, according to the literature, the most promising diagnostic approach for determining tissue inflammation in experimental models such as cutaneous neurogenic inflammation [6, 7, 13] and psoriatic arthritis [12] is the assessment of microcirculation. This method is based on measuring microcirculation in rats in the plantar aponeurosis region using LDF. This method allows not only for identifying individual variability in microcirculation but also for investigating the mechanisms of its regulation [4, 13].

Thus, assessing microcirculation using LDF in a carrageenan-induced edema model in mice to determine the degree of inflammation over time is a highly promising method. When compared with the plethysmography, LDF allows for in vivo and dynamic assessment of microcirculation status. It also provides a preliminary indication of the effectiveness of initiating therapy with anti-inflammatory drugs under development. At the same time, a high level of correlation is observed between the data obtained using LDF and a plethysmograph (the primary method for assessing the severity of edema in biological test systems).

CONCLUSION

Thus, based on results obtained in a mice model of carrageenan-induced edema, dynamic assessments of tissue blood flow were performed using the LDF method, and the resulting data were compared with plethysmography measurements.

It was established that LDF:

1) enables the assessment of microcirculatory status at different stages of carrageenan-induced edema with a high correlation between data sets;
2) is characterized by high accuracy and sensitivity, which allows to determine changes in microcirculatory blood flow at early stages, before the “visual” manifestation of edema.

Based on the above, this method can be used in preclinical practice to evaluate the therapeutic effects of drugs under development that affect regional blood

circulation and microcirculation, as well as to facilitate early diagnosis.

ADDITIONAL INFORMATION

Author contribution. E.V. Belyanina — development of the research concept, conducting the experimental study, analysis of the obtained results, writing the original text of the article; A.A. Ovsepyan — consultation on the research concept, scientific editing of the article; M.S. Aksenova — statistical processing of the results; Yu.V. Ishkova, Yu.S. Arilina, V.N. Garanova — assistance in conducting the experimental study; N.V. Belskaya — scientific and technical editing of the article; M.V. Lykov — consultation on the research concept, scientific and technical editing of the article.

All authors read and approved the final version before publication.

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

Experiments with animals were carried out in accordance with international rules (Directive 2010/63/EU of the European Parliament and of the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes).

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Effect of hypo- and hyperthyroidism on kidney morphology in experimental prostate hyperplasia in rats

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Abstract. ***Introduction.*** The influence of thyroid status on the morphogenesis of obstructive nephropathy, which develops against the background of benign prostatic hyperplasia, remains unexplored, despite the presence of contradictory clinical data on the relationship of hypo- and hyperthyroidism with the risk of developing benign prostatic hyperplasia. There are no experimental studies on this issue. ***The aim*** — to evaluate the effect of experimental hypo- and hyperthyroidism on the morphological characteristics of the kidneys in conditions of testosterone-induced benign prostatic hyperplasia and concomitant obstructive uropathy in rats. ***Materials and methods.*** Benign prostatic hyperplasia was modeled on 32 male Wistar rats using daily injections of testosterone propionate (5 mg/kg). The animals were divided into 4 groups (n=8): intact control, “pure” benign prostatic hyperplasia, benign prostatic hyperplasia + hyperthyroidism (L-thyroxine, 10 mcg/100 g/day) and benign prostatic hyperplasia + hypothyroidism (propylthiouracil, 0.05% with drinking water). On day 36, macro- and micromorphometry of the kidneys was performed using light microscopy, hematoxylin and eosin staining, and digital image analysis (ImageJ). The mass of the organ, the thickness of the cortical substance, the area of the glomeruli, the diameter of the lumen of the proximal and distal tubules, the density of capillaries were evaluated, and a semi-quantitative assessment of hydronephrosis (0–4 points) and inflammatory infiltrate (0–3 points) was performed. The thyroid status was confirmed by measuring the levels of thyroxine and thyroid-stimulation hormone using the ELISA method. ***Results.*** Hyperthyroidism on the background of benign prostatic hyperplasia led to the maximum severity of obstructive changes: the relative mass of the kidneys increased by 38.1% compared to the control ($p < 0.05$), the mass of residual urine exceeded the control value by 10.25 times ($p < 0.05$), and the thickness of the cortical substance decreased by 36.7% (to 0.95±0.12 mm, $p<0.05$). Micromorphometry revealed pronounced dilation of the distal tubules (diameter 48.2±5.9 microns versus 21.0±2.8 microns in the control, $p < 0.001$), an increase in glomerular area by 15% ($p<0.05$), an increase in capillary density by 50% ($p < 0.05$), as well as the development of grade 3 hydronephrosis and moderate inflammation (2 points). In the “benign prostatic hyperplasia + hypothyroidism” group, all parameters were much closer to the control: tubule dilation was minimal (25.3±3.2 microns), cortical thickness was preserved (1.40±0.17 mm), inflammatory infiltrate was absent, and hydronephrosis was estimated at 1 point. ***Conclusion.*** experimental hyperthyroidism potentiates structural kidney damage in obstructive uropathy, while hypothyroidism, on the contrary, exhibits a pronounced protective effect.

Keywords: kidney, obstructive nephropathy, hypothyroidism, hyperthyroidism, benign prostatic hyperplasia, rats

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Влияние гипо- и гипертиреоза на морфологию почек при экспериментальной гиперплазии предстательной железы у крыс

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Резюме. ***Введение.*** Влияние тиреоидного статуса на морфогенез обструктивной нефропатии, развивающейся на фоне доброкачественной гиперплазии предстательной железы, остается неизученным, несмотря на наличие противоречивых клинических данных о взаимосвязи гипо- и гипертиреоза с риском развития гиперплазии предстательной железы. Экспериментальные исследования, посвященные этому вопросу, отсутствуют. ***Цель*** — оценить влияние экспериментального гипо- и гипертиреоза на морфологические характеристики почек в условиях тестостерон-индуцированной гиперплазии предстательной железы и сопутствующей обструктивной уропатии у крыс. ***Материалы и методы.*** На 32 самцах крыс линии Wistar смоделирована гиперплазия предстательной железы с помощью ежедневных инъекций тестостерона пропионата (5 мг/кг). Животные были разделены на четыре группы (n=8): интактный контроль, «чистая» гиперплазия предстательной железы, гиперплазия предстательной железы + гипертиреоз (L-тироксин, 10 мкг/100 г/сут) и гиперплазия предстательной железы + гипотиреоз (пропилтиоурацил, 0,05% с питьевой водой). На 36-е сутки проведена макро- и микроморфометрия почек с использованием световой микроскопии, окрашивания гематоксилином и эозином и цифрового анализа изображений (ImageJ). Оценивали массу органа, толщину коркового вещества, площадь клубочков, диаметр просвета проксимальных и дистальных канальцев, плотность капилляров, а также выполняли полуколичественную оценку гидронефроза (0–4 балла) и воспалительного инфильтрата (0–3 балла). Тиреоидный статус подтвержден измерением уровня тироксина и тиреотропного гормона методом иммуноферментного анализа. ***Результаты.*** Гипертиреоз на фоне гиперплазии предстательной железы привел к максимальной выраженности обструктивных изменений: относительная масса почек увеличилась на 38,1% в сравнении с контролем ($p < 0,05$), масса остаточной мочи превысила контрольный показатель в 10,25 раза ($p < 0,05$), а толщина коркового вещества уменьшилась на 36,7% (до 0,95±0,12 мм, $p < 0,05$). Микроморфометрия позволила выявить выраженную дилатацию дистальных канальцев (диаметр 48,2±5,9 мкм против 21,0±2,8 мкм в контроле, $p < 0,001$), увеличение площади клубочков на 15% ($p < 0,05$), повышение плотности капилляров на 50% ($p < 0,05$), а также гидронефроз III степени и умеренное воспаление (2 балла). В группе «гиперплазия предстательной железы + гипотиреоз» все параметры были значительно ближе к контролю: дилатация канальцев была минимальной (25,3±3,2 мкм), толщина коры сохранена (1,40±0,17 мм), воспалительный инфильтрат отсутствовал, а гидронефроз оценивался в 1 балл. ***Заключение.*** Экспериментальный гипертиреоз потенцирует структурное повреждение почек при обструктивной уропатии, а гипотиреоз, напротив, проявляет выраженный протективный эффект.

Ключевые слова: почка, обструктивная нефропатия, гипотиреоз, гипертиреоз, доброкачественная гиперплазия предстательной железы, крысы

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a morphologically heterogeneous condition leading to lower urinary tract obstruction and secondary obstructive nephropathy [1, 2]. In addition to the key role of androgens, systemic hormonal and metabolic disorders, including thyroid dysfunction, are attracting increasing attention as a contributing factor to BPH and its complications [3–5]. Recent epidemiological studies demonstrate a close association between thyroid dysfunction and renal pathology. For example, a large population-based NHANES study (2007–2012) identified a U-shaped relationship between levels of free triiodothyronine (T3), thyroxine (T4), and chronic kidney disease. Both hypothyroidism and hyperthyroidism are associated with an increased risk of developing and progressing renal dysfunction [5]. These findings are particularly relevant for patients with benign prostatic hyperplasia (BPH), since obstructive uropathy may exacerbate renal complications, and thyroid status may act as a critical modifier of pathogenesis.

AIM

The aim of this study was to evaluate how experimental hypothyroidism and hyperthyroidism affect renal morphological characteristics in a model of testosterone-induced prostatic hyperplasia and concomitant obstructive uropathy in rats.

MATERIALS AND METHODS

The experiment was conducted on 32 sexually mature male Wistar rats (weighing 220–250 g). The animals were housed under standard vivarium conditions at a temperature of 22±2 °C, relative humidity of 50–60%, and a 12-hour light cycle (from 8:00 a.m. to 8:00 p.m.) . All procedures complied with the principles of European Convention for the Protection of Vertebrate Animals (Strasbourg, 1986) and were approved by the local ethics committee.

Overall, the study lasted 35 days. All animals, except for intact controls, underwent total bilateral orchiectomy under thiopental sodium anesthesia (40 mg/kg) to induce androgen deprivation. Seven days after surgery, the animals began receiving testosterone propionate (5 mg/kg) to induce prostatic hyperplasia and model obstructive uropathy [1].

Group 1 (intact control): sham surgery + subcutaneous administration of olive oil (0.1 mL/100 g body weight) from day 7 through day 35. Group 2 (hyperplasia model, BPH): daily subcutaneous injections of testosterone propionate (5 mg/kg) in olive oil from day 7 to day 35. Group 3 (BPH + hyperthyroidism): 7 days prior to orchiectomy and continuously thereafter — L-thyroxine (dry substance, Belmedpreparaty State Unitary Enterprise, Republic of Belarus) at a dose of 100±10 μg per 100 g of body weight once daily + testosterone propionate according to the regimen for Group 2. Group 4 (Castration + Hypothyroidism): 7 days prior to orchiectomy and continuously thereafter — propylthiouracil (dry substance, Merck Selbstmedikation GmbH, Germany) at a dose of 2.0±0.15 mg per 100 g of body weight once daily, administered intragastrically via an atraumatic polyurethane tube + testosterone propionate according to the Group 2 regimen.

To ensure biochemical verification that the model corresponded to the planned endocrine status, blood was collected from the retroorbital sinus 24 hours prior to euthanasia in 4 randomly selected rats from each group under light ether anesthesia. Serum was obtained by centrifugation at 3,000 rpm for 15 minutes. Concentrations of free thyroxine (T4) and thyroid-stimulating hormone (TSH) were determined by solid-phase enzyme-linked immunosorbent assay (ELISA) using commercial kits manufactured by NVO Immunotech CJSC for the detection of T_4 (Immuno-FA-free T_4) and TSH (ImmunoFA-TSH).

On day 36, the animals were euthanized with an overdose of sodium thiopental (100 mg/kg, intraperitoneally). A total laparotomy was performed, and the kidneys were removed. The organs were weighed on analytical balances accurate to 0.1 mg, the thickness of the cortical substance (mm) was measured, and the organs were fixed in 10% neutral buffered formalin (pH 7.4) for 24 hours. After standard histological processing, the material was embedded in paraffin, and serial sections 3–4 μm thick were prepared. The sections were stained with hematoxylin and eosin. Morphometric analysis was performed on digital images of the sections obtained using a Carl Zeiss Axio Scope A1 light microscope equipped with a digital camera. Before measurements, the system was calibrated using an objective micrometer scale. ImageJ software (USA) was used.

For each parameter, 10 randomly selected fields of view were analyzed from a single animal. The following parameters were assessed: cortical thickness (mm; ×100); glomerular area (μm²), 30 randomly selected glomeruli in the cortical region of the section (×400); hemocapillary density (units/mm²), number of capillary profiles in 10 fields of view of the cortical substance (×400); height of the proximal tubule epithelium (μm), measured as the height of 30 epithelial cells with a distinct nucleus and basement membrane (×1000, immersion); lumen diameter of the proximal and distal tubules (μm), minimum internal diameter of 30 transverse tubule sections (×400).

In addition, a semi-quantitative assessment of hydronephrosis was performed (0–4 points): 0 — normal; 1 — slight dilatation of the renal pelvis; 2 — moderate dilatation of the renal pelvis, flattening of the papillae; 3 — marked dilatation of the renal pelvis, blurring of the pyramid borders; 4 — severe dilatation of the renal pelvis, thinning of the cortical and medullary layers. Semi-quantitative assessment of inflammatory infiltrate (0–3 points): 0 — absence of infiltrates; 1 — isolated lymphohistiocytic cells in the interstitium; 2 — moderate multifocal infiltrates; 3 — dense diffuse infiltrates.

The normality of quantitative data distribution was tested using the Shapiro–Wilk test. Data following a normal distribution are presented as the arithmetic mean and standard deviation (M±SD). One-way analysis of variance (ANOVA) with Tukey's post hoc test was used to compare parameters between groups. Semi-quantitative scores are presented as the median and interquartile range [Me (Q_{25}; Q_{75})]. To compare these scores between groups, the nonparametric Kruskal–Wallis test was used, followed by pairwise comparisons using the Mann–Whitney U test with Bonferroni correction. Differences were considered statistically significant at p <0.05. Morphometric results were recorded in tables and subsequently analyzed using STATISTICA 10.0, specifically the Nonparametric, ANOVA, and Discriminant Analysis modules.

RESULTS

Throughout the experiment, the animals in all groups remained in satisfactory condition. Weekly body weight measurements revealed no statistically significant differences between the groups prior to euthanasia (F=1.12; p=0.364), indicating that the drugs used had no toxic effect on the animals' general somatic condition. Biochemical analysis of blood serum confirmed that the target endocrine states had been achieved. The T4 level in the "PH + hyperthyroidism" group was significantly increased by 2.8-fold compared to controls (p <0.001), accompanied by a decreased TSH level (p <0.01). The "PH + hypothyroidism" group showed a 65% decrease in T_4 levels (p <0.001) and a compensatory 3.2-fold increase in TSH levels (p<0.001).Controls and the PH group did not significantly differ from each other in terms of T_4 and TSH levels (p >0.05).

Macromorphometric analysis revealed significant differences between the groups in parameters associated with obstructive uropathy (Table 1).

Table 1

The effect of experimental hypo- and hyperthyroidism on the macromorphometric characteristics of the kidneys

Таблица 1

Влияние экспериментального гипо- и гипертиреоза на макроморфометрические характеристики почек

Параметр Parameter	n	Группа Group					
		масса тела, г weight, g (M±SD)	почки kidneys			мочевой пузырь bladder	
			абсолютная масса, мг absolute weight, mg	относительная масса, мг/100 г relative weight, mg/100 g	толщина коркового вещества, мм thickness of the cortical substance, mm	относительная масса опорожнения, мг/100г relative weight of emptying, mg/100g	остаточная моча, мг residual urine, mg
Контроль Control	8	312,0±35,4	11 207±137,3	359,2±37,3	1,50±0,18	58,2±6,1	1,2±0,4
ГПЖ BPH	8	302,5±32,8	1347,8±131,2*	445,6±31,2*	1,25±0,15*	72,8±8,3*	8,5±2,1*
ГПЖ + T_4 BPH + T4	8	294,5±31,5	1583,5±130,1*#	537,8±30,1*#	0,95±0,12*#	85,4±9,7*#	12,3±3,5*#
ГПЖ + ПТУ BPH + PTU	8	290,5±31,9	1190,5±129,8†	409,8±29,8†	1,40±0,17†	65,1±7,2*†	3,8±1,2*†
ANOVA		F=1,12 (p =0,364)	F=15,45 (p <0,001)	F=18,90 (p <0,001)	F=22,30 (p <0,001)	F=15,43 p <0,001	F=28,91 (p <0,001)

Notes. * — differences with the control group are significant (p <0.05); # — differences with the "BPH" group are significant (p <0.05); † — differences with the "BPH group + hyperthyroidism" is significant (p <0.05). BPH — benign prostatic hyperplasia

Примечания. * — различия с группой контроля достоверны (p <0,05); # — различия с группой «ГПЖ» достоверны (p <0,05); † — различия с группой «ГПЖ+ + гипертиреоз» достоверны (p <0,05). ГПЖ — гиперплазия предстательной железы.

Table by the authors of this article
Таблица авторов данной статьи

As shown in Table 1, modeling testosterone-induced PH led to a statistically significant 20.4% increase in relative kidney mass compared to controls (p <0.05), which was accompanied by a significant increase in residual urine mass (7-fold; p <0.05). The most pronounced changes in macroparameters were observed in the "PH + + hyperthyroidism" group: relative kidney mass was highest (a 38.1% increase relative to the control group; p <0.05), and residual urine mass exceeded the control value by more than 10.25-fold (p <0.05).At the same

Table 2

The effect of experimental hypo- and hyperthyroidism on micromorphometric and semi-quantitative kidney parameters in rats with benign prostatic hyperplasia compared with the control group

Таблица 2

Влияние экспериментального гипо- и гипертиреоза на микроморфометрические и полуколичественные показатели почек у крыс с гиперплазией предстательной железы по сравнению с контрольной группой

Параметр Parameter	Группа Group				Статистическая значимость (основные сравнения) Statistical significance (main comparisons)
	группа 1 (контроль) group 1 (control)	группа 2 (ГПЖ) group 2 (BPH)	группа 3 (ГПЖ + гипертиреоз) group 3 (BPH + hyperthyroidism)	группа 4 (ГПЖ+ гипотиреоз group 4 (BPH + hypothyroidism)	
Толщина коркового вещества, мм (M±SD) Thickness of the cortical substance, mm (M±SD)	1,50±0,18	1,25±0,15*	0,95±0,12*#	1,40±0,17†	Гр. 3–Гр. 2: <0,05 Gr. 3–Gr. 2: <0.05; Гр. 4–Гр. 3: <0,00 Gr. 4–Gr.3: <0.001
Площадь клубочка, мкм² (M±SD) Glomerular area, mm² (M±SD)	8250±950	9100±1050	10 500±1200*#	8600±980	Гр. 3–Гр. 2: <0,05 Gr. 3–Gr. 2: <0.05; Гр. 3–Гр. 4: <0,01 Gr. 3–Gr. 4: <0.01
Плотность капилляров коры, шт/мм² (M±SD) Density of cortical capillaries, pcs/mm² (M±SD)	320±45	380±50*	480±60*#	290±40†	Гр. 3–Гр. 2: <0,01 Gr. 3–Gr. 2: <0.01; Гр. 4–Гр. 3: <0,001 Gr. 4–Gr. 3: <0.001
Высота эпителия проксимальных канальцев, мкм (M±SD) Height of the epithelium of the proximal tubules, microns (M±SD)	8,2±1,1	9,5±1,3*	10,8±1,5*#	7,8±1,0†	Гр. 3–Гр. 2: <0,05 Gr. 3–Gr. 2: <0.05; Гр. 4–Гр. 3: <0,001 Gr. 4–Gr. 3: <0.001
Диаметр просвета проксимальных канальцев, мкм (M±SD) Diameter of the lumen of the proximal tubules, microns (M±SD)	28,5±3,5	32,0±4,1	35,5±4,8*	29,2±3,7†	Гр. 3–Гр. 2: <0,05 Gr. 3–Gr. 2: <0.05; Гр. 4–Гр. 3: <0,01 Gr. 4–Gr. 3: <0.01
Диаметр просвета дистальных канальцев, мкм (M±SD) Diameter of the lumen of the distal tubules, microns (M±SD)	21,0±2,8	35,5±4,5*	48,2±5,9*#	25,3±3,2*†	Гр. 3–Гр. 2: <0,001 Gr. 3–Gr. 2: <0.001; Гр. 4–Гр. 3: <0,001 Gr. 4–Gr. 3: <0.001
Степень гидронефроза, баллы [Me (Q_{25}; Q_{75})] Degree of hydronephrosis, points [Me (Q_{25}; Q_{75})]	0 [0; 0]	2 [1,5; 2,5]*	3 [3; 4]*#	1 [0,5; 1]*†	Гр. 3–Гр. 2: <0,01 Gr. 3–Gr. 2: <0.01; Гр. 4–Гр. 3: <0,001 Gr. 4–Gr. 3: <0.001
Воспалительный инфильтрат, баллы [Me (Q_{25}; Q_{75})] Inflammatory infiltrate, scores [Me (Q_{25}; Q_{75})]	0 [0; 0]	1 [1; 2]*	2 [2; 3]*#	0 [0; 1]†	Гр. 3–Гр. 2: <0,05 Gr. 3–Gr. 2: <0.05; Гр. 4–Гр. 3: <0,001 Gr. 4–Gr. 3: <0.001

Notes. * — differences with the control group are significant (p <0.05); # — differences with the "BPH" group are significant (p <0.05); † — differences with the "BPH group + hyperthyroidism" is significant (p <0.05). The data are presented as mean±standard deviation (M±SD) or median and interquartile range [Me (Q25; Q75)]. BPH — benign prostatic hyperplasia.

Примечания. * — различия с группой контроля достоверны (p <0,05); # — различия с группой «ГПЖ» достоверны (p <0,05); † — различия с группой «ГПЖ + гипертиреоз» достоверны (p <0,05). Данные представлены как среднее±стандартное отклонение (M±SD) или медиана и интерквартильный размах [Me (Q25; Q75)]. ГПЖ — гиперплазия предстательной железы.

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Таблица авторов данной статьи

time, cortisol thickness in this group was the lowest (0.95±0.12 mm). Compared to the control group, there was a 36.7% decrease ($p < 0.05$). Despite the presence of the PH model in the "PH + hypothyroidism" group, all measured parameters (kidney weight, residual urine volume, cortical thickness) differed significantly from those of the hyperthyroidism group ($p < 0.05$) and were closer to the values of the "pure" PH group or controls, indicating that the obstruction was less severe.

Histological examination and subsequent morphometric analysis of kidney sections stained with hematoxylin and eosin allowed for a detailed description of structural changes.

The architecture of the cortical substance was preserved in intact controls. Glomeruli were of normal size and had well-defined contours. The proximal and distal tubules were lined with tall columnar and cuboidal epithelium, respectively; their lumens were uniform and not dilated. The stromal connective tissue layers were thin, with no signs of edema or cellular infiltration.

The "HP" group showed a pattern of early obstructive damage. Against a background of relatively intact glomeruli, focal dilation of distal tubules and collecting ducts was noted, with their lumens unevenly dilated. The epithelium of proximal tubules appeared flattened in some areas. Moderate edema and isolated lymphohistiocytic infiltrates, predominantly perivascular, were identified in the stroma.

The most pronounced and complex changes were observed in the "HP + hyperthyroidism" group. The cortical substance was thinned. The glomeruli often appeared enlarged, with well-vascularized loops. Another characteristic finding was marked, widespread dilation of the tubules, especially in distal segments, many of which were markedly dilated and lined with flattened epithelium. At the same time, hypertrophy of the proximal tubule epithelium was noted in unaffected areas. The stroma was moderately edematous, with multifocal, fairly dense inflammatory infiltrates. The microcirculatory bed (peritubular capillaries) appeared visually well-perfused and branched.

As for "HP + hypothyroidism" group, the histological picture of the cortex differed significantly. Signs of obstructive tubular dilatation were minimal and focal. The glomeruli and tubular epithelium were structurally closer to controls, although the stroma could appear somewhat denser, with signs of mild diffuse basophilic staining (edema). Inflammatory infiltration was generally absent. The capillary network did not appear well-perfused.

A quantitative assessment of the described histological changes is presented in Table 2.

Based on the results of morphometric analysis (see Table 2), a clear correlation was identified between structural changes in the kidneys and thyroid status during obstruction. Histological features of the kidneys in the intact control group were normal. The glomeruli had a standard area (8250±950 μm²), tubular lumens were uniform (distal tubule diameter 21.0±2.8 μm), and stroma was unremarkable; there was no inflammatory infiltrate.

The HP model group showed signs of early obstructive nephropathy: a statistically significant 69% increase in the diameter of the distal tubule lumen (to 35.5±4.5 μm; $p < 0.05$) and a moderate increased density of peritubular capillaries by 19% (to 380±50 per mm²; $p < 0.05$) compared with the control group. Semi-quantitative assessment revealed grade II hydronephrosis [2 (1.5; 2.5)] and a mild inflammatory infiltrate [1 (1; 2)].

Hypothyroidism was not only associated with a lower degree of obstruction (as confirmed by macroscopic parameters) but also exerted a suppressive effect on the vascular and proliferative components of renal tissue, preventing the development of hyperplastic and angiogenic reactions that are typical for obstruction. The "HP + hyperthyroidism" group exhibited the most pronounced and complex structural changes. In comparison with the "pure" HP group, this group demonstrated increased tubular dilation. First of all, the lumen diameter of the distal tubules was 36% larger than in the "HP" group (48.2±5.9 vs. 35.5±4.5 μm; $p < 0.05$), exceeding the control value by 2.3 times. Secondly, there was an increase in glomerular and vascular changes. The glomerular area expanded by 15% compared to the "HP" group (10,500±1,200 vs. 9,100±1,050 μm²; $p<0.05$), and cortical capillary density increased by 26% (480±60 vs. 380±50 per mm²; $p < 0.05$), which was 50% higher than the control level. Finally, there was progression of hydronephrosis and inflammation. The median hydronephrosis score (in points) was significantly higher than in the "HP" group [3 (3; 4) vs. 2 (1.5; 2.5); $p < 0.05$], and the inflammatory infiltrate reached a moderate degree [2 (2; 3)].

By contrast, the "PH + hypothyroidism" group showed the least pronounced changes in most parameters. Compared with the "HP + hyperthyroidism" group, distal tubule dilation was 48% lower (25.3±3.2 vs. 48.2±5.9 μm; $p < 0.05$), while remaining 20% higher than the control group ($p < 0.05$). The density of renal cortical capillaries was 40% lower (290±40 vs. 480±60 per mm²; $p < 0.05$), which was even 9% lower than control levels ($p < 0.05$). There was no glomerular or tubular epithelial hypertrophy: glomerular area and proximal tubular epithelial height did not differ statistically from control values ($p > 0.05$). Minimal signs of obstructive damage were noted: hydronephrosis was assessed at 1 point [1 (0.5; 1)], which was significantly

lower than in the “PH” group ($p < 0.05$). The inflammatory infiltrate was insignificant or absent [0 (0; 1)].

DISCUSSION OF THE RESULTS

Clinical data on associations between thyroid status and benign prostatic hyperplasia (BPH) are contradictory. Some studies indicate an association between hyperthyroidism and increased prostate volume [4], whereas others, using Mendelian randomization, show that hypothyroidism may be associated with a reduced risk of PH [6]. These contradictions underscore the complex nature of thyroid hormones influencing urinary system development. Current research demonstrates that experimental hypothyroidism and hyperthyroidism exert divergent effects on structural changes in the kidneys in the context of testosterone-induced obstructive uropathy in rats.

Hyperthyroidism potentiated, while hypothyroidism significantly reduced the severity of hydronephrosis, tubular dilatation, inflammation, and glomerular changes.The changes observed in hyperthyroidism may be associated with several interrelated mechanisms [7, 8]. First, this is linked to an increase in hemodynamic load. Excess thyroid hormones stimulate renal blood flow and glomerular filtration [9, 10], which, under conditions of obstruction, places an additional burden on the nephrons, contributing to glomerulomegaly and sclerosis. Second, they may be associated with oxidative stress [11, 12]. Hyperthyroidism is related to increased production of reactive oxygen species through NOX4 activation [13], which exacerbates damage to the tubular epithelium. Third, it is associated with modulation of the inflammatory response: thyroid hormones modulate NF-κB-dependent inflammation [14], enhancing the production of proinflammatory cytokines (interleukin-1β, tumor necrosis factor-α).

Macroscopic and microscopic parameters in the “PH + hypothyroidism” group were similar to those in the intact control group or the “pure” PH group. The protective effect of hypothyroidism may be associated with three factors. The macroscopic and microscopic parameters in the “PH + hypothyroidism” group were similar to those in intact controls or the “pure” PH group. The protective effect of hypothyroidism may be associated with three factors. First, there is a reduction in metabolism. Hypothyroidism decreases renal blood flow and the metabolic load on the nephrons [10], thereby slowing the rate of their damage and sclerosis. Second, there is a shift in the balance toward antioxidant factors. A reduction in the generation of reactive oxygen species [13] protects tubulocyte mitochondria from apoptosis. Finally, T3 deficiency in hypothyroidism attenuates TGF-β/SMAD signaling (transforming growth factor beta / Sma and Mad — a family of proteins), a key pathway in fibrogenesis [15, 16]. This may explain the preservation of cortical architecture and less severe tubular dilation in the “PH + hypothyroidism” group [17].

The results underscore importance of assessing thyroid status in patients with BPH as a potential risk factor for renal complications. Correction of hyperthyroidism can be considered an additional strategy to slow the progression of nephropathy.

CONCLUSION

Experimentally induced hyperthyroidism in the PH model potentiates structural kidney damage due to obstructive uropathy against a background of more pronounced prostatic hyperplasia and lymphogenic infiltration of the renal parenchyma, despite an increase in glomerular surface area and capillary density. In contrast, when hypothyroidism is induced, a pronounced protective effect occurs due to a reduction in signs of obstructive damage to the renal parenchyma and the absence of lymphogenic infiltration. When extrapolating these findings to clinical practice, it underscores the need for a comprehensive endocrinological approach for managing patients with PH.

ADDITIONAL INFORMATION

Author contribution. R.I. Glushakov — concept of the experiment, writing the original text; Z.V. Pachuliya — collection of material, preparation of histological preparations; A.L. Semenov — conducting the experimental study; V.V. Krishtop — description of morphological preparations, analysis of the obtained data, statistical analysis; A.R. Iskalieva — writing the text of the article, scientific and technical editing.

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

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

Experiments with animals. All manipulations complied with the principles of the European Convention for the Protection of Vertebrate Animals (Strasbourg, 1986) and were approved by the local ethics committee.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Р.И. Глушаков — концепция эксперимента, написание исходного текста; З.В. Пачулия — сбор материала, изготовление гистологических препаратов; А.Л. Семенов — проведение

экспериментального исследования; В.В. Криштоп — описание морфологических препаратов, анализ полученных данных, выполнение статистического анализа; А.Р. Искалиева — написание текста статьи, научное и техническое редактирование.

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Occlusive splint therapy complication prevention

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Abstract. ***Introduction.*** Currently, occlusal split therapy has become widely used in dental practice for pathology of the temporomandibular joint and/or parafunctions (hypertonia) of the masticatory muscles. At the same time, no in-depth studies on the effect of occlusal splint therapy on the condition of tooth enamel, as well as the prevention of its demineralization have been conducted so far. ***The aim*** — to study the influence of occlusal splint therapy on the state of dental enamel and also to estimate the effectiveness of using the individual oral hygienic care for remineralization of dental enamel. ***Materials and methods.*** There were 45 women aged from 19 to 44 years old being under observation for 2 months who were treated by occlusal splint therapy for temporomandibular joint and/or masticatory muscles diseases and were periodically examined once a month for 60 days to estimate functional resistance of tooth enamel by means of TER-test. The 1st, control, group consisted of 20 people, who performed their usual 2 times daily routine individual oral hygiene during occlusal splint therapy. The 2nd, main group, consisted of 25 people who additionally used ASEPTA remineralizing dental gel after oral hygiene treatment. ***Results.*** Indexes of functional resistance of tooth enamel to acid before occlusal splint therapy in the 1st and 2nd groups patients were almost the same and comprised respectively 2,73±0,19 and 2,81±0,18 conventional units. Patients of the 1st group had the tendency to decrease the functional resistance of tooth enamel to 2,85±0,17 conventional units during the period of dynamic observation while the patients of the 2nd group had the functional resistance of tooth enamel significantly increased up to 1,02±0,18 conventional units that is the evidence of the effectiveness of the remineralizing gel for teeth during the occlusal splinting therapy. Daily use of remineralizing ASEPTA dental gel by the patients of the main study group 2 in the course of 2 months of occlusal splint therapy allowed to provide 36,3% increase of digital indices of tooth enamel resistance, which is an important factor of prevention of dental caries development.

Keywords: occlusal splint therapy, teeth, dental caries, prevention of dental caries, functional enamel resistance, remineralizing agents for teeth, pathogenetic method of dental caries prevention

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Обзор

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Профилактика осложнений окклюзионной сплинт-терапии

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Резюме. ***Введение.*** В настоящее время в стоматологической практике при патологии височно-нижнечелюстного сустава и/или парафункциях (гипертонии) жевательных мышц стали широко применять окклюзионную сплинт-терапию. В то же время до сих пор не проводились углубленные исследования о влиянии окклюзионной сплинт-терапии на состояние эмали зубов, а также профилактики ее деминерализации. ***Цель работы*** — изучить влияние окклюзионной сплинт-терапии на состояние эмали зубов и оценить эффективность индивидуальных гигиенических мероприятий по уходу за полостью рта в отношении реминерализации эмали зубов. ***Материалы и методы.*** Под наблюдением в течение двух месяцев находились 45 женщин в возрасте от 19 до 44 лет, проходивших лечение окклюзионной сплинт-терапией по поводу заболеваний височно-нижнечелюстного сустава и/или жевательных мышц. Пациенток на протяжении 60 суток периодически, 1 раз в месяц, осматривали для оценки функциональной резистентности эмали зубов, которую выполняли с помощью ТЭР-теста. В 1-ю, контрольную, группу исследования вошли 20 человек, осуществлявших в ходе окклюзионной сплинт-терапии обычную для них двукратную общепринятую индивидуальную гигиену полости рта в сутки. Во 2-ю, основную, группу исследования вошли 25 человек, которые после осуществления индивидуального ухода за полостью рта дополнительно использовали гель для зубов реминерализующий АСЕПТА. ***Результаты.*** До начала окклюзионной сплинт-терапии показатели функциональной резистентности эмали зубов к кислоте у пациентов 1-й и 2-й групп были практически одинаковыми и составили 2,73±0,19 и 2,81±0,18 усл. ед. соответственно. У пациентов 1-й группы за период динамического наблюдения отмечена тенденция к снижению функциональной резистентности эмали зубов до 2,85±0,17 усл. ед., в то время как у пациентов 2-й группы функциональная резистентность эмали зубов достоверно повысилась до 1,02±0,18 усл. ед., что свидетельствует об эффективности применяемого ими геля для зубов в ходе окклюзионной сплинт-терапии. Ежедневное использование пациентами 2-й группы исследования геля для зубов реминерализующего АСЕПТА в ходе двухмесячной окклюзионной сплинт-терапии позволило повысить показатели резистентности эмали зубов на 36,3%, что является важным фактором профилактики развития кариеса зубов.

Ключевые слова: окклюзионная сплинт-терапия, зубы, кариес зубов, профилактика кариеса зубов, функциональная резистентность эмали, реминерализующие средства для зубов, патогенетический метод профилактики кариеса зубов

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INTRODUCTION

Currently, occlusal splint therapy has become widely used in dental practice for the management of temporomandibular joint (TMJ) disorders and/or parafunctions (hypertonicity) of the masticatory muscles [1–3]. Splints, also referred to as occlusal appliances or mouthguards, are placed on the dental arches of one or both jaws and alter the pattern of tooth occlusion as well as the position of the mandibular condyles within the glenoid fossae of the temporal bones. This contributes to the normalization of TMJ and masticatory muscle function and helps prevent excessive tooth wear [4–7]. Splints are usually fabricated from acrylic resin or silicone, and patients wear them for 8–24 hours per day depending on their intended purpose [3, 8, 9]. Prolonged use of splints creates a greenhouse-like effect beneath the appliance, promoting the proliferation of microorganisms capable of causing enamel demineralization, which may lead to the development of dental caries [10–12]. Therefore, adequate individualized oral and dental hygiene is an important aspect of splint use [7, 13, 14]. To date, no in-depth studies have been conducted on the effect of occlusal splint therapy on the condition of dental enamel or on the prevention of its demineralization.

AIM

To investigate the effect of occlusal splint therapy on the condition of dental enamel and to evaluate the effectiveness of individualized oral hygiene measures for the remineralization of dental enamel.

MATERIALS AND METHODS

Forty-five women aged 19 to 44 years with various TMJ disorders and/or parafunctions of the masticatory muscles who were prescribed silicone splints for the mandible were followed for three months. The patients were divided into two study groups. The first (control) group included 20 (46.51%) participants who, during splint therapy, performed conventional twice-daily individual oral hygiene consisting of tooth brushing with a manual toothbrush and toothpaste. The second (main) group included 25 (53.49%) participants who, after performing conventional individual oral hygiene, additionally used ASEPTA remineralizing dental gel (VERTEX JSC, Saint Petersburg, Russia). According to the manufacturer's information, the gel contains biomimetic hydroxyapatite, which promotes rapid and effective mineralization of hard dental tissues [1], making it a pathogenetically justified method for the prevention of this pathology. Using a toothbrush, the gel was distributed over the tooth surfaces and left in contact with the hard dental tissues for 1–2 minutes, after which the excess gel was spat out without subsequent rinsing of the oral cavity. Patients were instructed to perform oral hygiene in the morning after breakfast and in the evening after dinner before bedtime. After applying the remineralizing gel, they were advised not to eat or drink for 30 minutes.

To study the effect of occlusal splint therapy on dental enamel and to evaluate the effectiveness of individualized oral hygiene measures in terms of enamel remineralization, the enamel resistance test (TER test) proposed by V.R. Okushko [5] was used. Enamel resistance was assessed on one of the mandibular central incisors. The tooth crown was cleaned of possible plaque and dried, after which a 1% HCl solution was applied, creating a droplet up to 2 mm in diameter on the crown surface. After 5 seconds, the droplet was rinsed off with distilled water, the crown was dried with a cotton pellet, and a droplet of 1% methylene blue solution was applied to the etched area and immediately removed with a cotton pellet. Enamel acid resistance, i.e., its resistance, was then scored according to the intensity of staining that developed on the crown surface. The staining was compared with a standard 10-point blue color scale ranging from 0 (complete absence of staining of the etched area of the tooth crown) to 10 points (most intense blue staining of the etched area of the tooth crown). This examination was performed in each patient before the start of occlusal splint use and again after 30 and 60 days of use.

The significance of differences between mean values of independent samples was assessed using Student's t-test for normally distributed data and the Mann–Whitney test for non-normal distributions. Normality was assessed using the Shapiro–Wilk test. For statistical comparison of proportions, Pearson's χ^2 test with the Mantel–Haenszel likelihood correction was used. In all statistical analyses, the level of significance was set at $p<0.05$.

RESULTS

When enamel resistance was assessed in patients of Groups 1 and 2 before the initiation of occlusal splint therapy, the indicators of enamel functional resistance to acid were found to be virtually identical, amounting to 2.73±0.19 and 2.81±0.18 conventional units, respectively ($p \geq 0.05$). One month after the start of occlusal splint therapy, patients in the control group demonstrated a tendency toward decreased functional enamel resistance, which persisted throughout the two-month follow-up period (Fig. 1). After two months of occlusal splint therapy,

enamel functional resistance to acid in the control group was 2.85±0.17. Although this value still indicated high structural and functional enamel resistance [5, 10], the overall trend should be regarded as unfavorable, as it may contribute to the development of dental caries.

In patients of the main group, a significant trend toward increased enamel functional resistance to acid was observed throughout the entire study period (Fig. 1). Thus, 30 and 60 days after the initiation of occlusal splint therapy, enamel functional resistance improved to 1.56±0.19 and 1.02±0.18 conventional units, respectively ($p \leq 0.01$). Figure 2 presents the dynamics of TER test values in patients from the control and main study groups before treatment and during the 60-day period of splint therapy.

Silicone splints used for occlusal therapy impede the cleansing effect of saliva on the enamel surfaces located beneath the splint. Under conditions of routine oral hygiene alone, this contributed to a decrease in enamel resistance during the two months of occlusal splint therapy. This finding was demonstrated in patients of Group 1. Such an unfavorable trend in enamel functional resistance may become a predisposing factor for the development of dental caries in patients undergoing occlusal splint therapy, although the TER test value after two months of therapy still indicated high structural and functional enamel resistance in Group 1 patients.

Daily use of ASEPTA remineralizing dental gel by patients in Group 2 throughout the 60-day period of occlusal splint therapy resulted in a positive trend in enamel resistance indicators. These values differed significantly from those observed in Group 1 as early as 30 days after treatment initiation ($p \leq 0.05$), although according to the TER test assessment criteria they also indicated high structural and functional enamel resistance [10]. Nevertheless, for patients in Group 2, a favorable trend in TER test values can be confidently stated, indicating an increase in enamel functional resistance. This is likely to contribute to the prevention of dental caries development in patients using silicone dental splints (occlusal appliances) during occlusal splint therapy.

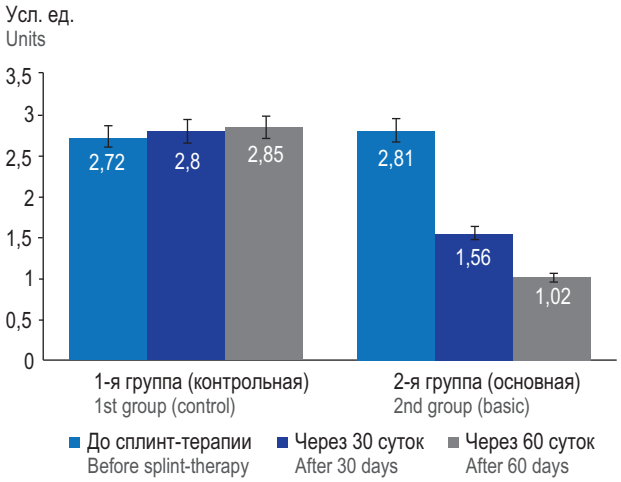


Fig. 1. **Functional acid resistance of tooth enamel in the control and main groups during follow-up (figure by the authors of this article)**

Рис. 1. Показатели функциональной резистентности эмали зубов к кислоте у обследованных контрольной и основной групп исследования на протяжении динамического наблюдения (рисунок авторов данной статьи)

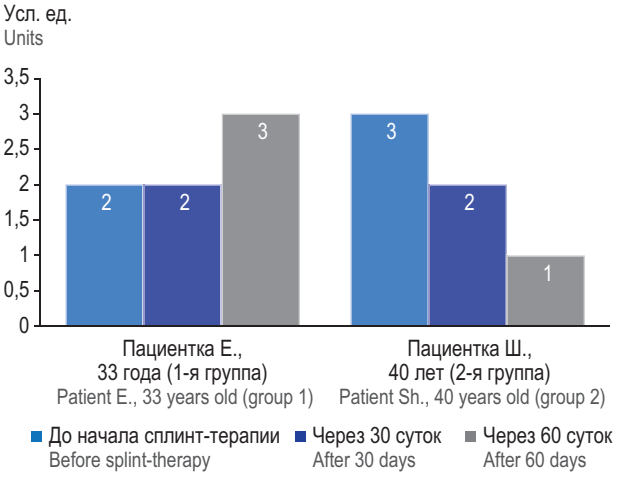


Fig. 2. **Changes in tooth enamel acid resistance in two patients from Groups 1 and 2 during follow-up (figure by the authors of this article)**

Рис. 2. Динамика показателей функциональной резистентности эмали зубов к кислоте у двух обследованных пациентов из контрольной и основной групп исследования на протяжении динамического наблюдения (рисунок авторов данной статьи)

CONCLUSION

1. Under conventional individual oral hygiene measures during occlusal splint therapy with silicone splints, a decrease in the functional resistance of dental enamel is observed, which may become a predisposing factor for the development of dental caries.

2. The use of the modern Russian-made ASEPTA remineralizing dental gel containing biomimetic hydroxyapatite makes it possible to increase the functional resistance of dental enamel by 36.3% over a 60-day period of occlusal splint therapy, which is an important factor in the prevention of dental caries. Therefore, the inclusion of ASEPTA remineralizing dental gel in individual oral hygiene measures may be recommended for patients during prolonged use of splints.

ADDITIONAL INFORMATION

Author contribution. A.K. Iordanishvili — developed the research concept, wrote the initial draft of the manuscript, performed the statistical analysis, and provided scientific and technical editing; A.A. Serikov — collected the research material, conducted the clinical study, analyzed the obtained results, and wrote the article text.

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

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. А.К. Иорданишвили — разработка концепции исследования, написание исходного текста, выполнение статистического анализа, научное и техническое редактирование; А.А. Сериков — сбор материала, проведение клинического исследования, анализ полученных результатов, написание текста статьи.

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

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

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Review
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Constructing products based on extracellular vesicles obtained from mesenchymal stem cells

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Abstract. Mesenchymal stem cells and products based on it are an effective means of treating diseases due to their proven effect on the tissue reparation. In recent years, large amount of data has accumulated showing that the therapeutic effect of mesenchymal stem cells is realized not by the cells themselves, but by it secretome. Preclinical studies using *in vitro* and *in vivo* disease models have demonstrated promising results with small extracellular vesicles derived from stem cells, including mesenchymal stem cells: reduction of oxidative stress, increased proliferation, survival and differentiation of cells, suppression of inflammation, which promotes regeneration at the site of damage. Isolation of the vesicular fraction of mesenchymal stem cells is the starting point for the production of products based on it. However, the path from the idea to the registration of such products is associated with many difficulties. A therapeutic strategy that allows achieving the effects of cell therapy without mesenchymal stem cells transplantation offers a number of advantages. The aim of this review is to highlight the multiple factors that contribute to the high variability of the vesicular fraction obtained from mesenchymal stem cells, the challenges of developing cell-free products, and the need for standardized protocols for the production and evaluation of extracellular vesicles.

Keywords: mesenchymal stem cells, mesenchymal stem cell secretome, extracellular vesicles, exosomes, extracellular vesicle-based products

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Создание продуктов на основе внеклеточных везикул из мезенхимальных стволовых клеток

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Резюме. Мезенхимальные стволовые клетки, а также продукты на их основе являются эффективным инструментом в лечении ряда заболеваний благодаря влиянию на процесс репарации тканей. В последние годы накапливается все больше данных о том, что терапевтический эффект мезенхимальных стволовых клеток реализуется не самими клетками, а их секретомом. Секретом представляет собой комбинацию везикулярной и невезикулярной фракции, которую секретируют клетки, в том числе мезенхимальные стволовые клетки. Доклинические исследования с использованием моделей заболеваний *in vitro* и *in vivo* продемонстрировали многообещающие результаты применения малых внеклеточных везикул, выделенных из стволовых клеток, включая мезенхимальные стволовые клетки: снижение окислительного стресса, усиление пролиферации, выживаемости и дифференцировки клеток, угнетение воспаления, что способствует регенерации в очаге повреждения. Изоляция везикулярной фракции мезенхимальных стволовых клеток служит отправной точкой для производства продуктов на ее основе. Однако путь от идеи до регистрации подобных продуктов сопряжен с массой сложностей. При этом терапевтическая стратегия, позволяющая добиться эффектов клеточной терапии, не прибегая к трансплантации мезенхимальных стволовых клеток, обеспечивает ряд преимуществ. Цель данного обзора — подчеркнуть множество факторов, обусловливающих высокую вариабельность везикулярной фракции, получаемую из мезенхимальных стволовых клеток, сложности разработки бесклеточных продуктов, а также необходимость создания стандартизованных протоколов получения и оценки малых внеклеточных везикул.

Ключевые слова: мезенхимальные стволовые клетки, секретом мезенхимальных стволовых клеток, внеклеточные везикулы, экзосомы, продукты на основе внеклеточных везикул

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

INTRODUCTION

Multipotent stem cells (MSCs) and MSC-derived products are opening new opportunities in biotechnology and regenerative medicine. MSCs are capable of differentiating into osteogenic, adipogenic, and chondrogenic lineages, express a set of surface markers (CD105, CD73, and CD90), and adhere to specialized plastic under standard culture conditions (Fig. 1) [1].

The therapeutic application of MSCs has been extensively investigated: as of August 2025, according to the U.S. National Institutes of Health database (https://clinicaltrials.gov), more than 1,300 clinical studies have been registered. Nevertheless, many unresolved issues remain. As a result, only 12 MSC-containing cell products have been registered to date, and only one has been approved by the U.S. Food and Drug Administration (FDA).

From the discovery of MSCs by Friedenstein in the 1970s [2] until the early 2000s, it was believed that the effects of MSCs were mediated by contact-dependent signaling to other cells, as well as by their accumulation at sites of injury, based on their capacity for multipotent differentiation [3]. This concept began to be reconsidered following the publication by Gnecchi, who demonstrated that MSCs exert their effects through the secretion and release of trophic molecules [4]. Furthermore, studies tracking MSCs after systemic administration showed that MSCs (and stem cells in general) do not become incorporated into the damaged tissue.

In recent years, increasing evidence has indicated that the primary mechanism of MSC action is their paracrine effect mediated by the release of biologically active molecules collectively known as the secretome. Over the past two decades, scientific interest in the cellular secretome, particularly its vesicular fraction, has increased dramatically. Investigation of the secretome composition has provided new insights into intercellular communication underlying numerous biological processes, both physiological and pathological. The composition of the secretome reflects the state of the secreting cell, and this property is already being utilized for disease diagnosis, prognostic assessment, and detailed studies of pathogenesis. In addition, strategies for targeted drug delivery using the vesicular fraction of the secretome are being actively developed, offering high specificity and efficiency..

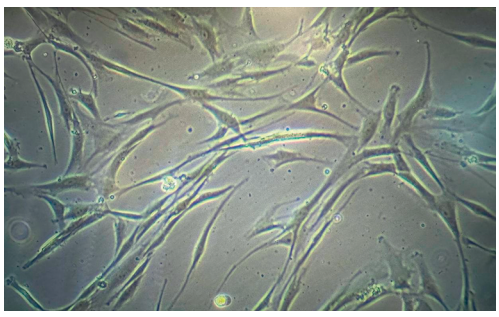


Fig. 1. **Mesenchymal stem cells (the figure is prepared by the authors)**

Рис. 1. Мезенхимальные стволовые клетки (рисунок подготовлен авторами)

COMPOSITION OF THE MESENCHYMAL STEM CELL SECRETOME

The cellular secretome has been described as a complex mixture of products released by virtually all cells of the body in the form of vesicular and non-vesicular fractions (Fig. 2) [5].

The vesicular fraction consists of vesicles that are classified according to their size. According to the recommendations of the International Society for Extracellular Vesicles (ISEV) issued on February 7, 2024, the term extracellular vesicles (EVs) refers to particles released from cells and enclosed by a lipid bilayer that are incapable of self-replication (i.e., do not contain a functional nucleus) [6]. ISEV recommends avoiding the use of the biogenesis-based terms exosomes and ectosomes, although these terms remain convenient for practical use. Instead, ISEV permits the use of the terms small extracellular vesicles (SEVs) (<200 nm) and large extracellular vesicles (LEVs) (>200 nm), with the size definition depending on the specific analytical method employed. In numerous scientific publications, extracellular vesicles are classified according to their biogenesis and release mechanisms as follows: exomeres (<50 nm), exosomes (30–150 nm), microvesicles (100–1000 nm), apoptotic bodies (1000–5000 nm), migrasomes (500–3000 nm), and oncosomes (1000–10000 nm) [7].

Non-vesicular extracellular particles (NVEPs) comprise all cell-derived particles belonging to one or more molecular classes that lack a delimiting lipid bilayer membrane [6]. NVEPs may be substantially smaller than extracellular vesicles, making their detection challenging, while MSC secretome isolation methods may result in the co-isolation of both vesicular and non-vesicular fractions [8]. The most common components of the non-vesicular fraction of the MSC secretome are presented in Table 1.

The most common components of the vesicular fraction of the MSC secretome are summarized in Table 2.

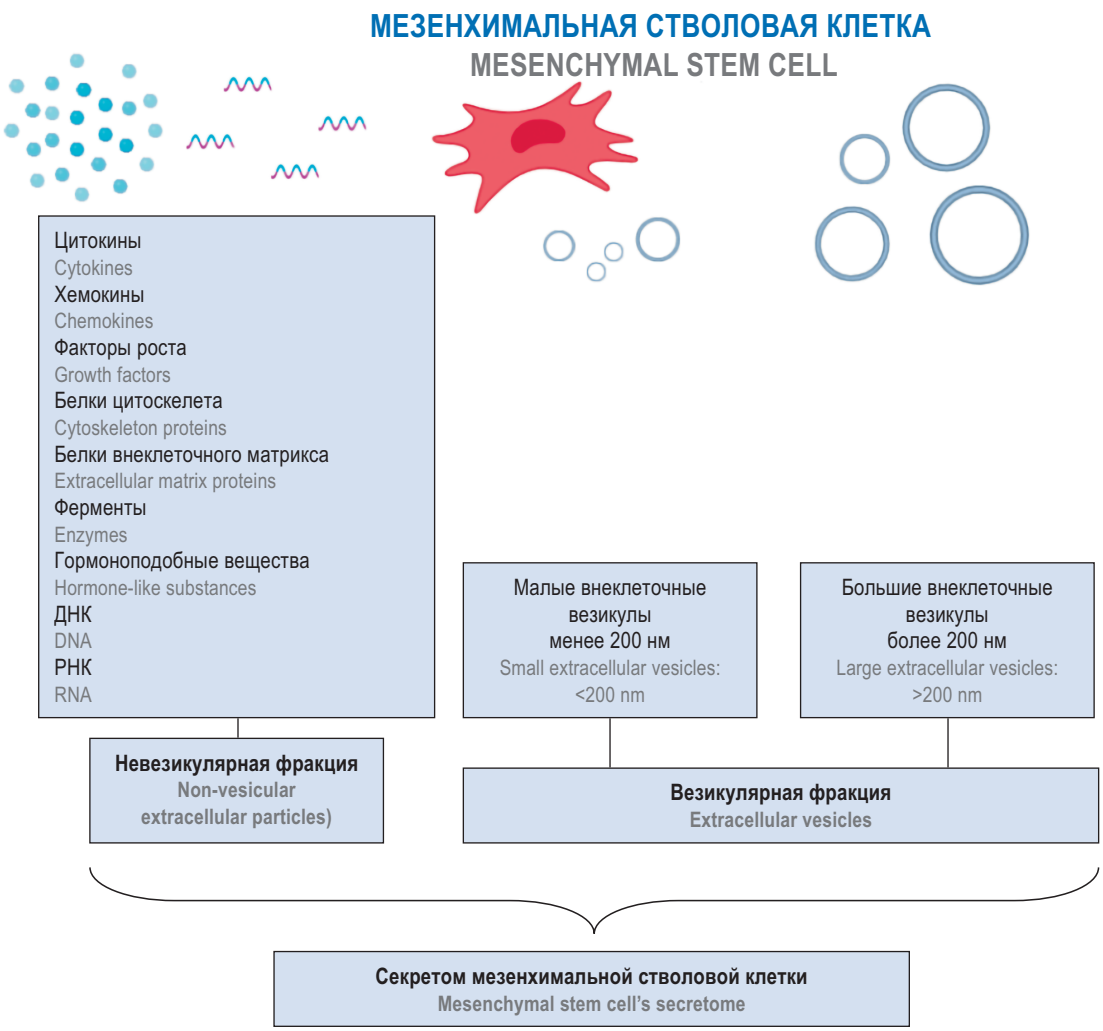


Fig. 2. **Mesenchymal stem cell`s secretome (the figure is prepared by the authors)**

Рис. 2. Секретом мезенхимальной стволовой клетки (рисунок подготовлен авторами)

Table 1

The most frequently encountered components of the non-vesicular fraction of the mesenchymal stem cells secretome

Таблица 1

Наиболее часто встречаемые компоненты невезикулярной фракции секретома мезенхимальных стволовых клеток

Компоненты невезикулярной фракции секретома мезенхимальных стволовых клеток Components of the non-vesicular fraction of the mesenchymal stem cells secretome	**Примеры** Examples	**Источник данных** Data source
Цитокины Cytokines	IL-1α, IL-1β, IL-6, IL-8, IL-10, IL-13	[8, 9]
Хемокины Chemokines	• Фактор стволовых клеток (SDF-1) Stem cell factor (SDF-1);	[8]
	• белок-хемоаттрактант моноцитов (MCP1) Monocyte chemoattractant protein (MCP1);	
	• хемокиновый лиганд мотива 12 (CXCL12) Chemokine ligand 12 motif (CXCL12);	
	• субъединица 8 полипептида 1, содержащего шаперонин (CCT8) Subunit 8 of polypeptide 1 containing chaperonin (CCT8);	
	• макрофагальный воспалительный белок 1-бета (MIP-1B) Macrophage inflammatory protein 1-beta (MIP-1B)	

Ending of the Table 1 / Окончание табл. 1

Компоненты невезикулярной фракции секретома мезенхимальных стволовых клеток Components of the non-vesicular fraction of the mesenchymal stem cells secretome	**Примеры** Examples	**Источник данных** Data source
Факторы роста Growth factors	• Фактор роста фибробластов 2 (FGF-2) Fibroblast growth factor 2 (FGF-2);	[8]
	• гранулоцитарно-макрофагальный колониестимулирующий фактор (GM-CSF) Granulocyte-macrophage colony-stimulating factor (GM-CSF);	
	• фактор роста гепатоцитов (HGF) Hepatocyte growth factor (HGF);	
	• субъединица А тромбоцитарного фактора роста (PDGF-1) Platelet-derived growth factor subunit A (PDGF-1);	
	• трансформирующий фактор роста бета (TGF-β) Transforming growth factor beta (TGF-β)	
Белки цитоскелета Cytoskeletal proteins	• Актин α2 (ACTA2), актин β (ACTB), α-актин сердечной мышцы (ACTC1) Actin α2 (ACTA2), actin β (ACTB), cardiac α-actin (ACTC1)	[10]
Белки внеклеточного матрикса Extracellular matrix proteins	• Фибриллин (FBN1), бета-цепь фибриногена (FGB) Fibrillin (FBN1), fibrinogen beta chain (FGB)	[10]
Ферменты Enzymes	• Глицеральдегид-3-фосфатдегидрогеназа индоламин 2 (GAPDH); супероксиддисмутаза (SOD) Glyceraldehyde-3-phosphate dehydrogenase indoleamine 2 (GAPDH); superoxide dismutase (SOD)	[8]
Гормоноподобные вещества Hormone-like substances	• Инсулиноподобный фактор роста-1 (IGF-1) Insulin-like growth factor-1 (IGF-1)	[8]

The table is prepared by the authors
Таблица составлена авторами

SEVs derived from MSCs express the same surface markers as MSCs themselves, including CD29, CD44, CD73, CD90, and CD105 [14]. These markers can be detected using various techniques, including flow cytometry and Western blotting.

SEVs are widely present in biological fluids such as saliva, urine, breast milk, cerebrospinal fluid, plasma, and serum [15]. Although their concentration varies among different biological fluids, the concentration of SEVs in 1 mL of blood plasma may reach 10^{10} particles [16]. Identified SEV components include approximately 10,000 proteins, 3,500 RNAs, 3,000 microRNAs, and 1,000 lipids [17].

Since SEVs retain the signature of their parent cells, determining their composition in blood plasma is of considerable diagnostic and prognostic value. At the same time, the overall composition of plasma SEVs is highly heterogeneous because they originate from cells of most tissues. Investigation of SEV composition may substantially expand our understanding of disease pathogenesis and serve as a starting point for the development of novel SEV-based therapeutics and vaccines [18].

The specific protein and RNA cargo of MSC-derived SEVs varies depending on the MSC source and culture conditions [19, 20]. Culture conditions such as hypoxia and cytokine stimulation can alter SEV composition and biological effects. Hypoxia enhances the secretion of pro-angiogenic factors by MSCs and their released SEVs, thereby improving neovascularization and bone tissue regeneration [21]. Cultivation with rapamycin and growth factor restriction increases SEV release [22]. Factors such as donor age, health status, and the method used for MSC isolation also influence SEV composition [23]. For example, SEVs derived from adipose tissue MSCs obtained by surgical excision and liposuction exhibit different characteristics, and differences in microRNA profiles have been observed even when the same isolation method is used for samples collected from different anatomical sites [24]. Age-related changes in donor cells affect the quality of released SEVs, limiting their anti-inflammatory and regenerative potential [25].

Increasing attention is being paid to the nucleic acid fraction of SEVs. Several studies have shown that DNA transported within SEVs participates in horizontal gene transfer between cells, including transformed cells, contributing to genetic diversity and potentially facilitating the spread of oncogenes during cancer progression [26].

Table 2

The most common components of the vesicular fraction of the mesenchymal stem cells secretome according to different sources

Таблица 2

Наиболее часто встречаемые компоненты везикулярной фракции секретома мезенхимальных стволовых клеток согласно разным источникам

Компоненты везикулярной фракции секретома мезенхимальных стволовых клеток Components of the vesicular fraction of the mesenchymal stem cells secretome	**Примеры** Examples	**Источник данных** Data source
Белки Proteins	• Актин Actin; • β-тубулин β-tubulin; • тетраспанины (CD9, CD63, CD81, CD82) tetraspanins (CD9, CD63, CD81, CD82); • белки теплового шока (HSP770, HSP90) heat shock proteins (HSP770, HSP90); • белок опухолевой предрасположенности 101 (Tsg101) tumor predisposition protein 101 (Tsg101); • белок, взаимодействующий с запрограммированной клеточной гибелью (Alix) programmed cell death-interacting protein (Alix); • белки главного комплекса гистосовместимости I и II классов (MHC I, MHC-II) proteins of the major histocompatibility complex classes I and II (MHC I, MHC-II)	[11]
Липиды Lipids	• Церамиды Ceramides; • сфингомиелин sphingomyelin; • фосфатидилсерин phosphatidylserine;	
	• фосфатидилинозитол phosphatidylinositol; • холестерин cholesterol	[12]
Нуклеиновые кислоты Nucleic acids	• Матричная РНК messenger RNA; • микроРНК microRNA • рибосомальная РНК ribosomal RNA • ДНК DNA	[13]

The table is prepared by the authors
Таблица составлена авторами

Because the DNA of SEVs derived from certain tumors contains characteristic genetic alterations, such as mutations and gene amplifications, SEVs represent promising targets for noninvasive diagnostic applications, including liquid biopsy. Furthermore, mitochondrial DNA contained in SEVs is associated with cellular stress responses and may play a role in immune system intercellular signaling [27].

Various forms of RNA have also been identified within SEVs, including messenger RNA (mRNA), microRNA, ribosomal RNA, circular RNA, long non-coding RNA and DNA. SEV-associated RNAs undergo horizontal transfer between cells, resulting in phenotypic changes in recipient cells due to their important role in gene regulation and participation in diverse physiological processes [28]. For example, SEVs derived from embryonic stem cells can reprogram hematopoietic progenitor cells through the delivery of mRNA [29]. During the immune response, unidirectional transfer of mRNA occurs from T lymphocytes to antigen-presenting cells, a process that may be antigen-dependent. Viral microRNAs contained in SEVs released by infected cells can be taken up by uninfected cells [30].

MicroRNAs are the most abundant RNA species found in human plasma SEVs, accounting for approximately 40% of the total RNA content, which makes them particularly advantageous for diagnostic applications.

FORMATION AND BIOLOGICAL EFFECTS OF EXTRACELLULAR VESICLES

The secretion of small extracellular vesicles by cells is a fundamental process required for intercellular communication under both physiological and pathological conditions [31] and has likely existed throughout evolution [32]. Under in vitro conditions, SEVs are released by cultured cells into the culture medium.

The process of vesicle formation begins with the invagination of the plasma membrane into the cell, leading to the formation of early endosomes, followed by the development of late endosomes or multivesicular bodies (MVBs) (Fig. 3) [33].

At this stage, MVBs contain proteins that were present on the plasma membrane, as well as RNA and proteins derived from the cytoplasm. Subsequently, proteins from the endoplasmic reticulum and Golgi apparatus are incorporated into MVBs. The *de novo* incorporation of various components into MVBs is regulated by the ESCRT protein complex (Endosomal Sorting Complexes Required for Transport) or mediated through ceramide-/tetraspanin-dependent pathways [34].

Some of the formed MVBs fuse with lysosomes, resulting in degradation of their contents. Another fraction of MVBs is “tagged” by ceramides; the outer membrane of the MVB fuses with the plasma membrane, and SEVs are released into the extracellular space [35].

The biogenesis and secretion of SEVs are controlled by specific GTPase proteins. Small GTPases of the Rab family regulate intracellular vesicular transport. For example, Rab5 participates in endosome formation, whereas Rab7 promotes degradation of MVB contents within lysosomes. Several Rab proteins (Rab35, Rab11, Rab27a, and Rab27b) regulate the secretion of SEVs into the extracellular space [31]. The formation and secretion of SEVs may be altered by intracellular processes or external

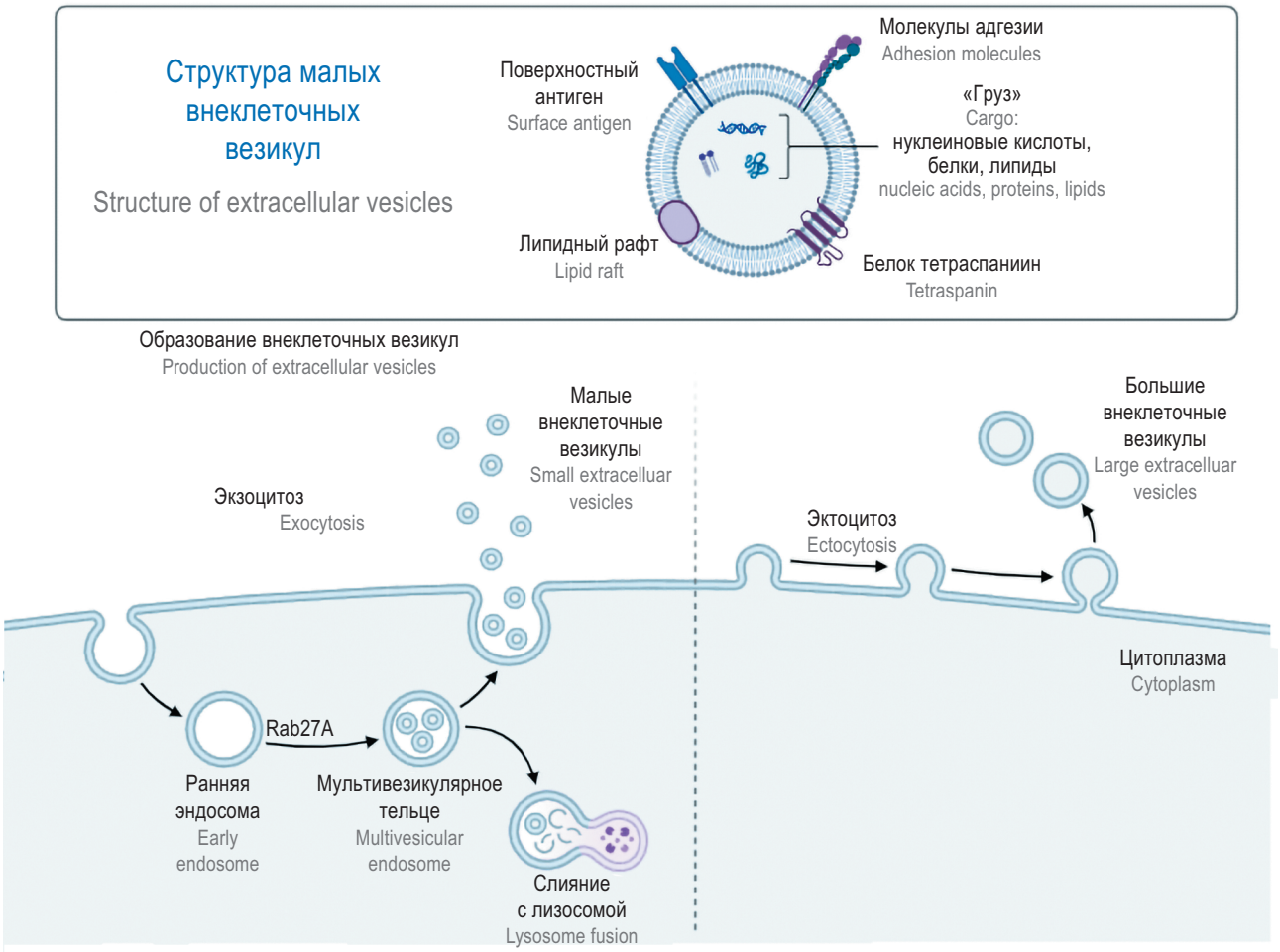


Fig. 3. **Structure and biogenesis of extracellular vesicles (the figure is prepared by the authors)**

Рис. 3. Структура и биогенез внеклеточных везикул (рисунок подготовлен авторами)

stimuli. For example, transformed tumor cells secrete significantly greater numbers of SEVs than non-transformed healthy cells [36]. Cellular stress is considered a possible factor that increases SEV release [37].

Following their release, SEVs adhere to the surface of target cells through the action of integrins and tetraspanins. For example, integrins αv (CD51), α3 (CD49c), β1 (CD29), as well as lactadherin and vitronectin, are involved in the adhesion of SEVs to leukocytes [33]. Tetraspanins present on the plasma membrane are also highly expressed on SEVs (CD9, CD81, CD63, and CD82), allowing their use as specific SEV markers. Tetraspanins play a key role in the adhesion, fusion, and selective uptake of SEVs by recipient cells [38]. Changes in the expression of specific tetraspanins may modulate the selective targeting and uptake of SEVs, thereby influencing the cellular response. The specificity of SEVs for target cells may be determined by the combination of antigens with MHC class I and II molecules [39].

The interaction of SEVs with recipient cells may lead to several outcomes: (1) signal transmission through intracellular signaling pathways (juxtacrine effect); (2) fusion with the cell membrane and release of vesicular contents into the cytoplasm of the recipient cell; and (3) uptake of SEVs through phagocytosis, macropinocytosis, or receptor-mediated endocytosis. Within the recipient cell, the contents of SEVs are either degraded or induce a cellular response. Although SEVs possess a wide range of biological activities, their principal significance lies in their ability to serve as carriers of information, facilitating long-distance intercellular communication. Compared with the diffusion of soluble signaling molecules, SEV-mediated intercellular communication is more effective both in terms of biological impact and specificity.

ADVANTAGES OF USING CELL-FREE PRODUCTS BASED ON COMPONENTS OF THE MESENCHYMAL STEM CELL SECRETOME

Despite numerous clinical studies, only 12 mesenchymal stem cell (MSC)-containing products have been approved to date, and only one of them has received FDA approval — Prochymal (Remestemcel-L) (Osiris Therapeutics Inc., Mesoblast Ltd.), which is used for the treatment of graft-versus-host disease. In this regard, the potential use of cell-free products based on the MSC secretome or its vesicular fraction offers several key advantages over MSC-containing cellular products, namely:

1) improved patient safety and avoidance of the low but potentially existing risks of tumorigenesis and transmission of infectious agents associated with the transplantation of living stem cell populations;
2) reduction in the number of invasive material collection procedures or their complete avoidance (depending on the MSC source);
3) assessment of safety and efficacy using approaches similar to those applied to pharmaceutical agents;
4) substantially prolonged storage life through cryopreservation or lyophilization without loss of biological activity; products containing viable cells are generally short-lived (from several hours to one day), requiring complex logistics for rapid delivery to patients;
5) large-scale manufacturing of cell-free products using specially established cell lines under controlled laboratory conditions (e.g., in bioreactors) to obtain MSC secretome components at desired concentrations and to tailor the secretome composition according to specific therapeutic goals;
6) reduced production time and cost, with immediate availability of ready-to-use products, which is particularly important for the treatment of acute conditions such as cerebral ischemia, myocardial infarction, and combat-related injuries.

CHALLENGES IN THE DEVELOPMENT OF CELL-FREE PRODUCTS BASED ON COMPONENTS OF THE MESENCHYMAL STEM CELL SECRETOME

Although cell-free products based on MSC secretome components offer potential advantages over MSC-containing cellular products, their production and regulatory approval are associated with numerous challenges.

1. Heterogeneity of SEVs derived from MSCs. The biological variability of SEV cargo, discussed above, poses a challenge for the standardization and predictability of therapeutic outcomes based on SEVs. Strict quality control measures, including the use of reference samples, development of calibration standards, and consensus guidelines for SEV research, may improve the reproducibility of SEV-related studies [40].

2. Use of different methods for SEV isolation and characterization.

To date, no standardized methods for SEV isolation, purification, and characterization have been

established [41]. This creates uncertainty regarding their expected biological effects and potential clinical outcomes, significantly complicating the assessment of efficacy and safety in both clinical and experimental studies. Commonly used methods for SEV isolation include ultrafiltration, ultracentrifugation, size-exclusion chromatography, and immunoaffinity-based approaches [42].

The small size of SEVs (30–150 nm), their heterogeneity within source samples, the presence of protein contaminants, and high economic costs hinder the selection of an optimal method for obtaining SEVs with predefined characteristics. Ultrafiltration, based on size separation, does not require expensive equipment but is time-consuming and associated with a high risk of membrane fouling by larger particles [43]. Ultracentrifugation, which relies on differences in density and size, is labor-intensive, costly, technically demanding, and may result in high levels of contaminants (RNA, proteins) as well as damage to SEV integrity [44]. Size-exclusion chromatography is used to obtain highly purified SEVs but requires expensive equipment and complex procedures. Immunoaffinity-based methods, which identify SEVs according to unique surface protein profiles using biotinylated antibodies, enable the isolation of tissue-specific SEVs with high purity; however, these methods are costly, low-throughput, and require extensive preparation [42].

Following isolation, SEVs must be characterized. Since SEVs contain nucleic acids, proteins, lipids, and a range of characteristic surface markers, each of these components may be measured as a surrogate indicator of SEV abundance. However, none of these parameters perfectly correlate with the actual number of SEVs. SEV purity and yield may be assessed using transmission or scanning electron microscopy, flow cytometry, Western blotting, and liquid chromatography–mass spectrometry [44]. A detailed description of these methods is beyond the scope of this review.

3. Low SEV yield. Although SEVs represent promising therapeutic agents, they are typically not secreted in quantities sufficient for clinical application, which limits the full realization of their therapeutic potential. Insufficient SEV production remains one of the major obstacles to their effective use [45]. For example, 1 mL of conditioned culture medium can produce approximately 10^9 SEVs, whereas an effective therapeutic dose is generally considered to be around 10^{10} SEV particles per milliliter [46]. Furthermore, no recommendations have yet been developed regarding the required in vivo dose of SEVs, taking into account their pharmacokinetics and pharmacodynamics [47].

Strategies to increase SEV release from cultured cells include three-dimensional (3D) culture systems using bioreactors and spheroids, physical stimulation (mechanical, electrical, or magnetic field-based), chemical stimulation, physiological modification, and genetic manipulation of the parent cell population producing SEVs [48]. In addition to difficulties associated with obtaining high SEV yields from cell cultures, it should also be considered that interactions between SEVs and target cells are accompanied by partial lysosomal degradation, ultimately reducing their therapeutic potential.

4. Variable stability of SEVs. Currently, there are no standardized requirements or conditions for SEV storage, despite their importance for planning the manufacture of SEV-containing products. Three principal methods are commonly used for SEV preservation: cryopreservation, spray drying, and freeze-drying (lyophilization).

Cryopreservation is typically performed at −80 °C or −196 °C. This process involves freezing, thawing, and potentially refreezing SEVs following partial use. To preserve SEV integrity during freeze–thaw cycles, various cryoprotective agents are employed; these should ideally possess low toxicity, water solubility, and low cost.

Factors such as the number of freeze–thaw cycles, pH, storage medium composition, and osmotic pressure influence the stability of SEV cargo, particularly proteins and microRNAs that mediate therapeutic effects, in MSC-derived SEVs [49]. For example, storage of SEVs in phosphate-buffered saline results in a rapid decline in SEV recovery within several days, whereas dilution of the buffer may reduce recovery within minutes [50]. The addition of human serum albumin and trehalose to the storage medium at −80 °C appears to be the most promising approach for long-term storage and preservation of stability through multiple freeze–thaw cycles.

Spray drying converts a liquid suspension containing SEVs into a dry powder through rapid exposure to hot gas. However, this process may denature many surface proteins and is therefore less suitable for SEVs containing thermosensitive components. During freeze-drying (lyophilization), a two-step preservation process involving freezing followed by water removal under reduced pressure, water is removed from SEVs in a manner that stabilizes them [51]. After lyophili-

zation, SEVs may be stored at room temperature for extended periods. Nevertheless, the choice of cryoprotectants remains crucial for preventing aggregation and maintaining functional integrity following reconstitution [52].

Despite the evident advantages of cell-free products, numerous challenges must be addressed before the first regulatory approval can be granted for a product containing the MSC secretome or its components. The most pressing issues in the development and registration of such products are the standardization and improvement of methods for the isolation, storage, and characterization of the vesicular fraction of the secretome. Therefore, the establishment of a reliable therapeutic platform for SEV-based products requires scalable manufacturing processes with clearly defined timelines and economic feasibility. Equally important are further studies on the composition, biogenesis, and biological effects of SEVs on target cells, which will enable a more detailed assessment of the efficacy and safety of SEV-based therapeutic products and facilitate modification of their composition according to specific clinical applications.

ADDITIONAL INFORMATION

Author contribution. R.V. Korablev — writing and editing, review`s concept; A.G. Vasiliev — writing and editing, review`s concept, supervision; S.S. Purveev, T.V. Brus, A.Yu. Pyrkh, Z.K. Emirgaev, A.E. Kurtukova, Yu.R. Ryzhov, Yu.A. Taminkina — writing and editing.

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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Pathophysiological role of the glucagon-like peptide-1 system in the regulation of stress-induced impairments of impulsive and compulsive behavior in rats

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Abstract. ***Introduction.*** The glucagon-like peptide-1 (GLP-1) system plays an important role not only in the regulation of energy metabolism but also in the control of motivational and reward-related behavior. Recent studies have demonstrated that GLP-1 receptor agonists can modulate the activity of mesolimbic brain structures involved in the development of impulsivity and addictive behavior. However, the effect of GLP-1 system activation on stress-induced disturbances of self-control remains insufficiently studied. ***Aim.*** To determine the role of the glucagon-like peptide-1 (GLP-1) system in regulating impulsive and compulsive behavior that develops in rats following early-life stress (temporary maternal separation), and to evaluate the effects of pharmacological activation of GLP-1 receptors on behavioral manifestations associated with impaired self-control and emotional regulation. ***Materials and methods.*** Experiments were carried out on Wistar rats exposed to maternal separation during the postnatal period. Impulsivity was assessed using a modified decision-making test with different reinforcement probabilities (analogous to the Iowa Gambling Task), and compulsivity was evaluated using the marble burying test. The GLP-1 receptor agonist exenatide (Byetta®, AstraZeneca, UK) was administered subcutaneously at a dose of 10 μg/kg daily for 7 days. Statistical analysis was performed using Student's t-test; data are presented as mean±SEM, and differences were considered significant at $p < 0.05$. ***Results.*** Administration of the GLP-1 agonist resulted in a significant reduction in impulsive behavior, expressed as a decreased frequency of risky arm choices in the probabilistic reinforcement task compared to saline-treated rats ($p < 0.05$). At the same time, no significant effect was observed on compulsive behavior in the marble burying test. ***Conclusions.*** Activation of GLP-1 receptors by exenatide exerts a selective anti-impulsive effect while maintaining the level of compulsive responses, indicating a modulatory role of the GLP-1 system primarily in the regulation of the impulsive component of behavior. The obtained results support the potential of GLP-1 receptor agonists as pharmacological agents for correcting stress-induced impairments of self-control and addiction-related behavioral disorders.

Keywords: glucagon-like peptide-1 (GLP-1), exenatide, impulsivity, compulsivity, stress, maternal deprivation, rat, mesolimbic system

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Патофизиологическая роль системы глюкагоноподобного пептида-1 в регуляции стресс-индуцированных нарушений импульсивного и компульсивного поведения у крыс

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Резюме. ***Введение.*** Система глюкагоноподобного пептида-1 (GLP-1) играет важную роль не только в регуляции энергетического обмена, но и в контроле мотивационно-подкрепляющего поведения. В последние годы установлено, что агонисты рецепторов GLP-1 способны модулировать активность мезолимбических структур, участвующих в развитии импульсивности и аддиктивных форм поведения. Однако влияние активации системы GLP-1 на стресс-индуцированные нарушения самоконтроля недостаточно изучено. ***Цель исследования*** — определить роль системы глюкагоноподобного пептида-1 (GLP-1) в регуляции импульсивного и компульсивного поведения, формирующегося у крыс после раннего стрессового воздействия (временной изоляции от матери), а также оценить влияние фармакологической активации рецепторов GLP-1 на поведенческие проявления, связанные с нарушением самоконтроля и эмоциональной регуляции. ***Материалы и методы.*** Эксперименты выполнены на крысах Вистар, подвергшихся временной изоляции от матери в постнатальном периоде. Для оценки импульсивности использовали модифицированный тест выбора с различной вероятностью подкрепления (аналог Iowa Gambling Task), а для оценки компульсивности — тест закапывания шариков. Препарат эксенатид (Byetta®, AstraZeneca, Великобритания) вводили подкожно в дозе 10 мкг/кг ежедневно в течение 7 дней. Статистическую обработку данных проводили с помощью t-критерия Стьюдента; результаты представлены в виде M±SEM, различия считали значимыми при $p < 0,05$. ***Результаты.*** Введение агониста GLP-1 приводило к достоверному снижению импульсивности, выражавшемуся в уменьшении частоты выбора рискованных рукавов в тесте вероятностного подкрепления по сравнению с группой, получавшей изотонический раствор натрия хлорида раствор ($p < 0,05$). При этом достоверного влияния на проявления компульсивного поведения в тесте закапывания шариков не выявлено. ***Выводы.*** Активация рецепторов GLP-1 с помощью эксенатида оказывает селективное антиимпульсивное действие при сохранении уровня компульсивных реакций, что указывает на модулирующую роль системы GLP-1 преимущественно в регуляции импульсивного компонента поведения. Полученные данные подтверждают перспективность агонистов GLP-1 как фармакологических средств для коррекции стресс-индуцированных нарушений самоконтроля и аддиктивных расстройств поведения.

Ключевые слова: глюкагоноподобный пептид-1 (GLP-1), эксенатид, импульсивность, компульсивность, стресс, материнская депривация, крыса, мезолимбическая система

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INTRODUCTION

Characteristic features of many psychiatric disorders, including substance use disorders, gambling disorder, obsessive–compulsive disorder, and binge-eating disorder, include impaired behavioral control [1]. Impulsivity is defined as "a predisposition toward rapid, unplanned reactions to internal or external stimuli, with diminished regard for the negative consequences of these actions for oneself or others" [2, 3].

Compulsivity, in contrast, is characterized by "the performance of repetitive and functionally maladaptive behaviors — overt or covert — carried out in a stereotyped manner, according to rigid rules or to prevent subjectively perceived negative consequences" [3].

Contemporary research indicates that both behavioral phenotypes represent multidimensional and multicomponent constructs involving distinct neurobiological and motivational mechanisms. Their relative contribution to the clinical presentation may vary depending on the type of psychopathology, individual personality traits, and the stage of the disorder [4].

In recent years, considerable efforts have been made to investigate the neurobiological basis of impaired self-control, including the development of behavioral tests for assessing impulsivity and compulsivity. Experimental evidence demonstrates pronounced impulsive and compulsive traits in obsessive–compulsive disorder [1], substance use disorders [5], and other addictive behaviors, such as gambling disorder [5].

Considerably less is known about how these processes relate to the pathogenesis of binge-eating disorder (BED). BED is characterized by the consumption of large amounts of food within a limited period of time, accompanied by a subjective loss of control over eating behavior [6]. The disorder is considered to share features with addictive disorders, including a positive correlation with impulsivity [7, 8].

According to current concepts of the neurobiology of addictive disorders, peripheral metabolic factors with central nervous system activity, such as glucagon-like peptide-1 (GLP-1), play an important role in regulating reward circuitry and reinforcement processes associated with psychoactive substances [15].

GLP-1 is an incretin hormone secreted by intestinal L-cells in response to food intake. It lowers blood glucose levels by stimulating insulin secretion from pancreatic β-cells, delays gastric emptying, and enhances satiety [8]. Based on these effects, GLP-1 analogs were developed and are used to improve glycemic control in patients with type 2 diabetes mellitus. In addition to its peripheral effects mediated through vagal afferents, GLP-1 is also synthesized in the brain—primarily by neurons of the nucleus of the solitary tract (NTS)—where it functions as a neuromodulator [10, 11]. GLP-1 receptors (GLP-1R) are expressed in several key brain regions, including the nucleus of the solitary tract, hypothalamus, ventral tegmental area (VTA), and nucleus accumbens (NAc), all of which are involved in the regulation of energy homeostasis, appetite, food reward, and drug-related reward [12].

A number of recent preclinical studies indicate an important role of the GLP-1 system in the regulation of addictive behavior. Publications from the last decade have demonstrated that exendin-4 suppresses conditioned place preference (CPP), cocaine self-administration, and the reinstatement of drug-seeking behavior induced either by the drug itself or by drug-associated cues during abstinence [13–15].

Given current understanding of the neurometabolic mechanisms regulating motivation and reward, investigation of the role of GLP-1 and its receptors in the pathogenesis of behavioral disorders appears highly relevant. While the influence of the GLP-1 system on energy balance, appetite, and glucose metabolism has been extensively studied, its involvement in the development of impulsive and compulsive behavioral patterns, addictive tendencies, and stress-induced disturbances of emotional regulation remains insufficiently explored.

AIM

To determine the role of the glucagon-like peptide-1 (GLP-1) system in the regulation of impulsive and compulsive behaviors developing in rats following early-life stress exposure (maternal separation), as well as to evaluate the effects of pharmacological activation of GLP-1 receptors on behavioral manifestations associated with impaired self-control and emotional dysregulation.

MATERIALS AND METHODS

Experimental Animals. The study was conducted on 72 Wistar rats weighing 250–300 g (62 males and 10 females). The animals were obtained from the Rappolovo breeding facility (Tosnensky District, Leningrad Region, Russia) and housed in the animal facility of St. Petersburg State Pediatric Medical University. Animals were maintained in standard

plastic cages (40×50×20 cm) under controlled conditions: temperature 22±2 °C, relative humidity 50–60%, and a reversed light–dark cycle (light: 20:00–08:00; dark: 08:00–20:00). Standard pelleted chow and water were provided *ad libitum*. Upon arrival, the animals underwent a two-week acclimatization period. All experimental procedures complied with Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes and were approved by the Local Ethics Committee of St. Petersburg State Pediatric Medical University (Protocol No. 58/03, September 25, 2025).

Breeding and Offspring Production. Female rats were housed in groups of five per cage with free access to food and water. One male was introduced into each cage. Vaginal smears were collected daily and examined under a light microscope. The presence of spermatozoa in a smear during proestrus was considered day 0 of pregnancy. After pregnancy was confirmed, females were housed individually. Gestation lasted 20±2 days.

Early-Life Stress Model. Maternal separation was used to model early postnatal stress. From postnatal day 2 to day 12, pups were separated from their mothers daily for 180 min and placed individually in plastic containers. Visual, tactile, and auditory contact with the mother was completely prevented. Following the deprivation period and subsequent nursing, offspring were housed in standard cages with five animals per cage. For behavioral testing, 20 male rats aged 90–100 days and weighing 200–250 g were selected [5]].

Randomization. Block randomization was performed at the litter level (1–2 pups from each litter assigned to each group). The experimental groups were: MS+NaCl (n=14); MS+Exenatide (10 μg/kg, s.c., once daily for 7 consecutive days; n=14).

Assessment of Impulsive Behavior: Probability–Reward Task (Modified Iowa Gambling Task). ДBehavioral impulsivity was assessed using the Probability–Reward Task, a rodent adaptation of the Iowa Gambling Task. The apparatus consisted of a start platform (33×50×35 cm) connected to three maze arms, each 50 cm long and 15 cm wide. An automatic food dispenser was located at the end of each arm (Fig. 1). Each return to the start platform initiated a new reinforcement cycle.

Animals were trained daily for 21 days under restricted feeding conditions (4 h of food access per day) with free access to water. Prior to each session, rats underwent 20 h of food deprivation.

During the first 5 days, a training reinforcement schedule was used: entry into arm 1 delivered one standard food pellet (0.1 g), arm 2 delivered two pellets, and arm 3 delivered three pellets.

Subsequently, animals proceeded to the main training phase. The reinforcement schedule was modified as follows: Arm 1: FR1 (one pellet on every entry); Arm 2: FR2 (two pellets on every second entry); Arm 3: FR3 (three pellets on every third entry).

Thus, no reward was delivered on 50% of entries into arm 2 and on 66.7% of entries into arm 3. Stable learning was defined as a consistent preference pattern maintained for at least three consecutive days. Animals that failed to enter the maze arms (≤15%) were excluded from the experiment [7].

Assessment of Compulsive Behavior: Marble Burying Test. Compulsive and anxiety-related behaviors were evaluated using the Marble Burying Test. Rats were placed individually in standard plastic cages (40×50×20 cm) containing a 5-cm layer of bedding. Twenty glass marbles (1.5 cm in diameter) were evenly distributed across the bedding surface.

Each animal remained in the cage for 30 min, after which the number of partially or completely buried marbles (buried to a depth exceeding two-thirds of their diameter) was recorded [7].

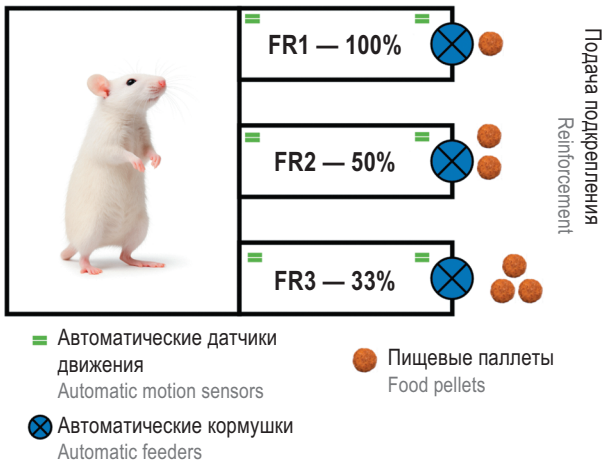


Fig. 1. **Experimental setup for the probability–reward task (modified Iowa Gambling Task). FR1 — one pallet per pass; FR2 — two pallets per every second pass; FR3 — three pallets per every third pass. (compiled by the authors)**

Рис. 1. Схема экспериментальной установки для теста вероятности и величины подкрепления (модифицированный Iowa Gambling Task). FR1 — одна паллета при каждом заходе; FR2 — две паллеты при каждом втором заходе; FR3 — три паллеты при каждом третьем заходе (рисунок составлен авторами)

The number of buried marbles was used as an indicator of compulsive behavior. Following each test session, both the bedding and marbles were replaced to eliminate olfactory influences.

Pharmacological Agents. The GLP-1 receptor agonist exenatide (Exendin-4; Byetta®, AstraZeneca, United Kingdom), a synthetic analogue of endogenous incretin with high affinity for GLP-1 receptors and resistance to degradation by dipeptidyl peptidase-IV, was used as the pharmacological agent.

According to published preclinical studies, exenatide is commonly administered to rodents at doses ranging from 2.4 to 10 μg/kg, producing pronounced behavioral and neurochemical effects without significant somatic adverse effects.

In the present study, exenatide was administered subcutaneously (s.c.) at a dose of 10 μg/kg in a volume of 1 mL/kg once daily for 7 days. Treatment began after the adaptation period. The selected dose and administration regimen were based on previously published data demonstrating the efficacy of GLP-1 receptor agonists in correcting stress-induced and addiction-related behavioral disturbances.

Statistical Analysis. Statistical analyses were performed using GraphPad Prism 10.1 (USA). Data distribution was assessed using the Kolmogorov–Smirnov test. Differences between groups were evaluated using Student's t-test.

Data are presented as mean ± standard error of the mean (M±SEM). Differences were considered statistically significant at $p < 0.05$.

RESULTS

A comparison of the proportion of visits to the first arm in groups subjected to maternal separation and treated either with isotonic sodium chloride solution (MS+NaCl) or a GLP-1 receptor agonist (exenatide, MS+GLP-1 agonist) revealed statistically significant differences.

Figure 2 presents the results of the Probability-Reward Task in rats after maternal separation (MS). Two groups of animals were compared: MS+NaCl rats receiving isotonic sodium chloride solution; and MS+GLP-1 agonist rats treated with a GLP-1 receptor agonist.

In the MS+Ex4 group, the proportion of visits to the first arm was 36.01±2.90%, which was significantly higher than in rats receiving isotonic sodium chloride solution (21.61±1.76%, $t(26)=4.238$, $p=0.0003$). The mean difference was 14.40% with a 95% confidence interval of 7.42–21.38. The coefficient of determination ($\eta^2=0.4085$) indicates that approximately 41% of the variance in this parameter is explained by GLP-1 receptor agonist administration.

When comparing the proportion of visits to the third arm between the same groups, a significant decrease was observed in animals treated with the GLP-1 receptor agonist. The mean proportion of visits to the third arm in the MS+NaCl group was 44.43±2.90%, whereas in the exenatide-treated group this value decreased to 24.40±2.90% ($t(26)=4.803$, $p < 0.0001$). The mean difference was −20.03% with a 95% confidence interval of −28.60 to −11.46. The coefficient of determination ($\eta^2=0.4702$) indicates that approximately 47% of behavioral variability is explained by the effect of GLP-1 receptor activation.

Thus, activation of GLP-1 receptors led to a redistribution of behavioral activity toward arms associated with guaranteed reinforcement, reflecting a shift in motivational decision-making patterns following early-life stress exposure.

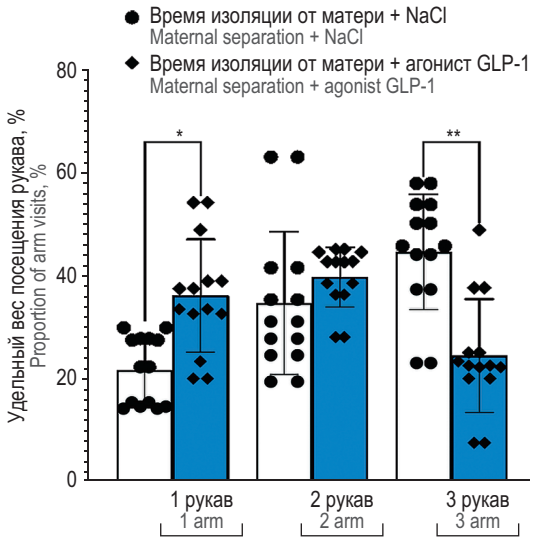


Fig. 2. **Changes in the proportion of arm visits with different reinforcement probabilities in rats after maternal separation following administration of saline or a GLP-1 agonist. Data are presented as mean ± SEM; statistical analysis was performed using Student's t-test; *p <0.01, **p <0.001 (compiled by the authors)**

Рис. 2. Изменение удельного веса посещения рукавов с различной вероятностью подкрепления у крыс после временной изоляции от матери при введении изотонического раствора натрия хлорида и агониста GLP-1. Данные представлены в виде средних значений ± SEM; статистическая обработка — t-критерий Стьюдента; * p <0,01, ** p <0,001 (рисунок составлен авторами)

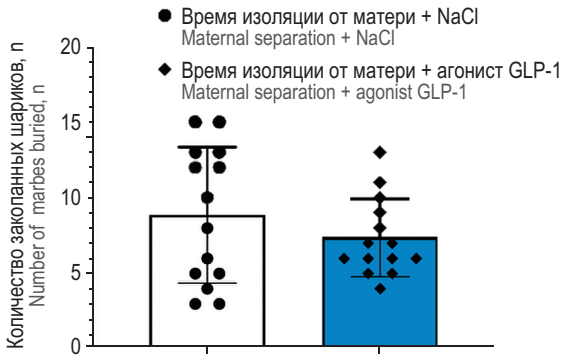


Fig. 3. **Number of marbles buried in the marble burying test in rats after maternal separation following administration of saline or a GLP-1 agonist. Data are presented as mean ± SEM (compiled by the authors)**

Рис. 3. Количество закопанных шариков в тесте закапывания шариков у крыс после временной изоляции от матери при введении изотонического раствора натрия хлорида и агониста GLP-1. Данные представлены как средние ± SEM (рисунок составлен авторами)

Figure 3 presents the results of the Marble Burying Test in rats subjected to maternal separation and treated with either isotonic sodium chloride solution (MS+NaCl) or a GLP-1 receptor agonist (MS+GLP-1 agonist). Both groups demonstrated a similar behavioral trend: animals actively interacted with the environment and buried marbles; however, administration of the GLP-1 receptor agonist did not produce statistically significant changes in the number of buried marbles compared with the control group ($p > 0.05$, Student's t-test).

The mean number of buried marbles was 8.2±0.7 in the MS+NaCl group and 7.1±0.6 in the MS+GLP-1 agonist group. Despite a slight trend toward reduction in the treated group, the differences were not statistically significant.

DISCUSSION

The maternal separation model used in this study represents one of the most valid and reproducible experimental approaches for modelling stress-induced disturbances of emotional and behavioral regulation [16, 17]. Prolonged separation of pups from the mother during the early postnatal period is accompanied by activation of the hypothalamic–pituitary–adrenal axis and the development of persistent alterations in dopaminergic and serotonergic brain systems, leading to increased impulsivity, anxiety, and the emergence of rigid behavioral patterns in adulthood [18].

The present data demonstrate that pharmacological activation of GLP-1 receptors with exenatide in animals exposed to early postnatal stress selectively corrects the impulsive component of decision-making, shifting behaviour from risky strategies toward predictable reinforcement. This is directly reflected in the redistribution of arm choices in the modified Probability–Reward Task: in rats treated with exenatide, the proportion of visits to the arm with guaranteed reinforcement (FR1) was significantly higher than in animals receiving isotonic sodium chloride solution (36.01±2.90% vs. 21.61±1.76%; $t(26)=4.238$; $p=0.0003$), whereas the number of visits to the "risky" arm (FR3) was significantly reduced (24.40±2.90% vs. 44.43±2.90%; $t(26)=4.803$; $p < 0.0001$). The absence of significant changes in the marble burying test highlights the selectivity of exenatide's effect: the intervention modulates impulsivity but does not affect compulsive or stereotyped behavioral patterns, where rigidity and perseveration play a dominant role. It should be noted that the marble burying test integrates an anxiety-related component as well, which limits its sensitivity to changes in cognitive rigidity; thus, the observed dissociation between impulsivity and compulsivity is not only methodologically plausible but also conceptually expected, supporting the relative independence of these constructs within a broader impulsive–compulsive spectrum.

These findings are consistent with evidence on the central role of the GLP-1 system in regulating motivational and reward-related behaviour. GLP-1 receptors are expressed in key reward-processing structures (NAc, VTA, amygdala, hypothalamus), and GLP-1 agonists are capable of modulating mesolimbic pathway activity [20, 21]. Inhibition of the GLP-1 system during early ontogenesis also produces significant behavioral changes: neonatal administration of the dipeptidyl peptidase IV inhibitor diprotin A, which blocks degradation of endogenous incretins, leads to a hyperactive phenotype and persistent increases in aggression in adult rats [22].

Against this background, the observed shift from risky to predictable behavioral strategies following exenatide administration extends the known effects of GLP-1 agonists (suppression of conditioned place preference, cocaine self-administration, and reinstatement of drug seeking) from the domain of "drug-related motivation" to stress-induced decision-making impulsivity [23–27].

Thus, the combined experimental and literature data support the view of the GLP-1 system as an important neuropeptidergic component integrating metabolic and motivational mechanisms of behavioral regulation.

CONCLUSION

1. The GLP-1 receptor agonist exenatide demonstrates a pronounced anti-impulsive effect, manifested by a reduction in risky choices and an increased preference for stable reinforcement in rats subjected to early-life stress, thereby supporting the regulatory role of the GLP-1 system in mechanisms of impulse control.

2. Administration of a GLP-1 receptor agonist does not significantly affect measures of compulsive behaviour in the marble burying test, which may indicate a selective action of the GLP-1 system predominantly on impulsivity-related behavioral components.

ADDITIONAL INFORMATION

Author contributions. N.S. Dedanishvili — experimentation, writing and editing; S.S. Purveev — experimentation, writing and editing, and study concept; A.A. Lebedev, A.G. Vasiliev, A.V. Vasilyeva, M.A. Pakhomova— writing and editing; P.D. Shabanov — writing and editing, and supervision.

All authors made a significant contribution to the concept development, study execution, and preparation of the article, and read and approved the final version prior to publication.

Conflict of interest. The authors declare no actual or potential conflicts of interest related to the publication of this article.

Experiments with animals were carried out in accordance with international rules (Directive 2010/63/EU of the European Parliament and of the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Н.С. Деданишвили — проведение экспериментов, написание и редактирование текста; С.С. Пюрвеев — проведение экспериментов, написание и редактирование текста, концепция исследования; А.А. Лебедев, А.Г. Васильев, А.В. Васильева, М.А. Пахомова — написание и редактирование текста; П.Д. Шабанов — написание и редактирование текста, руководство.

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

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

Эксперименты с животными проводили в соответствии с международными правилами (Директивой 2010/63/EU Европейского парламента и Совета Европейского союза от 22 сентября 2010 г. по охране животных, используемых в научных целях).

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Quantitative electroencephalography analysis data in outpatient patients with psychosomatic manifestations following COVID-19

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Abstract. ***Introduction.*** The electroencephalography is considered as the most important tool for assessing the spatiotemporal features of the electrical activity of the brain in the examination of patients with neurological manifestations of COVID-19, especially in cases of encephalopathy, seizures and epileptic status. ***Aim.*** It was planned to identify various electroencephalography patterns characteristic of the COVID-19 group of patients with visual electroencephalography analysis and to evaluate possible focal changes using quantitative methods such as spectral and coherent analysis. ***Materials and methods.*** The electroencephalography of 125 outpatient patients aged 16 to 68 years who were under observation at a neuropsychiatric dispensary with a history of COVID-19 and psychosomatic complaints at the time of the examination was recorded. The control group consisted of 45 healthy subjects. ***Results.*** The obtained results made it possible to divide the results of electroencephalography registration and analysis into three types of patterns: polymorphic low-frequency activity; low-frequency polymorphic activity with a predominance of slow waves (delta and theta bands); high-frequency electroencephalography with a dominant in the beta1 band. ***Conclusions.*** The formation of focal changes of a slow-wave nature with a characteristic localization in the right temporal region is noted in 20% of patients. The correlation index in the alpha range is stable for the electroencephalography of the control group, where 90% of the subjects had correlation coefficients in the alpha range of more than 0.6. On the contrary, a polymorphic pattern is observed among patients, stable indicators with a coefficient of more than 0.6 for all studied connections, both between the hemispheres and within the hemispheres, were recorded only in 25% of cases. The analysis of coherence coefficients in patients, on the contrary, shows a higher stability of interhemispheric connections and various options for reducing connections within the hemispheres, which often have a mirror character.

Keywords: electroencephalography, post-COVID condition, EEG spectral analysis, EEG coherence analysis

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Количественный анализ электроэнцефалографии у амбулаторных пациентов с психосоматическими проявлениями после COVID-19

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Резюме. ***Введение.*** Электроэнцефалографию рассматривают как наиболее важный инструмент для оценки пространственно-временных особенностей электрической активности мозга при обследовании пациентов с неврологическими проявлениями COVID-19, особенно при проявлении энцефалопатии, судорог и эпилептического статуса. ***Цель исследования*** — выделить различные паттерны электроэнцефалограммы, характерные для группы пациентов, перенесших COVID-19, при визуальном анализе электроэнцефалограммы и с помощью количественных методов — спектрального и когерентного анализа, оценить возможные очаговые изменения. ***Материалы и методы.*** Регистрировали электроэнцефалограмму 125 амбулаторных пациентов в возрасте от 16 до 68 лет, находящихся под наблюдением в психоневрологическом диспансере с COVID-19 в анамнезе и психосоматическими жалобами на момент обследования. Контрольную группу составили 45 здоровых испытуемых. ***Результаты.*** Данные регистрации и анализа электроэнцефалограммы были разделены на три типа паттернов: полиморфная низкочастотная активность; низкочастотная полиморфная активность с преобладанием медленных волн (дельта- и тета-диапазоны); высокочастотная электроэнцефалограмма с доминантой в бета-1-диапазоне. ***Выводы.*** Отмечено формирование очаговых изменений медленноволнового характера с характерной локализацией в правой височной области у 20% пациентов. Индекс корреляции в альфа-диапазоне стабилен для электроэнцефалографии контрольной группы, где у 90% испытуемых коэффициенты корреляции в альфа-диапазоне были более 0,6. Напротив, среди пациентов наблюдалась полиморфная картина, стабильные показатели с коэффициентом более 0,6 для всех изученных связей как между полушариями, так и внутри полушарий были зарегистрированы только в 25% случаев. При анализе коэффициентов когерентности у пациентов отмечены более высокая стабильность межполушарных связей и различные варианты ослабления связей внутри полушарий, которые часто носят зеркальный характер.

Ключевые слова: электроэнцефалография, ЭЭГ, постковид, спектральный анализ, когерентный анализ ЭЭГ

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INTRODUCTION

The period of the spread of coronavirus infection (COronaVIrus Disease 2019, COVID-19) was marked by an explosive surge in research across virology, epidemiology, infectious diseases, clinical physiology, and pharmacology. It became evident that the changes induced by the infection pertain to the interests of the most diverse, and often highly specialized, fields of medical science. Numerous specialists in laboratories around the world are observing a variety of specific and nonspecific manifestations of the consequences of coronavirus infection, both proximate in the history and quite remote. Scientific debate continues as to whether the nonspecific, yet similar, findings in a series of published cases of COVID-19-associated encephalopathy (disorganized background activity with diffuse slowing and frontal predominance, accompanied by low reactivity) can be considered distinctive features of COVID-19 or whether, conversely, these findings stem from a multifactorial origin not directly caused by the virus [1–7]. Furthermore, the interest in electroencephalography (EEG) findings in COVID-19 is driven by analogous results observed in a number of neurological conditions — viral encephalitis/encephalopathy associated with COVID-19, epilepsy, as well as demyelinating and neurodegenerative processes [1, 8, 9]. Neurological complications arise in one-third (34.6%) of patients with severe COVID-19 and include stroke, headache, and seizures [10]. In publications addressing EEG in COVID-19, the number of patients ranges from isolated cases [8, 11, 12] to 100 [13, 14]. The findings of these studies are heterogeneous, encompassing both normal EEG [15] and diffuse slowing in all cases [16–18]. Some works have demonstrated a predominance of frontal changes [1, 7, 19, 20].

The most common EEG finding, observed in two-thirds (68.6%) of patients, is a generalized reduction in the mean frequency of oscillations [21–23]. This may serve as a marker of diffuse nonspecific encephalopathy, the most prevalent brain abnormality in this disease. Other EEG signs indicative of diffuse encephalopathy include generalized rhythmic delta activity and generalized periodic discharges with triphasic morphology [24–26]. Lateralized periodic and rhythmic patterns, characteristic of concomitant focal dysfunction in some patients, are also recorded. Epileptiform abnormalities are not uncommon in the studied EEGs (13.0%), suggesting heightened cortical excitability preceding seizure events. Indeed, 5.5% of patients experienced seizures or status epilepticus [27, 28]. Studies occasionally note characteristic frontal abnormalities, which correlates with the presumed entry of COVID-19 into the brain [8, 16, 17, 19, 20].

Early clinical manifestations of COVID-19, such as anosmia and ageusia, are thought to be linked to viral entry into the nasal and oral mucosa, a process facilitated by ACE-2 receptors (angiotensin-converting enzyme 2) [27–29]. Subsequent spread to the orbitofrontal region [29] via afferent nerves leads to predominant involvement of the olfactory bulb and orbitofrontal/frontal areas, which may explain the emergence of focal EEG changes in frontal leads [28]. Several authors have proposed frontal epileptiform discharges as biomarkers of COVID-19 [8, 12, 16, 32, 33]. Approximately half of all recorded epileptic events (10 of 22) originate in the frontal lobes, compared with 18% (4 of 22) in the occipital lobe. Beyond the frontal lobe, COVID-19 may also affect the piriform cortex, limbic structures, thalamus, hypothalamus, brainstem, and autonomic structures [30, 31, 34–36]. Investigators have sought to link diverse EEG findings in patients with prior COVID-19 to other factors, such as lung injury with subsequent hypoxia, cardiac arrest, metabolic derangements, systemic inflammatory response syndrome, hypercoagulability, vasculitis, and stroke, among others. Evidence indicates that the severity of EEG abnormalities correlates with blood oxygen saturation upon hospital admission, though this relationship has yet to be confirmed by neuroimaging data [37]. In addition, EEG changes may also be attributable to pre-existing neurological conditions, such as epilepsy [19, 38, 39]. Thus, to date, no single EEG pattern has been identified that would develop within a short time frame from the onset of COVID-19 spread. The spectrum of neurophysiological changes will undoubtedly be very broad and polymorphic; however, a statistically robust analysis of large datasets will reveal avenues for further investigation. Furthermore, intriguing incidental findings remain a distinct possibility.

AIM

The aim of this study was to identify EEG patterns characteristic of the patient group by means of both classical visual EEG analysis and quantitative methods — spectral and coherence analysis — and to detect possible focal changes emerging on EEG as sequelae of COVID-19.

MATERIALS AND METHODS

Outpatient patients undergoing routine diagnostic workup and treatment at the Saint Petersburg State Budgetary Healthcare Institution “Psychoneurological Dispensary No. 1” (PND) were examined. Two groups, A and B, were formed for the analysis. Group A comprised 125 patients (age range 18–68 years, 68 women

and 57 men) who had sustained COVID-19 3 to 12 months prior to examination and presented with various psychosomatic complaints that had prompted them to seek psychotherapeutic care. Group B (control) consisted of 45 healthy subjects (with an age and sex distribution matching that of Group A) undergoing fitness-for-duty evaluation with no history of coronavirus infection.

EEG was recorded in accordance with the international 10–20 system using 16 monopolar leads (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, P3, P4, O1, O2) in a standard reference montage (the reference electrode was placed over the subjects' left zygomatic region). EEG recordings were obtained using the Mitsar-EEG-202 hardware-software system. Routine functional tests were performed during the examination, including eyes-open and eyes-closed tests, intermittent photic stimulation at varying frequencies (1–15 Hz range), and a three-minute hyperventilation test with forced breathing.

Computer analysis was performed using WinEEG 2.1 and Loreta-Key Viewer 04 software. EEG recordings were initially assessed visually with respect to frequency and amplitude parameters, rhythm distribution over the convexital surface, and the degree of rhythm desynchronization upon eye opening and/or the appearance of single photic stimuli. Using quantitative EEG methods, spectral power was determined in the main frequency bands, with correlation coefficients taken into account when comparing intrahemispheric and interhemispheric interactions.

The parameters for spectral power estimation were as follows: an epoch of 10 s duration was selected, with an analysis period of 5 s. The following additional parameters were applied: 50% overlap between analysis periods, a Hann window, and a low-frequency signal filter in the 0.25–1.25 Hz range. Furthermore, the mean power spectrum was calculated for all recording channels of the selected artifact-free EEG segments. The results obtained were converted into percentages such that the total sum across all frequency bands for each lead under study equaled 100%.

Local changes in spectral power were visualized by means of low-resolution electromagnetic tomography (LORETA), the results of which were presented as two-dimensional maps of distribution across anatomical structures. Statistical data processing was carried out using Microsoft Office Excel, SPSS, and Statistics 17.0 software. The reliability of the findings was assessed using Student's t-test. Differences were considered statistically significant at a significance level of $p < 0.05$.

RESULTS

Visual analysis of EEG recordings from COVID-19 convalescent outpatients revealed a tendency toward diminished alpha rhythm expression. Alpha activity emerged with a delay both at recording onset and upon resumption following the eyes-open/eyes-closed test or single photic stimuli. It is well established that in healthy individuals, the emergence of a stable, high-amplitude alpha rhythm at the beginning of an EEG recording under standard conditions (dimmed light, muscle relaxation, silence) varies temporally (from 1 s to 1 min in 90% of those examined).

For data comparison, we employed the alpha rhythm recovery test after eye opening followed by eye closure, with the «eyes closed» timestamp in the EEG file serving as the reference point. Among healthy participants (control group), a stable alpha rhythm emerged within 1–2 s in 80% of cases. In study Group A, alpha rhythm recovery occurred within 5–10 s in 60% of participants.

Fig. 1 presents a fragment of the baseline EEG illustrating this phenomenon. The patient, a 48-year-old man, complained of poor sleep, inability to concentrate, and impaired attention and memory. He had sustained coronavirus infection 4 months prior, had been managed on an outpatient basis, with an acute phase lasting no fewer than 20 days; computed tomography revealed pneumonia typical of COVID-19. Notably, Group A participants exhibited a reduction in alpha rhythm amplitude. Concurrently, the frequency values of this rhythm in these patients lay closer to the upper boundary of the range (11–12 Hz versus 9–10 Hz in the control group).

In the present study, comparison of EEG spectral power between the two groups revealed a consistent reduction in the alpha-band index in patients who had sustained COVID-19, whereas the EEG of healthy individuals demonstrated a clear predominance of the alpha rhythm on both visual analysis and spectral power estimation. Fig. 2 shows a "brighter" red-to-yellow spectrum corresponding to a high level of alpha-band oscillations, together with its symmetrical distribution and a maximum value in the occipital region. This pattern of spectral power distribution is characteristic of 70% of healthy individuals. Visually, such EEG recordings are assessed as patterns with a dominant alpha rhythm.

In Group A (outpatients), a broader distribution of spectral power variants across different EEG frequency bands is observed, satisfying the criterion of statistical significance ($p < 0.05$) relative to the spectral power data from the healthy group. The traditional



Fig. 1. **Electroencephalogram of a 48-year-old man who recovered from COVID-19. Delayed alpha rhythm recovery after eye closure. Markers indicate a steady increase in the alpha frequency range index from the 5th second (photo from the archive of PND No. 1, 2022–2023)**

Рис. 1. Электроэнцефалограмма мужчины, перенесшего COVID-19, 48 лет. Замедление восстановления альфа-ритма после закрытия глаз. Маркеры указывают на устойчивое увеличение индекса альфа-диапазона с 5-й секунды (фото из архива ПНД № 1, 2022–2023 гг.)

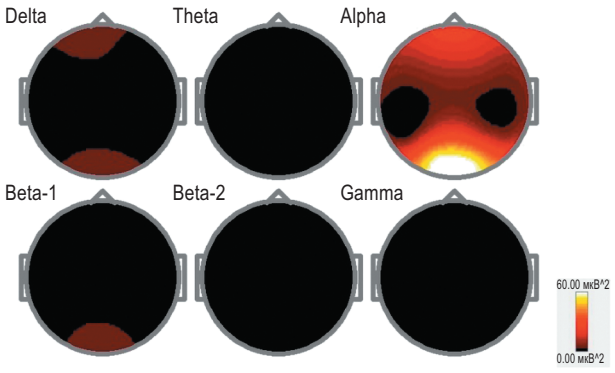


Fig. 2. **Distribution of electroencephalogram spectral power in a healthy subject (male, 45 years old) from control group B (photo from the archive of PND No. 1, 2022–2023)**

Рис. 2. Распределение спектральной мощности при выполнении электроэнцефалографии у здорового испытуемого (мужчина, 45 лет) из контрольной группы В (фото из архива ПНД № 1, 2022–2023 гг.)

alpha rhythm dominance occurs considerably less often (20%). In the majority of patients (62%), the EEG is characterized by a distribution of biosignals spanning all bands from delta to beta-2 waves. In such cases, no stable dominant rhythm can be identified (Fig. 3).

Figs. 3 and 4 present EEG frequency analysis maps along with the electromagnetic brain tomography results of a 50-year-old male patient who had sustained moderate COVID-19. Six months earlier, he had been treated in a general hospital with subsequent transfer to an infectious disease unit. Although the patient considers himself recovered and has resumed work, he complains of persistent signs of asthenia with autonomic dysfunction: general weakness, excessive sweating, and, consequently, a loss of vital energy.

Analysis of the data revealed the formation of a localized focus of slow-wave activity in the delta range (and, to a lesser extent, in the theta range) in the right cerebral hemisphere, with the greatest prominence in the temporal region. This local phenomenon is clearly visualized on the two-dimensional map generated by low-resolution electromagnetic tomography (LORETA): the red arrow marks a zone of increased spectral power in the right temporal lobe (see Fig. 4). Such focal dominance was recorded in 20% of the patients comprising Group A. Notably, on visual assessment, EEG recordings of this type are classified as low-amplitude polymorphic activity.

The third EEG variant observed in the patient group (approximately 20%) is characteristic of a broad range of psychosomatic patients and is therefore regarded as nonspecific. This variant is distinguished by a shift of spectral power into the beta-1 and beta-2 bands, with the emergence of two “centers of activity” — in the alpha and beta regions (Fig. 5). Visually, such EEG variants are assessed as high-frequency patterns with a noticeable beta-1 band dominance and fragmentary, weakly expressed alpha activity. In their reports, specialists frequently employ the phrase “flat EEG”.

Table 1 presents summarized data on spectral power (μV) across the frequency bands studied. Cells demonstrating an accent of spectral power in the right temporal region are highlighted.

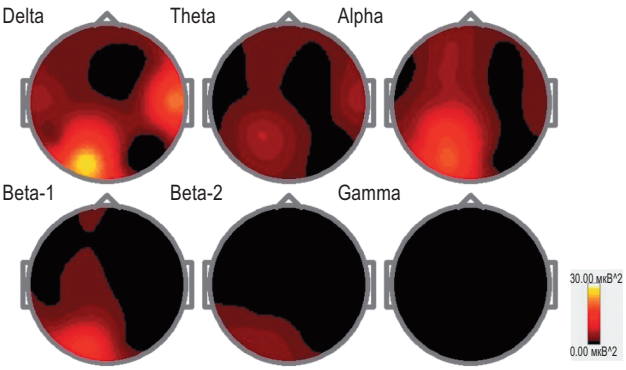


Fig. 3. **Spectral power of the electroencephalogram in the subject of the experimental group A (male, 55 years old). The signal distribution is visible in all ranges from delta to beta-2 (photo from the archive of PND No. 1, 2022–2023)**

Рис. 3. Спектральная мощность электроэнцефалографии у испытуемого опытной группы А (мужчина, 55 лет). Видно распределение сигнала по всем диапазонам от дельта до бета-2 (фото из архива ПНД № 1, 2022–2023 гг.)

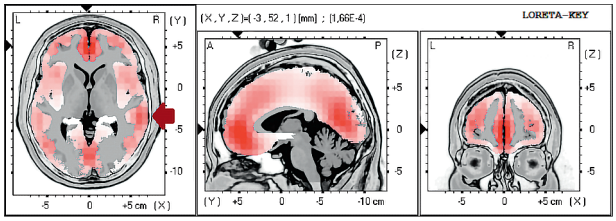


Fig. 4. **Low-resolution electromagnetic tomography of the LORETA — visualization of local changes in the right temporal region (the same subject, Fig. 3) (photo from the archive of PND No. 1, 2022–2023)**

Рис. 4. Электромагнитная томограмма низкого разрешения LORETA — визуализация локальных изменения в правой височной области (тот же испытуемый, рис. 3) (фото из архива ПНД № 1, 2022–2023 гг.)

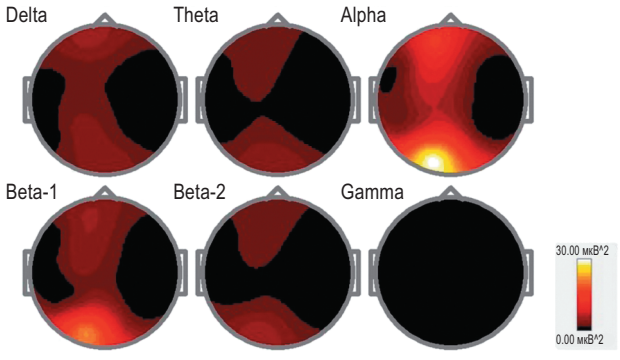


Рис. 5. **Распределение спектральной мощности у пациента группы А (женщина, 38 лет). Отмечается формирование двух акцентов в бета-1- и альфа-диапазонах (фото из архива ПНД № 1, 2022–2023 гг.)**

Fig. 5. Spectral power distribution in a patient, group A (female, 38 years old). Two accents in the beta-1 and alpha bands are noted (photo from the archive of PND No. 1, 2022–2023)

Among the systemic findings, the considerable divergence in EEG spectral power between patients and healthy subjects with respect to oscillations in the slow bands — delta and theta rhythms — is particularly noteworthy. Although the amplitude of these rhythms is reduced in patients, their spectral expression is considerably higher. A certain predominance in the right temporal EEG recording sites is also notable. The spectral power of the alpha rhythm is higher in healthy individuals than in patients; however, substantial differences are recorded only in the frontal and occipital regions. Following the determination of EEG spectral power, coherence analysis was performed to compare interhemispheric and intrahemispheric interactions. In healthy subjects (Group B), high correlation coefficients are consistently observed both between hemispheres (in the Fp1–Fp2, C3–C4, F7–F8, T3–T4, T5–T6, P3–P4, and O1–O2 pairs) and within hemispheres (in the Fp1–T3, Fp1–C3, Fp2–C4, Fp2–T4, T3–O1, C3–O1, T4–O2, and C4–O2 pairs) (Fig. 6).

In the control group, the alpha correlation index remained stable throughout the 10-second EEG segment selected for analysis. In 90% of the subjects in this group, alpha rhythm correlation coefficients exceeded 0.6. By contrast, the patients exhibited a heterogeneous EEG picture. Stable values with a coefficient above 0.6 across all interhemispheric and intrahemispheric connections studied were recorded in only 25% of participants, a statistically significant difference from the control group ($p < 0.05$). In the majority of the remaining cases, weakened interaction between individual pairs of leads was noted, predominantly in the temporal regions (T3 and/or T4).

As an illustration of coherence analysis, we present the case of Patient S., a 50-year-old man who sustained moderate COVID-19 requiring hospitalization and intensive care unit treatment (Fig. 7). Six months after recovery, the patient complained of intermittent muscle pain, reduced work capacity, and poor sleep. EEG analysis revealed a decreased interhemispheric correlation coefficient at T3–T4, along with reduced intrahemispheric interactions in the Fp1–T3 and T4–O2 derivations.

Examination of coherence measures in Group A patients demonstrated enhanced stability of interhemispheric interaction against a background of diverse manifestations of weakened intrahemispheric connectivity, often exhibiting mirror symmetry. As an example of coherence analysis, Fig. 8 presents the case of Patient K., a 55-year-old woman who had sustained moderate coronavirus infection approximately six months earlier, with initial admission to a general hospital and

Table 1

Electroencephalography spectral power (μV) in delta, theta, and alpha bands

Таблица 1

Спектральная мощность электроэнцефалографии (мкВ) в дельта-, тета- и альфа-диапазонах

ЭЭГ-отведение EEG-Ableitung	Опытная группа (A) An experienced group (A)			Контрольная группа (B) The control group (B)		
	дельта delta	тета theta	альфа alpha	дельта delta	тета theta	альфа alpha
Fp1	5±1,2**	10±4,2**	12±4,5**	0,2±0,1	5±2,2	21±7,8
Fp2	6±2,1**	11±4,6**	17±6,4	0,3±0,1	5±2,3	19±7,5
F3	5±2,2**	9±3,9**	16±5,4	0,1±0,1	4±1,9	17±6,8
F4	4±1,9**	10±4,1**	17±6,5	0,2±0,1	3±1,6	19±7,6
F7	5±2,3**	11±4,5**	15±5,0	0,3±0,1	3±1,7	16±6,5
F8	4±1,7**	8±3,8*	19±7,9	0,3±0,1	4±1,8	22±8,1
C3	2±1,4*	10±4,1**	11±3,9	0,3±0,1	3±1,6	12±4,7
C4	1±0,6*	9±3,7**	10±3,6	0,2±0,1	3±1,6	10±4,4
T3	3±1,6**	11±4,3**	16±5,6	0,3±0,1	2±1,4	17±6,7
T4	6±4,5**	15±5,9**	14±4,8	0,4±0,1	3±1,5	15±4,3
T5	3±1,7**	10±4,5**	18±7,6	0,3±0,1	3±1,6	20±7,5
T6	7±5,6**	14±5,7**	16±5,4	0,2±0,1	2±1,4	18±6,9
P3	4±1,9**	9±3,8**	19±7,8*	0,4±0,2	3±1,6	25±10
P4	4±1,9**	10±4,1**	20±8,1	0,3±0,1	3±1,5	22±9,5
O1	6±4,3**	11±4,4**	22±8,8**	0,2±0,1	4±1,8	35±11,3
O2	6±4,5**	10±4,2*	24±10,1**	0,3±0,1	5±2,0	32±11,1

Reliability * p <0.05; **p <0.01.
Достоверность * p <0,05; **p <0,01.

The table is prepared by the authors
Таблица составлена авторами

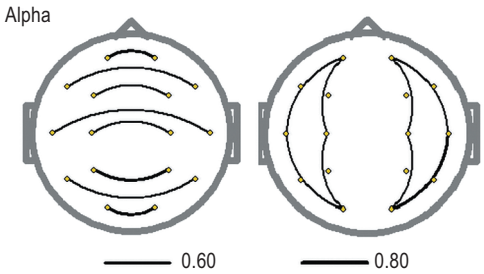


Fig. 6. **The ratio of interhemispheric and intrahemispheric interaction between points according to the 10/20 system in the alpha band in the studied control group (female electroencephalogram, 35 years old) (photo from the archive of PND No. 1, 2022–2023)**

Рис. 6. Соотношение межполушарного и внутриполушарного взаимодействия между точками в соответствии с системой 10/20 в альфа-диапазоне в исследуемой контрольной группе (электроэнцефалограмма женщины, 35 лет) (фото из архива ПНД № 1, 2022–2023 гг.)

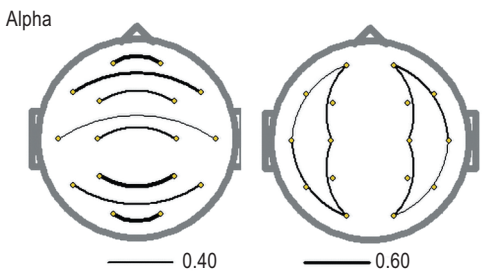


Fig. 7. **Ratio of interhemispheric and intrahemispheric interaction between leads according to the 10/20 system in the alpha band, patient C. (male electroencephalogram, 50 years old) (photo from the archive of PND No. 1, 2022–2023)**

Рис. 7. Соотношение межполушарного и внутриполушарного взаимодействия между отведениями в соответствии с системой 10/20 в альфа-диапазоне, пациент С. (электроэнцефалограмма мужчины, 50 лет) (фото из архива ПНД № 1, 2022–2023 гг.)

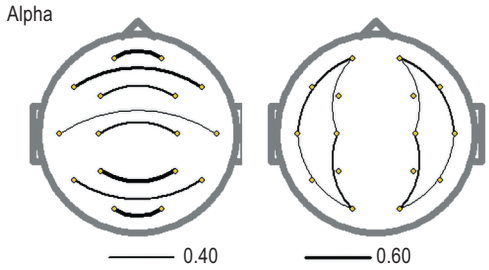


Fig. 8. **The ratio of interhemispheric and intrahemispheric interaction between the leads according to the 10/20 system in the alpha range. Group A, electroencephalogram of a woman, 55 years old (photo from the archive of PND No. 1, 2022–2023)**

Рис. 8. Соотношение межполушарного и внутриполушарного взаимодействия между отведениями в соответствии с системой 10/20 в альфа-диапазоне. Группа А, электроэнцефалограмма женщины, 55 лет (фото из архива ПНД № 1, 2022–2023 гг.)

subsequent transfer to an infectious disease unit. The patient rates her condition as "recovered" and has returned to work; however, she complains of symptoms of asthenia with autonomic dysfunction, namely loss of strength, excessive sweating, and, consequently, diminished interest in life. A reduction in the interhemispheric coherence coefficient is observed exclusively in the T3–T4 derivation, whereas weakened intrahemispheric interactions are evident in four lead pairs: Fp1–C3, T3–O1, Fp2–C4, and T4–O2.

DISCUSSION

Analysis of the EEG findings in patients with COVID-19, together with data from the literature spanning 2020–2025, indicates that the principal EEG observations center on reduced voltage (amplitude) of biosignals and various patterns of polymorphic activity, with a predominance of particular EEG rhythms in localized areas of the convexital surface. In patients with a neuropsychiatric profile, sustained coronavirus infection is characterized on EEG by a number of distinctive features. These include diminished cortical reactivity and, most notably, altered alpha rhythm parameters [40]. A marked shift in the EEG spectral power picture is observed, driven by an expansion of the dominant frequency bands to encompass those closest to the alpha range — namely, the beta and theta bands. Coherence analysis reveals that high interhemispheric correlation coefficients are preserved, whereas intrahemispheric connections, by contrast, are reduced in number, often involving the temporal leads.

As an intriguing and potentially specific feature of the analysis, we highlight a characteristic shift in spectral power within the slow-wave bands, accompanied by a phase of excitation in the right temporal region. Low-amplitude EEG patterns are recorded in approximately 10% of normal healthy individuals [27, 41]. These patterns do not exhibit the generation of a dominant alpha rhythm, show reduced reactivity, and display an intermingling of beta and alpha frequencies. In a series of studies, an EEG amplitude not exceeding 20 μV, with rare instances of reactivity, has been documented in 100% of patients.

During standard sleep EEG recording, it has been demonstrated that, upon spontaneous sleep onset, sleep spindles are either absent or poorly expressed. Follow-up examinations of patients with a favorable COVID-19 outcome have revealed a posterior dominant theta rhythm, thereby ruling out a physiological absence of the posterior alpha rhythm [15, 27, 29, 42–44].

Low-voltage EEG patterns, or those of generalized suppression, are frequently associated with extensive cortical and subcortical injury, such as anoxic encephalopathy or severe traumatic brain injury. This pattern has been found to precede an unfavorable prognosis (a score of 4 on the 11-grade qualitative EEG classification scale) or irreversible processes [45, 46]. Similar findings have been reported in ischemic encephalopathy [47, 48], with the notable exception of hypothyroid encephalopathy, which is considered reversible [27]. Low-voltage EEG has also been described in cases of diffuse neuronal dysfunction induced by hypothermia or intoxication with central nervous system depressants [48].

A review of the literature reveals a substantial body of fragmented data on the sensitivity of spectral power in both acquired and congenital conditions that pathologically alter brain activity. In particular, increased power in the slow delta and theta bands has been demonstrated in patients with acute cerebrovascular accidents, with clear positive dynamics by day 14 in the absence of localized foci of slow activity [44, 49]. Several authors report increased delta band spectral power in patients with concomitant organic brain lesions [9, 44, 49]. At the same time, significant changes in the spectral characteristics of the EEG in schizophrenia have been identified solely through the analysis of responses to auditory or visual stimuli [42, 43].

It must be borne in mind that the brain cannot function in "isolation" from the rest of the body. Alterations in the functioning of multiple internal organs influence brain activity via psychosomatic connections, which implies corresponding changes in EEG spectral power. For instance, increased spectral power in the beta-1 and alpha bands has been described in various endocrine pathologies [27]. A number of articles on EEG and COVID-19 make reference to background stress arising from physi-

cal activity [50–52]. Some authors detect low-amplitude EEG oscillations yet attribute these to metabolic or ischemic changes.

One particular concern is that EEG studies are at times conducted using a methodology that deviates from the standard—specifically, employing fewer than 10 electrodes rather than the recommended 21 (to reduce the risk of COVID-19 transmission). According to currently accepted normative amplitude values, as well as the criteria set forth by the American Clinical Neurophysiology Society for the standardization of EEG terminology, 21-electrode EEG caps are employed in intensive care settings and are regarded as the "gold standard". It is well established that interelectrode distance influences oscillation amplitude; consequently, recordings obtained with fewer electrodes double the interelectrode spacing and yield higher amplitudes, and should therefore be interpreted against their own normative values [37, 53]. These considerations, however, pertain more to bipolar than to monopolar recordings [54].

Nonspecific EEG changes have also been described in patients with COVID-19, distinct from those seen in other infectious or metabolic encephalopathies. A reduction in spectral power has been documented as a distinguishing feature, resembling the pattern observed in severe encephalopathic states associated with a poor prognosis. This picture was noted both in intensive care units and on standard wards, and in patients with either favorable disease progression or progressive deterioration alike. At the same time, among patients with a favorable outcome, these changes tended toward EEG normalization. On the basis of these EEG findings, a metabolic/hypoxic mechanism appears improbable. The low EEG amplitude, possibly attributable to desynchronization, may account for the minimal prevalence of epileptiform activity reported in patients with COVID-19 [28].

Thus, EEG represents an important tool in the management and diagnosis of patients with neurological manifestations of COVID-19, particularly in those with encephalopathy, seizures, and status epilepticus. Abnormalities, where present, encompass slowing, periodic discharges, epileptiform discharges, seizures, and status epilepticus—findings indicative of localized dysfunction, nonspecific encephalopathy, and cortical hyperexcitability in this condition. The extent of EEG abnormalities depends on the diagnosis of COVID-19, the duration of follow-up, pre-existing neurological conditions such as epilepsy, and disease severity. EEG abnormalities affecting the frontal lobes appear to be prevalent in patients with COVID-19-associated encephalopathy and may be proposed as a potential biomarker, provided they are consistently documented.

CONCLUSION

1. Visual EEG analysis permits the classification of post-COVID-19 sequelae into three distinct groups. In the majority of those examined (62%), the EEG demonstrates a uniform distribution of bioelectrical activity across all frequency bands studied, from delta to beta-2 waves. In such instances, clear identification of a dominant frequency proves challenging. This phenomenon may be interpreted as a variant of polymorphic low-frequency activity.

2. The EEG recordings of the second group are characterized by polymorphic low-frequency activity with prominent delta and theta rhythms.

3. The third group comprised EEG recordings marked by a predominance of the high-frequency beta-1 band and minimal alpha rhythm presence, a pattern designated as "flat EEG".

4. Focal slow-wave changes with a characteristic localization in the right temporal region are noted in 20% of patients.

5. In the control group, the alpha band exhibits stable correlation coefficients, with correlation coefficients exceeding 0.6 in the overwhelming majority (90%) of participants. By contrast, the patients present a heterogeneous picture: consistently high values (above 0.6) across all connections studied—both interhemispheric and intrahemispheric—were recorded in only a quarter (25%) of subjects. Coherence analysis in patients revealed an inverse trend: enhanced stability of interhemispheric connections accompanied by variable attenuation of intrahemispheric interactions, often exhibiting mirror symmetry.

ADDITIONAL INFORMATION

Author contribution. N.Yu. Kipyatkov — collection of materials, writing the original text; S.A. Lytayev — development of the research concept, scientific and technical editing; N.V. Skrebtsova — analysis of the obtained results, performing statistical analysis; V.V. Gaivoronskaia — analysis of the obtained results, selection of literary sources; K.A. Belskaya — selection of literary sources, performing statistical analysis.

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

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Н.Ю. Кипятков — сбор материала, написание исходного текста; С.А. Лытаев — разработка концепции исследования, научное и техническое редактирование; Н.В. Скребцова — анализ полученных результатов, выполнение статистического анализа; В.В. Гайворонская — анализ полученных результатов, подбор литературных источников; К.А. Бельская — подбор литературных источников, выполнение статистического анализа.

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

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

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

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Endovascular revascularization in case of femoropopliteal artery occlusion

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Abstract. Effective revascularization for patients with peripheral artery disease is much more than an elementary procedure. The approach to the patient with symptom-limiting intermittent claudication or limb-threatening ischemia begins with understanding the population at risk and variation in clinical presentation. The urgency of revascularization varies significantly by presentation; from patients with intermittent claudication who should undergo structured exercise rehabilitation before revascularization (if needed) to those with acute limb ischemia, a medical emergency, who require revascularization within hours. Recent years have seen the rapid development of new tools including wires, catheters, drug-eluting technology, specialized balloons, and biomimetic stents. Open surgical bypass remains an important option for those with advanced disease. The strategy and techniques employed vary by clinical presentation, lesion location, and lesion severity. There is limited level 1 evidence to guide practice, but factors that determine technical success and anatomic durability are largely understood and incorporated into decision-making. Following revascularization, medical therapy to reduce adverse limb outcomes and a surveillance plan should be put in place. There are many hurdles to overcome to improve the efficacy of lower extremity revascularization, such as restenosis, calcification, microvascular disease, silent embolization, and tools for perfusion assessment. Endovascular revascularization is a critical strategy in managing total occlusions of the femoropopliteal artery, a significant challenge in patients with peripheral artery disease. This review provides a comprehensive analysis of procedural strategies, highlighting the role of drug-coated balloons, atherectomy devices, and advanced crossing techniques like subintimal recanalization and re-entry methods. It discusses the importance of lesion-specific considerations, such as the use of atherectomy devices for un-crossable or un-dilatable lesions and the effectiveness of drug-coated balloons in reducing restenosis. Emerging techniques, including the PIERCE needle-cracking method and intravascular lithotripsy, offer novel approaches for treating heavily calcified plaques. Moreover, the review compares endovascular interventions with surgical bypass, noting that while minimally invasive techniques are preferred for high-risk patients, a hybrid approach may be optimal for selected cases. Despite advances, challenges remain regarding long-term outcomes and the management of complex calcified lesions, emphasizing the need for ongoing research and innovation in this field.

Keywords: endovascular surgery, femoropopliteal segment, peripheral artery disease, balloon angioplasty, stenting, bypass

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Эндоваскулярная реваскуляризация при окклюзии бедренно-подколенной артерии

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Резюме. Эффективная реваскуляризация пациентов с заболеваниями периферических артерий — это больше, чем просто процедура. Подход к пациентам с симптоматической перемежающейся хромотой или ишемией, угрожающей потерей конечности, начинается с понимания группы риска и различий в клинической картине. Срочность реваскуляризации значительно варьирует в зависимости от клинической картины: от пациентов с перемежающейся хромотой, которым следует пройти структурированную физическую реабилитацию перед реваскуляризацией (при необходимости), до пациентов с острой ишемией конечности, требующей неотложной медицинской помощи, которым реваскуляризация необходима в течение нескольких часов. В последние годы быстро развиваются новые инструменты, включая проводники, катетеры, стенты и баллоны с лекарственным покрытием, специализированные баллоны и биомиметические стенты. Открытое хирургическое шунтирование остается важным вариантом для пациентов с «запущенным» заболеванием. Стратегия и методы варьируют в зависимости от клинической картины, локализации и тяжести поражения. Имеются ограниченные доказательства 1-го уровня для практического применения, но факторы, определяющие технический успех и анатомическую прочность, в значительной степени изучены и учитываются при принятии решений. После реваскуляризации следует проводить медикаментозную терапию для снижения частоты неблагоприятных исходов в отношении конечностей и разрабатывать план наблюдения. Для повышения эффективности реваскуляризации нижних конечностей необходимо преодолеть множество препятствий, таких как рестеноз, кальцификация, микрососудистое заболевание, бессимптомная эмболизация и оценка перфузии. Эндоваскулярная реваскуляризация — критически важная стратегия при тотальных окклюзиях бедренно-подколенного сегмента, представляющих значительную проблему при заболеваниях периферических артерий. В статье выполнен всесторонний анализ стратегий, подчеркивающий роль баллонов с лекарственным покрытием, устройств для атерэктомии и передовых методов пересечения, таких как субинтимальная реканализация и повторный вход. Обсуждаются важность учета особенностей поражения, устройств для атерэктомии при непроходимых или нерасширяемых поражениях, а также эффективность баллонов с лекарственным покрытием для снижения рестеноза. Новые методы, включая PIERCE с применением иглы и внутрисосудистую литотрипсию, предлагают новые подходы к лечению выраженно кальцинированных бляшек. В обзоре сравниваются эндоваскулярные вмешательства с хирургическим шунтированием. Отмечено, что, хотя минимально инвазивные методы предпочтительны для пациентов с высоким риском, гибридный подход может быть оптимальным в отдельных случаях. Несмотря на успехи, сохраняются проблемы, связанные с отдаленными результатами и лечением сложных кальцинированных поражений, что подчеркивает необходимость исследований и инноваций в этой области.

Ключевые слова: эндоваскулярная хирургия, бедренно-подколенный сегмент, заболевание периферических артерий, баллонная ангиопластика, стентирование, шунтирование

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

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INTRODUCTION

Over the past few decades, endovascular revascularization has become a key treatment method, offering a minimally invasive alternative to traditional surgical bypass in patients with peripheral artery disease (PAD). This approach has gained recognition for its ability to restore perfusion while reducing morbidity and hospital stay duration, especially in high-risk groups such as elderly patients and those with multiple comorbidities [1, 2].

The treatment of femoropopliteal segment occlusions includes various advanced techniques tailored to the characteristics of the lesion, such as drug-coated balloons (DCBs), atherectomy devices, and innovative crossing strategies [3–5]. Despite these advances, achieving stable long-term outcomes remains a significant challenge, particularly in the presence of complex or calcified lesions [6]. Moreover, ongoing debates about the comparative efficacy of DCBs versus stents, as well as the optimal use of atherectomy devices, underscore the need for further research and clinical refinements in this field.

Technological innovations have expanded the scope of endovascular interventions, incorporating strategies such as subintimal recanalization, catheter re-entry devices, and hybrid techniques combining antegrade and retrograde approaches. These developments aim to improve intervention efficacy, reduce restenosis, and address complications associated with complex lesion morphology. The emergence of new tools, including balloons, intravascular lithotripsy, and atherectomy devices, has further enhanced treatment options, providing clinicians with a broader arsenal for managing various types of lesions. Recent evidence suggests that combining multiple endovascular techniques may optimize outcomes. For example, drug-coated balloons in conjunction with atherectomy or intravascular lithotripsy have been used to treat calcified lesions [7–9].

This review provides a comprehensive analysis of endovascular revascularization strategies for femoropopliteal segment occlusions, detailing procedural aspects, comparative outcomes, and emerging innovations. The review also addresses challenges and controversies in this field, such as the management of patients with heavily calcified plaques and the role of revascularization techniques. By integrating recent data with clinical practice, this review aims to support decision-making and stimulate further advancements in PAD treatment.

ENDOVASCULAR INTERVENTIONS

Vascular access

Most interventions on the femoropopliteal arteries are typically performed via contralateral femoral access (Fig. 1), which provides excellent angiographic visualization of the iliac, superficial femoral, and deep femoral arteries, as well as comprehensive visualization of total femoropopliteal artery occlusions and associated collateral vessels.

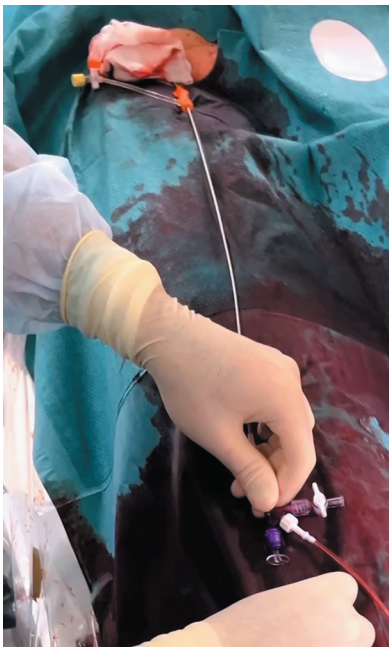


Fig. 1. **Contralateral access is used to perform interventions on the iliac segment, femoropopliteal and tibiofemoral segment of the contralateral limb when antegrade femoral access is impossible. For example, scars, abdominal obesity, lesions of the common femoral artery, ostial lesions of the superficial femoral artery (photos by Arshed A. Kuchay and Nikita N. Gruzdev)**

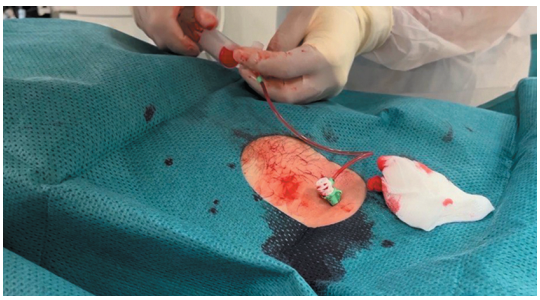


Fig. 2. **The antegrade femoral access is the primary approach for interventions on lower extremity arteries. It is the most convenient and common tactic. It provides good support and coaxial instrumentation, improving control compared to other methods. It is performed for lesions of the femoropopliteal segment (if both can be punctured) and the tibial segment of the foot (photos by Arshed A. Kuchay and Nikita N. Gruzdev)**

Usually, a braided introducer sheath of 6 F (45 or 55 cm) is used for these procedures, although a 7 F introducer is preferred when using atherectomy systems. After angiography, which visualizes the anatomy of the aorto-iliac region, a diagnostic catheter (JR or

IM, 5 or 6 F) is advanced into the contralateral iliac or femoral artery as deeply as possible using a 0.035-inch glide wire. The introducer can then be advanced over the diagnostic catheter to position it proximally at the target sites.

In cases of severe iliac tortuosity or calcification, either a stiff supportive guidewire (0.035 inch) or a balloon anchor technique can be used to facilitate introducer passage. In some cases, ipsilateral access (Fig. 2) is preferred, as it provides improved guidewire control and greater flexibility for device advancement. Despite technical challenges, particularly with proximal segment stenosis or superficial femoral artery occlusion, this method may not increase vascular complications compared to contralateral access when performed by experienced surgeons [10, 11].

Alternative vascular access sites, such as the radial or brachial arteries, may be considered when femoral access is not feasible. However, several factors must be evaluated, including the distance from access to target (with or without sufficiently long devices), radial artery vessel size, abdominal aortic tortuosity, and the angle between the subclavian artery and aortic arch.

Crossing strategy

In cases of total occlusion, advancing a guidewire through the affected area can be challenging. Currently, guidewires with diameters of 0.035 or 0.018 inches (0.035 or 0.045 mm) are commonly used. To enhance guidewire maneuverability, it is necessary to facilitate guidewire exchange, perform fixation with a hinge, or enable catheter tip insertion for angiography. The use of a support catheter (microcatheter or balloon catheter advanced over the guidewire) is mandatory.

Compared to microcatheters, balloon catheters have the advantage of dilating the occluded vessel, facilitating catheter advancement and improving guidewire efficacy. For extensive and long total occlusions, a balloon catheter is recommended as a support catheter rather than a microcatheter. To enhance the balloon catheter's ability to penetrate segments of total occlusion over the guidewire, a smaller-diameter balloon catheter (0.018 inch preferred over 0.035 inch) is recommended.

For total occlusion, various crossing strategies may be applied depending on the situation, such as antegrade or retrograde dissection with or without re-entry. Subintimal recanalization often requires subsequent stenting; however, current evidence does not favor one approach (intraluminal or subintimal recanalization) over another, nor the use of bare metal stents versus drug-coated stents [12, 13]. In most cases, antegrade advancement is recommended as the first step.

In the absence of severe calcification, guidewires with a hydrophilic polymer coating and low tip load are recommended for soft tissue trajectories, while guidewires with medium tip load are preferred for traversing fibrotic or calcified plaques to cross the total occlusion zone. Guidewires with high tip load, suitable for penetrating heavily calcified occlusions over distances of several millimeters to centimeters, should be advanced cautiously over long distances due to the risk of wire exit.

If traditional wire manipulation fails, the wire hinge technique may be considered, involving the creation of a loop with a hydrophilic wire supported by a catheter. This technique is particularly useful for subintimal tracking in total occlusions, with the catheter advancing behind the guidewire loop to maintain its small size. It is crucial to monitor re-entry into the distal true lumen to prevent excessive advancement of guidewires or catheters.

If re-entry into the distal true lumen fails with the wire hinge technique or conventional high-tip-load guidewire advancement, antegrade dissection using re-entry devices such as the Outback catheter (Cordis) may be applied. Alternatively, a retrograde approach may be attempted for recanalization, involving puncture of distal arteries such as the superficial femoral, popliteal, or below-knee arteries, followed by advancement of a guidewire and microcatheter. In cases of severe calcification, a 4 F introducer may be retrogradely inserted into distal vessels to improve support and facilitate device exchange.

To connect antegrade or retrograde guidewires, subintimal arterial wiring with antegrade-retrograde intervention (SAFARI) is performed [14]. After antegrade balloon angioplasty to create a subintimal space, the retrograde guidewire can be successfully advanced into the subintimal space, followed by wire externalization with a retrograde guidewire into an antegrade catheter or introducer to facilitate subsequent antegrade advancement of balloon or stent devices.

In other cases, if retrograde guidewire passage fails, retrograde balloon angioplasty may be performed to create a subintimal space for antegrade guidewire passage. In rare cases, the double-balloon technique may be used, involving simultaneous inflation of antegrade and retrograde balloons without overlap, allowing connection of different subintimal spaces [14].

Compared to antegrade dissection with re-entry using re-entry devices, the retrograde approach may be preferable in cases where antegrade guidewire passage fails due to its lower cost, fewer complications, and comparable success rates [15–17]. However, antegrade dissection techniques with re-entry devices may still be necessary if recanalization with SAFARI or other methods fails.

TREATMENT STRATEGY

Balloon angioplasty

For intraluminal recanalization, we recommend balloon angioplasty with extended inflation time. This study shows that a longer inflation time (180 s vs. 30 s) significantly reduces the likelihood of dissection and restenosis (14 vs. 43%, p=0.009) [18]. The diameter of the balloon catheter for preparation prior to drug-coated balloon (DCB) or stent placement should be 1 mm smaller than the diameter of the target artery [19]. For fibrotic or calcified plaques resistant to traditional angioplasty, we recommend switching to:

- a high-pressure balloon catheter (0.035 inch);
- a cutting or scoring balloon catheter.

Balloons with a full-length nitinol mesh coating are designed to maintain a uniform diameter during inflation. This design feature helps minimize the risk of edge dissection in the proximal or distal arterial segments. A study demonstrated a significant reduction in the rate of severe dissection: 4.2% in the percutaneous transluminal angioplasty group (n=48) versus 25% in the traditional angioplasty group (n=63), p=0.003 [20].

Drug-coated balloons, metallic stents, drug-eluting stents, and atherectomy

A meta-analysis included 51 randomized controlled trials involving 8430 patients/lesions. It was found that DCBs outperform traditional balloon angioplasty in terms of primary patency and demonstrate lower rates of target lesion revascularization (TLR) with comparable all-cause mortality across short-term (<1 year), mid-term (1–2 years), and long-term (>2 years) follow-up periods.

DCBs were associated with:

- higher odds of primary patency (short-term: odds ratio [OR] 3.21; 95% confidence interval [CI] 2.44–4.24; long-term: OR 2.47; 95% CI 1.93–3.16);
- lower TLR rates (short-term: OR 0.33; 95% CI 0.22–0.49; long-term: OR 0.42; 95% CI 0.29–0.60);
- similar all-cause mortality risk compared to traditional balloon angioplasty [21].

Compared to drug-eluting stents (DES), such as the paclitaxel-eluting Zilver PTX stent, DCBs demonstrated similar rates of restenosis and clinically driven TLR. At 12 months, target lesion restenosis was observed in 22% of DCB-treated patients versus 21% of DES-treated patients (p=0.90). Clinically driven TLR was required in 14% of DCB patients versus 17% of DES patients (p=0.50) [22].

Based on these results, we recommend:

- DCB angioplasty when no long or flow-limiting dissections are observed after traditional balloon angioplasty;
- stenting in cases of long or flow-limiting dissections after angioplasty, preferring DES over bare-metal stents due to their superior outcomes [23].

Regarding DES comparison, the Eluvia stent (Boston Scientific, Marlborough, MA, USA) was evaluated against the Zilver PTX stent (Cook, Bloomington, IN, USA). Non-inferiority was demonstrated for both efficacy and safety endpoints at 12 months. Primary patency was 86.8% (231/266) in the Eluvia group and 81.5% (106/130) in the Zilver PTX group, with a difference of 5.3% (one-sided lower bound of 95% CI 0.66; p <0.0001) [24].

In cases of total occlusion containing thrombus, various strategies may be considered, including primary stenting, thrombolysis, thrombectomy, or a combined approach.

It is important to note that atherectomy or intravascular lithotripsy catheters should not be routinely used in total occlusions with severe calcification, as there is no clinical evidence supporting a reduction in restenosis or TLR risk [7–9]. However, in special cases where lesions cannot be crossed or dilated, or insufficient stent expansion is anticipated, devices such as directional atherectomy (HawkOne), orbital atherectomy (Diamondback 360), rotational and aspiration atherectomy (Jetstream), laser, or intravascular lithotripsy catheters may be considered for lesion preparation.

Specific lesions

For impassable lesions, a low-profile coronary balloon may be used initially to create access through dense occlusions. Additionally, externalization techniques such as the “push-and-pull” method may be applied, where the guidewire is carefully advanced through the lesion to facilitate access for interventional devices.

Atherectomy devices have proven effective in such cases, particularly when hard or calcified tissue impedes passage. The percutaneous intravascular needle puncture of calcified plaque (PIERCE) technique, which involves needle fracturing, is another innovative method used to penetrate particularly resistant lesion areas. Applying precise needle force allows access through dense occlusions without causing excessive vessel trauma [25].

For non-dilatable lesions that do not respond to balloon dilation despite adequate balloon size, an atherectomy device remains necessary, as it can help reduce the volume of hard plaque and prepare the vessel for further intervention.

Coronary non-compliant balloons (CNBs) are also critical in these cases, as their rigidity allows for higher inflation pressures, making them more effective in dilating rigid lesions. When CNBs are insufficient, escalation to larger (0.035 inch) peripheral CNBs provides

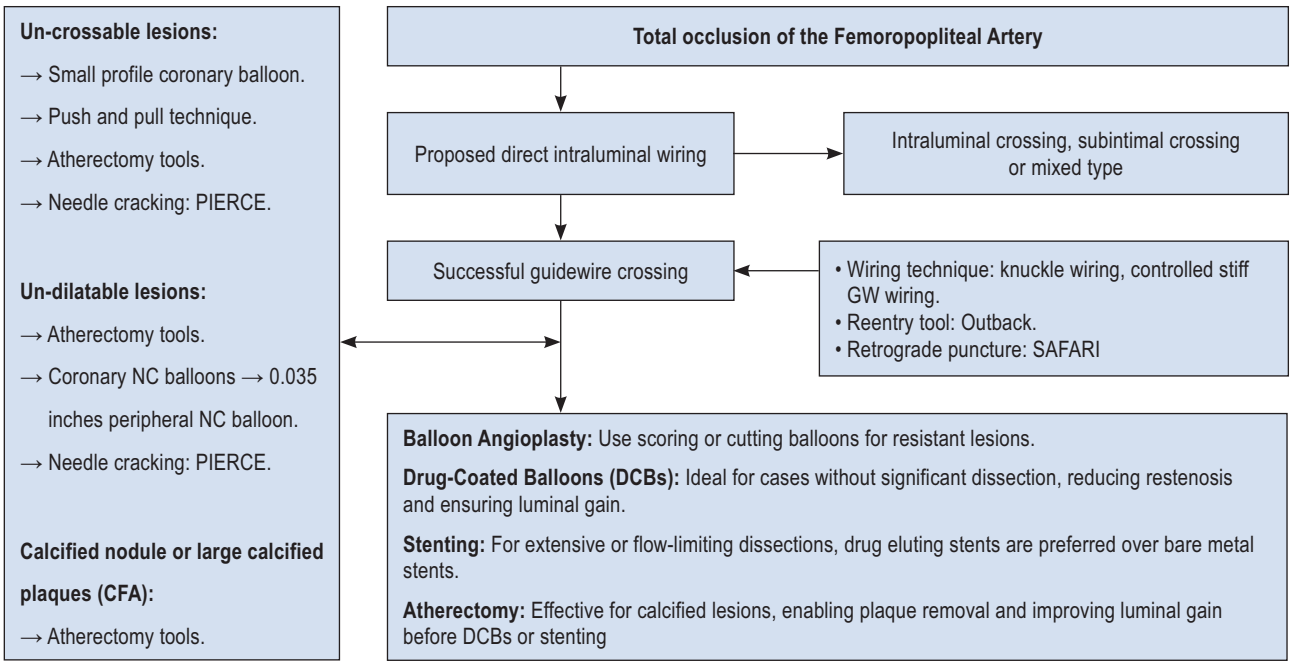


Fig. 3. **Algorithm of procedural and treatment strategies for total occlusion of the femoropopliteal artery (the figure by the authors of this article)**

additional force to address the lesion, particularly in larger peripheral arteries.

In more complex cases involving calcified nodules or large calcified plaques, such as those in the common femoral artery (CFA), advanced devices such as the Jetstream or HawkOne atherectomy systems are particularly useful. The Jetstream device combines resection and aspiration for effective removal of severe calcification while reducing the risk of distal embolization [26]. The HawkOne device, designed for directional atherectomy, is similarly developed to excise large plaques, especially when precise plaque removal and lumen enlargement are critical for restoring blood flow and preventing future restenosis [27]. These devices offer significant advantages in treating complex, heavily calcified lesions where other methods may be ineffective.

COMPARISON OF ENDOVASCULAR REVASCULARIZATION AND SURGICAL BYPASS

Endovascular revascularization and surgical bypass are the two main approaches to treat total occlusions of the femoropopliteal artery/segment, each with its own advantages and limitations.

Endovascular methods have gained popularity due to their minimal invasiveness, which ensures shorter recovery time, reduced hospital stay, and lower initial costs compared to surgical bypass. These advantages are particularly important for patients at high surgical risk due to comorbidities such as advanced age, diabetes, or cardiovascular disease [28].

However, surgical bypass remains an acceptable option, especially for patients with long or complex occlusions, long-segment involvement, or those with previous failed endovascular interventions. Bypass surgery, often using autologous venous grafts, has been shown to provide superior long-term patency rates in certain patient subgroups. Despite this, the invasiveness of the procedure, combined with higher risks of morbidity and mortality associated with major surgery, often makes it a less favorable option for frail or elderly patients [1, 2, 28, 29].

The UK Bypass vs Angioplasty in Severe Ischemia of the Leg (BASIL-1) trial, involving 452 participants, showed that patients with chronic limb-threatening ischemia (CLTI) expected to survive two years or more and having a suitable vein for bypass should be offered venous bypass as a first option instead of balloon angioplasty [30]. The **Best Endovascular vs Best Surgical Therapy in Patients with Critical Limb Ischemia (BEST-CLI)** trial, which enrolled 1,830 participants — mostly from the United States — evaluated patients with optimal (single-segment) venous grafts. Among the 1,434 such patients, the rate of the composite primary endpoint (major adverse limb events or death) was significantly lower in the venous bypass group compared to the best endovascular therapy group.

Major adverse limb events occurred in 302 of 709 patients (42.6%) in the surgical group versus 408 of 711 patients (57.4%) in the endovascular group (hazard ratio [HR] 0.68; 95% CI 0.59–0.79; p <0.001).

However, in a second cohort of 396 participants without optimal venous grafts, outcomes were similar between the two treatment groups. Major adverse limb events occurred in 83 of 194 patients (42.8%) in the surgical group and in 95 of 199 patients (47.7%) in the endovascular group (HR 0.79; 95% CI 0.58–1.06; p=0.12) [31].

The **randomized BASIL-2 trial** specifically compared venous bypass with the best endovascular therapy as the first-line revascularization strategy for patients with critical limb ischemia requiring below-knee, proximal infrainguinal revascularization (or without it). Between July 22, 2014, and November 30, 2020, a total of 345 participants were enrolled and randomly assigned either to the venous bypass group (n=172) or to the best endovascular therapy group (n=173).

Major amputation or death occurred in 108 of 172 patients (63%) in the venous bypass group and in 92 of 173 patients (53%) in the best endovascular therapy group (adjusted HR 1.35 [95% CI 1.02–1.80]; p=0.037).

Mortality occurred in 91 of 172 patients (53%) in the venous bypass group and in 77 of 173 patients (45%) in the best endovascular therapy group (adjusted HR 1.37 [95% CI 1.00–1.87]) [32].

These data suggest that the severity and anatomical distribution of atherosclerosis, as well as the quality of venous grafts, may influence treatment decisions and outcomes in critical limb ischemia.

Emerging evidence indicates that a **hybrid approach** — combining endovascular and surgical techniques [33–42] — may yield the best outcomes for selected patients by maximizing patency rates and minimizing recovery time [42–54]. Further studies directly comparing these strategies across different patient populations will be critical for guiding clinical decision-making.

CHALLENGES AND CONTROVERSIES IN ENDOVASCULAR REVASCULARIZATION

Despite substantial advances in the field, several challenges and controversies remain in the endovascular management of femoropopliteal occlusions.

One major debate centers on the use of DCBs versus stents. Although DCBs have shown promising results in reducing restenosis, their efficacy in complex or heavily calcified lesions remains under scrutiny. Similarly, the choice between DES and bare-metal stents often depends on lesion characteristics and individual patient factors, with no clear consensus on the optimal approach for all cases.

The role of **atherectomy** in treating calcified occlusions is another ongoing topic of discussion. While atherectomy devices can facilitate lesion preparation and improve stent expansion, their routine use is not universally recommended due to concerns about procedural complications and a lack of robust evidence supporting long-term benefits.

Moreover, the management of **chronic total occlusions** presents particular challenges, as various techniques — such as subintimal recanalization and re-entry devices — are employed with variable success rates. The choice of the most appropriate strategy often depends on the surgeon's expertise and the specific features of the occlusion.

CONCLUSION

Endovascular revascularization has evolved significantly, offering a range of effective treatments for femoropopliteal occlusions. Drug-coated balloons, atherectomy devices, and advanced crossing techniques have improved procedural success; however, challenges persist in managing complex calcified lesions.

Although drug-coated balloons show promise in reducing restenosis, their role in heavily calcified disease remains debated. The use of hybrid strategies — combining endovascular and surgical methods may provide optimal outcomes in selected patients.

Further research is needed to refine these techniques and improve long-term patency, ultimately leading to better outcomes for patients with PAD.

ADDITIONAL INFORMATION

Author contribution. Conceptualization of the work, A.A. Kuchay, A.N. Lipin; acquisition, A.A. Kuchay, A.N. Lipin, K.L. Kozlov and N.N. Gruzdev; analysis, A.A. Kuchay, N.N. Gruzdev; interpretation of data for the work, A.A. Kuchay, A.N. Lipin; drafting and revising the work, A.N. Lipin, K.L. Kozlov; final approval of the version to be published and agree to be accountable for all aspects of the work, A.A. Kuchay, A.N. Lipin, K.L. Kozlov and N.N. Gruzdev.

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

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

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Вклад авторов. А.А. Кучай, А.Н. Липин — разработка концепции работы; А.А. Кучай, А.Н. Липин, К.Л. Козлов и Н.Н. Груздев — сбор данных; А.А. Кучай, Н.Н. Груздев — анализ данных; А.А. Кучай, А.Н. Липин — интерпретация данных

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

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The problem of obesity and overweight in Vietnam. Part 3. (Literature review of research in Vietnam)

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Abstract. The third and final review of the double burden of malnutrition in Vietnam systematizes the concepts of the prevalence, causes and methods of correction of overweight and obesity in light of its negative consequences for public health. The analysis of literary sources clearly demonstrates an increase in the prevalence of overweight and obesity in school-age children and adolescents from 2–5% in 2007–2013 to 20–30% in 2002–2013 and 40–60% in 2024. In younger children and adults, this indicator did not differ throughout the observation period and corresponded to an average of 18% (from 6 to 35%) for children and 27% (from 11 to 70%) for adults. Women in Vietnam are at higher risk of developing overweight, the prevalence of which is 2–10% higher in them than in men. The prevalence of obesity in urban children and adults was 2.5–2.7 times higher than that in rural areas. The reasons for the increase in the prevalence of excess body weight and obesity are the traditional preferences of the Vietnamese for carbohydrate foods, incorrect ideas about obesity as a sign of health in men, the spread of fast food, freeze-dried products and sweets, especially among urban residents, combined with the refusal to exercise. Thus, it is obvious that the double burden of malnutrition, despite the measures taken by the Vietnamese government to protect public health, is still relevant for the country's residents. This requires the development of priority programs to simultaneously combat malnutrition and obesity.

Keywords: Vietnam, obesity, overweight, double burden of malnutrition

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Обзор

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Проблема ожирения и избытка массы тела во Вьетнаме. Часть 3. (Литературный обзор исследований во Вьетнаме)

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Резюме. В третьем, заключительном, обзоре, посвященном двойному бремени неполноценного питания во Вьетнаме, систематизированы представления о распространенности, причинах и методах коррекции избытка массы тела и ожирения в свете его негативных последствий для здоровья населения. Анализ литературных источников наглядно демонстрирует увеличение распространенности избытка массы тела и ожирения у детей школьного возраста и подростков с 2–5% в 2007–2013 гг. до 20–30% в 2002–2013 гг. и 40–60% в 2024 г. У младших детей и взрослых этот показатель не различался весь период наблюдений и соответствовал в среднем 18% (от 6 до 35%) для детского и 27% (от 11 до 70%) для взрослого контингентов. Женщины Вьетнама подвержены большему риску развития избытка массы тела, частота встречаемости которого у них на 2–10% выше, чем у мужчин. У городских детей и взрослых распространенность ожирения превосходила в 2,5–2,7 раза этот показатель у жителей сельских регионов. Причинами роста распространенности избытка массы тела и ожирения являются традиционные пристрастия вьетнамцев к углеводистой пище, неверные представления о полноте как признаке здоровья у мужчин, увеличение потребления фастфуда, сублимированных продуктов и сладостей, особенно у городских жителей в сочетании с отказом от занятий спортом. Таким образом, двойное бремя неполноценного питания, несмотря на принимаемые правительством Вьетнама меры по защите общественного здоровья, все еще актуально для жителей страны. Это требует разработки приоритетных программ одновременной борьбы с недоеданием и ожирением.

Ключевые слова: Вьетнам, ожирение, избыток массы тела, двойное бремя неполноценного питания

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

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INTRODUCTION

The double burden of malnutrition in Vietnam is characterized by the coexistence of undernutrition and underweight in one part of the population and obesity in another [1]. An analysis of Vietnamese studies published between 2003 and 2024, presented in previous reviews[1], demonstrated an approximately threefold decline in the prevalence of underweight [2–4]. Nevertheless, the country remains far from fully eliminating undernutrition — as of 2024, up to 25% of children were still underweight [5, 6]. Concurrently, iron deficiency and anemia currently affect 20–25% of school-age children and women, along with 30–35% of newborns [6, 7]. Up to 20% of the Vietnamese population have deficiencies of vitamins A and B_{12}, and up to 50% have deficiencies of vitamin D and micronutrients (zinc, selenium, magnesium, calcium) [4–6]. This third review presents the findings of studies that shed light on the prevalence and causes of overweight and obesity among the Vietnamese population — the "other side of the coin" of the double burden of malnutrition. The present review represents an attempt to systematize the data accumulated over a nearly thirty-year period on the prevalence, causes, and management strategies for overweight and obesity in Vietnam in light of their adverse impact on public health.

PREVALENCE AND CAUSES OF OVERWEIGHT AND OBESITY IN VIETNAM: AN ANALYSIS

The data summarized in Table 1 clearly illustrate a rising prevalence of overweight and obesity among school-age children and adolescents, from 2–5% in 2002–2013 to 20–30% in 2007–2013 and further to 40–60% in 2024. These figures are in partial agreement with the published literature. T.K. Hong et al. (2007) and N.H. Trang et al. (2012) reported that between 2002 and 2004 and between 2004 and 2009, the increase in adolescent overweight and obesity reached +8.1% and +7.6%, respectively [8, 9]. According to the National Survey of Non-Communicable Disease Risk Factors (2015–2016) and the Vietnam National Nutrition Survey (2019–2020), the prevalence of overweight rose by 16% among children and by 8% among adults from 2002 to 2020.

For younger children and adults, this indicator remained stable throughout the observation period covered in Table 1, averaging 18% (range, 6–35%) in the pediatric population and 27% (range, 11–70%) in adults. These findings are likely attributable to the wide time span of the metabolic disorder prevalence data included in Table 1, as they stand in contrast to results discussed in the literature. For example, H.T. Dieu et al. (2009) reported a 52.9% increase in the incidence of overweight and obesity among children aged 4–5 years between 2002 and 2005 [10]. This observation is inconsistent with the findings of B. Norov et al. (2023) and L.M. Do et al. (2017), who documented a 6–8% rise in the prevalence of these conditions among older and younger children, respectively, over the period 2000–2016 [11, 12].

A number of authors have noted that the prevalence of obesity in adults also exhibits an upward trend. M.D. Nguyen et al. (2007) published findings from the 1992–1993 Vietnam Living Standards Survey, reporting a twofold increase in the prevalence of overweight during that period, from 3% to 6% [13]. P.H. Nguyen et al. (2018) documented a change in this indicator from 2% to 15% between 1993 and 2015 [14]. According to data from a stepwise cross-sectional survey conducted between 2009 and 2015, the prevalence of obesity increased by 5% among adult men and by 7% among adult women [15]. Vietnamese women are at greater risk of developing overweight, with prevalence rates among them being 2–10% higher than among men (see Table 1).

Several studies have reported on the prevalence of abdominal obesity as a component of the metabolic syndrome in Vietnam, which ranged from 8.7% to 30.2% between 2004 and 2019 [16–18]. Drawing on an analysis of medical records of 652 adult outpatients with diabetes mellitus at Ho Chi Minh City General Hospital, H. Yokokawa et al. (2010) identified a markedly higher prevalence of metabolic syndrome in women than in men (70.5% vs. 39.4%) [19]. N.T. Ho et al. (2024), in a comparison of 30- and 60-year-old Vietnamese residents, found that although the overall prevalence of the metabolic syndrome increased with age, its manifestations were more pronounced in women than in men [20].

Several studies do not support the notion that women are at elevated risk of metabolic disorders [1, 21–24]. Traditional beauty ideals in Vietnam hold that girls should have a petite physique, whereas men should have a larger body build [1]. This fuels greater weight-related concern among women [25] and leads to excessive parental control aimed at preventing obesity in girls, but not in boys [26]. In Vietnam, families typically prioritize the needs of boys over those of girls [26], which, in turn, contributes to longer periods of physical

[1] This article is the final part of the series of publications "The Double Burden of Malnutrition in Developing Countries as a Global Problem. Part 1. (Literature Review of Research in Vietnam)" (Russian Biomedical Research. 2025;10(3):44–54. https://doi.org/10.56871/RBR.2025.80.56.005) and "Growth Retardation, Nutritional Deficiency, and Micronutrient Insufficiency in Vietnam. Part 2. (Literature Review of Research in Vietnam)" (Russian Biomedical Research. 2025;10(4):18–48. https://doi.org/10.56871/RBR.2025.22.44.002).

inactivity among the latter. Research conducted in Hai Phong showed that boys consumed a wider variety of energy-dense foods than girls [21]. Boys also consume fast food more often than girls [27], spend more time watching television, and use smartphones more frequently [28]. Programs aimed at reducing overweight and obesity among schoolchildren in Vietnam should therefore take into account sex-specific differences in the risk of developing these conditions [29].

Notably, across the entire more than 30-year period of monitoring the prevalence of overweight and obesity, a consistent trend has been observed: these indicators have been 2.5–2.7 times higher among both children and adults residing in urban settings than among their rural counterparts (see Table 1). T.T. Nguyen et al. (2018) and N.K. Pham et al. (2020) reported that, between 2010 and 2015, the prevalence of this condition rose by 6% among urban children and by only 4% among rural children [30, 31]. The mean prevalence of being at risk of overweight and obesity increased nearly 9-fold (from 0.7% in 1992 to 6.2% in 2000) in urban areas and 3-fold (from 0.4% in 1992 to 1.2% in 2000) in rural areas [32]. In general, affluence — which has traditionally been higher in urban regions — correlates positively with the risk of overweight [6, 31, 33–37]. A contrasting view, however, also exists. For instance, X. Tan et al. (2024) found no significant association between overweight and wealth index, ethnicity, geographic region, or area of residence [5]. The relationships between excess body weight and socioeconomic status are complex, depending on sex and the intensity of economic development [38]. A recent study conducted in Ho Chi Minh City highlighted that children living in low-income households in urban areas face a higher likelihood of obesity than their peers living in high-income households [1]. This may be attributable to various barriers to healthy eating and lifestyle that are characteristic of urban settings: the increased availability of inexpensive, energy-dense foods; a shortage of grocery stores offering fresh produce; a lack of opportunities for physical activity; and insufficient nutrition knowledge [39].

The causes underlying the high prevalence of overweight and obesity are widely discussed in the literature. The rising consumption of foods with added sugar (such as highly processed breads, cakes, sweetened dairy products, fruit drinks, and carbonated beverages) now represents a serious public health concern in Vietnam [30]. Rapid urbanization and economic development have driven a nutrition transition in Vietnam, away from traditional diets rich in fresh fruits, vegetables, and rice and toward diets high in processed foods, refined grains, meat, dairy products, saturated fats, and sugar, and low in fiber [23]. Food prices in Vietnam, particularly those of sugar-rich and highly processed items, declined during the country's economic expansion, making them more affordable [23]. Such products are increasingly marketed to children in supermarkets, convenience stores located near residential areas, school canteens [1, 40], and shopping malls [12]. The per capita availability of sugar and sweets in Vietnam rose by 176% from 1961 to 2013 [41]. In 2018, total sugar consumption in Vietnam was estimated at 46.5 g per capita per day, nearly double the maximum level of 25 g per capita per day recommended by the World Health Organization [30]. These products are readily accessible in urban areas, where a greater density of supermarkets caters to higher-income populations [42, 43]. Children from urban areas also eat out more often, and a greater share of the energy consumed in these settings comes from fat, sugar, fast food [44], hard candies, and chocolate [45]. A study involving children aged 11–15 years revealed that 36% of participants consumed at least one sugar-sweetened beverage every day [46]. Among schoolchildren, the mean daily energy contribution from sweetened beverages was 256.4 kcal, corresponding to approximately 10% of total daily energy intake (~2,484 kcal/day) [46]. In a study by T.T.P. Pham et al. (2019), the proportion of children who consumed confectionery more than five times per week in Thanh Hoa province reached 13.81% [47]. Overweight and obesity in adolescents were considerably less prevalent among those who frequently ate vegetables and fruits; the likelihood of overweight and obesity was lower when fruits were available at home [33].

In addition, Vietnamese households have been shown to be receptive to the marketing of energy-dense, nutrient-poor foods [48]. Food advertising has been found to influence dietary preferences, purchasing behavior, consumption patterns [49], and children's food choices [24]. The marketing of energy-dense, nutrient-poor foods may therefore contribute to childhood obesity [50]. The low political priority assigned to tackling childhood obesity has allowed commercial interests — particularly those of companies producing sugar-sweetened beverages and processed foods — to lobby successfully for the inclusion of their products in the school food system [11]. A study by H.T.D. Ngan et al. (2018) in Hai Phong established that women who attained higher levels of education were able to secure better jobs with long working hours, which, in turn, reduced the time available for preparing meals for their children and increased children's reliance on fast food [21].

The traditional lifestyle of Vietnamese people living in rural villages is characterized by high energy

Table 1

Prevalence of overweight and obesity in Vietnam according to various authors

Таблица 1

Распространенность избытка массы тела и ожирения во Вьетнаме по данным различных авторов

Автор Author	Контингент Contingent	Возраст Age	Избыток массы тела Overweight	Ожирение Obesity
Son le N.T. et al., 2005 [70]	Смешанная выборка взрослых[1] Mixed sample of adults[1]	≥20 лет ≥20 years	12%	
Cuong T.Q. et al., 2006 [71]	Смешанная выборка 1488 взрослых из г. Хошимина Mixed sample of 1,488 adults from Ho Chi Minh City	20–60 лет 20–60 years	♂ — 31,6% ♀ — 33,6%	
Tang H.K. et al., 2007 [72]	Смешанная выборка 1504 подростков из г. Хошимина, равное количество мальчиков и девочек Mixed sample of 1,504 adolescents from Ho Chi Minh City, equal numbers of boys and girls	Средний возраст 13,1 года Average age 13,1 years	4,9%	0,6%
Dieu H.T. et al., 2007 [73]	Смешанная выборка 670 детей из г. Хошимина Mixed sample of 670 children from Ho Chi Minh City	3–6 лет 3–6 years	20,5%	16,3%
Khan N.C. et al., 2008 [74]	Смешанная выборка взрослых[2] Mixed sample of adults[2]	45–54 года 45–54 years	Городские — 43% City — 43% Сельские — 17% Rural — 17%	
van Lierop A. et al., 2008 [75]	Смешанная выборка 2613 детей из провинции Биньтхуан A mixed sample of 2,613 children from Binh Thuan Province	6–10 лет 6–10 years	Городские — 4,6% City — 4.6% Сельские — 1,6% Rural — 1.6% Общая — 2,7% Total — 2.7%	
Walls H.L. et al., 2009 [76]	Смешанная выборка 4846 взрослых из г. Ханоя Mixed sample of 4,846 adults from Hanoi	25–74 лет 25–74 years	Общее Total — 28.6% ♂ — 29,7% ♀ — 31,5%.	2,1%
Dieu H.T. et al., 2009 [10]	Повторное поперечное исследование 1162 детей в 2002–2005 гг. A repeat cross-sectional study of 1,162 children in 2002–2005.	4–5 лет 4–5 years	21,4%	36,8%
Ha do T.P. et al., 2011 [77]	Смешанная выборка взрослых[3] Mixed sample of adults[3]	25–64 года 25–64 years	В 2000 году — 11,7% In 2000 — 11.7%	
			В 2005 году — 16,3% In 2005 — 16.3%	
Hong T.K. et al., 2012 [9]	Смешанная выборка взрослых[4] Mixed sample of adults[4]	13–16 лет 13–16 years	4,6%	
Nguyen P.H. et al., 2013 [78]	4983 небеременных женщин г. Тхай Нгуен 4,983 non-pregnant women in Thai Nguyen City	–	–	5%
Nguyen P.V. et al., 2013 [79]	Смешанная выборка 1989 детей из г. Хошимина Mixed sample of 1,989 children from Ho Chi Minh City	11–14 лет 11–14 years	♂ — 22% ♀ — 13,3% Общее — 17,8% Total — 17.8%	♂ — 5,4% ♀ — 1,3% Общее —3,2% Total —3.2%
Ly K.A. et al., 2013 [80]	Смешанная выборка взрослых[5] Mixed sample of adults[5]	≥35 лет ≥35 years	33,7%	–
Binh T.Q. et al., 2014 [16]	Смешанная выборка взрослых[6] Mixed sample of adults[6]	Средний возраст Middle age	16,3%	–

Continuation of the Table 1 / Продолжение табл. 1

Автор Author	Контингент Contingent	Возраст Age	Избыток массы тела Overweight	Ожирение Obesity
Do L.M. et al., 2015 [49]	2677 городских и сельских детей из г. Ханоя 2,677 urban and rural children from Hanoi	Средний возраст 4,3 года Average age 4.3 years	Городской — 21,1% City — 21.1% Сельский — 7,6% Rural — 7.6%	
Carrillo-Larco R.M. et al. 2016 [34]	Данные продольного исследования Young Lives 6000 детей Data from the Young Lives longitudinal study of 6,000 children	4–8 лет 4–8 years	1,5%	
		11–15 лет 11–15 years	0,3%	
Nguyen P.V. et al., 2016 [35]	Смешанная выборка 2024 из г. Хошимина Mixed sample 2024 from Ho Chi Minh City	11–14 лет 11–14 years	21,1%	
Nguyen N.M. et al., 2017 [37]	Смешанная выборка 2943 детей Mixed sample of 2,943 children	Средний возраст 5,3 года Average age 5.3 years	2,4%	0,4%
		Средний возраст 8 лет Average age 8 years	5,8%	4,7%
Nguyen C.L. et al., 2017 [81]	2030 беременных на 24–28-й неделе беременности 2,030 pregnant women at 24–28 weeks of pregnancy	–	12,8%	
Dat T.Q. et al., 2018 [82]	Смешанная выборка 6514 из провинции Биньдинь Mixed sample 6,514 from Binh Dinh province	6–10 лет 6–10 years	30,1%	
Hoang N.T.D. et al., 2018 [24]	Смешанная выборка 2334 детей из г. Хайфона Mixed sample of 2,334 children from Hai Phong City	6–9 лет 6–9 years	22,1%	31,0%
Ngan H.T.D. et al., 2018 [21]	Смешанная выборка 276 детей из г. Хайфона A mixed sample of 276 children in Hai Phong City,	6–10 лет 6–10 years	11,2%	10,1%
Chuc D.V. et al., 2019 [83]	Смешанная выборка 327 детей из г. Хынъена в 2017 г. Mixed sample of 327 children in Heungyeong City, 2017	1–3 года 1–3 years	1,2%	
Giao H. et al., 2019 [84]	Смешанная выборка 768 детей из г. Хошимина Mixed sample of 768 children from Ho Chi Minh City	1–2 года 1–2 years	10,7%	
Pham T.T.P. et al., 2019 [47]	Смешанная выборка 821 детей из г. Ханоя Mixed sample of 821 children from Hanoi	11–12 лет 11–12 years	17,1%	19,1%
Le T.T. et al., 2019 [85]	16 177 детей из горных районов, разные этнические группы 16,177 children from mountainous areas, different ethnic groups	2–5 лет 2–5 years	От 0 до 2,3% у разных этнических групп From 0 to 2.3% in different ethnic groups	
Phan H.D. et al., 2020 [86]	Смешанная выборка 2788 детей Mixed sample of 2,788 children	11–14 лет 11–14 years	17,4%	8,6%
Mai T.M.T. et al., 2020 [1]	Смешанная выборка 10 949 детей из г. Хошимина Mixed sample of 10,949 children from Ho Chi Minh City	6–18 лет 6–18 years	20–30%	20–30%
Pham N.K. et al., 2020 [31]	Смешанная выборка 1806 детей из г. Хошимина Mixed sample of 1,806 children from Ho Chi Minh City	7–9 лет 7–9 years	♂ — 24,7% ♀ — 12,3%	
Nguyen T.T. et al., 2020 [51]	Поперечное исследование 367 взрослых из г. Ханоя A cross-sectional study of 367 adults from Hanoi	18–25 лет 18–25 years	16,6%	

Ending of the Table 1 / Окончание табл. 1

Автор Author	Контингент Contingent	Возраст Age	Избыток массы тела Overweight	Ожирение Obesity
Ha et al., 2021 [69]	280 взрослых пациентов с сахарным диабетом 2-го типа 280 adult patients with type 2 diabetes mellitus	–	35,4%	
Kim T.V. et al., 2022 [65]	Смешанная выборка 103 детей Mixed sample of 103 children	3–4 года 3–4 years	22,3%	
Le G.B., Dinh D.X., 2022 [28]	Смешанная выборка 782 детей из г.Тханьхоа Mixed sample of 782 children from Thanh Hoa city	6–11 лет 6–11 years	21,61%	14,32%
Truong D.T.T. et al., 2022 [87]	Смешанная выборка 1556 детей Mixed sample of 1,556 children	Средний возраст 12 лет Average age 12 years	9,4%	
Dang A.K. et al., 2022 [18]	Смешанная выборка взрослых[6] Mixed sample of adults[6]	–	16,1%	
Thuyen T.Q. et al., 2022 [88]	Данные распространенности метаболического синдрома у 1150 взрослых Prevalence data of metabolic syndrome in 1,150 adults	40–64 лет 40–64 years	23,4%	
Vu K. et al., 2022 [89]	Смешанная выборка взрослых Mixed sample of adults	25–64 года 25–64 years	20,57%	
Tan P.Y., Chan C.L. et al., 2024 [6]	Смешанная выборка детей[8] Mixed sample of children[8]	<5 лет <5 years	9,7%	
		5–18 лет 5–18 years	41,3%	
Pham T.T.P. et al., 2024 [90]	Смешанная выборка 733 детей г. Ханоя Mixed sample of 733 children from Hanoi	11–12 лет 11–12 years	25%	11%
Tan P.Y. et al., 2024 [5]	Смешанная выборка 2039 детей Mixed sample of 2,039 children	6 месяцев — 2 года 6 months — 2 years	♂ — 2,3% ♀ — 2,6% Общее — 2,5% Total — 2.5%	♂ — 0,7% ♀ — 0,5% Общее — 0,6% Total — 0.6%
Mai T.M.T. et al. 2024 [91]	Смешанная выборка 221 ребенка в возрасте 18 лет из г. Хошимина Mixed sample of 221 children aged 18 years in Ho Chi Minh City	9–11 лет 9–11 years	59,3%	
Ho N.T. et al. 2024 [92]	Смешанная выборка взрослых[9] Mixed sample of adults[9]	<40 лет <40 years	16%	

Notes. [1] — Study on the prevalence of metabolic syndrome in adults in Ho Chi Minh City; [2] — National Overweight and Obesity Survey Summary Statistics; [3] — data from a study of 31,665 adults in 2000 and 2005 from the 2000 National Nutrition Examination Survey (14,452 subjects) and the 2005 National Adult Obesity Survey (17,213 subjects); [4] — prevalence of Metabolic Syndrome in Children in Ho Chi Minh City; [5] — 1,713 adult residents from Da Nang City from 900 households in 6 of 56 urban, rural and mixed urban-rural communities in Da Nang; [6] — prevalence of metabolic syndrome in 2,443 adults; [7] — meta-analysis of the prevalence of metabolic syndrome in 35,421 adult subjects; [8] — data on overall prevalence and prevalence stratified by sex and region were obtained from WHO/UNICEF/World Bank Group databases and national nutrition surveys (2018–2020); [9] — prevalence of metabolic syndrome in 57,997 adults examined from 300 Vietnamese companies from Vinmec Healthcare System.

Примечания. [1] — Исследование распространенности метаболического синдрома у взрослых жителей г. Хошимина; [2] — сборная статистика Национального исследования избыточного веса и ожирения; [3] — данные исследования 31 665 взрослых в 2000 и 2005 гг. Национального опроса по питанию 2000 г. (14 452 субъекта) и Национального опроса по ожирению у взрослых 2005 г. (17 213 субъектов); [4] — распространенность метаболического синдрома у детей в г. Хошимине; [5] — 1713 взрослых жителей из г. Дананг из 900 домохозяйств в 6 из 56 городских, сельских и смешанных городских и сельских общин в Дананге; [6] — распространенность метаболического синдрома у 2443 взрослых; [7] — метаанализ распространенности метаболического синдрома у 35 421 взрослых испытуемых; [8] — данные об общей распространенности и распространенности, стратифицированной по полу и региону, были получены из баз данных ВОЗ/ЮНИСЕФ/Группы Всемирного банка и национальных обследований питания (2018–2020); [9] — распространенность метаболического синдрома у 57 997 взрослых на основе осмотра сотрудников 300 вьетнамских компаний из Vinmec Healthcare System.

Table by the authors of this article
Таблица авторов данной статьи

expenditure[1] arising from the physical demands of agricultural labor [51]. Urban Vietnamese, by contrast, need to focus on increasing their physical activity during leisure time. Survey data from the Ministry of Health indicate that 70% of Vietnamese adults do not engage in physically active pursuits. Office workers, in particular, lead an almost entirely sedentary lifestyle, averaging only 600 steps per day instead of the recommended 10,000. Moreover, only 18% of fifth-grade students in Ho Chi Minh City adhere to physical activity guidelines [52]. A recent international study ranked Vietnam among the countries with the lowest average daily step counts in the world [51]. Low levels of physical activity have been reported for both urban and rural populations [53]. Participation in recreational physical activities remains rare among the Vietnamese population [54]. Common barriers to physical activity in South and Southeast Asia include ambivalent attitudes toward exercise; limited time due to long working hours and cultural obligations to family; a lack of adequate facilities and infrastructure; a limited number of safe public spaces; unfavorable climate; and environmental pollution [53]. Women may face additional cultural barriers stemming from norms of modesty or the avoidance of mixed-gender activities [53].

The risk of overweight or obesity was 1.39 times higher among physically inactive children and 2.5 times higher among those residing in urban areas [55]. Additional determinants of overweight include living in an affluent household [8]; not being required to walk to school [1, 22, 28]; reduced physical activity during school breaks owing to a scarcity of open spaces and playgrounds [9, 28]; having overweight parents [23]; and household food insecurity [23]. Study findings indicate a marked decline in the prevalence of walking to school among adolescents, from 27.8% in 2004 to 19.6% in 2009 [9]. A number of additional factors have been associated with elevated odds of overeating and obesity. These include being born to overweight or obese mothers, together with their sedentary lifestyle and unhealthy dietary habits [6, 56]; early discontinuation of breastfeeding [36]; prolonged screen time on smartphones; low levels of physical activity in the child; and excessive intake of energy, sugar, oils, and salt, as well as fast food [1, 6, 21, 28, 30, 31, 36, 49]. Further determinants comprise high birth weight; delivery by cesarean section [57, 58]; nighttime sleep duration of less than 8 hours per day [57]; daytime napping [16]; high levels of maternal and paternal education [21, 47, 58]; parental underestimation of the risks posed by childhood obesity [1]; neuroticism in the population [59]; and infrequent breakfast consumption [31]. Finally, polymorphisms in the brain-derived neurotrophic factor gene [57] and the β_3-adrenergic receptor gene [60], as well as an increased abundance of *Firmicutes* coupled with a reduced abundance of *Bacteroidetes* in the gut microbiota [61], have also been linked to higher odds of overeating and obesity. A survey conducted by L.M. Do et al. (2016) revealed that some Vietnamese mothers find the appearance of a "chubby" child appealing and regard excess weight in a child as a sign of good health [12]. At the same time, the women surveyed expressed concern about overeating, the reduced physical activity of their overweight children, and the high likelihood of developing diabetes mellitus and cardiovascular complications in the future [12]. When asked about the causes of obesity, the women pointed to hereditary factors, economic living conditions, and the presence of unsafe hormones in meat [12]. The mothers admitted that they find it difficult to control their children's diet, limit fast-food consumption, and restrict television viewing and the use of electronic gadgets; they also reported challenges in persuading older-generation relatives (grandparents) of the need to regulate the children's nutrition and physical activity [12]. Y.T.H. Nguyen et al. (2022) reported broadly similar findings when describing the results of interviews with elderly Vietnamese residents [62].

Accelerometer-based measurements of physical activity among schoolchildren, conducted by T.H. Nguyen et al. (2010), demonstrated that the risk of metabolic disturbances rises when time spent in moderate or light physical activity falls below 43 minutes per day [63]. N.T. Nguyen et al. (2024) found that more than 70% of secondary school students devoted less than 60 minutes per day to physical activity. These same students spent more than 120 minutes per day on sedentary pursuits [64].

In a sociodemographic study, Q.G. To et al. (2020) established that high levels of affluence were significant predictors of overweight and obesity among Vietnamese schoolchildren. Such affluence enabled children to own two or more electronic devices (smartphones, tablets) and to attend private tutoring [46]. These children displayed the lowest levels of physical activity, as they were either engaged in academic study or spent their time using smartphones or tablets [46]. Secondary school students aged 11–14 years in Ho Chi Minh City spent more than 2 hours per day watching television [35]. The number of hours of television viewing was positively associated with obesity, and a clear dose–response relationship was observed [33]. T.V. Kim et al. (2022) established that more than 50% of preschool children in Ho Chi Minh City failed to meet the recommendations regarding physical activity duration, sleep length, and screen time [65].

[1] World Health Organization. Guideline: Sugars Intake for Adults and Children. Geneva: WHO; 2015. Available at: https://www.who.int/publications/i/item/9789241549028. Accessed January 14, 2026.

A fast eating speed was significantly associated with higher alcohol and sugar consumption and a greater prevalence of abdominal obesity [34]. Furthermore, a significant association was detected between adults who participated in sports with their children and the weight status of adolescents. The likelihood of being overweight was twice as high among those children whose parents never engaged in sports with them [33].

Children living with their father only were at an elevated risk of overweight and obesity compared with their peers living in two-parent families [66]. This may be attributable to the fact that fathers are less likely to restrict access to food and to monitor their children's dietary intake [67]. Parental divorce has been associated with excess body weight and obesity [68].

Family support and counseling delivered by health care professionals play a decisive role in establishing and sustaining healthy dietary habits and appropriate physical exercise among both patients with diabetes mellitus and healthy individuals, thereby helping to reduce the risk of overweight and obesity [1, 69]. Patients who received no support from their families or who were not counseled by health care professionals on matters of nutrition and physical activity proved more vulnerable to overweight and obesity [69].

Taken together, the analysis of the published literature points to a steady rise in the prevalence of overweight and obesity among children of various ages as well as among adults. The factors regarded as the most important contributors to the development of metabolic disorders in the Vietnamese population include male sex, urban residence, a shift away from a healthy diet toward fast food and foods rich in fat and sugar, low levels of physical activity, and excessive reliance on television and smartphones.

MAIN APPROACHES TO THE PREVENTION AND MANAGEMENT OF OVERWEIGHT AND OBESITY IN VIETNAM

With the aim of preventing and managing overweight and obesity, the Government of Vietnam developed the National Strategy for the Prevention and Control of Non-Communicable Diseases for the period 2015–2025, setting the target of keeping the prevalence of these metabolic disorders below 10% among children and below 15% among adults [30]. A central pillar of this strategy is a comprehensive lifestyle modification program that encompasses dietary changes, behavioral modification, and increased physical activity, the last of which plays a fundamental role in combating obesity. For initial weight reduction and subsequent weight maintenance in adults, individualized dietary correction is recommended; this intervention should reduce total energy intake by at least 500 kcal per day while providing adequate amounts of protein, vitamins, and minerals. When selecting a dietary intervention, health care professionals should take into account the individual's motivation, personal and cultural preferences, and any associated comorbidities. Health care providers should recommend that adults with overweight or obesity engage in 30–60 minutes of moderate-intensity aerobic exercise per day on at least five days per week (≥150 minutes in total). The maintenance of a reduced body weight may necessitate longer-duration or higher-intensity exercise (200–300 minutes of moderate-intensity activity per week or ≥150 minutes of vigorous-intensity activity per week). To increase muscle strength and improve physical function, resistance exercise performed 2–3 times per week should be recommended. Activity interventions should be advanced gradually over time in order to reach the target level and should be tailored to the individual's age, current level of functioning and physical fitness, as well as to any existing complications and risk factors.

For the prevention and management of childhood obesity, physicians should counsel parents or guardians on the importance of establishing healthy dietary and physical activity habits in the child. These habits include consuming regular meals; limiting the intake of energy-dense snacks, unhealthy foods, and sugar-sweetened beverages; and ensuring daily opportunities for active play or other forms of physical activity. The National Plan of Action for Nutrition further recommended improving maternal nutrition to support prolonged breastfeeding, limiting salt intake to less than 300 g per person per month, restricting the consumption of sugar and fats, and increasing protein intake [93]. In the absence of weight loss within three months, intensive lifestyle therapy, pharmacotherapy, or referral for surgical intervention may be considered. The published literature attests to the effectiveness of such intervention programs in adults [94] and in children aged 11–12 years [90].

Vietnam currently has no regulations governing the sale and marketing of ultra-processed foods [91], a situation that makes their advertising highly pervasive [48]. Consequently, in order to curb the rising consumption of unhealthy foods, public health efforts should focus not only on modifying the behavior of children and their parents but also on the pressing need to develop government policies aimed at regulating the food environment. This can be accomplished through the introduction of higher taxes on selected ultra-processed foods and sugar-sweetened beverages, the regulation of the marketing of unhealthy products high in fat, sugar, and salt, and the implementation of front-of-pack nutrition labeling [91, 95, 96]. A recent study by L.T.T. Nguyen et al. (2023) demonstrated that

raising the price of "unhealthy" foods by up to 20% led to a 12.7% and 12.4% reduction in the prevalence of overweight and obesity, respectively, while saving an estimated 27 million US dollars in direct medical costs [97].

CONCLUSION

Studies consistently report a marked increase in the prevalence of obesity and overweight, which, according to some estimates, has ranged from 6% to 15% over the period 1990–2024. This rise has been driven by a combination of factors: the traditional Vietnamese predilection for carbohydrate-rich foods; deeply ingrained misconceptions equating plumpness, particularly in men, with good health; the growing consumption of fast food, ultra-processed products, and sweets, especially among urban residents; and a widespread shift away from physical exercise. It is therefore evident that the double burden of malnutrition remains a pressing public health challenge for the Vietnamese population, notwithstanding the measures implemented by the Government of Vietnam to safeguard public health. Addressing this challenge will require the development of priority programs designed to simultaneously tackle both undernutrition and obesity.

ADDITIONAL INFORMATION

Authors' contribution. V.O. Erkudov — conceptualization, literature search, writing the draft, final approval; V.V. Gaivoronskaya — literature search, editing, final approval; N.V. — Screbcova — editing, final approval; S.S. Rogozin — literature search, final approval.

All authors read and approved the final version before publication.

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Lecture

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Contemporary concepts of the vertebral column additional cervical ribs anatomy

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Abstract. The additional ribs of the cervical spine, or cervical ribs, are a fairly rare developmental anomaly that occurs as a result of a mutation of the *HOX* genes responsible for the formation of the bone system. This developmental feature is most often localized in the C_7 region, however, there are also possible formation variants in which it can be found in the C_4–C_6 projection. Cervical ribs are classified according to their size and the presence of a fibrous junction with the first rib. Different authors disagree on which variant of formation prevails, one-sided or two-sided. It is also believed that the cervical ribs mainly develop on the left. This feature is more common in the female population. For the most part, the anomaly is asymptomatic. However, sometimes, in the presence of certain developmental features of the body, as well as a number of provoking factors, a condition called thoracic outlet syndrome may occur. This syndrome may differ clinically depending on the effect of the cervical ribs on nearby structures: the brachial plexus, subclavian artery and/or subclavian vein. The diagnosis is made on the basis of a physical examination, instrumental diagnostic data methods and certain provocative tests. Treatment can be both conservative and surgical if medication and physiotherapy are ineffective. Surgical treatment may include resection of the first rib and scalenotomy. This article presents a literary review of scientific papers using PubMed and eLibrary resources and scientific journals over the past 5 years. The aim of the work is to summarize the available data on the prevalence, causes of formation and clinical symptoms caused by additional cervical ribs.

Keywords: additional cervical ribs, thoracic outlet syndrome, interscalene space

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Современные представления об анатомии добавочных ребер шейного отдела позвоночного столба

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Резюме. Добавочные ребра шейного отдела позвоночного столба, или шейные ребра, довольно редкая аномалия развития, возникающая в результате мутации *HOX*-генов, ответственных за формирование костной системы. Данная особенность развития чаще всего локализуется в области VII шейного позвонка (C_7), однако возможны также варианты формирования, при которых она может обнаруживаться в проекции C_4–C_6. Шейные ребра классифицируют в зависимости от размера и наличия фиброзного соединения с I ребром. Различные авторы расходятся во мнении, какой вариант формирования преобладает, односторонний или двусторонний. Также считается, что шейные ребра преимущественно развиваются слева. Чаще данная особенность встречается у женского населения. В большинстве своем аномалия клинически не проявляется. Однако иногда, при наличии определенных особенностей развития организма, а также ряда провоцирующих факторов, может возникнуть состояние, называемое синдромом грудного выхода. Данный синдром может клинически различаться в зависимости от влияния шейных ребер на расположенные рядом структуры: плечевое сплетение, подключичную артерию и/или подключичную вену. Диагноз ставят на основании физикального обследования, а также благодаря инструментальным методам исследования и определенным провокационным пробам. Лечение может быть как консервативным, так и хирургическим при неэффективности медикаментозной и физиотерапии. Оперативное вмешательство может включать резекцию I ребра и скаленотомию. В данной статье представлен литературный обзор научных трудов с использованием таких ресурсов, как поисковые системы PubMed и eLibrary, а также научных журналов за последние 5 лет. Целью работы является обобщение данных о распространенности, причинах формирования и клинических симптомах, вызываемых добавочными шейными ребрами.

Ключевые слова: добавочные шейные ребра, синдром грудного выхода, межлестничное пространство

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HISTORY

Accessory ribs of the cervical spine are supernumerary ribs that represent an elongation arising at the level of the transverse process, most commonly of the C_7 vertebra [1, 2]. This anomaly, known as the "rib of Eve," is referenced in the works of Galen from the 2nd century AD and later in the writings of Vesalius from the 16th century AD [3, 4].

EMBRYOGENESIS

The skeleton develops from the mesoderm. Mesodermal cells give rise to somites on either side of the neural tube, which further subdivide into a ventral sclerotome and a dorsal dermatome. The cells of the sclerotome transform into mesenchymal cells that will give rise to the future ribs during the fourth week of embryogenesis. These cells are guided by *HOX* genes and growth differentiation factor 11 (GDF11). Initially, 29 pairs of rudimentary ribs form from the mesenchyme, after which the 12 pairs of ribs projecting from the 1–12 thoracic vertebrae continue to develop. The remaining 17 pairs normally undergo regression; however, should this fail to occur for any reason, they may ossify and present either as elongated transverse processes or as fully formed accessory ribs [5–8]. Given that the rudiments regress in a craniocaudal direction, accessory ribs arising from C_7 are encountered most frequently in clinical practice, followed by those arising from C_6 and C_5 [1]. The rarest variant is the formation of this anomaly at the C_4 level [9, 10]. Early in development, cervical ribs are thought to arise from a mutation in *HOX* gene expression [11, 12].

ANATOMY

A cervical rib consists of a head, a neck, and a tubercle. The rib ends may terminate freely within the soft tissues or articulate with the 1st rib near the insertion of the anterior scalene muscle [1, 13] (Fig. 1). The literature contains conflicting data regarding the prevalence and incidence of the various morphological forms of this anomaly. Some sources report that unilateral cervical ribs are more common than bilateral ones (Fig. 2, 3), with a predilection for the left side [1, 13, 14]. Other sources, however, indicate that cervical ribs are bilateral in 50–80% of cases [5] (Fig. 4, 5). This discrepancy is most likely attributable to differences in the patient cohorts studied. There is also evidence that this developmental anomaly occurs twice as frequently in women as in men [5, 15]. The most authoritative work on cervical ribs is the monograph by the Russian anatomist W.L. Gruber. His classification, based on the degree of osseous development and the presence of an articulation with the 1st rib, delineates four types of cervical ribs (Table 1) [5, 16, 17].

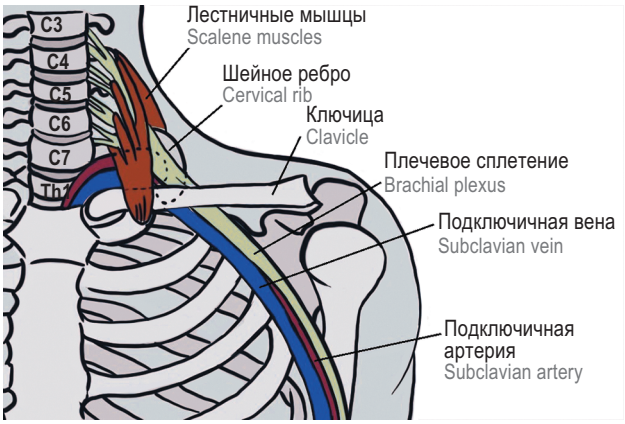


Fig. 1. **Relative position of the structures of the upper chest aperture in the presence of an accessory cervical rib (the author of the illustration is A.V. Kogan)**

Рис. 1. Взаимное расположение структур верхней апертуры грудной клетки при добавочном шейном ребре (автор иллюстрации А.В. Коган)

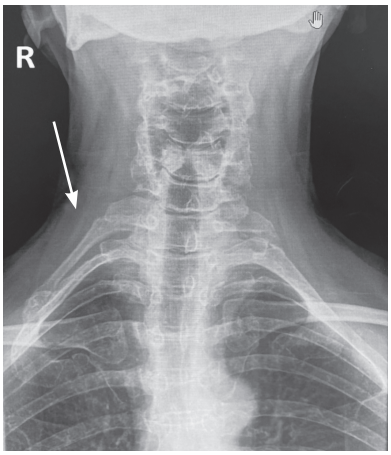


Fig. 2. **X-ray of patient F. A full-fledged accessory cervical rib is detected on the right, and hypertrophy of the transverse process of C7 on the left. The arrow points to the right-hand fully formed cervical rib (from personal photo archive of L.M. Strelkova)**

Рис. 2. Рентгенография пациента Ф. Определяются полноценное добавочное шейное ребро справа, гипертрофия поперечного отростка С7 слева. Стрелка указывает на правостороннее полностью сформированное шейное ребро (из личного фотоархива Л.М. Стрелковой)

CLINICAL MANIFESTATIONS

Despite the spectrum of developmental variations, cervical ribs serve no established physiological function in the body [18]. In most instances, cervical ribs are incidental findings on routine chest or cervical spine

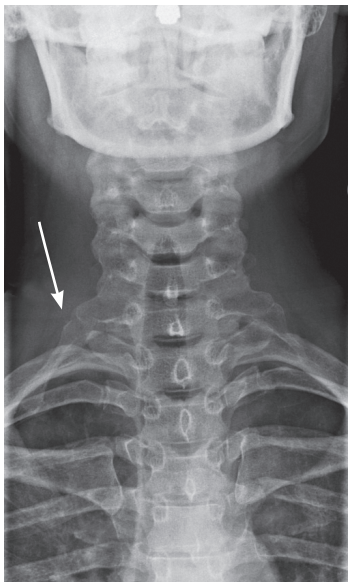


Fig. 3. **X-ray of patient M. A full-fledged accessory cervical rib is detected on the right, as well as a fragment of a rib on the left. The arrow points to the right-sided underdeveloped cervical rib) (from personal photo archive of L.M. Strelkova)**

Рис. 3. Рентгенография пациентки М. Определяется полноценное добавочное шейное ребро справа, а также фрагмент ребра слева. Стрелка указывает на недоразвитое шейное ребро с правой стороны (из личного фотоархива Л.М. Стрелковой)

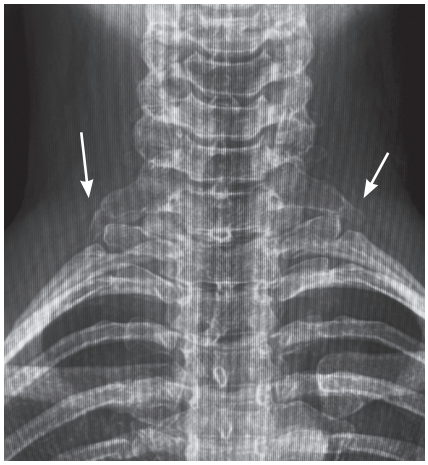


Fig. 4. **X-ray of patient G. Bilateral underdeveloped cervical ribs are detected. The arrows point to the underdeveloped bilateral cervical ribs (from personal photo archive of L.M. Strelkova)**

Рис. 4. Рентгенография пациента Г. Определяются двусторонние слаборазвитые шейные ребра. Стрелки указывают на недоразвитые двусторонние шейные ребра (из личного фотоархива Л.М. Стрелковой)

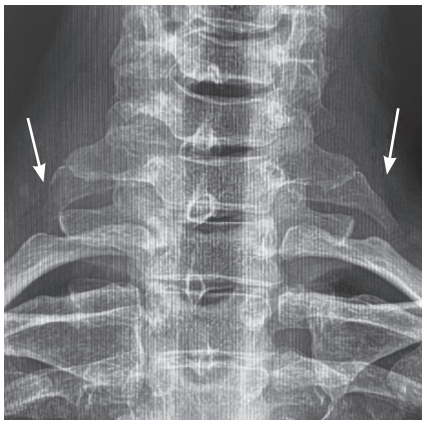


Fig. 5. **X-ray of patient T. Bilateral cervical ribs are detected with a more pronounced left rib. The arrows point to the underdeveloped bilateral cervical ribs (from personal photo archive of L.M. Strelkova)**

Рис. 5. Рентгенография пациентки Т. Определяются двусторонние шейные ребра с более выраженным левым ребром. стрелки указывают на недоразвитые двусторонние шейные ребра (из личного фотоархива Л.М. Стрелковой)

Table 1

Classification table of cervical ribs based on their length according to W.L. Gruber [5, 16]

Таблица 1

Таблица классификации шейных ребер в зависимости от их длины по В.Л. Груберу [5, 16]

Типы шейных ребер Cervical ribs types	Степень развития костных структур Degree of bone structures development
I тип Type I	Ребро чуть больше поперечного отростка C_7 длиной менее 2,5 см Rib less than 2.5 cm
II тип Type II	Ребро длиной более 2,5 см Slightly over 2.5 cm
III тип Type III	Полное шейное ребро, которое соединяется с I ребром фиброзной связкой A complete cervical rib connected to rib 1 by a fibrose ligament
IV степень 4th degree	Полное шейное ребро, которое соединяется с I ребром посредством хряща A complete cervical rib connected to rib 1 by a cartilage

radiographs. The anomaly is predominantly clinically asymptomatic [13, 14, 19, 20]. In a subset of cases, however, thoracic outlet syndrome (also termed superior thoracic aperture syndrome in some publications) may arise, particularly in the presence of specific additional anatomical variants and secondary changes in the adjacent structures [14]. A congenital cervical rib constitutes one of the predisposing factors and is implicated in up to 5% of cases of this condition [21].

Superior thoracic aperture syndrome was characterized as a distinct clinical entity in 1958 [22]. The superior thoracic aperture is the space between the thorax and the axilla, transmitting the subclavian vein, subclavian artery, and brachial plexus [23]. The space is bounded by the scalene muscles, the 1st rib, the clavicle, and, in some individuals, a cervical rib [24]. Thoracic outlet syndrome is an uncommon condition (1–3 cases per 100,000 population) caused by compression of the neurovascular bundle at the superior thoracic aperture. In some cases, the condition is exacerbated by hypertrophy of the anterior scalene muscles, which may impinge upon the brachial plexus and/or the subclavian vessels [19, 25, 26]. Thoracic outlet syndrome is categorized as neurogenic, arterial, or venous, according to the compromised structure [27, 28]. It is postulated that short, incomplete ribs tend to produce neurogenic compression, whereas long or complete ribs predominantly contribute to vascular manifestations [29]. The neurogenic form is the most common in both sexes, representing up to 95% of all diagnosed cases [30]. In the pediatric population, the venous type is the most frequent presentation of thoracic outlet syndrome [1, 31]. While anatomical and mechanical factors, together with sex-based differences in pain perception, are thought to contribute, the definitive reasons for the disparity in incidence between men and women remain incompletely elucidated [32]. Compression of the neurovascular bundle occurs most frequently at the following anatomical sites. These include: 1) the superior pleural sulcus; 2) the interscalene triangle (between the anterior and middle scalene muscles); 3) the costoclavicular space (between the clavicle and the 1st rib); and 4) the subpectoral space (between the pectoralis minor and subscapularis muscles) [33]. A cervical rib is regarded as the second most prevalent anatomical anomaly giving rise to neurovascular bundle compression [34, 35].

The pathogenesis of thoracic outlet syndrome is form-dependent. In the neurogenic form, pectoralis minor hyperactivity predominates, resulting in altered scapular position and narrowing of the retropectoral space. As a result, arm elevation leads to compression of the brachial plexus. In the vascular form (both arterial and venous), contraction of the scalene muscles elevates the 1st rib, thereby narrowing the costoclavicular space. The subclavian vein is the primary structure compressed, while the subclavian artery is affected to a lesser degree. Cervical ribs exacerbate these changes by reducing the interscalene space. Persistent pulsation of the subclavian artery generates friction between the vessel wall and the adjacent osseous structures, which may lead to fibrosis of the arterial wall, as well as stenosis or aneurysm formation, potentially complicated by intraluminal thrombus development [36–39]. This may be further complicated by subclavian artery thrombosis and, in rare instances, by stroke resulting from retrograde thromboembolism [40].

The majority of patients present with neurological symptoms: numbness and paresthesia in the little and ring fingers within the ulnar nerve distribution (C_8 and Th_1 nerve roots). Compression of the subclavian vein causes the affected limb to become swollen and cyanotic due to impaired venous return to the heart [13]. When an accessory rib lies in close proximity to the arterial vessel (the subclavian artery), compression may occur, up to and including critical impairment of blood supply. This condition has been termed Sistine Chapel syndrome, which develops secondary to an abrupt reduction in vertebral artery blood flow and consequent brainstem ischemia [16]. In some cases, secondary Raynaud's phenomenon — a peripheral circulatory disorder attributable to vasospasm — is identified [6].

DIAGNOSIS

Superior thoracic aperture syndrome may be diagnosed on the basis of clinical symptoms and physical examination findings; however, the diagnosis must be corroborated by instrumental investigations [27]. The diagnostic workup includes radiography, magnetic resonance imaging, multislice computed tomography angiography, electroneuromyography, and ultrasound [5, 42, 43]. Ultrasound has a sensitivity of merely 60–70% and is operator-dependent. The principal limitations of this modality relate to the difficulty of visualizing structures and the inability to adequately assess osseous anomalies. Moreover, challenges are encountered during provocative maneuvers: upon arm abduction, the acoustic window becomes obscured by the clavicle [44]. A range of clinical tests are also employed to elicit compression, including the Adson test, the abduction test, the hyperabduction test, the military posture test, and the three-minute stress test [5, 45].

Thoracic outlet syndrome may result from various types of trauma, repetitive movements, anatomical anomalies within the space bounded by the first thoracic vertebra, the 1st rib, and the manubrium of the sternum, as well as postural abnormalities and an excessively developed chest [33, 46] (Fig. 6). Sustained occupational loads may provoke fibrosis of the scalene muscles or displacement of a cervical rib,



Fig. 6. **3D volumetric reconstruction obtained by performing a CT scan of the cervical spine. Bilateral accessory ribs are visualized at the C7 level (https://radiopaedia.org/cases/cervical-rib-12?lang=us)**

Рис. 6. Объемная 3D-реконструкция, полученная при проведении компьютерной томографии шейного отдела позвоночного столба. Визуализируются двусторонние добавочные ребра на уровне C7 (https://radiopaedia.org/cases/cervical-rib-12?lang=us)

which, in turn, may lead to compression of the brachial plexus [27, 47, 48].

TREATMENT

Most authors agree that treatment of thoracic outlet syndrome should be initiated with conservative measures: pharmacotherapy, physiotherapy, therapeutic exercise, and massage [5]. Surgical treatment is also recommended following unsuccessful conservative therapy of a total duration ranging from 6 months to 2 years, as well as in cases where arterial complications arise [49, 50]. The primary surgical procedure is complete rib resection. The operative approach may vary; the most commonly performed procedures are brachial plexus decompression and scalenotomy (division of the scalene muscles with or without resection of the 1st rib) [13, 27, 51]. The history of thoracic outlet syndrome surgery dates back to 1927, when scalene muscle division was first performed. In 1962, the first resection of the 1st rib via a posterior approach was undertaken, and in 1966, a less invasive transaxillary approach was introduced. At present, no consensus exists regarding the choice of surgical technique; however, the majority of surgeons favor the supraclavicular approach, which permits scalenotomy, exploration of the brachial plexus branches, resection of the 1st rib, and decompression of the subclavian artery [5, 52].

CONCLUSION

Thus, accessory cervical ribs are a relatively uncommon developmental anomaly of osseous structures in the general population (>1% of the population) and are frequently asymptomatic. In most instances, they represent an incidental finding on routine radiographic examinations. Accessory ribs per se do not require treatment or ongoing surveillance; therapy is prescribed only when complications develop, such as thoracic outlet syndrome. Thoracic outlet syndrome, depending on the structure affected, may be neurogenic, arterial, or venous and may be attended by a range of neurological and/or vascular disturbances. The choice between conservative management and surgical intervention is determined by the severity and intensity of the presenting symptoms.

ADDITIONAL INFORMATION

Author contribution. D.N. Strelkov — development of the concept, collection of material, writing, formatting of the article; E.Yu. Kalinina — development of the concept, approval of the final version of the work; E.V. Shcherbakova — preparation and editing of the work; A.M. Fedyuk — collection of material, editing of the work; A.A. Sevruk — development of the concept; A.M. Kramarenko — editing of the work; K.I. Lazareva — collection of materials; A.V. Kogan, L.M. Strelkova — registration and provision of materials from the personal archive.

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Д.Н. Стрелков — разработка концепции, сбор материала, написание, оформление статьи; Е.Ю. Калинина — разработка концепции, утверждение итоговой версии работы; Е.В. Щербакова — подготовка и редактирование работы; А.М. Федюк — сбор материала, редактирование работы; А.А. Севрук — разработка концепции; А.М. Крамаренко — редактирование работы; К.И. Лазарева — сбор материала; А.В. Коган, Л.М. Стрелкова — оформление и предоставление материалов из личного архива.

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

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

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Leonid Iosifovich Smirnov — outstanding soviet scientist-neuromorphologist

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Abstract. The article is dedicated to the life and creative path of an outstanding Soviet scientist-pathologist, organizer and educator, one of the founders and classics of Soviet neuromorphology, Doctor of Medical Sciences, Professor, corresponding member of the USSR Academy of Medical Sciences Leonid Iosifovich Smirnov (03/08/1889 — 01/08/1955), who was born in the district Soligalich of the Kostroma province in a large family of a priest, archpriest and rector of the Soligalich Cathedral of the Nativity of the Blessed Virgin Mary and his mother Smirnova (nee Krutikova) Alexandra Evgenievna. In 1918, his father was repressed and shot as a "perpetrator of a counter-revolutionary uprising". Leonid received his primary education at a parochial school and a theological college. In 1906, he passed the external matriculation exam at the Kostroma Gymnasium and entered the Physics and Mathematics Faculty of the Imperial Saint Petersburg University. After graduating, in 1910 he became a student at the Medical Faculty of the University of Warsaw, and in 1914, due to the events of the First World War, he transferred to the Faculty of Medicine of the Imperial Moscow University and successfully graduated, receiving a doctor's diploma in 1916. From 1916 to 1938, L.I. Smirnov worked in hospitals and medical institutes in various positions. From 1938 to 1955, at the invitation of N.N. Burdenko and under his patronage, L.I. Smirnov headed the Morphological Department of the Central Neurosurgical Institute. In 1940, the Higher Attestation Commission awarded Leonid Iosifovich a doctorate degree without defending his dissertation. In 1940, L.I. Smirnov was a voluntary participant in the war with Finland and from 1941 to 1944 in the Great Patriotic War with Nazi Germany. The scientist's scientific interests throughout his creative career were the study of issues of central nervous system pathology. L.I. Smirnov is the author of more than 80 scientific publications, including a number of monographs that laid the foundation for neurophysiology and contributed greatly to the study of the pathomorphology of mental, traumatic, and tumor diseases of the brain and spinal cord. The remarkable modesty and extraordinary work ethic of this unique scientist, who made significant contributions to medicine, will serve as an example for the younger generation of scientists. L.I. Smirnov died on January 8, 1955, at the age of 66, and was buried at the Donskoy Cemetery in Moscow.

Keywords: Leonid Iosifovich Smirnov, an outstanding Russian scientist-pathologist, founder of Soviet neuromorphology, organizer, educator

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Резюме. Статья посвящена жизненному и творческому пути выдающегося отечественного ученого-патолога, организатора и педагога, одного из основоположников и классиков советской нейроморфологии, доктора медицинских наук, профессора, члена-корреспондента АМН СССР Леонида Иосифовича Смирнова (08.03.1889 — 08.01.1955), родившегося в уездном Солигаличе Костромской губернии в многодетной семье священника. Отец — протоиерей и настоятель Солигаличского собора Рождества Пресвятой Богородицы, мать — Смирнова (урожденная Крутикова) Александра Евгеньевна. В 1918 году его отец был репрессирован и расстрелян как «виновник контрреволюционного восстания». Начальное образование Леонид получил в церковно-приходской школе и духовном училище. В 1906 году он сдал экстерном экзамен на аттестат зрелости в гимназии Костромы и поступил на физико-математический факультет Императорского Санкт-Петербургского университета. Окончив его, в 1910 году стал студентом медицинского факультета Варшавского университета, а в 1914 году из-за событий Первой мировой войны перевелся на медицинский факультет Императорского Московского университета и успешно окончил его, получив диплом лекаря в 1916 году. С 1916 по 1938 год Л.И. Смирнов работал в больницах и медицинских институтах на различных должностях. С 1938 по 1955 год по приглашению Н.Н. Бурденко и под его протекцией Л.И. Смирнов возглавил морфологическое отделение Центрального нейрохирургического института. В 1940 году Высшая аттестационная комиссия присудила Леониду Иосифовичу докторскую степень без защиты диссертации. В 1940 году Л.И. Смирнов — добровольный участник войны с Финляндией, с 1941 по 1944 год — Великой Отечественной войны с фашистской Германией. Научные интересы ученого на протяжении всей его творческой деятельности включали вопросы патологии центральной нервной системы. Л.И. Смирнов — автор более 80 научных публикаций, в том числе ряда монографий, заложивших фундамент нейрофизиологии. Леонид Иосифович много сделал в изучении патоморфологии психических, травматических и опухолевых заболеваний головного и спинного мозга. Удивительная скромность и чрезвычайная работоспособность этого неповторимого ученого, внесшего значительный вклад в медицину, будут примером для молодого поколения ученых. Л.И. Смирнов умер 8 января 1955 года на 66-м году жизни и похоронен на Донском кладбище г. Москвы.

Ключевые слова: Леонид Иосифович Смирнов, выдающийся отечественный ученый-патолог, основоположник советской нейроморфологии, организатор, педагог

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

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On January 8, 2025 we have celebrated the 70th anniversary of the death of the outstanding Russian pathologist, scientist, educator and organizer, one of the founders and classics of Soviet neuromorphology, Corresponding Member of the USSR Academy of Medical Sciences, Doctor of Medical Sciences, Professor Leonid Iosifovich Smirnov (Fig. 1) [1].

Leonid Iosifovich Smirnov was born on March 8 (according to the Julian calendar) in 1889 in the district of Soligalich in the Kostroma province (now the Kostroma region) of the Soligalichsky district was born into a large family of a priest, archpriest and rector of the Soligalichsky Cathedral of the Nativity of the Blessed Virgin Mary and his mother, Smirnova (née Krutikova) Alexandra



Fig. 1. **Leonid Iosifovich Smirnov (03/08/1889–01/08/1955). Photo of the 1950s of theXX century. URL: https://bibl-kostroma.ru/фотографии/галереи-17-19/nggallery/page/5 (accessed: 11/05/2025).**



Fig. 2. **Leonid Iosifovich Smirnov's father — Iosif Sergeevich Smirnov. Photo from the Soldovskikh family archive (Soligalich)**



Fig. 3. **Leonid Iosifovich Smirnov's mother is Alexandra Evgenievna Smirnova. Photo of the Soldovskikh family archive (Soligalich) of the 10s of the XX century**

Evgenievna, the daughter of an official, who belonged to the clergy by birth (Fig. 2, 3)[1].

Father, Smirnov Iosif Sergeevich (03/03/1864 — 03/07/1918), was born in the village of Zharki, Kostroma district, Kostroma province in the family of fr. Sergiy Smirnov is a priest of the Church of the Assumption of the Same Faith. In 1871, fr. Sergiy and his mother died almost simultaneously. Six of their orphans were taken in by the unmarried 30-year-old sister of the deceased mother, Evdokia Osipovna Florenskaya, who lived in her own house in the village of Teterinsky in the Nerekhtsky district.

In 1874, Iosif entered the Soligalich Theological College, after graduating in 1879, he was enrolled in the Kostroma Theological Seminary for state support (Fig. 4). Throughout his seminary years, studying was not easy for Iosif Smirnov, which can apparently be explained by the difficult situation of the orphan [2].

After graduating from the seminary, Iosif Sergeevich was appointed to the position of assistant teacher at the parish school in Soligalich, and on June 2, 1886, he married Alexandra Krutikova. The wedding of the young couple took place in the Cathedral of the Nativity of the Blessed Virgin Mary. The Smirnov family settled in the house that belonged to the wife of fr. Iosif. Subsequently, the Smirnov couple had eight children, namely: Sergiy (04/23/1887), Leonid (03/08/1889 — 01/08/1955; Fig. 5), Anna (01/01/1891, died in 1913), Elizaveta (10/06/1892), Maria (03/28/1894), Nikolay (01/11/1899), Natalia (03/09/1902) and Serafim (11/14/1904)[2].

[1] Dudin V.A. Our countrymen. L.I. Smirnov. URL: https://soligalich.prihod.ru/2015/03/08/v-a-dudin-nashi-zemlyaki-l-i-smirnov/ (accessed: 11/05/2025).

[2] Smirnov Iosif Sergeevich. Drevo. URL: https://drevo-info.ru/articles/13674237.html?ysclid=mi0nv9r489108666594 (accessed: 11/15/2025).

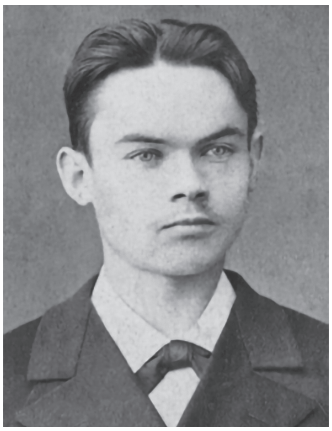


Fig. 4. **Iosif Smirnov is a graduate of the Kostroma Theological Seminary. Photo from 1883. URL: https://bibl-kostroma.ru/фотографии/галереи-17-19/nggallery/page/5 (accessed: 11/05/2025)**



Fig. 5. **Leonid Smirnov, son of Archpriest Iosif. Photo of the 10s of the XX century. URL: https://bibl-kostroma.ru/фотографии/галереи-17-19/nggallery/page/5 (accessed: 05.11.2025)**

On June 22, 1886, fr. Iosif was ordained a deacon by Bishop Alexander (Kulchitsky) of Kostroma and Galich, and on June 24 of the same year, a priest by the same bishop and assigned to the clergy of the Cathedral of the Nativity of the Blessed Virgin Mary in Soligalich.

Since 1888, fr. Iosif began to provide free spiritual care to prisoners held in the Soligalich prison castle. In 1897, the Nikolsky prison church was built, which was consecrated in January 1898 and became attached to the Cathedral of the Nativity of the Blessed Virgin Mary.

In 1895, a parish school was opened at the cathedral, where fr. Iosif became a religious teacher, and in 1904 he was appointed director of the school.

From 1896 to 1907, fr. Iosif served as an observer of parish schools in the Soligalich district.

On September 27, 1905, he was appointed rector of the Cathedral of the Nativity of the Blessed Virgin Mary in Soligalich, and on July 22, 1907, he was elevated to the rank of archpriest.

From 1906 to 1907 — a deputy of the City Duma, since August 1907 — a member of the district sanitary-executive commission of the Soligalich district, since 1909 — a deputy of the Soligalich district assembly, a member of the district committee of guardianship for public sobriety and a member of the board of the Soligalich theological college, since 1911 — a law teacher of the city college and real college, and on June 25, 1914 he was appointed dean of the Bogoroditse-Feodorovsky Monastery. Archpriest Iosif Smirnov performed many other church and public duties, deservedly enjoyed the respect and love of parishioners and was marked various awards.

At the end of February 1918, an attempt by the Soviet authorities to plunder and effectively liquidate the Bogoroditse-Feodorovsky Monastery led to an uprising in the city, as a result of which power in the city passed to a temporary council, but its activities lasted only a few days. Upon the arrival of the punitive detachment in the city, began arresting of “counter-revolutionaries”, including the local clergy, followed by a massacre.

In March, archpriest Iosif Smirnov was sentenced to execution by the military tribunal of the Soligalich Military District as “a culprit of a counterrevolutionary uprising”. Shot on March 7, 1918 in Soligalich. The execution took place late at night on the territoty of the Nikolsky prison church, the construction of which fr. Iosif had done so much. The report of the managing bishop Evdokim (Meshchersky) states that those shot were “so mutilated that, according to eyewitnesses, not a single corpse could be recognized. The executed martyrs were buried almost naked in one pit without a funeral service, and there was no one to perform the funeral service: the clergy of the city of Soligalich are in hiding and are being sought”. Those executed were buried in a mass grave in the city cemetery, near the walls of the Peter and Paul Church, early in the morning on March 8. A cross and a fence were erected at the site of the mass grave, which were demolished by atheists in the thirties. The cross on the grave was restored in 1996 (Fig. 6).

On July 4, 1996, Iosif Sergeevich Smirnov was rehabilitated by the Prosecutor’s Office of the Kostroma Region for the 1918 repressions and canonized as a new martyr and confessor of Russia in August 2000 at the Bishops’ Council of the Russian Orthodox Church[1].

Mother — Alexandra Evgenievna Smirnova (née Krutikova), widow of fr. Iosif, lived with her children for

[1] Smirnov Leonid Iosifovich. Wikipedia. URL: https://ru.wikipedia.org/wiki/Смирнов,_Леонид_Иосифович (accessed: 06/10/2025).



Fig. 6. **The cross on the mass grave of the victims of the shooting. Photo from 2003. URL: https://drevo-info.ru/articles/13674237.html?ysclid=mnqno9pmk1661378100 (accessed: 11/05/2025)**



Fig. 7. **Leonid Iosifovich Smirnov with his wife and son. Photographer I.I. Nedeshev, Petrograd, 1915–1917. URL: https://vk.com/wall-98221643_387132 (accessed: 09/20/2025)**

some time in Soligalich and died of a stroke in Kyiv in November 1943.

Their son, Leonid Iosifovich Smirnov, was married to Ekaterina Konstantinovna Smirnova (née Kalaganova), who was also from Soligalich and died in 1967. They had an only son, Iosif (Fig. 7) [3].

Leonid received his primary education at a parochial school and a theological college, which he graduated in 1902. Then he studied at the Kostroma Theological Seminary, but was expelled from it in 1905. In 1906, Leonid passed the external matriculation exam at the Kostroma gymnasium and entered the Physics and Mathematics Faculty of the Imperial Saint Petersburg University. After graduating, in 1910 he became a student at the Medical Faculty of the Warsaw University, and in 1914, due to the events of the First World War, he transferred to the Medical Faculty of the Imperial Moscow University (IMU) and successfully graduated it, receiving a doctor's diploma in 1916.

From 1916 to 1920, he was a resident at the Moscow Nerve Clinic, which were headed by IMU Professors V.A. Muratov and G.I. Rossolimo. In 1920, Leonid Iosifovich moved to Kursk, where he headed the Nervous Department of the Psychiatric Hospital and was also a prosector there. In 1925 — an Associate Professor at the Kiev Medical Institute and simultaneously the head of the histopathological laboratory of the Institute for Advanced Medical Training and a prosector at the Kiev Psychiatric Hospital. From 1932 to 1938 — the head of the Pathology Department at the Psychoneurological Faculty of the 2nd Kharkov Medical Institute and a prosector of the Psychoneurological Academy.

In 1938, at the suggestion of N.N. Burdenko, L.I. Smirnov was transferred to Moscow and from 1938 to 1955 headed the Morphological Department of the Central Neurosurgical Institute (CNHI) — now the "National Medical Research Center of Neurosurgery named after Academician N.N. Burdenko" of the Ministry of Health of the Russian Federation [4]. In early 1940, Nikolai Nilovich appealed to the Higher Attestation Commission (HAC) with a request to award L.I. Smirnov the title of Doctor of Medical Sciences without defending his dissertation, as a leading scientist in the field of pathological anatomy of the nervous system, having diverse scientific, pedagogical, and production achievements.

In December 1940, the HAC awarded Leonid Iosifovich Smirnov a doctorate degree, and two months later in 1941, approved him with the academic title of "Professor" in the specialty "Morphology".

In 1940, L.I. Smirnov — a voluntary participant in the war with Finland and from 1941 to 1944 in the Great Patriotic War (GPW) with Nazi Germany on the South-Western and Stalingrad fronts in evacuation hospital No. 2386 with the rank of lieutenant colonel of the medical service (Fig. 8)[1]. It should be noted that during the GPW, L.I. Smirnov initiated a series of fundamental studies on the problem of brain injury. These studies, based on the combined principles of etiology, pathological anatomy, pathophysiological mechanisms of development, outcomes, and complications of traumatic brain injury, later led to the development of the doctrine of traumatic brain disease, which significantly influenced the treatment of

[1] Leonid Iosifovich Smirnov: Memory of the People. URL: https://pamyat-naroda.ru/heroes/person-hero91472389/?ysclid=miasyfsrmg432420181 (accessed: 11/23/2025).



Fig. 8. **Smirnov Leonid Iosifovich — voluntary participant of the Great Patriotic War (1941–1945). URL: https://pamyat-naroda.ru/heroes/person-hero91472389/ (accessed: 11/05/2025)**

head wounds. After demobilization, the scientist returned to his position at the Institute of Neurosurgery[1].

Leonid Iosifovich's scientific interests throughout his creative career were the study of issues of central nervous system pathology.

L.I. Smirnov was distinguished by his selfless love for his profession and science, talent, goodwill, nobility, and had a broad erudition in morphology and related sciences, which was facilitated by his knowledge of German, French and English, and to a lesser extent Italian and Spanish; he was completely devoid of any squeamishness (he carried a saucepan of porridge and brains preserved in formalin, wrapped in a rag and newspaper, in a single string bag), indifferent to his appearance, hairstyle, beard, and extremely careless in his clothes. A man of science, he did not confine himself to his profession and remained a lifelong admirer of the Maly Theatre, especially the plays of A.N. Ostrovsky, he read classics at home, preferred Leskov. He enjoyed singing folk songs with his colleagues and was a keen fisherman. His dedication and passion for his work were contagious and uniting to all his staff [5, 6].

In 1940, Leonid Iosifovich was a member of the All-Union Communist Party (Bolsheviks), and in 1944–1947 — a member of the party bureau, secretary of the party organization of the CNHI, and then a member of the plenum of the Sverdlovsk District Party Committee in Moscow [7].

In 1944, as part of a delegation of prominent scientists, he carried out the exhumation of victims of the occupation of Nazi Germany.

In 1945, Nikolai Nilovich appointed L.I. Smirnov as his deputy for scientific and theoretical work of the CNHI. Soon, the USSR Academy of Medical Sciences (AMS) and the USSR People's Commissariat of Health approved Leonid Iosifovich as the first deputy director of the CNHI. After the death of N.N. Burdenko in 1946, L.I. Smirnov served as acting director of the institute for several months. As early as May 1946, N.N. Burdenko, seeing the outstanding scientific achievements of L.I. Smirnov, nominated him for full membership in the USSR AMS, established in 1944, emphasizing: "We have no equal to him specialist in pathological anatomy in the Union, no equal to him researcher of the pathological process abroad," and in the same year, Professor L.I. Smirnov was elected a corresponding member of the USSR AMS[2, 3].

L.I. Smirnov's main scientific and pedagogical activities were related to issues in the field of neurophysiology, the morphology of mental illnesses, including schizophrenia, studied issues in the field of topography, histogenesis, and histology of the meninges, as well as tumors of the brain and spinal cord. Under the leadership of L.I. Smirnov, fundamental research into the problems of brain injury was developed, where the natural sequence of development of pathological processes in the brain after traumatic brain injury was demonstrated for the first time.

The Morphology Department, in which L.I. Smirnov worked passionately, was a unique institute center, where young and old staff, morphologists sent from all over the country, and even guests from abroad, were constantly clarifying things. Leonid Iosifovich never refused to help anyone and traditionally served as the head of the morphological sections of all dissertations. Incidentally, Nikolai Nilovich, as well as the institute's leading neurosurgeons and neurologists, eagerly analyzed all the sectional cases with Leonid Iosifovich, concentrating on analyzing errors and observational features. This was an extremely useful discussion, in which everyone together enriched neuromorphology with first-class researches. At the same time, for the first time, regularly alternating periods during traumatic brain disease were identified [8, 9].

The main thing that characterizes the pathomorphological picture after craniocerebral trauma at any period of the disease development and in each individual case, according to the conclusion of L.I. Smirnov, is: a) the state of the foci of traumatic crushing, in other words, the stage of healing of the primary damage to the brain tissue caused by the direct impact of mechanical energy;

[1] Uranova N.A. Smirnov Leonid Iosifovich (1889–1955). URL: https://m.ncpz.ru/sotr/57.php (accessed: 10/07/2025).

[2] Kursk Encyclopedia. Compiled by Sh.R. Goizman. 2025. URL: https://www.mke.su/wide.html (accessed: 11/05/2025).

[3] Baibakov Yu.I. Smirnov Leonid Iosifovich. URL: https://www.mke.su/doc/SMIRNOV%20LI.html (accessed: 11/05/2025).

b) the state of circulatory mechanisms (hemodynamics and cerebrospinal fluiddynamics and the presence of consequences of their disorders); c) the absence or presence of complications and their nature. Based on this, Leonid Iosifovich identified the following five periods in the development of pathological processes.

1. Initial — the period of direct pathogenic action of mechanical energy with the phenomena directly caused by it, with passivity of tissue elements or, more precisely, the rudimentary expression of tissue and cellular reactions at the site of direct application of the traumatic agent, with maximum expression of functional disorders, circulatory mechanisms and in the absence of complications.

2. Early — the period of tissue reactions, characterized by the processes of cleansing the tissue defect from the decay products of brain tissue and blood, the development of reactive, non-purulent inflammation at a distance, lability of circulatory mechanisms and early complications.

3. Intermediate — the period of developing scar formation and later complications.

4. Late — the period of ending scar formation and complete elimination of complications of the early and intermediate (intermediate) periods.

5. Residual state — the period of the formed scar. The duration of each of these periods varies in different cases and is determined by many factors. Of these, the vastness of tissue damage, depending on the intensity of the traumatic agent, and the nature of complications that occur during the course of the disease (bacteriological factor) are in the first place. Of no small importance in this regard are the individual characteristics of the organism, the mechanism of action of the traumatic agent, the type and kinetic energy of the wounding projectile at the moment of its application, the topography of the lesion, the nature of the damage to the bones of the skull and their condition [10].

L.I. Smirnov's research in the field of the central nervous system tumors was distinguished by its focus on general pathological processes, the depth of its generalizations, combined with the brilliance of its morphological analysis.

He developed an original classification of neuroectodermal and meningeal tumors, taking into account their clinical and surgical significance. The scientist deeply and convincingly studied such tumor factors as topic, interaction of parenchyma and stroma, differentiation, cataplasia, metastasis, etc. L.I. Smirnov confirmed his histogenetic conclusions using the tissue culture method. He developed the theory of diffuse tumors of the central nervous system and identified previously unknown and clinically important forms of purulent complications.

L.I. Smirnov made many new contributions to the study of the pathomorphology of schizophrenia, developing the concept of organic and functional unity and interaction of processes in neurons, glia, and blood vessels, and emphasizing the importance of identifying histopathological syndromes in schizophrenia.

L.I. Smirnov has written more than 80 scientific publications, including 6 monographs that laid the foundation for neurophysiology and in which, in particular, epidemic diseases of the nervous system, the basics of morphology of the nervous system in normal and pathological conditions, the pathological anatomy and pathogenesis of traumatic diseases of the nervous system, as well as the topography, histology and histogenesis of brain tumors are highlighted. and the spinal cord and meninges, which have gained worldwide fame.

L.I. Smirnov was noted the following awards: He was awarded the Order of the Red Star, the Medal "For the Defense of Stalingrad" and a number of other high awards [11].

Professor Smirnov's research results are classic and have not yet lost their exceptional relevance and significance, while Leonid Iosifovich's monographs and printed works have not lost their significance to this day and are the reference books for neuromorphologists and pathologists in our country.

The remarkable modesty and extraordinary work ethic of this unique scientist, who made significant contributions to medicine, will serve as an example for the younger generation of scientists.

L.I. Smirnov died on January 8, 1955 in Moscow at the age of 66. He was buried at the ancestral site of the Donskoy cemetery in Moscow (Fig. 9) [12].



Fig. 9. **The tombstone monument to Leonid Iosifovich Smirnov at the ancestral site of the Donskoy cemetery in Moscow. Photo by Evgeny Danilov**

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7. Tumors of the brain and spinal cord. Moscow: MEDGIZ Publishing House; 1962. 188 p. (In Russ.).

ПЕРЕЧЕНЬ ОСНОВНЫХ НАУЧНЫХ РАБОТ Л.И. СМИРНОВА В ХРОНОЛОГИЧЕСКОЙ ПОСЛЕДОВАТЕЛЬНОСТИ

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ADDITIONAL INFORMATION

The author read and approved the final version before publication.

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

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Автор прочитал и одобрил финальную версию перед публикацией.

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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