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ОБЗОР
REVIEW

Shaping the future of radiotherapy: the role of electron beams and flash techniques

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Abstract. *Relevance.* Radiation therapy (RT) remains a cornerstone of oncology, offering targeted treatment for various cancers. With its roots tracing back to the discovery of X-rays by Wilhelm Röntgen and radium research by Marie Curie, RT has evolved into a sophisticated field encompassing a range of techniques. However, the rising global cancer burden highlights the need for continuous advancements to enhance efficacy while minimizing collateral damage. Traditional modalities such as X-rays and gamma rays have established their role in cancer treatment, yet they often lead to unintended damage to healthy tissues. Electron therapy has emerged as a promising alternative, leveraging distinct dosimetric properties that enable precise targeting with limited penetration depth. Low-energy electron beams are ideal for superficial tumors, while Very High-Energy Electrons (VHEEs) extend the reach to deep-seated tumors, rivalling proton and heavy-ion therapies. Furthermore, the FLASH effect — a phenomenon reducing healthy tissue toxicity at ultra-high dose rates, offers a breakthrough in electron therapy, improving patient quality of life. Despite these advancements, challenges persist. Limited penetration depth, secondary radiation from bremsstrahlung, and complexities in dose delivery systems constrain broader clinical adoption. Moreover, unresolved biological uncertainties, such as variability in relative biological effectiveness (RBE), necessitate further research. This review explores the historical evolution, unique benefits, and limitations of electron therapy compared to traditional modalities. It highlights advancements like VHEEs, FLASH therapy, and hybrid approaches, while addressing technological challenges and the future potential of electron beams in oncology. *Conclusion.* Integrated with recent technological breakthroughs, electron therapy may redefine the future of radiotherapy by offering safer, more precise, and individualized cancer treatment strategies.

Keywords: radiation therapy, very high-energy electrons, accelerators, ultra-high dose rate FLASH therapy, oncology

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Introduction

Radiation therapy (RT), one of the fundamental methods for cancer treatment worldwide, has a rich history spanning over 130 years (Figure 1) [1]. Wilhelm Röntgen's discovery of X-rays in 1895 marked a revolutionary turning point in medicine, enabling the use of ionising radiation to treat various types of malignant tumours. Building on this foundation, Marie Curie's pioneering research on Radium [2, 3], for which she received a Nobel Prize, laid the groundwork for modern radiotherapy, making it a critical component in oncology and helping to save countless lives. Today, radiotherapy is supported by a multidisciplinary team of radiation oncologists, medical physicists, dosimetrists, and radiotherapists, all working collaboratively to ensure precise planning and delivery of treatment.

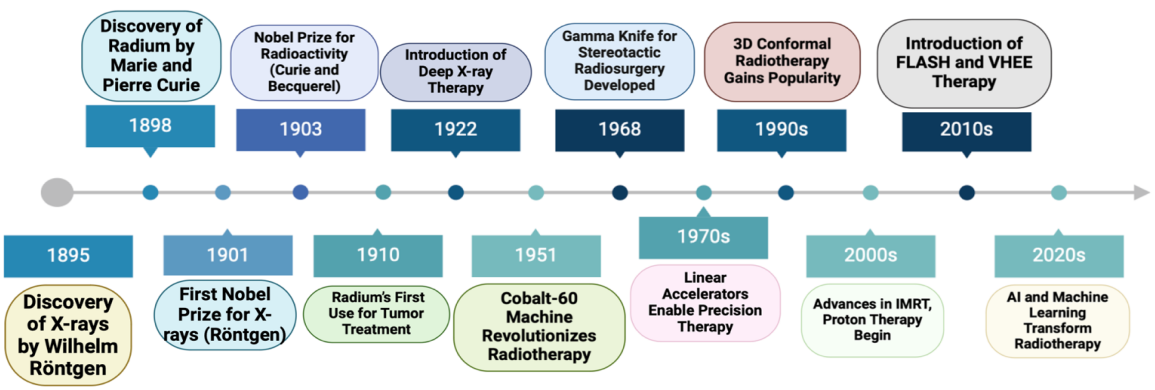

Fig. 1. Milestones in the evolution of Radiation Oncology: from the discovery of X-rays by Wilhelm Röntgen to modern advancements like FLASH and VHEE therapy

The field faces growing challenges as cancer cases are projected to increase by 77% by 2050, according to the World Health Organization [4]. This anticipated rise underscores the pressing need for continuous advancements in radiation therapy to meet the increasing demand for effective cancer treatment.

Radiation therapy has become an indispensable modality in modern oncology, serving both as a standalone treatment for malignant neoplasms (MN) and as an adjunct to other therapeutic approaches, including surgical interventions, chemotherapy, targeted molecular therapies, and immunotherapy [5]. The choice of radiation therapy method depends on various factors, such as the type, localization, and stage of cancer, highlighting the necessity of personalized treatment strategies for each patient.

Among its numerous applications, radiation therapy has shown particular efficacy in the treatment of breast cancer, where it plays a central role in both curative and palliative settings [6]. Techniques such as three-dimensional conformal radiation therapy (3D CRT), intensity-modulated radiation therapy (IMRT), and volumetric-modulated arc therapy (VMAT) are widely employed [7–9]. Their effectiveness varies depending on tumor location and stage, with VMAT often preferred for left-sided breast cancer to minimize cardiac and pulmonary toxicity, while 3D CRT remains the method of choice for right-sided cases to reduce myocardial exposure [10]. Additionally, hypofractionation schedules, which reduce the overall treatment duration, have been increasingly adopted to improve patient convenience while maintaining therapeutic efficacy [11].

Radiation delivery methods are broadly classified into external beam radiation therapy (EBRT), brachytherapy, and systemic radiation. EBRT utilizes high-energy beams such as X-rays, gamma rays, or particles like electrons and protons, targeting tumors with high precision through advanced imaging and planning technologies [12]. On the other hand, brachytherapy involves placing radioactive sources directly within or adjacent to the tumor, allowing for localized dose escalation while minimizing exposure to surrounding healthy tissues [13]. These approaches, combined with emerging techniques such as adaptive radiation therapy and proton therapy, aim to enhance the therapeutic index by achieving higher tumor control rates with reduced toxicity to normal tissues (Figure 2).

Recent advancements in radiation oncology have not only refined traditional approaches but have also integrated multi-modality treatment strategies. For instance, the combination of different radiation techniques with systemic therapies has enabled the targeting of radioresistant tumors, increasing the likelihood of achieving durable local control [14]. Furthermore, advanced imaging and treatment planning systems have improved dose conformity, enabling clinicians to optimize radiation delivery while protecting critical structures and minimizing long-term side effects [15].

However, despite the crucial position that RT occupies in the treatment of multiple cancers, the effects of ionizing radiation on the body are complex and affect biological structures at the cellular, molecular and other levels. Conventional methods of irradiation, including X-ray and gamma therapy, although effective, often result in collateral damage to healthy tissue, highlighting the need to develop better approaches that maintain therapeutic efficacy while minimizing harm.

Electron therapy has emerged as a promising alternative in this regard, offering distinct physical properties that allow for more targeted radiation delivery with reduced penetration depth. This feature enables electron therapy to be highly effective for treating tumors located near the skin surface or in shallow tissue areas [16], making it less likely to impact deeper organs and structures. Unlike photon-based radiotherapy, which can penetrate deeply and affect both the tumor and surrounding tissue, electron therapy's limited depth of action presents significant potential for reducing treatment-related side effects [17, 18].

Recent advances have broadened the potential of electron therapy. *Very High-Energy Electrons* (VHEEs, 100–250 MeV) now show promise for treating deep-seated tumors, approaching the precision of proton and carbon ion therapies while offering a more accessible and cost-effective alternative [19]. A key advantage of electron beams is their compatibility with the FLASH effect — a phenomenon in which ultra-high dose rates reduce toxicity to healthy tissue without

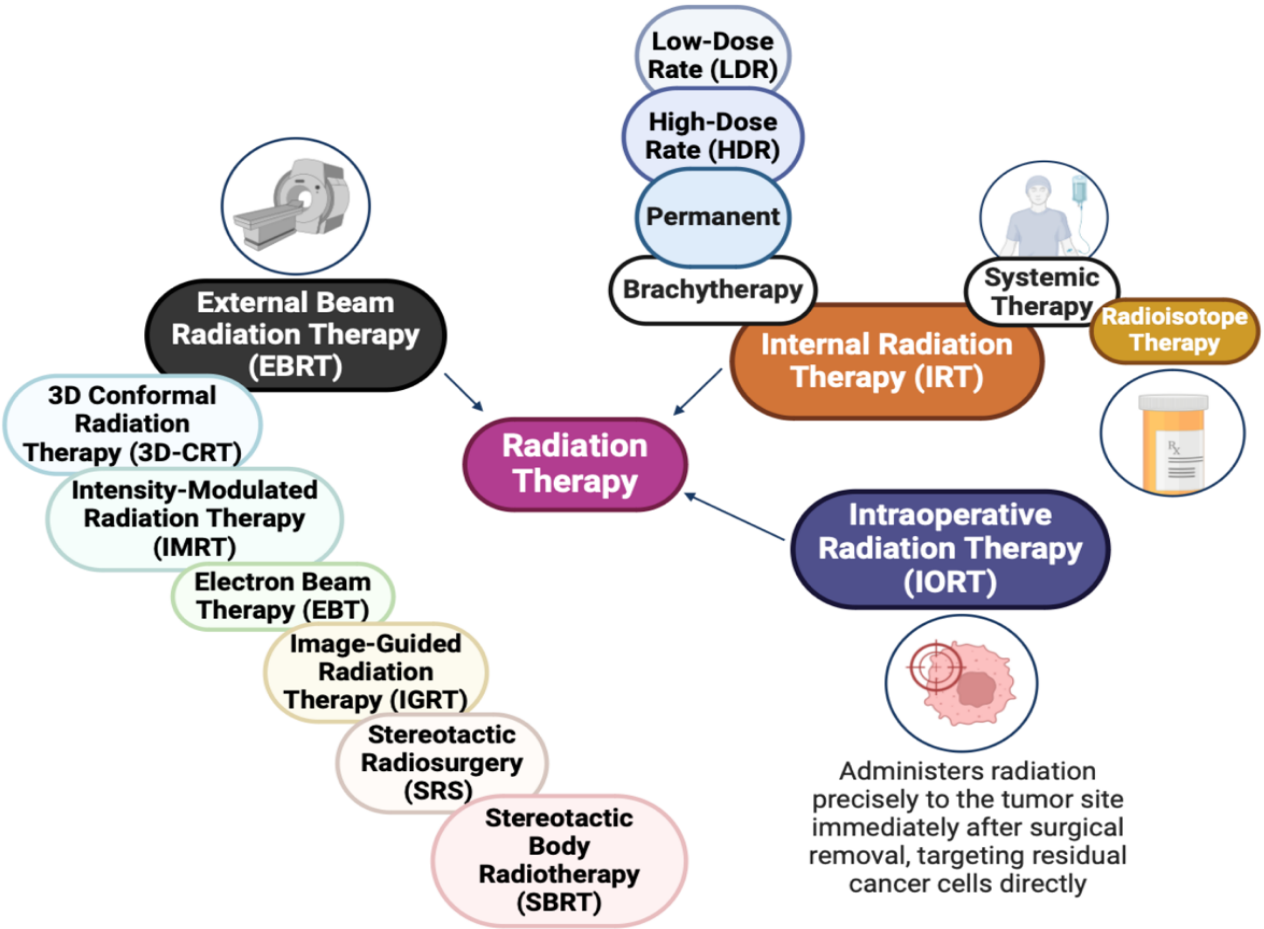

Fig. 2. Overview of modern Radiation Therapy Techniques and their applications

sacrificing tumor control [20]. By harnessing FLASH, electron therapy may dramatically reduce side effects and improve patients' quality of life.

We explore the potential of electron therapy within the broader scope of radiotherapy, emphasizing its unique benefits, limitations, and its comparison with other radiation types, such as X-rays and gamma rays. This paper also addresses current technological challenges and examines the promise of advanced techniques, such as the FLASH effect and *Very High-Energy Electrons*, in establishing electron therapy as a standalone and safer modality in radiation treatment. By offering a comprehensive overview of its advantages, limitations, and areas ripe for further research, this review aims to support advancements in oncology to enhance radiotherapy outcomes for patients.

Fundamental principles of radiation therapy

Radiation therapy is a cornerstone of oncology, utilizing high-energy particles or waves [21]. The targeted damage induces cell death in malignant tissues, making radiation therapy an effective strategy for treating a wide range of cancers. The success of this approach depends on several factors, including the type of radiation, linear energy transfer (LET), total dose, fractionation schedules, and the radiosensitivity of tumor cells [22].

A critical determinant of the biological effectiveness of radiation therapy is linear energy transfer (LET), which measures the energy deposited by radiation per unit distance travelled in tissue [23]. The High-LET radiation, such as alpha particles or neutrons, creates dense ionization tracks, resulting in more severe macromolecular damage and increased cell lethality compared to low-LET radiation like X-rays or gamma rays [24]. This heightened damage includes double-strand breaks (DSBs) in DNA [25], a pivotal factor in inducing apoptosis, necrosis, or cellular senescence. Also, The High-LET radiation could engage specific DNA repair pathways, with non-homologous end-joining (NHEJ) being particularly critical [24]. Notably, defects in NHEJ pathways lead to heightened radiosensitivity across various LET ranges, emphasizing the central role of repair mechanisms in determining radiation-induced cell fate (Figure 3) [25, 26].

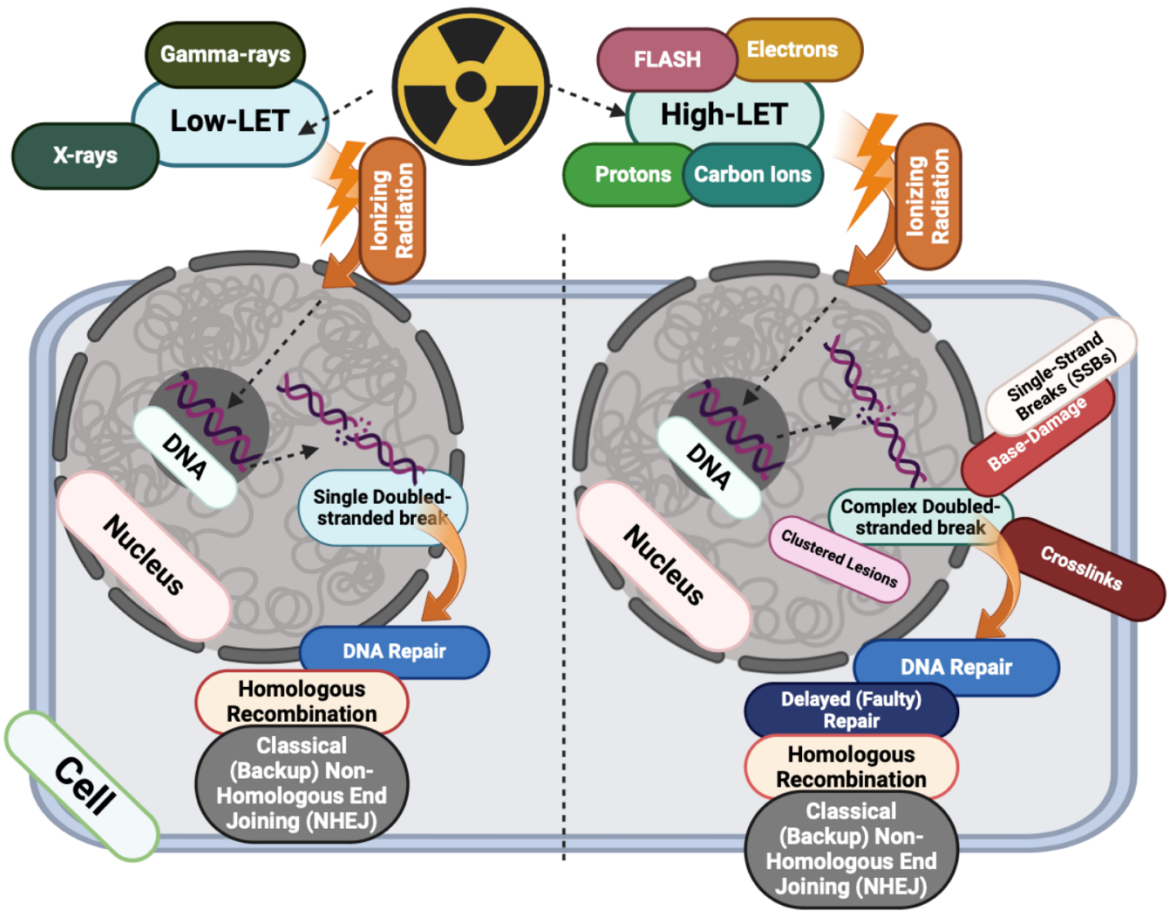

Fig. 3. Comparison of DNA damage and repair mechanisms induced by low-LET and high-LET radiation

The relationship between LET and relative biological effectiveness (RBE) is intricate. While the high-LET radiation is generally associated with increased RBE, this relationship varies depending on radiation quality, cellular characteristics, and biological endpoints under investigation. Recent studies highlight inconsistencies in how LET is defined and averaged across the literature, potentially undermining RBE modelling and its clinical

translation [27]. Resolving these inconsistencies is paramount to enhancing the precision of treatment planning and improving therapeutic outcomes.

Beyond DNA damage, the biological effects of LET encompass secondary mechanisms such as oxidative stress and bystander effects. Oxidative stress, driven by reactive oxygen species (ROS), exacerbates cellular damage, while bystander signalling propagates radiation effects to neighbouring cells, influencing both tumor control and normal tissue toxicity (Fig. 4) [28–30]. Understanding these mechanisms is particularly critical for advancing novel radiation modalities, including proton therapy and heavy-ion radiation, which inherently rely on the interplay between LET and biological response.

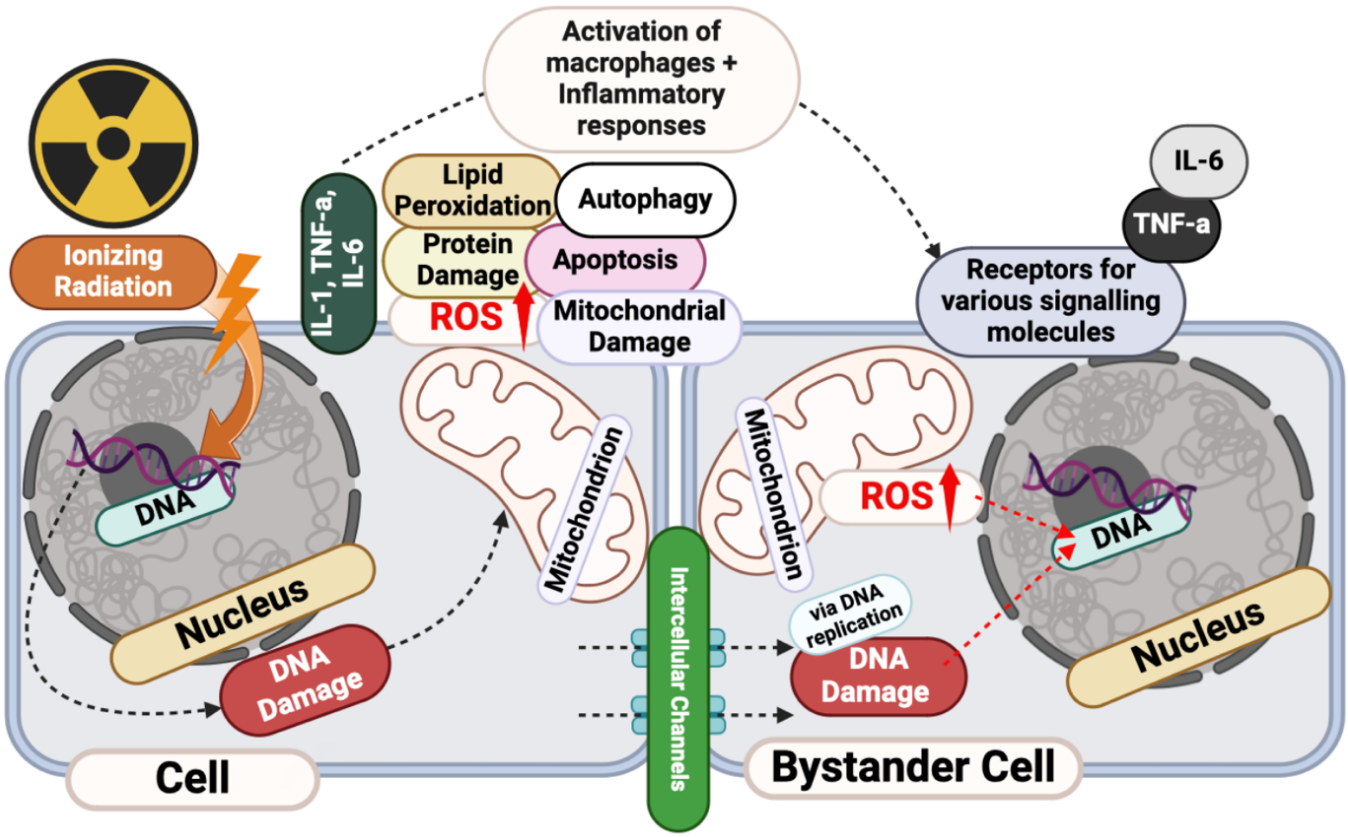

Fig. 4. Mechanisms of Radiation-induced cellular and Bystander effects

By integrating these insights, radiation therapy continues to advance as a precise and adaptable treatment modality in oncology. Nevertheless, challenges persist, including the variability of RBE predictions and the absence of universally accepted LET parameters. These hurdles underscore the need for ongoing research to refine biological models and optimize clinical application, paving the way for more effective and individualized cancer treatments.

Electron Irradiation

Electron irradiation presents significant potential in radiation oncology due to its distinct physical properties, particularly penetration depth and scattering

patterns [31]. These properties are critical for optimizing electron-based treatments, especially in scenarios where precision is required to target tumors while preserving adjacent healthy tissues.

The penetration depth of electron beams is highly dependent on their energy and the atomic composition of the irradiated material [32]. Low-energy electron beams (6–20 MeV) are well-suited for treating superficial malignancies, as their limited penetration depth ensures dose delivery primarily to the skin and shallow tissues, sparing underlying structures [33]. On the other hand, *Very High-Energy Electrons* (VHEEs), with energies exceeding 100 MeV, provide the capability to treat tumors located at depths of 5–15 cm while maintaining dose conformity even in heterogeneous tissues such as the lungs and bones [34, 35]. These properties position VHEEs as a potential alternative to photon and proton therapies for certain clinical applications (Figure 5).

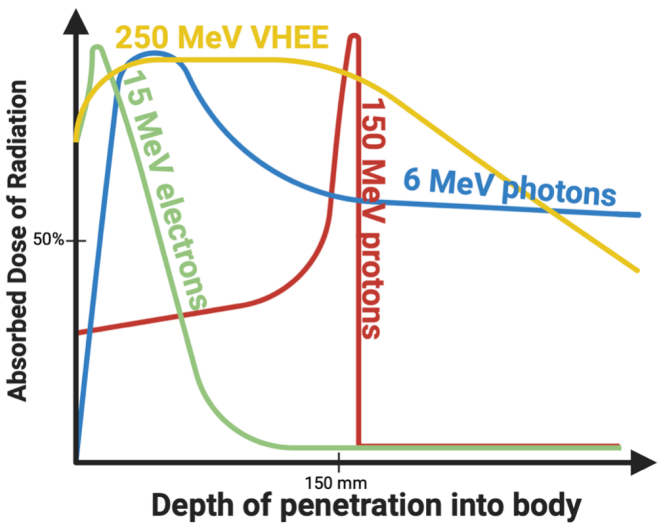

Fig. 5. Theoretical depth-dose distribution of radiation in water for various particle beams. The graph illustrates the absorbed dose of radiation as a function of penetration depth for different particle types, including 6 MeV photons, 15 MeV electrons, 150 MeV protons, and 250 MeV Very High-Energy Electrons (VHEEs)

Recent innovations, such as FLASH radiotherapy, have further expanded the potential of electron beams. FLASH therapy involves delivering ultra-high dose rates (>40 Gy/s), which have been shown to reduce normal tissue toxicity while preserving tumor control [36]. Although most FLASH studies in medical literature have focused on low-energy electrons, VHEEs could extend this modality to deeper-seated tumors. The precise mechanisms underlying the FLASH effect remain under investigation, with current hypotheses suggesting reduced oxygenation and suppression of reactive oxygen species as key factors [37].

Electron scattering is central to treatment planning, as elastic, inelastic, and bremsstrahlung interactions shape dose distribution, especially in anatomically complex regions [38, 39]. Monte Carlo simulations remain the gold standard for modeling these effects, accurately predicting energy deposition, range straggling, and lateral spread across media [40]. Notably, VHEE beams exhibit a stable, narrow profile at depth, delivering more uniform doses than photons in heterogeneous tissues [41]. Fermi-Eyges models, closely aligned with Monte Carlo data, further enable faster, high-precision calculations for VHEE therapy [42].

Advances in beam delivery systems, such as active scanning techniques and pencil beam scanning, have significantly enhanced the precision of electron therapy [43]. These technologies enable highly focused dose delivery, reducing exposure to surrounding tissues and accommodating complex tumor geometries. For example, a 160 MeV laser-wakefield accelerated electron beam has been focused to a 2.3 × 2.6 mm^2 spot, demonstrating the feasibility of stereotactic radiotherapy with sub-millimeter precision [41, 43]. Furthermore, integrating Monte Carlo methods with imaging modalities like dual-energy CT has refined treatment planning, improving the accuracy of stopping power ratios and dose predictions [44].

Combining different electron beam energies offers additional flexibility in treatment. For instance, mixed-energy beams can effectively expand the treatment region while maintaining steep dose “fall-offs”, enabling the precise targeting of irregularly shaped tumors [45]. This versatility highlights the adaptability of electron therapy for a wide range of clinical scenarios and emphasizes the different situation of use.

Gamma Irradiation

Another approach we would like to focus on is gamma irradiation. Gamma radiation, a high-energy form of electromagnetic radiation, stands out for its exceptional penetration capabilities, making it indispensable in radiotherapy and other applications [46]. Its uncharged, high-energy photons enable gamma rays to deeply penetrate matter, interact with tissues via ionization, and cause excitation at the atomic level [47]. These interactions underlie gamma radiation's ability to inactivate pathogens, extend food shelf-life, and perform critical roles in medical and industrial applications. In radiotherapy, gamma rays interact primarily through the Compton effect, leading to ionization and subsequent biological effects, including DNA damage [48].

Typically, gamma rays are generated through radioactive decay, nuclear fission, or advanced particle accelerators [49]. Cobalt^{60} and Cesium^{137} are among the most widely used isotopes, offering reliable gamma ray emission for therapeutic and research purposes [50]. These rays exhibit wavelengths ranging from approximately 0.25 to 0.005 angstroms, with energy levels spanning tens of thousands to several million electronvolts [51]. Due to their high energy, effective shielding using dense materials like lead or concrete is essential in clinical and, for example, industrial settings.

Additionally, gamma radiation is integral to radiosurgical techniques, with *the Gamma Knife* exemplifying its precision and effectiveness in treating localized conditions (Figure 6) [52]. This non-invasive method uses 201 Cobalt*60* sources to deliver focused beams, achieving high doses at targeted lesions while sparing adjacent healthy tissue [53]. *The Gamma Knife* has demonstrated success in managing arteriovenous malformations (AVMs) and inoperable brain tumors, with studies linking biologically effective doses to higher obliteration rates [54]. Recent advancements, such as frameless *Gamma Knife* radiosurgery, have enhanced patient experience, enabling fractionation without compromising spatial resolution [55]. These developments underscore gamma radiation's role in advancing neurosurgical outcomes.

Despite its extensive applications, the effective and safe use of gamma radiation relies on accurate dosimetry and individualized treatment planning [56]. Dosimetric verification methods, including gamma analysis, are vital for ensuring precise dose delivery in treatments like *Gamma Knife* radiosurgery. However, standard

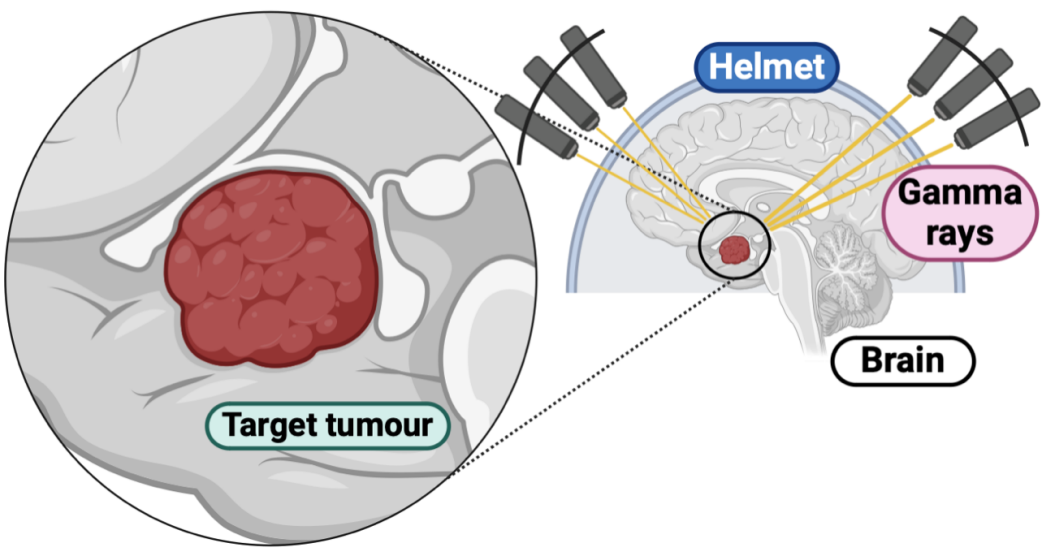

Fig. 6. Schematic representation of ***Gamma Knife*** radiosurgery. The diagram illustrates the precise targeting of a brain tumor (target tumour) using converging gamma rays, delivered through a specialized helmet. The focused radiation beams spare the surrounding healthy brain tissue, demonstrating the non-invasive and localized nature of the treatment

activity prescriptions often fail to account for individual patient differences, necessitating advancements in personalized dosimetry techniques. Challenges such as non-standardized protocols and the complexity of dose distribution modelling require further research and technical innovation to optimize patient outcomes.

Recent innovations, such as "mini-beam" collimator designs, have improved gamma-based dose conformity, allowing for narrower beams with high peak-to-valley dose ratios. Techniques like volumetric modulated arc therapy (VMAT) and intensity-modulated radiation therapy (IMRT) further enhance precision by modulating collimator positioning, dose rates, and gantry speeds [57]. These advancements minimize radiation exposure to surrounding tissues, reducing side effects and enhancing treatment outcomes.

Finally, it is important to consider that gamma radiation's biological efficacy is enhanced by its linear energy transfer, especially in radiosurgical applications. While low-LET radiation like gamma rays primarily causes single-strand DNA breaks, high-LET radiation, including α-particles and heavy ions, induces complex DNA damage such as clustered lesions and multiple double-strand breaks (DSBs) [58]. These DSBs activate homologous recombination repair pathways more effectively than non-homologous end-joining, contributing to the higher biological effectiveness of high-LET radiation [59]. Leveraging these differences in DNA repair mechanisms can optimize cancer therapy and aid in developing targeted radiosensitizers.

X-Ray Irradiation

X-rays, a high-energy form of electromagnetic radiation, have revolutionized both medical and industrial applications due to their remarkable penetration capabilities (Figure 7) [60]. These waves, with wavelengths ranging from 10 pm to 10 nm and energies typically between 100 eV and 500 keV, possess unique properties that allow them to penetrate dense materials, enabling imaging and therapeutic interventions across a broad spectrum of fields (Figure 8) [61]. In the medical realm, X-rays are indispensable for diagnostics, including radiography and computed tomography (CT), and for therapeutic applications such as sterilization of single-use devices, where X-ray sterilization is emerging as an alternative to traditional gamma radiation [62].

X-ray imaging remains a cornerstone of clinical diagnostics, with techniques like radiography and CT relying on the differential absorption of X-rays by various tissues to produce high-resolution internal images. These modalities are critical for detecting cancers, bone fractures, and other medical conditions [63]. Recent advances include the development of dual-energy and multi-spectral CT, which enable quantitative tissue analysis and material characterization, offering improved diagnostic accuracy and interventional guidance [64]. However, the associated risks of radiation exposure necessitate strategies to minimize harm to both patients and medical staff.

The mechanism of X-ray generation, known as bremsstrahlung or "braking radiation", occurs when high-energy electrons decelerate as they interact with atomic nuclei. This process produces a broad spectrum of X-ray energies, making it the cornerstone of X-ray production in medical and industrial settings [61, 65]. Recent advancements in bremsstrahlung include the development of electron wavefunction shaping techniques, which have demonstrated enhanced X-ray intensity and emission control when electrons interact periodically with crystalline materials [66]. Additionally, accurate modelling of bremsstrahlung production has refined predictions of X-ray energy and angular distributions, enhancing applications ranging from industrial inspection to advanced imaging techniques [67].

The biological effects of X-rays are primarily mediated through their interaction with DNA, leading to complex DNA damage (CDD), including double-strand breaks (DSBs) [68]. These lesions activate the DNA damage response (DDR), initiating pathways such as cell cycle arrest, DNA repair, and apoptosis [69]. Radiotherapy leverages this property to target cancer cells, exploiting their impaired repair mechanisms to induce cell death. Recent research highlights the potential of targeting DNA repair pathways to enhance radiosensitivity in tumors, thereby overcoming radioresistance while protecting normal tissue [70]. Emerging approaches, such as mitophagy enhancement, further illustrate innovative strategies

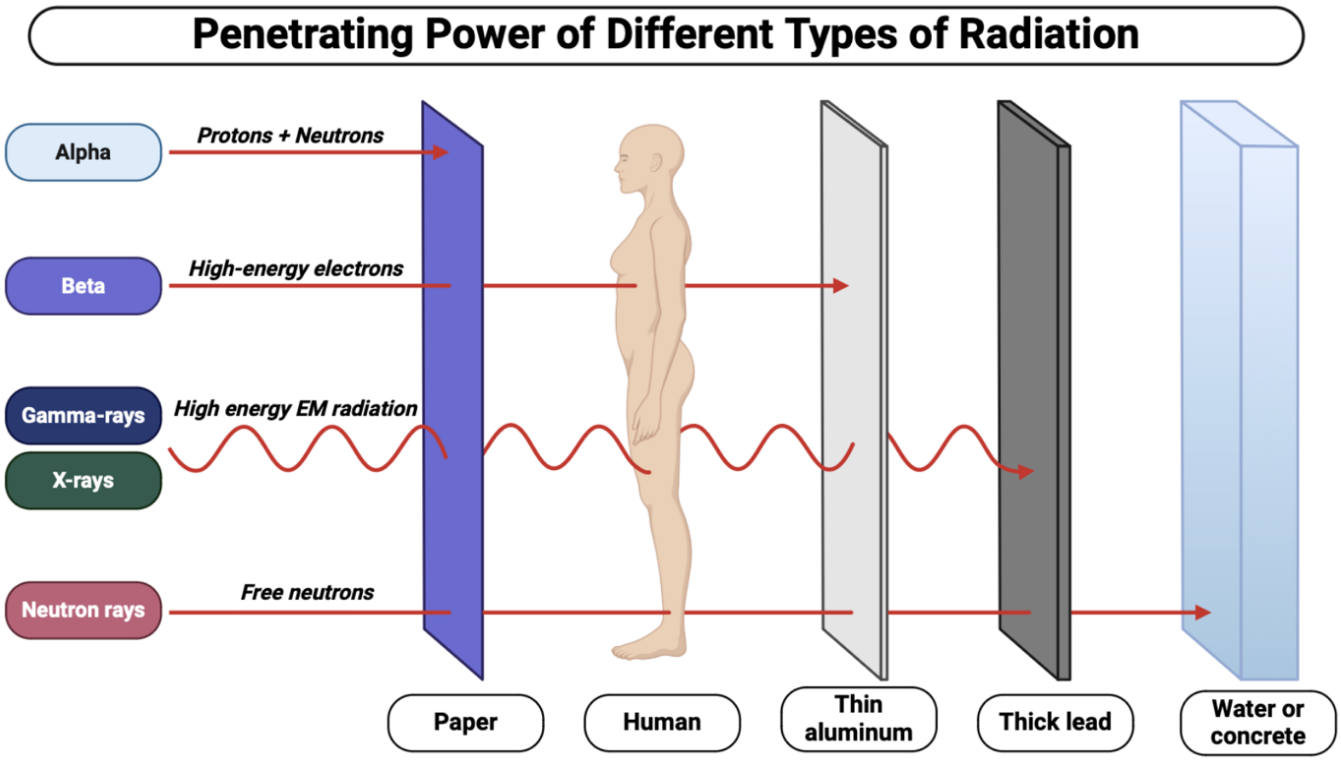

Fig. 7. Comparative penetrating power of various radiation types through different materials

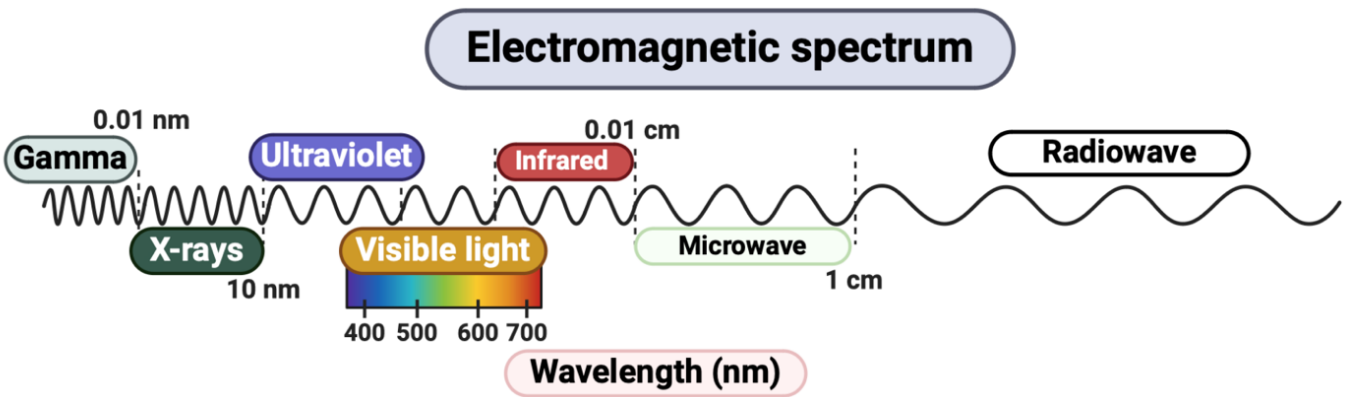

Fig. 8. Representation of the electromagnetic spectrum highlighting X-rays and other radiation types by wavelength range

to amplify radiation-induced DNA damage, paving the way for improved therapeutic outcomes [71].

X-rays also enable hybrid imaging techniques, such as X-ray-induced optical molecular sensing. These methods combine scintillation or Cherenkov radiation with molecular probes to achieve high-resolution imaging of tissue properties like oxygenation and pH, offering novel diagnostic opportunities [72]. Advances in scintillation materials, such as all-inorganic perovskite nanocrystals, have further improved X-ray detection efficiency, enhancing both medical and industrial imaging [62].

In industrial applications, X-rays are widely used for non-destructive testing and cargo screening. Dual-angle X-ray systems, such as those designed with 9 MV linear accelerators, have demonstrated improved contrast sensitivity and spatial resolution, ensuring precise inspections [73]. The development of wearable dosimeters for personnel protection, incorporating artificial intelligence and Internet of Things technologies, reflects the ongoing innovations aimed at optimizing X-ray safety in various fields.

Despite these advancements, challenges persist. Secondary radiation, such as that generated by bremsstrahlung, and the need for precise beam collimation complicate X-ray applications in both medical and industrial contexts [74]. Additionally, optimizing dose delivery while minimizing radiation-induced harm remains a critical area for research and development. As our understanding of X-ray interactions with biological tissues and materials deepens, future innovations will undoubtedly expand the potential of X-rays as a versatile tool for imaging, therapy, and diagnostics.

In-depth analysis of electron therapy in radiation treatment

To begin with, any therapeutic technique (whether established or emerging) must undergo rigorous evaluation from multiple perspectives, in context both its current advantages and inherent limitations. This approach is especially crucial in radiotherapy, where therapeutic decisions directly impact patient health and survival outcomes. Electron therapy, with its potential for high precision and adaptability, presents significant benefits across various clinical applications. However, a thorough understanding of its role demands not only an appreciation of its strengths but also a critical examination of its limitations and associated challenges. In this section, we aim to provide a comprehensive overview of electron therapy as an advancing modality. Through an analysis of current literature and recent innovations, we seek to offer a balanced perspective on its clinical promise, as well as the barriers that may influence its broader adoption in oncology.

Advantages of electron therapy in radiation oncology

Unique dosimetric properties of electron therapy

Electron therapy offers a distinct advantage in radiation oncology due to its unique dose distribution characteristics. Unlike traditional photon radiation, electron beams provide a homogeneous dose profile within the target area, with a sharp dose fall-off beyond a specific depth. This property makes them particularly effective for superficial tumors and cutaneous lymphomas, minimizing damage to underlying healthy tissues [75]. The steep dose gradients of electron beam also allow precise treatment of irregularly shaped targets while sparing adjacent organs and tissues [31]. Very High-Energy Electron (VHEE) beams, operating at energies above 100 MeV, have expanded the scope of electron therapy to include deep-seated tumors up to 15 cm depth. These beams offer improved dose conformity and reduced lateral scattering compared to photon beams, making them suitable for treating challenging anatomical regions [76].

Adaptability for Targeting Tumors at Various Depths

One of the most notable benefits of electron therapy is its adaptability. The ability to adjust beam energy allows for tailored treatments targeting tumors at varying depths. Low-energy beams are ideal for shallow lesions, while higher-energy beams address deeper tumors. For instance, electron therapy has shown efficacy in breast cancer treatments, particularly as a boost modality

after breast-conserving surgery. Studies demonstrate reduced radiation doses to critical structures such as the heart and contralateral breast, maintaining high target coverage [77]. Recent advancements in hybrid techniques, such as combining electron and photon therapy, have further optimized treatment outcomes [17]. The use of 3D-printed modulated electron boluses (MEBs) has improved dose conformity and reduced exposure to organs at risk, including the ipsilateral lung and left anterior descending artery [78]. These innovations underline the potential of electron therapy to enhance patient quality of life.

Advancements in Very High-Energy Electron Therapy

VHEE therapy becomes a pioneering technique in modern radiotherapy due to its unique physical properties and potential to treat complex cancer cases [19]. Using electrons with energies in a wide range, it is characterised by its ability to deliver therapeutic doses with remarkable precision, which makes it particularly suitable for the treatment of tumours in heterogeneous and anatomically complex areas such as the thoracic and pelvic cavities (including the retroperitoneum and pelvic organs) [34].

Comparative analyses have demonstrated that VHEE beams achieve dosimetric performance similar to advanced modalities like proton therapy, offering an effective yet potentially more accessible alternative for institutions without proton beam facilities. Advanced beam delivery systems, including collimation and modulation techniques, have further enhanced this precision. Recent innovations in treatment planning, such as adaptive optimization algorithms, have enabled tailored dose distributions to accommodate tumors with irregular geometries or varying densities [79], underscoring the versatility of VHEE in clinical practice. As research progresses, the application of VHEE beams continues to evolve, with ongoing studies focusing on optimizing treatment protocols, refining beam delivery systems, and enhancing patient outcomes. By addressing existing technical challenges and expanding its clinical capabilities, VHEE therapy holds immense promise as a cornerstone of next-generation radiation oncology.

Innovative Delivery Systems and Emerging Technologies

Technological innovations continue to expand the versatility of electron therapy. *Laser Wakefield Acceleration* (LWFA) offers a compact and cost-effective method for generating high-energy electron beams, potentially making electron therapy more accessible in clinical settings [80]. Researchers have demonstrated the generation of ultrarelativistic electron beams up to 50 MeV using terawatt-scale lasers, paving the way for advanced radiotherapy devices [81]. Advanced collimation and scanning systems are also under development to support the precise delivery of VHEE beams. These systems incorporate optimized magnetic fields and high-Z foils to sustain ultra-high dose rates while ensuring dose uniformity. Combined with PBS techniques, these innovations enhance the precision and safety of electron therapy, reinforcing its role as a cornerstone in modern radiation oncology.

Biological Applications and Potential of Electrons

Electron therapy has emerged as a versatile modality in radiation oncology, offering unique biological and dosimetric advantages. Low-energy electrons (LEEs) play a crucial role in inducing DNA damage, primarily through ionization and excitation, leading to double-strand breaks (DSBs) and oxidative stress in tumor cells [82]. These effects are highly localized, minimizing collateral damage to healthy tissues. Advanced computational tools, such as Monte Carlo simulations, have provided insights into the interactions of LEEs with biological molecules, aiding in precise future treatment planning.

Recent innovations, such as *Very High-Energy Electrons* have expanded the potential of electron therapy to treat deep-seated tumors [32]. Studies demonstrate that VHEEs can achieve dosimetric quality comparable to proton therapy, particularly for challenging cancers such

as glioblastoma and prostate cancer [57]. Furthermore, the integration of electron therapy with emerging modalities like FLASH radiotherapy has shown promise in enhancing the therapeutic index. VHEE beams are particularly suited for FLASH applications, offering both biological and ballistic advantages for treating deep-seated tumors.

Limitations and challenges of electron therapy

Despite its significant potential, electron therapy faces several limitations and challenges that restrict its broader clinical application. One of the primary limitations is the restricted penetration depth and dose modulation of conventional electron beams. Their shallow penetration depth makes them less effective for treating deep-seated tumors, even though there's a lot of research of this flaw. Thus, *Very High-Energy Electrons* partially address this limitation by providing improved dose matching for tumors located at a depth of 5–15 cm. However, achieving such precision requires energies above 100 MeV, for greater penetration depths — up to 30 or more centimeters deep, and advanced beam modulation techniques and highly specialized delivery systems. These setups, while promising, are not yet widely available and require further technological development.

Another critical issue is the presence of secondary radiation components, particularly *Bremsstrahlung* photons generated by high-energy electron beams. These secondary photons can contribute up to 8% of the absorbed dose [83], increasing the risk of unintended biological effects, particularly in high-energy applications. This underscores the importance of careful machine design and optimization of beam delivery systems to mitigate these risks. Accurate dosimetry and beam monitoring also present significant challenges, especially in ultra-high dose-rate applications such as FLASH therapy. Existing detectors struggle with saturation effects, limiting their ability to measure doses accurately at the speeds required for FLASH [84]. The development of robust monitoring tools and the standardization of dosimetry protocols are essential to ensure precise and safe dose delivery.

The scattering dynamics and lateral penumbra of electron beams further complicate their use, particularly in heterogeneous tissues. Advanced techniques such as pencil beam scanning (PBS) and magnetic focusing have demonstrated potential in reducing lateral penumbra and enhancing dose conformity [85]. However, these technologies are still in experimental stages and require further refinement to become clinically viable. In addition, the technical challenges associated with FLASH and VHEE therapy remain a significant bottleneck. Achieving the ultra-high dose rates necessary for FLASH therapy involves overcoming hurdles such as rapid energy adjustments and efficient pencil beam scanning for large treatment fields [84]. Current systems lack the capability to deliver FLASH dose rates across extensive areas, limiting their practical application. The development of advanced technologies is necessary to address these issues.

Finally, biological uncertainties surrounding electron therapy must be resolved. The relative biological effectiveness (RBE) of electrons, often assumed to be unity, may vary depending on factors such as energy levels, dose rates, and tissue types. While preliminary studies have reported differences in DNA double-strand break (DSB) induction between conventional and VHEE beams [86], the clinical significance of these findings remains unclear. A deeper understanding of the underlying radiobiological mechanisms is crucial to optimizing treatment outcomes and minimizing potential side effects.

Conclusion

Electron therapy represents a promising advancement in radiation oncology, offering unique physical and biological properties that enable precise and adaptable treatment strategies. Its dosimetric advantages, particularly the ability to deliver highly localized doses with minimal collateral damage, position it as a valuable modality for both superficial and deep-seated tumors. Recent innovations, such as *Very High-Energy Electrons* and FLASH radiotherapy, have expanded the scope of

electron therapy, demonstrating significant potential for improving therapeutic outcomes and patient quality of life.

But several challenges remain. The limited availability of advanced delivery systems, complexities in beam modulation, and biological uncertainties, like variations in relative biological effectiveness, underscore the need for continued research and technological development. Addressing these limitations through interdisciplinary collaboration and innovation will be essential for unlocking the full potential of electron therapy as a standard clinical modality.

By bridging the gap between emerging technologies and clinical application, future efforts in electron therapy hold the promise of transforming radiotherapy practices, enhancing precision, and ultimately improving outcomes for cancer patients worldwide.

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Формирование будущего лучевой терапии: роль электронов и FLASH-подхода

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Аннотация. Лучевая терапия (ЛТ) остается краеугольным камнем в онкологии, предоставляя целенаправленное лечение различных видов злокачественных новообразований (ЗНО). История ее развития уходит корнями к открытию рентгеновских лучей Вильгельмом Рентгеном и исследованиям радия Марии Кюри. Сегодня ЛТ превратилась в сложную область, охватывающую широкий спектр методов. Однако растущая глобальная проблема ЗНО различных органов подчеркивает необходимость постоянных инноваций для повышения эффективности лечения при минимизации побочных эффектов. Традиционные методы, такие как рентгеновские и гамма-лучи, доказали свою значимость в лечении различных

видов рака, но тем не менее, часто сопровождаются непреднамеренным повреждением здоровых тканей. Электронная терапия становится перспективной альтернативой благодаря уникальным дозиметрическим характеристикам, обеспечивающим точное воздействие с ограниченной глубиной проникновения. Низкоэнергетические пучки электронов идеально подходят для лечения поверхностных опухолей, в то время как электроны очень высокой энергией (ЭОВЭ) позволяют воздействовать на глубокие опухоли, соперничая с протонной и тяжело-ионной терапиями. Кроме того, эффект FLASH — феномен, снижающий токсичность для здоровых тканей при сверхвысоких дозах, открывает новые возможности для улучшения качества жизни пациентов. Однако, несмотря на эти достижения в данной области, остаются многочисленные вопросы и вызовы. Ограниченная глубина проникновения, вторичное излучение от тормозного излучения и сложности в системах доставки доз ограничивают широкое клиническое применение. Кроме того, нерешенные биологические вопросы, такие как изменчивость относительной биологической эффективности, требуют дальнейших исследований. Настоящий обзор посвящен обсуждению уникальных преимуществ и ограничений электронной терапии в сравнении с традиционными методами. В нем рассматриваются новейшие достижения (ЭОВЭ, терапия FLASH и гибридные подходы), а также обсуждаются технологические вызовы и будущий потенциал электронных пучков в онкологии. Выводы. Интеграция с последними технологическими достижениями позволяет электронной терапии переосмыслить терапевтические подходы, предлагая более безопасные и персонализированные стратегии лечения злокачественных новообразований.

Ключевые слова: лучевая терапия, электроны очень высокой энергией, ускорители частиц, сверхвысокодозная терапия, онкология

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ОБЗОР
REVIEW

Multidisciplinarity and interdisciplinarity in medicine and education as a tool for improving the quality of patients' antitumor treatment

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Abstract. *Relevance.* Despite the advances in modern medicine, the improvement of treatment methods for many diseases, the overall incidence of cancer, as well as mortality from cancer, remains high. At the same time, the approaches to antitumor treatment themselves often significantly reduce the quality of life of patients, limit their ability to work, which causes certain social and economic damage from these diseases. In this regard, issues of improving the quality of antitumor treatment are among the priority issues in healthcare today. The purpose of this study is to find new possible tools and approaches to improve the quality of antitumor treatment for patients at different levels, including clinical and educational. It is possible to significantly change and improve the quality of oncological care for patients through the tools and technologies of accompanying therapy, including dental support, the clinical significance of which is critically underestimated today. Improving the methods of accompanying therapy is a multidisciplinary problem that can and should be solved exclusively in the context of interdisciplinary interaction of specialists of different profiles. Currently, the development of dental support is limited by a number of factors, such as clinical or organizational, but one of the most significant factors is the insufficient focus on this problem in medical education. Of course, the current pace of development of medicine, the introduction of new technologies, including artificial intelligence, increase the requirements for a modern specialist doctor and require extensive knowledge that goes beyond one discipline, including the presence of interdisciplinary thinking. *Conclusion.*Thus, the introduction of interdisciplinary approaches in the training of future dentists and doctors specializing in «General Medicine», training students at the intersection of different specialties (oncology and dentistry, dentistry and hematology) can improve the quality of dental support in particular, and the quality of antitumor treatment in general.

Keywords: interdisciplinarity, supportive therapy, dental supporting care in cancer patients, medical education

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Introduction

The increase in the overall oncological incidence in the Russian Federation was more than 7%, compared in 2023 to the previous 2022 [1]. The overall incidence rate of malignant neoplasms per 100 thousand of the population of Russia was 428.4, which is higher than in previous years. The prevalence rate of oropharyngeal tumors is no more than 3%. At the same time, 66% of tumors were detected in the late stage of the disease (stages III–IV), which certainly often determines the negative prognosis for tumors of this localization [2].

Search for ways to improve the effectiveness of antitumor treatment methods

Malignant neoplasms (MN) of the oropharyngeal region are very difficult to treat, associated with many factors (anatomical and functional disorders, speech limitations, nutrition, aesthetic disorders), significantly limit the ability of patients to work and cause high mortality. In this regard, the issues of prevention, early diagnosis and treatment of oropharyngeal tumors are one of the key tasks of healthcare today [3–5]. It is difficult to determine the most rational and optimal method of treating malignant neoplasms of this localization; in most cases, the approach is individual. At the same time, clinicians and researchers are constantly searching for new treatment methods in all areas of antitumor therapy [6].

The main method of treatment is a surgical approach, but the resulting traumatic and aesthetic disorders significantly limit its radicality [7], which leads to more active development of non-surgical approaches to treatment, namely radiation therapy and chemotherapy.

Radiation therapy is a common method of non-surgical treatment of head and neck tumors, allowing to avoid severe traumatic consequences, dysfunction of the maxillofacial organs, aesthetic disorders, which is an extremely important aspect for the patient, since it is associated with the psychological individual characteristics of the personality. At the same time, modern methods of 3D radiation therapy, 3D radiation therapy planning allow to exclude or at least minimize the negative impact on the surrounding, peritumor healthy tissues [8].

Chemotherapy in the treatment of malignant neoplasms of the maxillofacial and oropharyngeal region is also widely used and today is one of the most promising and rapidly developing areas in oncology. The most common drugs in the treatment of tumors of this localization are platinum drugs (cisplatin),

5-fluorouracil and taxanes. [9]. At the same time, these drugs do not have a selective effect on other cells of the oropharyngeal epithelium, which leads to their damage and the development of complications such as chemotherapeutic mucositis. Relatively recently, about 20 years ago, a new direction in chemotherapy appeared — targeted therapy [10], capable of targeting the cellular mechanisms of carcinogenesis [11, 12]. This method of chemotherapy is associated with its prospects in general. The possibilities of combining chemotherapy with radiotherapy show good results in overall relapse-free survival of patients with malignant neoplasms of this localization [13, 14], which generally leads to a shift in the vector of development of antitumor treatment methods towards organ-preserving ones.

Despite the promise of non-surgical methods of treating tumors, a significant drawback of these methods is the high risk of developing side effects [15–17]. Side effects of radiation and chemotherapy reduce the positive results of the treatment. Oncologists are often forced to stop or interrupt treatment, for example, due to the development of severe oral mucositis. At the same time, various factors are distinguished in the etiology of the development of side reactions during chemotherapy or radiation therapy: both local and general (Figure). Taking into account these factors (comorbidity [18], genetic markers[19], nutritional status[20], psychological state [21], microflora of the oral cavity [22–24], level of dental sanitation) when preparing the patient for the upcoming treatment can reduce the number and intensity of side reactions.

Dental support of patients as part of accompanying therapy in oncology

A set of measures for the preparation and support of a patient during antitumor treatment is called accompanying therapy. The creation of programs and development of accompanying therapy technologies that can improve the quality and effectiveness of antitumor

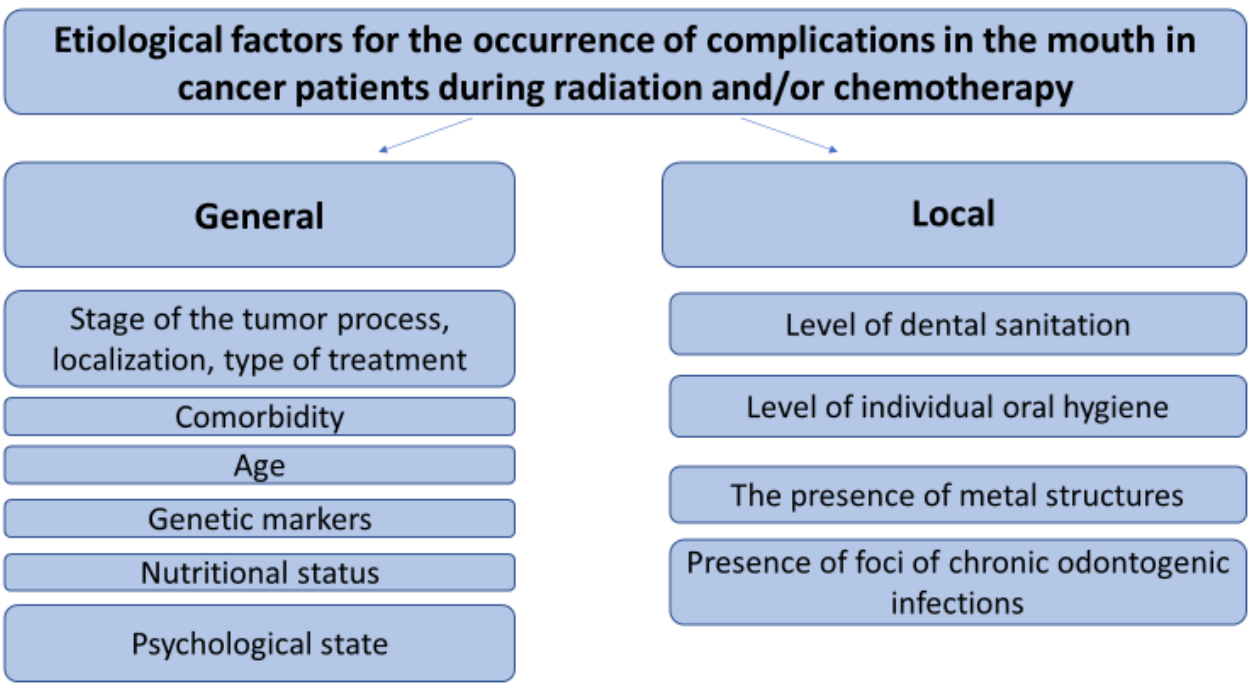

Fig. Etiological factors for the occurrence of complications in the mouth in cancer patients during radiation and/or chemotherapy

treatment of patients is a complex multidisciplinary problem. Currently, professionally performed expensive antitumor treatment without accompanying therapy often does not provide the patient with the quality of life necessary, which negatively affects the overall results [25, 26]. Accompanying therapy occupies an important place in oncology. The main goal of accompanying treatment of cancer patients is to reduce the frequency and severity of adverse events of antitumor treatment. The section of accompanying therapy dealing with issues of preventing adverse reactions in the mouth is dental accompanying therapy. Dental support allows to reduce the severity of developing complications, such as oral mucositis, which are often quite predictable, thereby increasing the effectiveness of antitumor treatment in general, given that the absence of complications or their mild severity allows for the treatment of patients without interruption, which has a beneficial effect on the overall prognosis of the disease [27–29]. Improving the methods of dental support is also a complex multidisciplinary problem that can and should be solved exclusively in the context of interdisciplinary interaction of specialists of different profiles [30–32]. This includes improving the methods of clinical prevention and treatment of complications arising in the oral cavity against the background of antitumor treatment (development and testing of new patient treatment protocols, search for new treatment tools and technologies) [33–35], and organizational aspects (legislative justification for the need for dental training of cancer patients), and, most importantly, improving the quality of medical education, namely the training of dental personnel with the appropriate competencies. In reality, cancer patients are often not examined by dentists at the pre-hospital stage for various reasons: on the one hand, patients are not informed about the need to contact a dentist to prepare for the upcoming antitumor treatment, on the other hand, there is often nowhere to refer the patient — there are no dental departments and dentists with the skills and knowledge to provide dental care to cancer patients.

The concept of interdisciplinarity and multidisciplinarity in clinical practice and medical education

We call the training of future doctors, including dentists, in the field of clinical medicine and clinical dentistry interdisciplinarity. Of course, the current pace of development of medicine, the introduction of new technologies, including artificial intelligence, increase the demands on a modern medical specialist and require extensive knowledge that goes beyond one discipline, including the presence of interdisciplinary thinking. That is, interdisciplinarity meets the modern nature of the development of medicine in general and medical education in particular [36,37].

The need to create and work interdisciplinary or multidisciplinary teams in oncology, consisting of doctors of different specialties, is much discussed at international and domestic conferences. Up to 10–15 different specialists should be involved in the treatment of an oncological patient, including, of course, oncologists, radiotherapists, chemotherapists, rehabilitation specialists, nutritionists, narrow specialists, including dentists, otolaryngologists, anesthesiologists, defectologists, speech therapists, mid-level medical specialists, etc. This is a huge team, whose work is based on constant interaction and monitoring of the patients' condition. Unfortunately, in reality, the work of multidisciplinary teams is often implemented formally. Organizing such work in the context of practical healthcare is associated with many limiting factors. These include time costs, organizational difficulties, for example, the lack of necessary specialists in a medical institution, and others [38]. In any case, participation in a multidisciplinary team of specialists, or the practical application of interdisciplinary approaches requires a modern doctor to expand his knowledge in a certain area. Namely, a dentist must have sufficient knowledge in oncology, etc. That is, such multidisciplinary and interdisciplinary approaches are, among other things, difficult to implement due to the lack of trained personnel to solve such problems. That is, the problem of interdisciplinarity in medicine is a problem of interdisciplinarity in medical education. It should be noted that the entire educational process is built on the idea of obtaining knowledge on the structure of various disciplines, including in medical education. From the first year, medical institutes study various

disciplines — subjects that are often not related to each other. And a student cannot independently conduct and establish interdisciplinary connections between these disciplines-subjects. Also, the very structure of medical institutes and universities is built on departmental division, where within the framework of one department, specialists of one direction are united, who are aimed at solving one scientific problem. Departments that include specialists from different fields, such as oncologists, radiotherapists and dentists, are rare, and the problems that these departments are able to solve are interdisciplinary. The introduction of interdisciplinarity in teaching disciplines in universities should begin with the development of interaction between teachers of different departments and disciplines at the intersection of different areas: dentistry and oncology, dentistry and hematology.

The issues of improving the quality of education in universities, including medical ones, lead to the search for approaches to modernizing the education system in Russia. One of the problems in the pedagogical environment is the difficulties that students encounter when mastering educational material that requires combining knowledge from previous disciplines, analyzing acquired knowledge and interdisciplinary thinking. Students experience difficulties in combining their knowledge from different fields even within the framework of one specialty (for example, therapeutic dentistry and surgical dentistry), so targeted work of methodologists and teachers is needed to find new approaches in medical education to improve the quality of material assimilation by students. The most accessible methodological approach in this case is the analysis and demonstration of clinical examples from the teacher's experience with a detailed analysis of all clinical and organizational stages [39]. Interdisciplinarity and multidisciplinarity in medicine and education are a modern necessity also due to the fact that the main goal of Russian healthcare is to increase the average life expectancy of the population. An increase in the average life expectancy of the population inevitably leads to an increase in the percentage of people who suffer from chronic diseases, and not one, but several. And this reveals another problem of clinical medicine associated with the treatment of such patients with combined pathologies. What is today called comorbidity. Despite the large number of publications on this topic, the healthcare system still uses an approach in which each individual nosology is treated by a separate specia leaf, according to individual clinical guidelines, complex approaches to the treatment of a comorbid patient are practically not used [40]. An oncological patient is most often a comorbid patient suffering from several diseases — this includes diabetes mellitus, cardiovascular pathology, and others. Taking into account the comorbidity of an oncological patient when planning antitumor treatment, including accompanying therapy programs, is a priority task for modern oncology. That is, an interdisciplinary approach to patient treatment is a clinical necessity today, due to a number of factors, including an increase in the average life expectancy of the Russian population. A gradual and comfortable transition to interdisciplinarity for all participants in the treatment process is a priority task for primary health care [41–43].

Conclusion

Thus, improving the quality of antitumor treatment of patients is a complex multidisciplinary and interdisciplinary problem that can and should be solved at different levels. First of all, at the educational level — the introduction of interdisciplinary clinical approaches in educational programs in medical universities from the early years of study (I, II year) for medical students of all specialties, both dentists and the specialty «General Medicine». This approach will allow students to develop clinical interdisciplinary thinking and in the future successfully become part of a multidisciplinary team for the treatment of patients with combined pathology, including oncological, as well as implement in practice programs of accompanying therapy, including dental support. Training medical personnel with knowledge in several specialties will improve the quality of oncological care and medical care in general.

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Мультидисциплинарность и междисциплинарность в медицине и образовании как инструмент повышения качества противоопухолевого лечения пациентов

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Аннотация. *Актуальность.* Несмотря на успехи современной медицины, совершенствование методов лечения многих болезней, общая онкологическая заболеваемость, а также смертность от онкологии остается на высоком уровне. При этом сами подходы к противоопухолевому лечению часто существенно снижают качество жизни пациентов, ограничивают их работоспособность, что обусловливает определенный социальный и экономический ущерб от этих заболеваний. В связи с чем вопросы повышения качества противоопухолевого лечения являются одними из приоритетных вопросов в здравоохранении сегодня. Целью настоящего исследования является поиск новых возможных инструментов и подходов для повышения качества противоопухолевого лечения пациентов на разных уровнях, в том числе клиническом и образовательном. Существенно изменить и улучшить качество онкологической помощи пациентам возможно за счет инструментов и технологий сопроводительной терапии, в том числе и стоматологического сопровождения, клиническая значимость которого сегодня критически недооценивается. Совершенствование методов сопроводительной терапии — мультидисциплинарная проблема, которая может и должна быть решена исключительно в контексте междисциплинарного взаимодействия специалистов разного профиля. В настоящее время развитие стоматологического сопровождения ограничено рядом факторов, например клинических или организационных, но одним из наиболее значимых факторов, является недостаточное акцентирование внимания на данной проблеме в рамках медицинского образования. Безусловно, современные темпы развития медицины, внедрение новых технологий, в том числе и искусственного интеллекта, повышают требования к современному врачу-специалисту и требуют от него обширных знаний, выходящих за рамки одной дисциплины, в том числе и наличие междисциплинарного мышления. Выводы. Таким образом, внедрение междисциплинарных подходов в обучении будущих врачей-стоматологов и врачей специальности «Лечебное дело», обучение студентов на стыке разных специальностей (онкология и стоматология, стоматология и гематология) способно повысить качество стоматологического сопровождения в частности и качество противоопухолевого лечения в целом.

Ключевые слова: междисциплинарность, сопроводительная терапия, стоматологическое сопровождение онкологических пациентов, медицинское образование

Информация о финансировании. Работа выполнена без финансовой поддержки.

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Killing potential of circulating neutrophils in renal tumors

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Abstract. *Relevance*. Currently, the study of the role of neutrophils in the development of renal cancer is of considerable interest. The study of the immunopathogenesis of renal cancer is determined by the need to use combined treatment with immunotherapy. It is known that neutrophils have both pro- and antitumor properties, which are associated with the level of surface receptors CD11b, CD16, CD63, CD66b and the killing activity of neutrophils. *The aim* of the study was to assess the killing potential of circulating neutrophils in renal tumors. *Materials and Methods.* The object of the study was circulating neutrophils of patients with verified renal cancer (n = 74), patients with renal benign neoplasms (n = 18) and conditionally healthy donors (n = 22). The study of the phenotype of the isolated neutrophils was carried out by flow cytometry. Neutrophil extracellular traps were counted using the method by I.I. Dolgushin. *Results and Discussion.* Analysis of the percentage of neutrophil extracellular traps showed an increase in their number in the groups of patients with renal cancer, both stages I–II and III–IV, relative to the control group and the group of patients with renal benign neoplasms. An increase in the neutrophil trap index was found in the groups of patients with renal cancer stages I–II and III–IV relative to the control group and the group of patients with renal benign neoplasms. When assessing the phagocytic activity and the phagocytic activity index, a significant increase in these indicators was found in the groups of patients with renal cancer relative to the control group and the group of patients with renal benign neoplasms. A correlation was found between the percentage of neutrophil extracellular traps (r = 0.438, p = 0.001), the phagocytic activity (r = 0.431, p = 0.001) and the phagocytic activity index (r = 0.507, p = 0.001) of neutrophils and the stage of renal cancer. A significant increase in the percentage of neutrophils expressing CD66b receptors was found both at the initial and widespread stages of renal cancer relative to the group with renal benign neoplasms and the control group. Multivariate Cox regression revealed an increase in the risk of renal cancer with an increase in CD66b expression, the neutrophil extracellular traps index, the phagocytic activity and the phagocytic activity index of circulating neutrophils (R^2 = 0.728, χ^2 = 58.1, p = 0.001). For differential diagnostics between renal benign neoplasms and renal cancer, the percentage of CD66b+ neutrophils, the neutrophil extracellular traps index, the phagocytic activity of neutrophils and the phagocytic activity indexneutrophils demonstrated statistical

significance together. The area under the curve (AUC) of the model was 0.983, and could be diagnosed with a probability of 94.3% (Spec. = 0.889, Sens. = 0.962). *Conclusion.* Thus, an increase in CD66b+ neutrophils and activation of extracellular trap release indicate an increase in the killing activity of neutrophils in renal cancer. Simultaneous determination of the amount of CD66b+ neutrophils, the index of neutrophil extracellular traps, phagocytic activity and the index of phagocytic activity can be used for differential diagnosis between the renal benign neoplasms and renal cancer.

Keywords: neutrophils, renal cancer, CD11b, CD16, CD66b, CD63, neutrophil extracellular traps

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Introduction

Clear cell renal cell carcinoma (RC) is the most common type of renal cancer (about 70% of cases). The leading role in its treatment belongs to the surgical method. However, already at the time of diagnosis, a significant proportion of patients are diagnosed with disseminated RC, which determines the need for combined treatment with immunotherapy [1]. Currently, the number of studies aimed at studying the role of neutrophils (Nph) in RC is growing [2, 3]. The ability of Nph to exhibit both pro- and antitumor properties has been shown [4].

The level of expression of surface receptors determines the functional activity of Nph. Thus, CD11b, CD16, CD63 and CD66b allow identifying mature and activated Nph [5]. Thus, CD11b mediates chemotaxis of Nph to the site of inflammation, adhesion, phagocytosis, respiratory burst and degranulation [6]. CD16 (FcγRIII) is a marker of Nph capable of cytotoxic action, degranulation, oxygen burst and proliferation [6]. CD66b receptors are expressed by mature, activated and degranulating Nph [7]. CD11b+CD16+ is a subpopulation of mature Nph capable of phagocytosis and degranulation [8]. The receptors of maturity, activation, degranulation and cytotoxicity CD16, CD63, CD66b determine the phenotype of neutrophils, which have a high capacity to form extracellular neutrophil traps (NETs) [9].

It is known that NETs play an important role in the occurrence and development of pathological processes

[10,11]. While the positive effects of NETs in the fight against pathogens have already been largely described, their negative role has also become known, including in carcinogenesis. NETs can have potential antitumor effects due to the direct destruction of cancer cells or activation of the immune system, releasing a number of cytotoxic substances that destroy tumor cells, block tumor growth and the formation of metastases [12, 13]. However, many studies indicate that NETs, ensuring the spread of tumor cells to organs and tissues, are capable of exerting a protumorogenic effect and play an important role in the progression and metastasis of tumors, including in RC [14]. The phenotype of Nph is associated with the tumor process and stage, and can determine the growth and progression of RC [9]. However, this question has not been fully studied.

The aim of this work was to evaluate the killing potential of circulating Nph in renal tumors.

Materials and methods

The object of the study were circulating Nph of patients with verified RC (Table 1), conditionally healthy donors (control group) and patients with renal benign neoplasms (RBN) (oncocytoma, angiolipoma, renal cyst) (Table 1). Nph were isolated from leukocyte suspension on a double density gradient of Ficoll-Verografin solutions. The isolated Nph were brought to a concentration of 5×10^6 cells/ml. The purity of the Nph fraction was 92–94%. The viability of Nph in the test with 0.5% trypan blue was 95%. The phenotype of the isolated Nph was studied by flow cytometry (BioSino, China) using monoclonal antibodies (Sony Biotechnology, USA) labeled with FITC (fluoresceinisothiocyanate), PE (phycoerythrin), PC5 (phycoerythrin-cyanin 5): CD11b, CD16, CD63, CD66b, CD95. NETs were counted according to the method of Dolgushin I.I. et al. (2010). The number traps (NT,%) of neutrophil was determined — the number of neutrophil traps containing yeast activator cells from 100 counted network-like structures and the neutrophil trap index (TI, c.u.) — the number of yeast activators in 100 counted traps per 1 structure, phagocytic activity (PA,%) and phagocytic index (PI, c.u.).

Statistical analysis

The sets of quantitative indicators, the distribution of which differed from the normal one, were described using the median (Me) values and the lower and upper quartiles ($Q_1 – Q_3$). The statistical significance of the differences was assessed using the Mann-Whitney U-test. To study the relationship between quantitative variables, the Spearman correlation coefficient was calculated. To assess the association of the studied indicators and the degree of differentiation, sensitivity and specificity were calculated, as well as ROC analysis. Statistical processing was performed using Statistica v. 13 and Jamovi 2.3.28 software. Differences were considered statistically significant at $p < 0.05$.

Table 1

Clinical characteristics of patients included in the study

Group	Clinical characteristics	Meaning
Renal cancer, n = 74	Age — median ($Q_1 – Q_3$), years	66 (58–70)
	Absolute leukocyte count x10^9/l	7.02 (5.80–8.31)
	Absolute neutrophil count x10^9/l	3.46 (2.70–4.90)
	NLR ($Q_1 – Q_3$)	1.33 (1.01–2.19)
	Sex	
	male	36
	female	38
	Histotype:	
	Clear cell carcinoma	74
	Stage of the disease:	
	I–II	40
	III–IV	34

Ending tabl. 1

Group	Clinical characteristics	Meaning
Renal benign neoplasms n = 18	Age — median (Q_1– Q_3), years	68 (56–75)
	Absolute leukocyte count x10^9/l	4.60 (4.30–5.65)
	Absolute neutrophil count x10^9/l	2.58 (2.10–2.68)
	NLR (Q_1– Q_3)	1.19 (1.18–1.68)
	Sex	
	male	0
	female	18
Control groupn = 22	Age — median (Q_1– Q_3), years	54(52–66)
	Absolute leukocyte count x10^9/l	6.10 (5.28–6.88)
	Absolute neutrophil count x10^9/l	3.30 (2.82–3.97)
	NLR (Q_1– Q_3)	1.73 (1.23–1.88)
	Sex	
	male	8
	female	14

Note: NLR — neutrophil-lymphocyte ratio.

Results and discussion

During the study, we did not find any significant change in the absolute amount of Nph in the blood of patients in the study groups. According to studies [15, 16], NETs are associated with tumor cell proliferation and affect tumor development. Analysis of the percentage of NETs showed an increase in their number in groups of patients with RC, both I–II and III–IV stages of RC, relative to the control group and the group of patients with RBN (Table 2).

Table 2

Indicators of neutrophil extracellular traps and phagocytic activity of circulating neutrophils in the study groups, Me (Q_1– Q_3)

Indicators	Control group (*n* = 22)	Renal benign neoplasms (*n* = 18)	Renal cancer stage I–II (*n* = 50)	Renal cancer stage III–IV(*n* = 34)
Number traps, %	4.00 (3.00–4.75)	3.00 (3.00–4.00)	5 (4.00–7.00)*	6.00 (5.00–8.00)*
p	-	-	p1 = 0.001, p2 = 0.001	p1 = 0.001, p2 = 0.001
Index trap, y. e.	1.33(1.00–1.90)	1.55 (1.45–1.60)	1.69 (1.48–1.85)*	1.63 (1.50–2.00)*
p	-	-	p1 = 0.007, p2 = 0.022	p1 = 0.012, p2 = 0.024
Phagocyticactivity, %	13.00 (10.30–12.30)	7.00 (5.00–11.00)*	10.00 (8.75–12.30)*	14.00 (10.00–17.00)*
p	-	p1 = 0.001	p2 = 0.006	p1 = 0.189, p2 = 0.001, p3 = 0.001
Phagocytic activity index, y. e.	0.24 (0.19–0.29)	0.17 (0.07–0.39)	0.26 (0.20–0.39)*	0.32 (0.29–0.36)*
p	-	-	p2 = 0.026	p1 = 0.004, p2 = 0.024, p3 = 0.001

Note: p1 — reliability of differences in indicators from the values of the control group; p2 — reliability of differences in indicators from the values in the group with benign neoplasms; p3 — reliability of differences in indicators from the values of the previous stage of renal cancer; reliability of differences according to the Mann-Whitney criterion: * ($p < 0.05$).

We also found an increase in IT in the groups of patients with stages I–II and III–IV RC relative to the control group and the group of patients with RBN. When assessing PA and PI, a significant increase in these parameters was found in the groups of patients with RC relative to the control group and the group of patients with RBN. In addition, PA and PI of circulating Nph changed depending on the prevalence of RC, so a significant increase in these parameters was noted in the group of patients at stages III–IV RC relative to the group with stages I–II RC. According to previous studies [17], at the initial stages of lung cancer, NETs had cytotoxic properties in relation to cancer cells, and at later stages they demonstrated a pro-tumor effect. There is evidence that in breast cancer, Nph more actively form NETs in the presence of a tumor with G3 differentiation than G1 [18]. The formation of NETs is one of the mechanisms of "evasion" or shielding of cancer cells from the antitumor mechanisms of the immune system [19].

Our data indicate an increase in the ability of circulating Nph to form NETs, as well as an increase in their killing activity in groups with RP relative to patients with RBN and the control group. The correlation we found between the percentage of NETs ($r = 0.438$, $p = 0.001$), PA ($r = 0.431$, $p = 0.001$) and IP ($r = 0.507$, $p = 0.001$) of Nph with the stage of RC may indicate an increase in their cytotoxic properties depending on the prevalence of RC. We assessed the expression of surface receptors that determine activation, degranulation, phagocytic activity and maturity of Nph. A significant increase in the number of Nph expressing CD66b receptors was found both at the initial and widespread stages of RC (Table 3). An increase in the number of CD66b+ Nph may indicate an increase in activated, mature, degranulating circulating Nph in patients in the study groups. There is evidence of an increase in the number and ability to form IL-1 in CD66b+ Nph in other types of cancer [20], which is consistent with the results of our study in RC.

Table 3

Changes in the expression of surface receptors of circulating neutrophils in the study groups, Me (Q_1-Q_3)

Indicators		Control group (*n* = 22)	Renal benign neoplasms (*n* = 18)	Renal cancer stage I–II (*n* = 50)	Renal cancer stage III–IV(*n* = 34)
$CD11b^+$	%	89.10 (82.00–90.90)	93.30 (85.00–93.90)	87.40 (72.64–95.20)	94.40 (73.30–97.90)
	10^9/л	2.94 (2.70–3.00)	2.4 (2.19–2.50)	3.02 (2.51–3.30)	3.27 (2.53–3.38)
$CD16^+$	%	86.10 (82.00–89.70)	83.40 (82.00–89.50)	89.00 (72.20–95.00)	88.30 (61.20–94.40)
	10^9/л	2.84 (2.71–2.96)	2.15 (2.11–2.42)	3.08 (2.49–3.31)	3.06 (2.12–2.27)
$CD66b^+$	%	66.50 (57.80–77.20)	65.60 (60.10–67.60)	75.70 (62.80–86.90)	70.30 (59.50–79.30)
	10^9/л	2.26 (2.18–2.76)	2.24 (2.14–2.51)	2.62 (2.17–3.01)*	2.43 (2.06–2.74)*
p		-	-	p2 = 0.001	p1 = 0.012, p2 = 0.001
$CD63^+$	%	82.80 (78.10–95.60)	78.30 (67.00–98.00)	86.10 (68.30–96.00)	81.30 (35.10–92.00)
	10^9/л	2.73 (2.58–3.15)	2.02 (1.72–2.53)	2.98 (2.36–3.32)	2.81 (1.21–3.18)
$CD11b^+CD16^+$	%	86.30 (77.70–89.40)	81.70 (80.30–89.50)	82.00 (64.40–90.60)	86.50 (61.10–93.50)
	10^9/л	2.84 (2.56–2.95)	2.10 (2.07–2.31)	2.84 (2.23–3.13)	2.99 (2.11–3.24)

Note: p1 — reliability of differences in indicators from the values of the control group; p2 — reliability of differences in indicators from the values in the group with benign neoplasms; reliability of differences according to the Mann-Whitney criterion: * ($p < 0.05$).

Changes in the expression values of CD11b, CD16, CD63 receptors of circulating Nph in the study groups were statistically insignificant. In multivariate Cox regression, an increase in the risk of developing RC was revealed with an increase in the expression of CD66b, TI, PA and the PI of circulating Nph ($OR^2 = 0.728$, $\chi^2 = 58.1$, $p = 0.001$). In the univariate logistic regression analysis for the differential diagnosis between renal

RBN and RC, the following factors showed statistical significance: the percentage of CD66b+ Nph (OR 0.344 95% CI 0.128–0.559, $p = 0.002$), the TI (OR 9.173 95% CI 1.474–16.872, $p = 0.020$), PA of Nph (OR 1.555 95% CI 0.437–2.672, $p = 0.006$) and PIof Nph(OR 42.940 95% CI 12.259–73.622, $p = 0.006$). The area under the curve (AUC) of the model was 0.983, and RC could be diagnosed with a probability of 94.3% (Spec. = 0.889, Sens. = 0.962) (Figure).

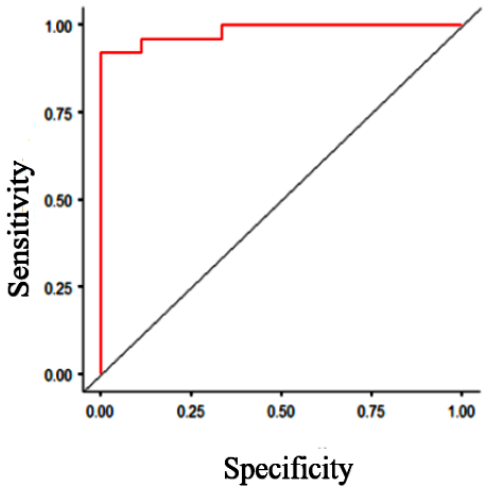

Fig. ROC curve for the regression model of differential diagnosis of renal cancer and renal benign neoplasms taking into account the expression indicators of the CD66b receptor, the neutrophil extracellular traps index, phagocytic activity and the phagocytic activity index

We found a direct correlation between the change in the expression of the CD66b receptor and CD16 ($r = 0.501$, $p = 0.001$), as well as the CD66b receptor and CD63 ($r = 0.688$, $p = 0.001$) in groups of patients with stages I–II and stages III–IV RC. This may indicate an increase in the killing activity of neutrophils in the studied groups, since these receptors are markers of maturity, PA, the ability to degranulate and form NETs [21].

Conclusion

Thus, an increase in CD66b+ Nph and activation of extracellular traps release indicate an increase in the killing activity of Nph in RC. Simultaneous determination of the amount of CD66b+ Nph, TI, PA and the PI can be used for differential diagnosis between RBN and RC.

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Киллинговый потенциал циркулирующих нейтрофилов при опухолях почки

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Аннотация. *Актуальность.* В настоящее время значительный интерес представляет изучение роли нейтрофилов в развитии рака почки. Исследование иммунопатогенеза рака почки определяется необходимостью использования комбинированного лечения с применением иммунотерапии. Известна способность нейтрофилов проявлять как про- так

и противоопухолевые свойства, которые связаны с уровнем поверхностных рецепторов CD11b, CD16, CD63, CD66b и киллинговой активностью нейтрофилов. *Цель* — оценить киллинговый потенциал циркулирующих нейтрофилов при опухолях почки. *Материалы и методы.* Объектом исследования явились циркулирующие нейтрофилы пациентов с верифицированным раком почки ($n = 74$), пациентов с доброкачественными новообразованиями почки ($n = 18$) и условно здоровых доноров ($n = 22$). Исследование фенотипа выделенных нейтрофилов проводили методом проточной цитометрии. Подсчет внеклеточных нейтрофильных ловушек проводили по методу Долгушина И.И. *Результаты и обсуждение*. Анализ процента внеклеточных нейтрофильных ловушек показал увеличение их количества в группах пациентов с раком почки, как I–II, так и III–IV стадий относительно группы контроля и группы пациентов с доброкачественными новообразованиями почки. Было обнаружено повышение индекса нейтрофильных ловушек в группах пациентов с раком почки I–II и III–IV стадий относительно контрольной группы и группы пациентов с доброкачественными новообразованиями почки. При оценке фагоцитарной активности и индекса фагоцитарной активности было обнаружено значимое увеличение данных показателей в группах пациентов с раком почки относительно контрольной группы и группы пациентов с доброкачественными новообразованиями почки**.** Обнаружена корреляционная связь между процентом внеклеточных нейтрофильных ловушек ($r = 0{,}438$, $p = 0{,}001$), фагоцитарной активностью ($r = 0{,}431$, $p = 0{,}001$) и индексом фагоцитарной активности ($r = 0{,}507$, $p = 0{,}001$) нейтрофилов со стадией рака почки. Установлено значимое повышение процента нейтрофилов, экспрессирующих рецепторы CD66b как на начальных, так и на распространенных стадиях рака почки относительно группы с доброкачественными новообразованиями почки и группы контроля. В мультивариантной регрессии Кокса выявлено возрастание риска возникновения рака почки при повышении экспрессии CD66b, индекса внеклеточных нейтрофильных ловушек, фагоцитарной активности и индекса фагоцитарной активности циркулирующих нейтрофилов ($R^2 = 0{,}728$, $\chi^2 = 58{,}1$**,** $p = 0{,}001$). Для дифференциальной диагностики между доброкачественными новообразованиями почки и раком почки статистическую значимость демонстрировали совместно процент CD66b+ нейтрофилов, индекс внеклеточных нейтрофильных ловушек, фагоцитарной активности нейтрофилов и индекса фагоцитарной активности. Площадь под кривой (AUC) модели составила 0,983, и рак почки мог быть диагностирован с вероятностью 94,3% (Spec. = 0,889, Sens. = 0,962). *Выводы*. Таким образом, увеличение CD66b+ нейтрофилов и активация высвобождения внеклеточных ловушек свидетельствует о повышении киллинговой активности нейтрофилов при раке почки. Одновременное определение количества $CD66b^+$ нейтрофилов, индекса внеклеточных нейтрофильных ловушек, фагоцитарной активности и индекса фагоцитарной активности может использоваться для дифференциальной диагностики между доброкачественными новообразованиями почки и рака почки.

Ключевые слова: нейтрофилы, рак почки, CD11b, CD16, CD66b, CD63, внеклеточные нейтрофильные ловушки

Информация о финансировании: авторы заявляют об отсутствии внешнего финансирования.

Вклад авторов: И.Р. Мягдиева — проточная цитометрия, исследование внеклеточных нейтрофильных ловушек, анализ полученных данных, написание текста статьи; Т.В. Абакумова — научное руководство, разработка концепции и дизайна исследования; Д.Р. Долгова — подбор моноклональных антител, научное редактирование; О.Ю. Горшков — подбор групп пациентов, сбор клинических данных; Т.П. Генинг — научное редактирование; Г.В. Галиева — исследование внеклеточных нейтрофильных ловушек. Все авторы внесли значительный вклад в подготовку рукописи, прочитали и утвердили окончательную версию перед публикацией.

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Elemental homeostasis in children and adolescents after completion of antitumor therapy for malignant neoplasms

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Abstract. *Relevance.* As medical research develops, more and more attention is being paid to the study of elemental changes in cancer patients not only as a marker of the disease, but also as a possible complication of the disease. The aim was to study changes in the level of essential and toxic trace elements in patients who have undergone antitumor therapy (AT) for malignant neoplasms (MN). *Materials and Methods.* As part of a retrospective monocenter study, a group of 214 patients from the Russian Field Medical and Rehabilitation Research Center aged 4 to 17 years was formed. All patients were in remission after the completion of antitumor treatment: 107 patients with hemoblastosis and 107 with solid tumors. The age of the participants ranged from 4.2 to 17.6 years, with an average age of 11.4 years. For a comprehensive assessment of the elemental status in children, hair and blood serum were used, measurements were carried out by mass spectrometry after mineralization of the samples. *Results and Discussion.* The results of the study of hair samples and blood serum showed that the elemental profile of patients after AT has both similar patterns and distinctive features depending on the histological type of tumor. *Conclusions.* Patients with solid tumors had a higher accumulation of toxic metals compared to samples taken from patients with tumors of the hematopoiesis organs. Nevertheless, no serious specific changes in elemental homeostasis were observed depending on the histological structure. The results obtained emphasize the importance of careful monitoring of homeostasis parameters to prevent the development of complications of antitumor therapy associated with elemental homeostasis.

Keywords: trace elements, macronutrients, essential elements, toxic elements, the element status, elemental imbalance, carcinogenesis, solid tumors, tumors of the hematopoiesis system, hair, the serum, late effects, inductively coupled plasma mass spectrometry

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Consent for publication. The informed voluntary consent was obtained to take part in the investigation and to publish the results from the parents and guardians of children and adolescents.
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Introduction

The modern theory of carcinogenesis is attracting more and more attention to the role of elemental changes in the induction of tumor growth [1]. In particular, associations of essential and toxic chemical elements with several types of malignant neoplasms have been identified [2]. In studies devoted to the role of elemental changes in experimental or clinical models, toxic elements are most associated with carcinogenic activity [3, 4]. In addition, the imbalance of the main elements contributes either to the metabolic restructuring of proteins, providing activation or inhibition of enzymatic reactions, affecting the permeability of cell membranes [5, 6], or to changes in the cellular microenvironment and immune status [7], which can also modulate the progression of cancer. Some organic and inorganic compounds of essential elements, such as selenium (Se) or zinc (Zn), can affect the redox status of cells [8, 9], provoking the formation of reactive oxygen species (ROS), interfering with proapoptotic signaling pathways [10], an appropriate amount of ROS can promote carcinogenesis and support transformation and proliferation of tumor cells [11].

Unfortunately, antitumor therapy (AT) has limited selectivity, and its components can cause various early and late metabolic complications. The direct cytotoxic effect of chemotherapeutic drugs and radiation therapy, along with potential iron overload as a result of repeated transfusions, can lead to adverse effects on the nervous, cardiovascular, and urinary systems. On the other hand, nutritional deficiency and metabolic homeostasis disorders are accompanied by clinical changes in the form of osteoporosis, nutritional deficiency, etc. Specific disorders of the elemental composition of tissues (Figure) are also observed in patients after AT [12, 13].

In particular, after treatment, there may be an excessive accumulation of toxic elements that can be considered as possible carcinogens, which directly leads to disruption of mitochondrial function, cell growth processes, and DNA damage [14]. It has also been shown that changes in the concentration of certain essential elements can affect oxidative stress

Fig. The components of elemental homeostasis (elemental portrait) of a person

and suppress or enhance proliferative processes due to a violation of the redox balance [15]. Many elements show a correlation with oxidative stress in the blood of cancer patients [16, 17], therefore, excessive accumulation of individual elements affecting the redox status of tissues can be considered as a factor associated with oncogenesis. Based on this, the elemental imbalance after AT should be considered as a significant factor preventing or provoking cancer recurrence. The available data indicate a possible specificity of the elemental status in patients with tumors of various histological origin. For example, tumors of hematopoietic tissue differ from solid tumors not only in the variant of cell differentiation, but also in other related features: biochemical and tissue atypism, metastatic activity, signaling pathways, etc. [18], which can affect metabolism in different ways, contributing to the appearance of specific biomarkers of the disease [19]. Features of the microenvironment associated with the activation of matrix metalloproteinases [20], the distribution of metals in tissues due to their participation in ion transport [21], and their action as cofactors [22], changing the elemental composition of the malignant neoplasms MN bio substrate. In modern literature, the profile of microelements and macronutrients often appears as a possible application point for targeted diagnosis, treatment or prevention of MN [23], however, it is necessary to take into account the histological affiliation of the tumor and the features of AT in this type of neoplasm. In this study, we sought to identify the specifics of the elemental changes after AT, depending on the histological structure of the tumor. Increased attention should be paid to the detection of carcinogenic elements: cadmium (Cd), nickel (Ni), arsenic (As), beryllium (Be), and chromium (Cr), which are already known and described in the literature [24]. The non-invasiveness and speed of the screening method using the analysis of chemical elements in blood serum and hair make it very promising in oncology.

Research objectives

To compare the elemental composition of biological substrates, such as hair and blood serum, depending on the histological types of tumors in children and adolescents who were in remission after completion of antitumor therapy (AT).

Materials and methods

Ethical standards

The study was developed and conducted in accordance with the requirements of the Helsinki Declaration and its later amendments. Before being included in the study, the informed consent of the parents of the examined children was obtained.

Research design

The one-cent cross-sectional retrospective study included patients of the Russian Field Clinical Research and Rehabilitation Center of the Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Oncology and Immunology in 2019–2021 (Moscow, Russia), these were children and adolescents of both sexes aged 4 to 17 years.

The study group consisted of 214 children in remission of MN (malignant neoplasms), of which 107 were patients (group 1) who had completed treatment and were in remission according to the International Classification of Diseases version 10 (ICD) with disease codes C 91, C 92; C 81–84 and 107 patients (Group 2) who received AT according to regarding solid tumors with disease codes according to ICD C 22-C 76, with the exception of tumors of the central nervous system. The age of the children and adolescents included in the study ranged from 4.2 to 17.6 years. The average age was 11.4 years. The duration of MN remission ranged from 2.6 to 8.0 years, with an average of 3.9 ± 1.1 years. The treatment of hemoblastosis included BFM, MB, and DAL-HD protocols. Treatment of solid neoplasms was carried out in accordance with international protocols recommended in the clinical guidelines for the treatment of hypertension in children by the Russian Ministry of Health (SIOP, EURAMOS, etc.). The structure of the cytotoxic agents used excludes the use of the studied chemical elements in patients included in the study.

Criteria for inclusion in the study: (I) confirmed remission of malignant tumors in accordance with ICD 10: C 91; C 92, C 81–84, C 22–76; (II) patients under the age of 18; (III) signed informed consent by parents of children <14 years old and adolescents ≥ 14 years old.

The exclusion criteria were: (I) the patient's somatic or psychological condition that prevents participation in the study, (II) eating habits (including a vegetarian diet), (III) metal implants (including dental fillings made of amalgam), (IV) surgical and traumatic diseases, (V) acute inflammatory and infectious diseases. The presence of any of these factors led to the exclusion of the patient from the study.

The control group was based at the Center for Biotic Medicine (Moscow, Russia). The study included 213 children aged 4 to 17 years without a history of cancer and other chronic somatic diseases. In addition, all participants in the control group reported that they had not consumed drugs containing macro- and microelements during the last year before the study. The appropriate exclusion criteria were applied to the participants of the control group.

Sample collection and preparation

Bio substrates were used for a comprehensive mass spectrometry assessment: hair and blood serum. Only the proximal sections of the strands, which are less susceptible to exogenous contamination, were used for the study. Sample preparation included washing and microwave treatment procedures to remove contaminants. Hair samples were degreased with acetone (Chimmed, Russia) for 10–15 minutes, washed three times with deionized water with a concentration of 18.2 MΩ•cm (Labconco Corp., Kansas City, Missouri, USA) and dried at 60 °C. Dry hair samples were kept in Teflon tubes with 5 ml of concentrated (65%) nitric acid (Sigma-Aldrich Co., St. Louis, Missouri, USA) for 20 minutes at a temperature of 170–180 °C. Hair samples were also acid-treated using a microwave oven in the Berghof SpeedWave-4 DAP-40 system (Berghof Products + Instruments GmbH, 72800 Ehningen, Germany) at a frequency of 2.46 GHz with a power of 1450 watts. Distilled deionized water with a total volume of 15 ml was then added to the resulting solutions. The resulting solution was used for subsequent ICP-MS analysis.

Blood samples were taken from the ulnar vein using Vacutest tubes (Greiner Bio-One International AG, Austria) with blood clotting activator. The serum was obtained by centrifugation of blood for 10 min at 1800 rpm. The analysis was performed only on blood serum samples, in which no signs of hemolysis were found. All samples were diluted 1:15 with an acidified (pH = 2.0) diluent containing (by volume) 1-butanol 1% (Merck KGaA, Darmstadt, Germany), Triton X-100 0.1% (Sigma-Aldrich, Co., St. Louis, Missouri, USA) and HNO3 0.07% (Sigma-Aldrich, Co., St. Louis, Missouri, USA) in distilled deionized water.

ICP-MS analysis (inductively coupled plasma mass spectrometry)

The content of macro- and microelements in hair and blood serum, including Na, P, K, Mg, Ca, Al, As, Be, Co, Cr, Cu, Fe, Hg, I, Mn, Ni, Pb, Se, Sn, V, Zn, Li, Mo, Rb, Tl, Cd, Bi, B were determined using inductively coupled plasma mass spectrometry (ICP-MS) on a NexION 300D device (PerkinElmer Inc., Shelton, CT 06484, USA) equipped with an ESI SC-2 DX4 autosampler (Elemental Scientific Inc., Omaha, NE 68122, USA). The use of Dynamic Reaction Cell (DRC) technology has eliminated most of the polyatomic interference in the system. The system was calibrated using a universal set of data collection standards (PerkinElmer Inc., Shelton, CT 06484, USA), diluted with distilled deionized water (acidified with 1% HNO3) to final concentrations of 0.5, 5, 10 and 50 micrograms/l. 10 micrograms/l of yttrium solution prepared from a single-element standard of pure yttrium (Y) (PerkinElmer Inc., Shelton, CT 06484, USA) was used as an internal online standard prepared on a matrix containing 8% 1-butanol (Merck KGaA, Darmstadt, Germany), 0.8% Triton X-100 (Sigma-Aldrich, Co.), 0.02% tetramethylammonium hydroxide (Alfa-Aesar, Ward Hill, Massachusetts 01835 USA) and 0.02% ethylenediaminetetraacetic acid (Sigma-Aldrich, St. Louis, Missouri, USA).

Laboratory quality control

Laboratory quality control was carried out using a control analysis of GBW09101 certified human hair reference material (Shanghai Institute of Nuclear Research, Shanghai, China) and ClinCheck plasma control (batch 129, levels 1 and 2, RECIPE Chemicals + Instruments GmbH, Germany). The recovery rates of all analyzed trace elements were in the range of 90–110%. In addition, the values obtained for all metals and metalloids were within the limits that, according to the estimates of the manufacturer of the reference samples, were acceptable. The laboratory also participates in the External quality assessment system in the field of occupational medicine and the environment (EMAS OELM).

Statistical analysis

The search and calculations of statistically significant deviations in the elemental status of patients were carried out using the Jupyter Notebook software development environment in Python 3.9. The algorithm was based on open source libraries: Pandas, NumPy and Pingouin.

The nature of the data distribution was assessed using the Shapiro-Wilk criterion. The significance of the intergroup differences was assessed using the nonparametric Mann-Whitney test for data with an abnormal distribution. The boundaries of the median (Me) and interquartile range (IQR) were also calculated to compare the statistical significance of the observations. The difference between the values in the groups was considered significant at $p < 0.05$.

Results and discussion

The trace element composition in patients with tumors of the hematopoietic system was characterized by a significant decrease in the content of Co, Mn, I, Fe, Al, Ni, Pb (p-value < 0.05). It is noteworthy that an elemental imbalance with a predominantly reduced concentration in the hair was detected significantly more often in the cohort of patients with tumors of the hematopoiesis system than in the group of solid tumors.

In patients with solid tumors, the spectrum of manifestations of the elemental composition in the hair is different: reduced values of Na, P, Mg at unchanged concentrations of Ca and K. As for trace elements, the Mn level decreased significantly (p-value < 0.05), and the concentration of V, Cr, I, Sn, Se, Co, on the contrary, increased (Table 1).

Blood serum, as a biochemical active substrate, is represented by a wide variety of elements. In the samples of patients with MN of the hematopoietic system, an increase in the content of trace elements Al, Mn, Ni, V, Tl, Cu, Zn, Fe, B, Bi and a decrease in the content of Co, Rb, Mo (p-value < 0.05) was observed. Deviations from the control values were observed for metals of the toxic and essential groups: increased levels of P, Al, Mn, Ni, V, Tl, Cd, Be, Bi (p-value < 0.05) and decreased values of Co, Cr, Rb, Mo in solid tumors (Table 2).

Table 1

Hair elemental status according to the main diagnosis

Trace elements, μg/g	Me(Q1-Q3) Tumors of the hematopoietic tissues (*n*=107)	P-value	Me(Q1-Q3) Solid tumors (*n*=107)	P-value	Me(Q1-Q3) Control group (*n*=213)
Al	3,632(2,303–5,398)	0.0291	4,51(3,05–7,57)	0.524	4,202(2,839–6,882)
As	0,029(0,020–0,044)	0.846	0,029(0,018–0,041)	0.582	0,029(0,019–0,046)
Be	0,00048(0,0001–0,001)	0.146	0,0003(0,0002–0,0009)	0.161	0,00039 (0,0001–0,0007)
Co	0,0089(0,004–0,014)	0.039	0,015(0,007–0,027)	0.0102	0,0105 (0,006–0,016)
Cr	0,123(0,059–0,241)	0.553	0,835(0,469–0,90)	0.000	0,1291 (0,082–0,269)
Cu	11,007(8,69–14,47)	0.805	11,98(9,38–15,51)	0.064	10,76(8,74–13,76)
Fe	12,86(9,01–18,21)	0.0008	16,73(12,62–26,04)	0.372	17,038 (11,28–24,02)
Hg	0,089(0,03–0,15)	0.083	0,108(0,05–0,18)	0.668	0,1145(0,05–0,18)
I	0,341(0,21–0,55)	0.029	0,793(0,33–1,64)	0.004	0,4776(0,26–0,94)
Mn	0,241(0,15–0,43)	0.000	0,343(0,19–0,68)	0.041	0,4702(0,22–1,52)
Ni	0,148(0,101–0,239)	0.015	0,173(0,118–0,407)	0.959	0,173(0,132–0,282)
Pb	0,293(0,155–0,651)	0.0001	0,533(0,235–1,12)	0.325	0,566(0,268–1,33)
Se	0,4704(0,382–0,56)	0.003	0,441(0,381–0,572)	0.044	0,409(0,369–0,491)
Si	23,3(14,2–36,66)	0.152	23,13(12,99–34,86)	0.099	25,45(17,94–36,35)
Sn	0,092(0,054–0,238)	0.104	0,167(0,087–0,472)	0.030	0,1208(0,07–0,282)
V	0,025(0,015–0,047)	0.111	0,045(0,026–0,08)	0.000	0,021(0,013–0,035)
Zn	175,84(128,94–216,16)	0.217	179 (127–227)	0.373	189,63 (153,1–225,61)

Table 2

Serum elemental status according to the main diagnosis

Trace elements, μg/g	Me(Q1-Q3) Tumors of the hematopoietic tissues (*n*=38)	P-value	Me(Q1-Q3) Solid tumors (*n*=38)	P-value	Control group (*n*=213)
Al	0,0338(0,024–0,095)	0.0003	0,0336(0,027–0,036)	0.0003	0,0151(0,008–0,024)
As	0,0018(0,001–0,001)	0.98	0,0016(0,001–0,002)	0.66	0,0018(0,001–0,006)
Be	0,00004(0,000–0,00007)	0.052	0,0001 (0,00007–0,0001)	0.0000	0,00001 (0,000–0,00002)
Co	0,00069(0,0005–0,0009)	0.0000	0,00062 (0,0004–0,0008)	0.0000	0,0054(0,001–0,011)
Cr	0,0026(0,001–0,002)	0.1	0,0025(0,001–0,002)	0.01	0,0351(0,001–0,13)
Cu	1,196(1,093–1,386)	0.0002	1,079(0,99–1,24)	0.11	0,991(0,9–1,082)
Fe	2,59(1,78–3,574)	0.0000	1,69(1,44–1,845)	0.06	1,37(1,153–1,699)
Hg	0,00018(0,0001–0,0001)	0.72	0,00018 (0,0001–0,0001)	0.29	0,00018 (0,0001–0,0001)
I	0,059(0,051–0,069)	0.78	0,058(0,053–0,067)	0.47	0,05(0,052–0,066)
Mn	0,0024(0,001–0,003)	0.0000	0,0018(0,001–0,002)	0.02	0,0014(0,001–0,001)
Ni	0,0054(0,003–0,006)	0.0000	0,0051(0,003–0,006)	0.0000	0,0019(0,001–0,002)
Pb	0,0005(0,0002–0,001)	0.57	0,0004 (0,0002–0,001)	0.46	0,0005 (0,0004–0,0007)
Se	0,084(0,072–0,098)	0.57	0,091(0,073–0,099)	0.68	0,087(0,08–0,095)
Sn	0,0001(0,00006–0,0004)	0.46	0,0001 (0,00003–0,0001)	0.07	0,00017 (0,0001–0,0002)
V	0,0029(0,0004–0,004)	0.0000	0,00525 (0,0005–0,006)	0.0000	0,00008 (0,0000–0,0004)

Ending table 2

Trace elements, μg/g	Me(Q1-Q3) Tumors of the hematopoietic tissues (*n*=38)	P-value	Me(Q1-Q3) Solid tumors (*n*=38)	P-value	Control group (*n*=213)
Zn	1,809(1,636–1,981)	0.0000	1,12(0,967–1,54)	0.25	1,09(1,013–1,21)
Li	0,0014(0,0009–0,001)	0.8	0,0014 (0,0008–0,002)	0.46	0,0014 (0,0009–0,001)
Mo	0,0009(0,0006–0,001)	0.0005	0,00095 (0,0007–0,001)	0.0002	0,0015(0,001–0,001)
Rb	0,169 (0,134–0,22)	0.0088	0,187(0,161–0,227)	0.03	0,251(0,191–0,35)
Tl	0,00002(0,000–0,00003)	0.03	0,00002 (0,000–0,00002)	0.003	0,00001 (0,000–0,00001)
Cd	0,00002(0,000–0,00007)	0.21	0,00008 (0,000–0,0001)	0.0066	0,00002 (0,000–0,00003)
Bi	0,00002(0,000–0,00002)	0.004	0,00001 (0,000–0,00002)	0.018	0,000006 (0,00–0,0000)
B	0,0531(0,023–0,082)	0.018	0,0202(0,011–0,037)	0.53	0,0242(0,012–0,033)

In addition, we presented a table that more clearly shows a statistically significant change in concentration in all three analyzed biosubstrates depending on the histological nature of the tumor (Table 3).

Table 3

Changes of elemental status depending on substrate and tumor nature ($p < 0.05$)

Significant change in the concentration of elements	Tumors of the hematopoietic tissues		Solid tumors	
	Hair	Serum	Hair	Serum
'↑'	Se	Al, Mn, Ni, V, Tl, Cu, Zn, Fe, B, Bi	V, Cr, I, Sn, Se, Co	Al, Mn, Ni, V, Tl, Cd, Be, Bi
'↓'	Al, Co, Fe, I, Mn, Ni, Pb	Co, Rb, Mo	Mn	Co, Cr, Rb, Mo

Note: signs '↓' and '↑' denote elements with statistically significant ($p < 0.05$) change in concentration.

In this study, the levels of 23 trace elements in blood serum and hair were compared in 107 patients after chemotherapy with tumors of hematopoietic tissues and 213 healthy individuals in the control group, as well as in 107 patients after AT with solid tumors and 213 healthy individuals in the control group. The results showed that significant changes in the concentration of trace elements were observed in both groups of patients. Thus, in the cohort of patients who completed treatment of hematopoietic tumors, higher concentrations of Al, Mn, Ni, V, Tl, Cu, Zn, Fe, B, Bi ($p < 0.05$) in the blood serum were found, but lower concentrations of Co, Rb, Mo ($p < 0.05$) in blood serum. In addition, in the same patients, a higher content of Se ($p < 0.05$) and a lower content of Al, Co, Fe, I, Mn, Ni, Pb ($p < 0.05$) were found in the hair. In addition, patients treated for solid tumors had higher serum levels of Al, Mn, Ni, V, Tl, Cd, Be, Bi ($p < 0.05$) and lower serum levels of Co, Cr, Rb, Mo ($p < 0.05$) However, higher levels of V, Cr, I, Sn, Se, Co ($p < 0.05$) and lower levels of Mn ($p < 0.05$) were found in the hair.

The results obtained confirm the presence of an imbalance of trace elements in patients with cancer, including in the period after the end of the sweat. The elemental imbalance was slightly different depending on the type of neoplasm, although the trends were similar. The trends in the concentration of chemical elements in the blood serum of patients in both groups partially coincided: an increase in the content of manganese (Mn), aluminum (Al), vanadium (V), nickel (Ni), thallium (Tl) and a decrease in the content of magnesium (Mg), cobalt (Co), rubidium (Rb) and molybdenum (Mo). The concentration of Mn in hair decreased in both solid and hematopoietic tumors; the concentration of Se increased similarly (Table 3).

Trace elements with significant changes can be divided into 2 categories: essential trace elements and toxic trace elements [25]. It is known that exposure to certain toxic elements contributes to the development of

MN, affects the processes associated with mutagenesis (apoptosis, proliferation, neoplastic transformation) [26], therefore, their increased content can be considered as a factor of unfavorable prognosis of the disease [27].

In our study of patients with tumors of the hematopoietic system, we observed changes in the content of toxic elements in the levels of Al, Be, Cd, Tl, Bi, and Pb. Changes in the levels of Al, Tl, Cd, Be, and Bi in the hair and blood serum of patients with solid tumors were also detected.

A number of publications have shown that high serum levels of aluminum (Al) are also characteristic of patients with breast tumor tissue, but there is no evidence that this is directly related to carcinogenic effects [28]. No information was found on an increase in Al levels in the hair and blood serum of patients with tumors of the hematopoiesis system.

It cannot be excluded that the increase in thallium (Tl) content is a consequence of previously realized mechanisms of carcinogenesis. Tl can carry out carcinogenic activity by interfering with important processes, replacing potassium, in particular, in the (Na+/K+)-ATPase. However, the antitumor role of thallium salts has been described and shown in individual cell cultures [29]. Participation in oncogenesis is confirmed by the effectiveness of Tl-scintigraphy for detecting malignant tumors such as breast cancer and lymphoma [30].

It was also reported that bismuth-Bi (BisBAL NPs) nanoparticles obtained from the bis (p-aminophenyl) compoundlumazine can inhibit the growth of TNF cells, and the effectiveness directly depends on the dose used [31]. This is an important discovery because it suggests that BisBAL nanoparticles may have potential as a targeted therapy for breast cancer, specifically targeting tumor cells without affecting healthy tissues. Interestingly, our data showed a decrease in serum Bi levels after completion of the AT. Lead (Pb) exposure is also associated with various health risks, including harmful effects on the nervous system, reproductive system, and kidneys [32]. However, the relationship between lead exposure and the development of AT is less obvious. It should be noted that our data indicate a low level of Pb in the hair of patients with tumors of the hematopoiesis system.

In addition, a group of patients with solid tumors had elevated concentrations of cadmium (Cd) and beryllium (Be), which the International Agency for Research on Cancer (IARC) has recognized as carcinogens for humans or animals. Numerous studies have shown that chronic exposure to these metals is associated with the development of solid tumors [33, 34]. This may be due to their ability to disrupt the repair of nucleotide fragments, which leads to genome instability [35] and subsequent tumor growth. Notably, high levels of Cd and Be were found only in the blood serum of patients with solid tumors. Patients from the group of tumors of the hematopoiesis system were characterized by the absence of changes in the content of these toxic metals in the blood serum.

It has been reported that significant deviations from the norm in the content of essential elements may be the cause of toxicity due to homeostasis disorders. Among the essential trace elements in the group with tumors of the hematopoietic system, changes in the levels of Se, Mn, Ni, V, Cu, Zn, Fe, B, Co, I, Rb, Mo, as well as V, Cr, I, Sn, Se, Co, Mn, Ni, V, Co, Rb, Mo was found in the group with solid tumors. The described significant elemental imbalance in the blood serum in the group with tumors of hematopoietic tissues largely coincides with the data obtained by other authors.

Thus, we found similar patterns of increased serum levels of Fe, Cu, and Ni, known from previous studies [36, 37]. It has been found that nickel (Ni) can stimulate the proliferation of cancer stem cells through the NADPH oxidase/ROS-dependent mechanism [38]. It has also been reported that high Ni levels have been associated with breast cancer, and this may be a risk factor for carcinogenesis [39]. Some authors note the predominance of epigenetic modulation in nickel carcinogenesis, which may include changes in histone acetylation, methylation, ubiquitation, and changes in DNA methylation affecting gene expression [40]. In addition, Ni may be involved in the hypoxic signaling pathway leading to nickel-induced carcinogenesis, since Ni has been found to be a strong inducer of HIF-1a protein and an activator of HIF-dependent transcription [41], which may provide conditions for resistance to apoptosis. Although nickel (Ni) and iron (Fe) are very

similar and can alter each other's metabolism [42], the effects of Fe are more based on the regulation of oxidative stress and subsequent carcinogenesis [43]. Excess Fe, which is a cofactor of hematopoietic cell proliferation, can also stimulate the growth of tumor cells [44]. Caroline L. et al. It has been shown that in patients with acute leukemia, the level of iron in the blood serum is increased [45].

Copper (Cu) is a trace element that plays an important role in the functioning of the cellular substrate. Elevated serum Cu levels may increase oxidative stress associated with the PI3K/Akt metabolic pathway, which may be a beneficial factor for the development of oncogenic processes [46], and this is consistent with our results, since serum Cu levels were elevated in patients with hematopoietic tumors. Numerous studies have unequivocally confirmed a significant increase in Cu levels both in tumors and in the blood serum of cancer patients, which is significantly higher than in healthy people [47]. So, Li Y. et al. It has been shown that an increased level of copper in the blood serum increases the risk of colorectal cancer, therefore, a high level of copper in the blood serum can be considered as an indicator of a risk factor for the development of the disease [48].

We can also note a higher concentration of vanadium (V) in the blood serum compared to the control. V can affect many enzyme systems, such as phosphatases, ATPases, peroxidases, ribonucleases, protein kinases, and oxidoreductases, and a number of animal cancer models have shown that vanadium provides protection against all stages of carcinogenesis [49]. V promotes cellular instability, in some cells, induces tyrosine kinase phosphorylation and, thus, can affect oncogenesis [50]. Due to its physiological duality, V becomes toxic in excessive amounts and probably has procancerogenic properties [51].

Numerous studies have shown that a number of boron (B) derivatives have proven effective in fighting cancer [52]. Various types of compounds and structures in B have the ability to inhibit the progression of MN and are associated with a decrease in the incidence of various types of cancer. B exhibits its antitumor effects by participating in the regulation of specific molecular mechanisms, such as induction of apoptosis and cell cycle arrest [53]. However, many aspects of this effect remain unclear. We found an increase in serum B levels in patients with hematopoietic tumors.

In addition, in patients with solid tumors, the concentration of chromium (Cr) in the blood serum was lower than in patients with hematopoietic tumors. Carcinogenesis associated with Cr(VI) is described in the literature and includes mutational inactivation of p53, base substitutions in A/T pairs, and double missense mutations [54]. Cr(VI) belongs to the first group of carcinogens. In patients with solid tumors, changes in the Cr content were observed in the hair and blood serum, while the Cr content in the serum decreased and in the hair increased. Zekavat et al. It was shown that serum Cr levels decreased after completion of combined chemotherapy [55], which is consistent with our results. In the same study, a decrease in the concentration of manganese (Mn) in the blood serum was recorded. On the other hand, Diez et al. Higher Mn levels have been found in patients with lung cancer [56]. Our results indicate a decrease in Mn levels in the hair, but the level of Mn in the blood serum is increased compared to the control group. Mn^{2+} induces apoptosis in cells and participates in the antitumor immune response through the cGAS-STING signaling pathway, which means it is usually characterized by antitumor action [57].

Iodine (I) is one of the main antioxidants. Antitumor, antiproliferative, and cytotoxic effects of I in cancer have been described [58]. We found a decrease in the level of I in the hair in the group of patients with tumors of the hematopoiesis organs and an increase in the level of I in the blood serum in the group of solid tumors.

Tin (Sn) compounds also have the described antitumor properties. Sn-DBPTF-1 has been reported to be effective against cancer or oncogenic cell lines because Sn-DBPTF-1 (dibenzylphosphinoyl dithioformate) It can induce apoptosis and double-stranded DNA breaks [59]. It is noteworthy that we found an increased level of Sn in the hair of patients with solid tumors.

Also pay attention to the general patterns of decreasing levels of Co, Rb, Mo in blood serum in patients with both solid and hematopoietic tumors.

Cao G.H. et al. It was reported that the cobalt (Co) content in hair and blood serum in patients with stomach cancer was lower than in healthy people in the control group [60]. The introduction of Mo compounds promotes apoptosis and the formation of reactive oxygen species, which demonstrates their potential use for the treatment of metastatic cancer cells [61]. The case-control study conducted by Yetişgin F. and co-authors. Studies have shown that Co levels were elevated in the group of patients with myeloproliferative neoplasms [62]. Several studies have shown that Co(II) ions are genotoxic due to the formation of reactive oxygen species and inhibition of DNA repair [63]. It is also worth noting the discovery of Wang X. and co-authors. that Rb levels correlate with a lifetime risk of cancer, which may be related to possible involvement in the etiology of MN [64].

Special attention should be paid to the effects of trace elements such as selenium (Se) and zinc (Zn), since they are considered to have the maximum antitumor effect among trace elements. The Zn level was assessed as a marker for predicting the response to perspiration. It has also been reported that zinc deficiency is common in hematopoietic and solid tumors [65]. Apparently, this relationship can be explained by the properties of zinc to inhibit MT expression and additionally induce an increase in ROS content [66]. Some studies show that impaired redox activity can lead to the progression of tumor growth by affecting signal transduction pathways that cause the expression of anti-apoptotic genes regulating cell death [67, 68]. However, redox-active trace elements can be useful in AT. Thus, Se-based compounds are considered as chemotherapeutic agents that mediate the activation of apoptosis receptors expressed on the cell surface and the production of ROS, which leads to necrosis [69]. Increased Se levels in hair contradict the data of other studies on decreased Se levels in patients with leukemia and lymphoma [70].

Since our study considered the delayed effects of AT, an increase in Se levels can be interpreted as a violation of the elimination process. In addition, essential trace elements may have therapeutic applications when used synergistically with AT, especially due to their ability to modulate the toxicity of therapy and promote the restoration of healthy tissues [71, 72]. It is important to take this into account, since an imbalance of essential trace elements can lead to impaired immune function, an increased risk of side effects of AT, and a deterioration in the quality of life of patients [72–74].

Our study has some limitations, such as the number of participants, the lack of measurement of the elemental profile before the start of treatment, and the lack of follow-up after measuring the elemental status after the start of the AT, which makes it impossible to accurately determine whether the apparent violations of the elemental status are caused by the disease or treatment. Our goal was not to study the relationship between the elemental imbalance caused by AT and metabolic disorders associated with the tumor process. This should be evaluated in subsequent studies.

Conclusions

Thus, we found a statistically significant difference between the content of elements in blood serum and hair in patients with different histological structures of the tumor and in the control group. As clinical data accumulate, it is advisable to take into account metabolic changes in the levels of essential and toxic elements.

Our data indicate that neoplasms of the hematopoiesis system are characterized by more pronounced changes in the composition of essential elements in hair and blood serum, and solid tumors exhibit a more pronounced accumulation of certain toxic metals compared to tumors of the hematopoiesis system. However, no significant or specific differences were found between the groups. Depending on the type of tumor and treatment, a more differentiated approach to nutritional support may be required.

Further research is needed to assess the causes of the elemental imbalance, the associated toxic effects, and the possible role of nutritional support as supportive therapy. It is necessary to study the long-term effects of AT on changes in the homeostasis of trace elements and the associated deterioration of general health, the effects of treatment and the risk of tumor recurrence.

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Элементный гомеостаз у детей и подростков после завершения противоопухолевой терапии злокачественных новообразований

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Аннотация. *Актуальность.* По мере развития медицинских исследований все больше внимания уделяется изучению элементных изменений у онкологических больных не только как маркера заболевания, но и как возможного осложнения заболевания. Целью данного исследования является изучение изменений уровня эссенциальных и токсичных микроэлементов у пациентов, прошедших противоопухолевую терапию (ПОТ) по поводу злокачественных новообразований (ЗНО). *Материалы и методы.* В рамках проведения ретроспективного моноцентрового исследования была сформировано группа из 214 пациентов лечебно-реабилитационного научного центра “Русское поле” в возрасте от 4 до 17 лет. Все пациенты находились в состоянии ремиссии после завершения противоопухолевого лечения: 107 человек — по поводу гемобластозов и 107 — солидных опухолей. Возраст участников составлял от 4,2 до 17,6 лет, средний возраст — 11,4 года. Для комплексной оценки элементного статуса у детей использованы биосубстраты (волосы и сыворотка крови), измерения проводили методом масс-спектрометрии после минерализации образцов. *Результаты и обсуждение.* Результаты исследования образцов волос и сыворотки крови показали, что элементный профиль пациентов после ПОТ имеет как сходные закономерности, так и отличительные особенности в зависимости от гистологического типа опухоли. *Выводы.* Наши данные показывают, что у пациентов с солидными опухолями наблюдалось более высокое

накопление токсичных металлов по сравнению с образцами, взятыми у пациентов с опухолями органов кроветворения. Тем не менее, серьезных специфических изменений элементного гомеостаза в зависимости от гистологической структуры не наблюдалось. Полученные результаты подчеркивают важность тщательного мониторинга параметров гомеостаза для предотвращения развития осложнений противоопухолевой терапии, связанных с элементным гомеостазом.

Ключевые слова: микроэлементы, макроэлементы, эссенциальные элементы, токсичные элементы, элементный статус, элементный дисбаланс, канцерогенез, солидные опухоли, опухоли системы кроветворения, волосы, сыворотка, поздние эффекты, масс-спектрометрия с индуктивно связанной плазмой

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Экспрессия иммуно-ассоциированных генов в изолированных классических моноцитах при преэклампсии

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Аннотация: *Актуальность.* Преэклампсия — это тяжелое осложнение беременности, встречающееся в 8 % случаев и являющееся причиной высокой материнской и перинатальной смертности и заболеваемости. Этиология преэклампсии до сих пор остается предметом исследования, однако все больше данных свидетельствуют о вовлеченности клеток врожденного иммунитета, моноцитов, в патогенез данной опасной патологии. *Целью* нашей работы было изучить экспрессию ряда иммунно-асоциированных генов в классических моноцитах крови при преэклампсии и физиологической беременности. *Материалы и методы.* Использовались методы градиентного центрифугирования, магнитного сортинга, цитометрический анализ, ПЦР в реальном времени. *Результаты и обсуждение*. Впервые описано повышение экспрессии псевдогена адгезионного рецептора, сопряженного с G-белком, *ADGRE4P,* в классических моноцитах при преэклампсии. Также был выявлен значимо низкий относительный уровень экспрессии гена интерлейкина 8 – CXCL8 — при преэклампсии. *Выводы.* Роль отдельных моноцитарных субпопуляций в развитии преэклампсии еще уточняется. Очевидно, что моноциты могут изменять цитокиновый профиль плазмы крови пациенток с преэклампсией, усиливать реакции врожденного иммунитета,

в том числе воспаление. Хемокин ИЛ8 и кодирующий его ген, а также псевдоген адгезионного рецептора могут стать потенциальной терапевтической мишенью при лечении данной опасной гестационной патологии.

Ключевые слова: моноциты, преэклампсия, CD14, ПЦР в реальном времени, цитометрия

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Информация о конфликте интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией данной статьи.

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Expression of immune-associated genes in isolated classical monocytes in preeclampsia

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Abstract: *Relevance*. Preeclampsia is a severe complication of pregnancy, occurring in 8 % of cases and causing high maternal and perinatal mortality and morbidity. The etiology of preeclampsia is still a subject of research; however, more and

more data indicate the involvement of innate immune cells, monocytes, in the pathogenesis of this dangerous pathology. The aim of our work was to study the expression of a number of immune-associated genes in classical blood monocytes in preeclampsia and physiological pregnancy. *Materials and Methods*. The work used the methods of gradient centrifugation, magnetic sorting, cytometric analysis, real-time PCR. *Results and Discussion*. For the first time, an increase in the expression of the pseudogene of the adhesion receptor coupled to the G protein, ADGRE4P, in classical monocytes in preeclampsia is described. A significantly low relative level of expression of the interleukin 8 gene — CXCL8 — in preeclampsia was also revealed. *Conclusion*. The role of individual monocytic subpopulations in the development of preeclampsia is still being clarified. It is obvious that monocytes can change the cytokine profile of blood plasma of patients with preeclampsia, enhance the reactions of innate immunity, including inflammation. The chemokine IL8 and the gene encoding it, as well as the pseudogene of the adhesion receptor, can become a potential therapeutic target in the treatment of this dangerous gestational pathology.

Keywords: monocytes, preeclampsia, CD14, real-time PCR, cytometry

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Введение

Преэклампсия (ПЭ) — это серьезное осложнение беременности, характеризующееся повышенным кровяным давлением в сочетании с протеинурией или проявлениями полиорганной недостаточности после 20 недели беременности [1]. ПЭ может привести к прогрессирующим нарушениям со стороны органов матери (например, печени, почек) и угрозе для здоровья плода. Симптомы ПЭ могут включать головные боли, отеки, зрительные нарушения и боль в верхней части живота [2]. Лечение данной опасной гестационной

патологии обычно включает медикаментозный контроль артериального давления и экстренное родоразрешение при развитии тяжелых форм ПЭ. Несмотря на большой массив исследований, посвященных ПЭ, ее точные причины до сих пор не установлены [3], что связано в том числе со сложностью получения биоматериала для исследований.

Иммунологический аспект развития ПЭ представляет наибольший интерес для исследователей и в большей степени изучается со стороны матери [4]. И если роль NK-клеток, Treg и резидентных макрофагов в патогенезе ПЭ наиболее изученная область [5–7], то участие моноцитов в развитии ПЭ активно исследуется. Развитие нормальной беременности опосредовано тонким балансом прокоагулянтных, воспалительных реакций и ангиогенеза, о чем свидетельствуют результаты single-cell РНК секвенирования мононуклеарной фракции крови пациентов с ПЭ и физиологической беременностью и in vitro изучение взаимодействия моноцитов и тромбоцитов посредством тканевого фактора CD142 и маркера активации тромбоцитов CD61 [4, 8]. В ряде работ показано, что при ПЭ в крови повышается доля неклассических моноцитов (CD16+) [9, 10], участвующих в фагоцитозе клеточного дебриса в кровяном русле и являющихся основным источников провоспалительного цитокина TNFa. Однако в недавнем исследовании [11] анализ результатов single-cell РНК секвенирования плацент ПЭ с ранней и поздней манифестацией было выявлено, что доля неклассических моноцитов была снижена при поздней ПЭ. При этом также наблюдается снижение уровня классических моноцитов (CD14+) [12], составляющих в норме до 90 % всей моноцитарной популяции и служащих основным источником макрофагов в ткани, куда они попадают после экстравазации из сосудистого русла.

Прицельное изучение транскрипционного профиля моноцитов периферической крови матери встречается в единичных работах, чего нельзя сказать о цельной крови или мононуклеарной фракции. На основе результатов *microarray* клеток периферической крови женщин с ранней и поздней ПЭ авторы [13] предположили, что определение уровней экспрессии генов длинной некодирующей белок РНК — H19, фибронектина 1 (FN1), тубулина бета-6 класса V (TUBB6) и формилпептидного рецептора 3 (FPR3) можно использовать для прогнозирования ранней ПЭ на 22–28 неделе беременности. А определение уровней экспрессии генов *MMP11, SLC6A2* и *IL18BP* позволяет предсказать раннюю ПЭ на 11–17 неделе беременности. При анализе на уровне единичных клеток мононуклеарной фракции крови были выделены следующие подмножества моноцитов: моноциты экспрессирующие белки версикан и фиколин 1 (VCAN+ моноциты или VCAN+FCN1+), классические моноциты (CD14+FCN1+), IFN- неклассические моноциты (CD16+FCN1+IFNTM3-) и IFN+ неклассические моноциты (CD16+IFITM3+FCN1+) [4]. В данной работе было отмечено, что в крови пациенток с ПЭ увеличивается количество классических моноцитов и уменьшается количество IFN-неклассических моноцитов, что диаметрально противоположно ранее полученным результатам [12]. Это говорит о том, что результаты секвенирования на уровне единичных клеток дают огромный массив информации, нуждающейся в дополнительном подтверждении на уровне экспериментов *in vitro.*

Ранее нами был проведен анализ изолированных моноцитарных популяций, который выявил, что в классических моноцитах активируются сигнальные пути, связанные с воспалением, апоптозом, интерлейкиновым сигналингом и др. [14]. Среди подавленных сигнальных путей была активация Т клеток, EGF и PDGF сигналлинг. Нами были выбраны гены *CXCR1, CXCL8, JUN, ADGRE4P, IL7R и ARL17A* как те, что показали наибольшие различия. В контексте ПЭ гены *CXCR1* и *CXCL8* критичны для процесса ремоделирования спиральных артерий матки [15], а их активация вовлечена в нарушение инвазии трофобласта путем привлечения нейтрофилов, лимфоцитов, моноцитов и тромбоцитов [16]. Транскрипционных фактора *JUN* участвует в регуляции дифференцировки трофобласта [17].

В классических моноцитах при ПЭ эти и остальные выбранные нами гены ранее не изучались. Цель: оценить экспрессию генов *CXCR1, JUN, CXCL8, ADGRE4P, IL7R, ARL17A,* вовлеченных в клеточную адгезию и воспалительный ответ, в изолированных классических моноцитах у женщин с физиологической беременностью и пациенток с ПЭ.

Материалы и методы

Этическое разрешение

Все эксперименты с участием пациентов проводились в соответствии с Хельсинкской декларацией и были одобрены Комиссией по биомедицинской этике при НМИЦ Акушерства, гинекологии и перинатологии им. В.И. Кулакова Минздрава России, г. Москва (протокол № 5 от 27 мая 2021 г.). У всех пациенток было получено добровольное информированное согласие на участие в исследовании и обработку персональных данных согласно Хельсинкской декларации Всемирной медицинской ассоциации и в соответствии с требованиями Этического комитета.

Сбор образцов

Исследование проводилось в НМИЦ акушерства, гинекологии и перинатологии имени академика В.И. Кулакова Министерства здравоохранения Российской Федерации. В контрольную группу ($n = 9$) вошли пациентки, имеющие рубец на матке после предыдущего кесарева сечения, миопию высокой степени, миомоэктомию в анамнезе, пациентки с диспластическим сколиозом, пациентки с поперечным положения плода. Для группы ПЭ ($n = 8$) кесарево сечение было связано с нарастанием тяжести ПЭ, ухудшением состояния плода (нарушения кровотока в артериях пуповины или венозном кровотоке). Критерием исключения в обоих группах являлись женщины с отягощенным внеакушерским анамнезом. Классические моноциты выделяли из 15 мл цельной крови. Периферическую кровь собирали путем пункции локтевой вены перед операцией кесарево сечение в пробирки, обработанные ЭДТА (BD Vacutainer Plus).

Выделение мононуклеаров периферической крови и классических моноцитов

Периферическую кровь разбавляли промывочным раствором autoMACS (Miltenyi biotec, Германия) в соотношении 1:1. В новую стерильную пробирку добавляли 5 мл градиентной среды Lympholyte-H (Cedarlane, Канада) и наслаивали равный объем разведенной крови. Затем пробирку центрифугировали в течение 15 минут при 400 g, +18 °C, без торможения. С помощью дозатора фракцию мононуклеарных клеток, образовавшеюся на границе между плазмой и Lympholyte-H, собирали в новую центрифужную пробирку объемом 15 мл. Добавляли 10 мл промывочного раствора autoMACS, полученную смесь ресуспендировали и центрифугировали при 300 g в течение 15 минут, +11 °C, образовавшийся супернатант удаляли. Клеточный осадок ресуспендировали и проводили выделение CD14+ моноцитов с помощью магнитной сепарации частицами с конъюгированными антителами к рецептору CD14 (130-050-201, MicroBeads, human, Miltenyi Biotec, Германия) согласно протоколу производителя.

ПЦР в реальном времени

Тотальную РНК из выделенных классических моноцитов выделяли реагентом QiaZOL Lysis Reagent (Qiagen, США) согласно протоколу производителя. Обратная транскрипция проводилась с использованием 0,5 мкг РНК набором MMLV-RT («Евроген», Россия) при 40 °C в течение 40 мин. Смеси для ПЦР в реальном времени готовили в реакционном объеме 20 мкл, содержащем 150 нг кДНК, 0,3 мкМ праймеров и 4 мкл 5xSybrGreen-mix («Евроген», Россия) в трех технических повторах. Последовательности праймеров приведены в Таблице 1. ПЦР в реальном времени проводили в термоциклере ДТ-96 (ООО «ДНК-Технологии», Россия). Уровни экспрессии генов рассчитывали относительно референсного гена глицеральдегид-3-фосфатдегидрогеназы (GAPDH) в программе QGENE.

Таблица 1/ Table 1

Последовательности праймеров / Primer sequences

Название праймера / Primer name	Последовательность / Sequence Forward	Последовательность / Sequence Reverse
CXCR1	ATCTTCCTGCTTTGCTGGCT	GGTAACACGATGACGTGCCA
JUN	AGTCCTTGTTCCACTGTGCC	GGACTCTGCCACTTGTCTCC
CXCL8	AGTCCTTGTTCCACTGTGCC	CACAGCACTACCAACACAGC
ADGRE4P	GCTCTCATGTGCACAGCAAC	AGGTGCTGGTGTTCTGGATG
IL7R	ACGATGTAGCTTACCGCCAG	TAGGATCCATCTCCCCTGAGC
ARL17A	GTCGGCGGTGTTGTAGGTAG	TGTCTCCACACAGAAACCTACTG
GAPDH	GCACCGTCAAGGCTGAGAAC	TGGTGAAGACGCCAGTGGA

Проточная цитометрия

Классические моноциты, полученные из периферической крови от пациенток исследуемой и контрольной группы, окрашивали антителами к CD14 (Клон: REA599, Miltenyi Biotec, Германия) и CD16 (3G8, Beckman Coulter, США) для оценки чистоты выделенной популяции. Моноклональные антитела к CD14 человеку инкубировали с суспензией 1×10^5 клеток в 100 мкл autoMACS® Rinsing Solution (Miltenyi Biotec, Германия) с 0,1 % MACS® BSA Stock Solution (Miltenyi Biotec, Германия), при 4 °C в течение 10 мин в темноте. Клетки центрифугировали 500 g x 5 мин и ресуспендировали в PBS (натрий-фосфатный буфер) перед проведением анализа. Все образцы анализировались на проточном цитометре FACSCalibur (Becton Dickinson, США). В каждом измерении проводился набор не менее 10000 клеток. Данные проточной цитометрии были либо проанализированы в программе BD CellQuest (Becton Dickinson, США), либо экспортированы и проанализированы в программном обеспечении FlowJo™ v10 (FlowJo LLC, США).

Статистический анализ

Статистический анализ был проведен в программе Prism 7.0 (GraphPad, США) с использованием теста Шапиро–Вилка для оценки нормальности распределения, критериями Манна-–Уитни и t-test для попарного сравнения. Различия считались статистически достоверным при уровне значимости $p<0.05$.

Результаты и обсуждение

В ходе исследования были получены образцы от 17 пациенток, которые на основании поставленного диагноза были распределены на две группы: контрольная (далее контроль) — пациентки с неотягощенным внеакушерским анамнезом и физиологическим течением беременности ($n=9$) и пациентки с поздней ПЭ ($n=8$), развившейся после 34 недели беременности (Табл. 2).

Таблица 2

Демографические и клинические характеристики пациенток

Характеристики	Контроль	ПЭ
Количество	9	8
Возраст матери, лет	31,7 ± 3,4	31,4 ± 3,7
Срок гестации на момент родоразрешения	38,6 ± 0,8	37,1 ± 0,7
Систолическое артериальное давление, мм рт. ст.	115,4 ± 7,2	140,4 ± 8,3*
Диастолическое артериальное давление, мм рт. ст.	72,9 ± 5,0	91,0 ± 9,4*
Протеинурия, г/л	0,0	1,9 ± 2,6*
Масса новорожденного, г	3455,0 ± 488,8	2513,6 ± 362,9*

Окончание табл. 2

Характеристики	Контроль	ПЭ
Пол новорожденного (муж./жен.)	4/5	2/6
Задержка внутриутробного развития, количество случаев	0	3
Беременность по счету 1≥ 2, %	36	44
Анестезия	Эпидуральная	Эпидуральная/наркоз

Примечание: Данные представлены как среднее ± SD, **p* < 0,01

Table 2

Patents' demographic and clinical characteristics

Characteristics	Control	PE
Number	9	8
Maternal age, years	31,7 ± 3,4	31,4 ± 3,7
Gestational age at delivery, weeks	38,6 ± 0,8	37,1 ± 0,7
Systolic blood pressure, mm Hg	115,4 ± 7,2	140,4 ± 8,3*
Diastolic blood pressure, mm Hg	72,9 ± 5,0	91,0 ± 9,4*
Proteinuria, g/L	0,0	1,9 ± 2,6*
Newborn mass, g	3455,0 ± 488,8	2513,6 ± 362,9*
Newborn gender (Male/Female)	4/5	2/6
Intrauterine growth restriction, number of cases	0	3
Gravida 1≥ 2, %	36	44
Anesthesia	Epidural	Epidural/narcosis

Note: Data are presented as mean±SD, *p < 0.01.

Значения систолического и диастолического артериального давления, а также показатель протеинурии были достоверно выше в группах у пациенток с ПЭ, чем в контрольной группе. Также наблюдались достоверные различия по массе плода при рождении между группами ПЭ и контроля.

От всех пациенток, включенных в исследование, были получены образцы периферической крови, из которой выделяли классические CD14+ моноциты. Полученные фракции моноцитов окрашивались антителами против CD14 для проверки чистоты сортинга, которая составила более 80 % во всех полученных пробах. Минорный процент популяции окрашивался антителами к CD16, что может указывать на незначительную примесь клеток, экспрессирующих оба типа рецепторов. Такую субпопуляцию моноцитов относят к промежуточным. Репрезентативное окрашивание приведено на Рисунке 1.

В полученных классических CD14+ моноцитах исследовали уровни экспрессии генов *CXCR1*, *JUN*, *CXCL8*, *ADGRE4P*, *IL7R*, *ARL17A* методом ПЦР в реальном времени. Таблица, суммирующая функции каждого из генов, представлена ниже (табл. 3).

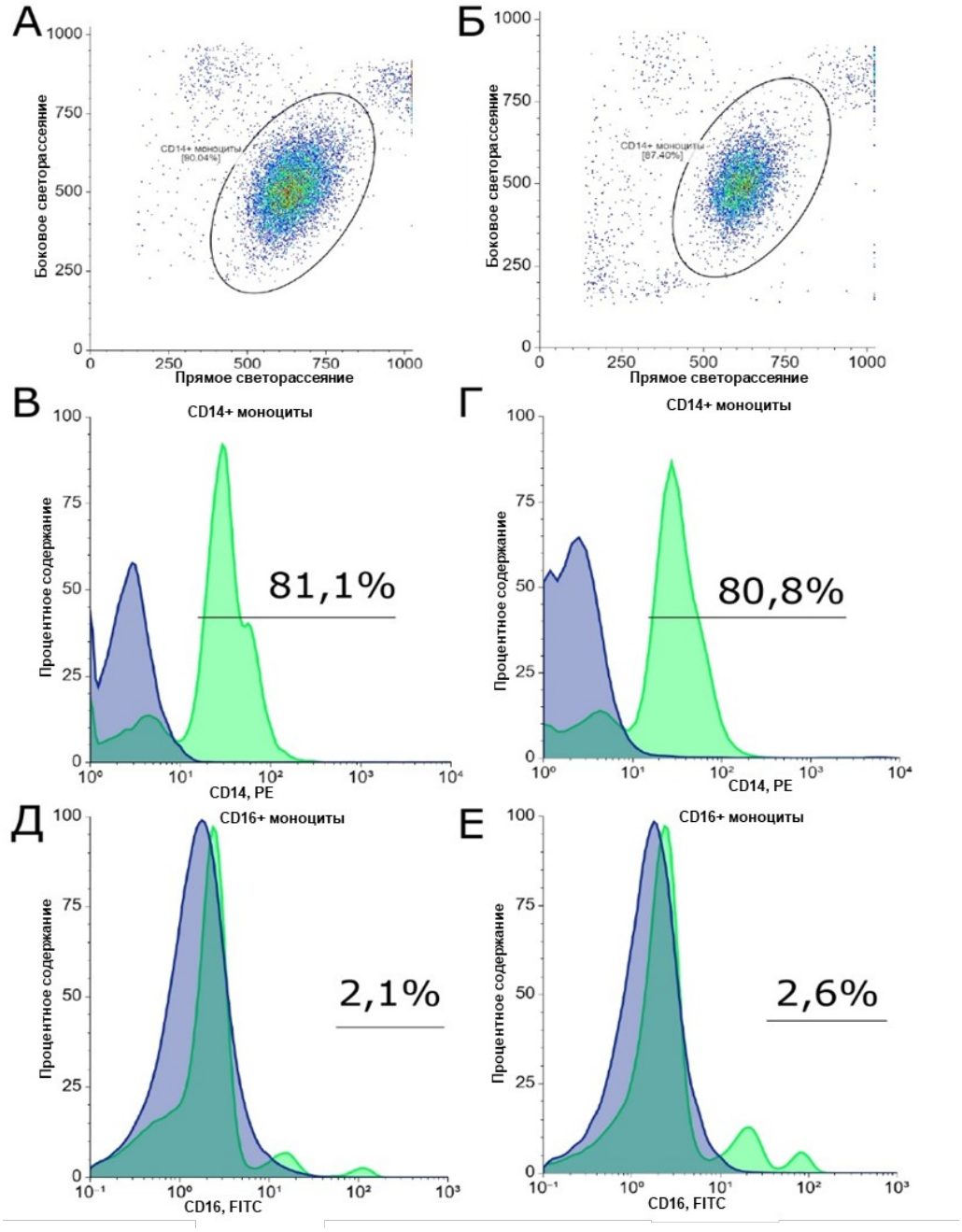

Рис. 1. Репрезентативные дот-плот диаграммы бокового и фронтального светорассеяния пробы контрольной группа (А) и группы ПЭ (Б). Репрезентативные гистограммы окрашивания анти-CD14 (В, Г) и анти-CD16 антителами (Д, Е) (зеленая заливка) пробы контрольной группа (В, Д) и группы ПЭ (Г, Е). Неокрашенный контроль — синяя заливка. Процент положительных клеток указан над маркером

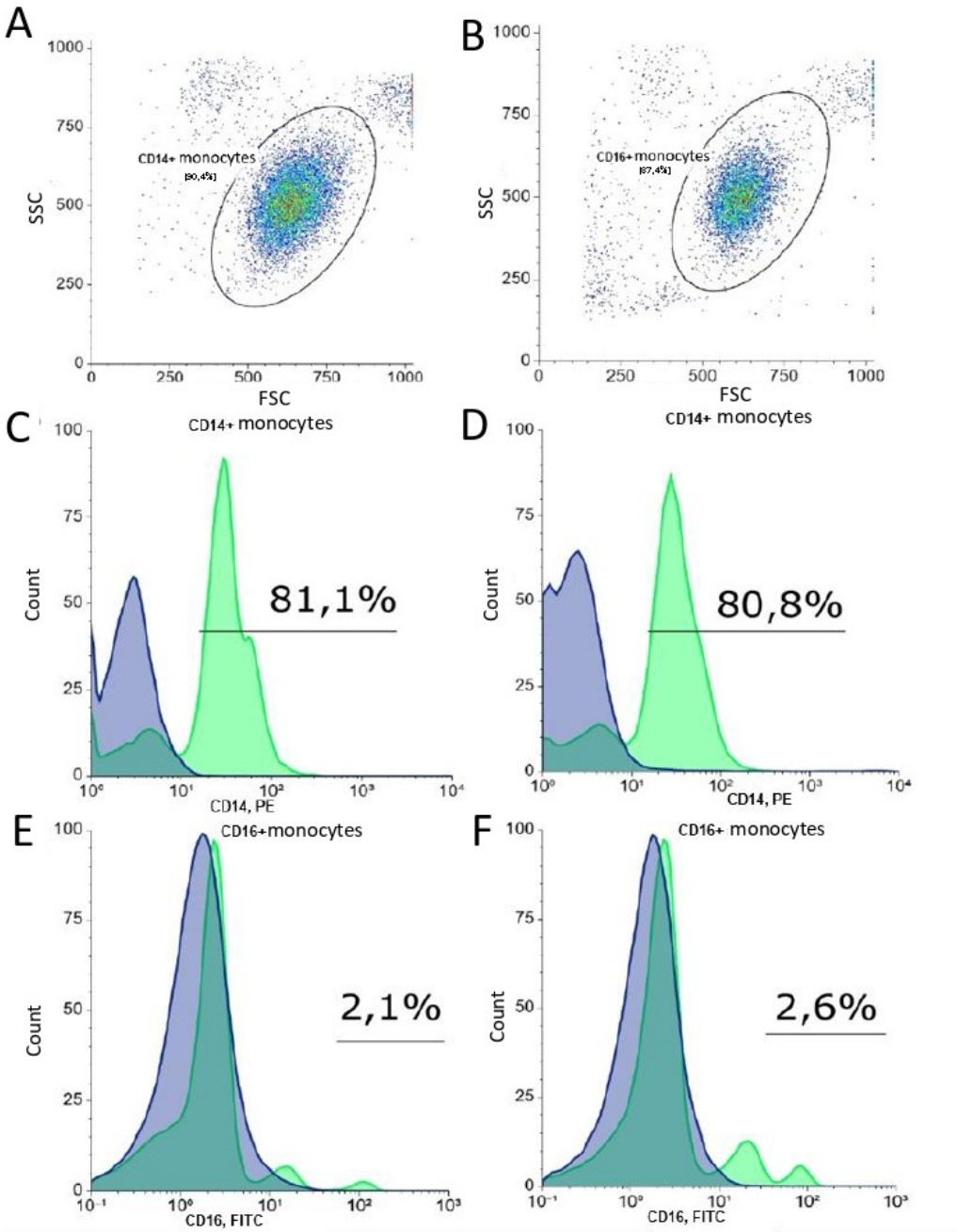

Fig.1. Representative dot plots of side and frontal scatter of the control group (A) and PE group (B) samples. Representative histograms of anti-CD14 (C, D) and anti-CD16 (E, F) staining (green shading) of the control group (C, E) and PE group (D, F) samples. Unstained control – blue. The percentage of positive cells is indicated above the marker

Таблица 3

Названия генов цитокинов, рецепторов и белков, их функции и роль в организме

Название гена	Функции	Роль в норме и при патологии	**Источник**
CXCR1(CD128; CD181; CKR-1; IL8R1 etc.)	Ген высокоаффинного рецептора IL-8. Экспрессируется в различных тканях, включая костный мозг, сетчатку глаза, сердце, легкие и плаценту.	Изменения экспрессии CXCR1 во время беременности может влиять на иммунную функцию и восприимчивость к инфекциям. Показано, что доля моноцитов, экспрессирующих CXCR1, уве-личивается во время беременности в ответ на активацию TLR3 пути. Снижение экспрессии CXCR1 в эндотелиальных клетках пуповины ассоции-рована с гибелью плода.	[18–20]
JUN(AP1; p39; AP-1; cJUN; c-Jun etc.)	Ген транскрипционного фактора, который регулирует экспрессию генов, участвующих в пролиферации, дифференцировке, выживании и воспалении клеток.	В клетках, лишенных Jun, повышается экспрессия p53 и p21, наблюдаются дефекты клеточного цикла. Экспрессия гена Jun помогает поддерживать иммунный гомеостаз. C-Jun участвует в активации макрофагов, регулируя экспрессию про- и противовоспалительных генов при стимуляции различными цитокинами, про- или противовоспалительными стимулами, а также микробными агентами. Максимальная экспрессия JUN наблюдается на ранних сроках беременности.	[21–23]
CXCL8(IL-8; NAF; GCP1 etc.)	Ген кодирует хемокин интерлейкин-8 (IL-8), который является одним из основных медиаторов воспалительной реакции.	IL-8 секретируется мононуклеарными макрофагами, нейтрофилами, эозинофилами, Т-лимфоцитами, эпителиаль-ными клетками и фибробластами. IL-8 играет роль в регулировании привлечения и активации нейтрофилов, что может быть важно для развития плода и защиты от воспаления. IL-8 играет гомеостатическую роль, в частности регулирует выход нейтрофилов из костного мозга и индукцию миграции нейтрофилов. При материнской аллоиммунизации (воспали-тельной реакции против белковых антигенов в эритроцитах плода) уровень IL-8 значительно повышается.	[24,25]
ADGRE4P (EMR4; FIRE; EMR4P; PGR16; GPR127)	Псевдоген рецептора GPCR, отвечающего за адгезию и миграцию лейкоцитов.	Экспрессируется в различных тканях человека, связанных с иммунитетом, включая тимус, селезенку, моноциты и дендритные клетки. Несмотря на то, что он является псевдогеном, существует предположение, что секретируемый белок из 232 аминокислот, образующийся в результате сдвига рамки считывания, может иметь биологическую функцию.	[26]
IL7R (ILRA; CD127; IL7RA etc.)	Ген кодирует рецептор для IL-7.	IL-7 — важнейший цитокин, регулирующий пролиферацию Th-17 клеток. Сообщается, что Th-17 клетки негативно влияют на имплантацию эмбриона. Повышенная экспрессия IL7 в децидуальных клетках при выкидышах указывает на его роль в сигнализации клеток плаценты. Чрезмерная экспрессия IL-7 может приводить к ранним потерям беременности.	[27, 28]
ARL17A (ARF1P2; ARL17P1)	Белок, кодируемый геном ARL17A, обладает способностью связывать ГТФ и участвует во внутриклеточном транспорте белков.	Участвует во многих регуляторных путях, имеющих отношение к канцерогенезу человека.	[29]

Table 3

Genes of cytokines, receptors and proteins, their functions and role in the organism

Gene	Function	Role	Ref.
CXCR1*(CD128; CD181; CKR-1; IL8R1*, etc.*)*	High-affinity IL-8 receptor gene. Expressed in various tissues including bone marrow, retina, heart, lungs, and placenta.	Alterations in CXCR1 expression during pregnancy may affect immune function and susceptibility to infections. The proportion of monocytes expressing CXCR1 has been shown to increase during pregnancy in response to TLR3 pathway activation. Decreased CXCR1 expression in umbilical cord endothelial cells is associated with fetal death.	[18–20]
JUN*(AP1; p39; AP-1; cJUN; c-Jun,* etc.*)*	A transcription factor gene that regulates the expression of genes involved in cell proliferation, differentiation, survival, and inflammation.	In cells lacking Jun, p53 and p21 expression increases, and cell cycle defects are observed. Jun gene expression helps maintain immune homeostasis. c-Jun is involved in macrophage activation by regulating the expression of pro- and anti-inflammatory genes upon stimulation by various cytokines, pro- or anti-inflammatory stimuli, and microbial agents. Maximum JUN expression is observed in early pregnancy.	[21–23]
CXCL8*(IL-8; NAF; GCP1,* etc.*)*	The gene encodes the chemokine IL-8, which is one of the main mediators of the inflammatory response.	IL-8 is secreted by mononuclear macrophages, neutrophils, eosinophils, T-lymphocytes, epithelial cells, and fibroblasts. IL-8 plays a role in regulating the recruitment and activation of neutrophils, which may be important for fetal development and protection against inflammation. IL-8 plays a homeostatic role, in particular, it regulates the release of neutrophils from the bone marrow and the induction of neutrophil migration. In maternal alloimmunization (an inflammatory reaction against protein antigens in fetal red blood cells), the level of IL-8 increases significantly.	[24, 25]
ADGRE4P (EMR4; FIRE; EMR4P; PGR16; GPR127)	A pseudogene of a GPCR receptor involved in leukocyte adhesion and migration.	It is expressed in a variety of human immune-related tissues, including the thymus, spleen, monocytes, and dendritic cells. Although a pseudogene, it has been suggested that the 232-amino acid secreted protein resulting from the frameshift may have a biological function.	[26]
IL7R (ILRA; CD127; IL7RA, etc.*)*	The gene encodes a receptor for IL-7.	IL-7 is a key cytokine that regulates the proliferation of Th-17 cells. Th-17 cells have been reported to negatively affect embryo implantation. Increased IL7 expression in decidual cells in miscarriages indicates its role in placental cell signaling. Excessive IL-7 expression may lead to early pregnancy loss.	[27, 28]
ARL17A (ARF1P2; ARL17P1)	The protein encoded by the ARL17A gene has the ability to bind GTP and is involved in intracellular protein transport.	It is involved in many regulatory pathways related to human carcinogenesis.	[29]

Экспрессия иммунно-ассоциированного гена IL7R не выявила различий между группами. *IL7R* кодирует рецептор для интерлейкина-7 (IL-7), который критически важен для развития и выживания Т-лимфоцитов и В-лимфоцитов. Он играет ключевую роль в иммунной системе, обеспечивая поддержание и развитие клеток, отвечающих за адаптивный иммунитет [27].

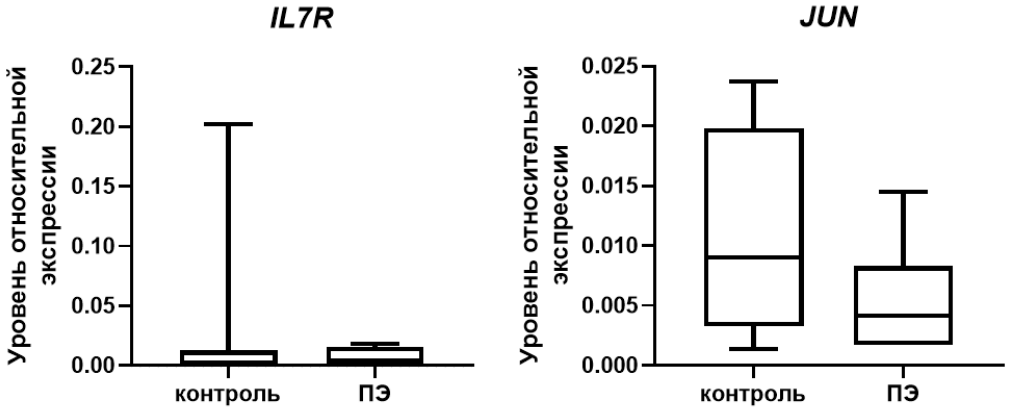

Рис. 2. Уровень относительной экспрессии генов *IL7R* и *JUN* в классических CD14+ моноцитах от пациенток с физиологической беременностью (контроль) и пациенток с ПЭ

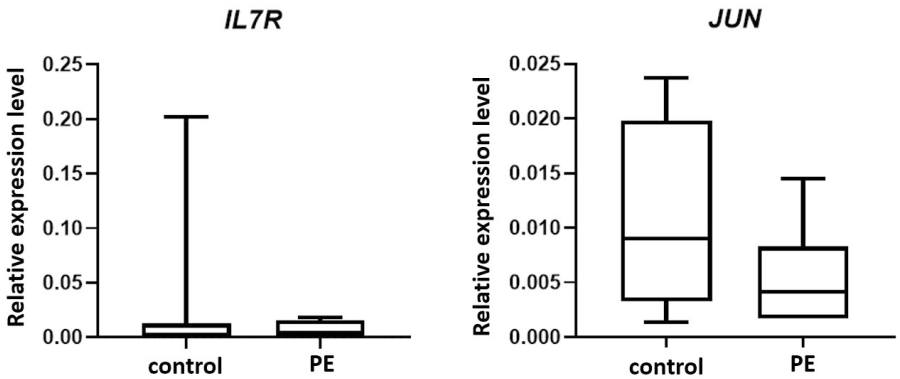

Fig. 2. Relative expression level of IL7R and JUN genes in classical CD14+ monocytes from patients with physiological pregnancy (control) and patients with PE

При анализе уровня относительной экспрессии гена *JUN* было показано, что он схож между группой контроля и ПЭ (рис. 2). Ген *JUN* кодирует один из компонентов транскрипционного фактора AP-1 (Activator Protein 1), который регулирует экспрессию генов, участвующих в клеточном росте, дифференцировке и апоптозе [21, 22]. JUN играет важную роль в реакциях на стресс и воспалительные процессы.

При исследовании гена *CXCR1* также не было получено значимых различий его экспрессии между группами (рис. 3). CXCR1 — это рецептор хемокина CXCL8 (IL-8). Он играет ключевую роль в иммунном ответе, регулируя миграцию нейтрофилов и других клеток иммунной системы к местам инфекции и воспаления [18, 20].

В случае гена *CXCL8* мы наблюдали значимое снижение его экспрессии в классических моноцитах от пациенток с ПЭ по сравнению с моноцитами от пациенток контрольной группы (рис. 3). CXCL8, также известный как интерлейкин-8 (IL-8), является хемокином-лигандом исследованного нами выше гена рецептора CXCR1 [24, 25].

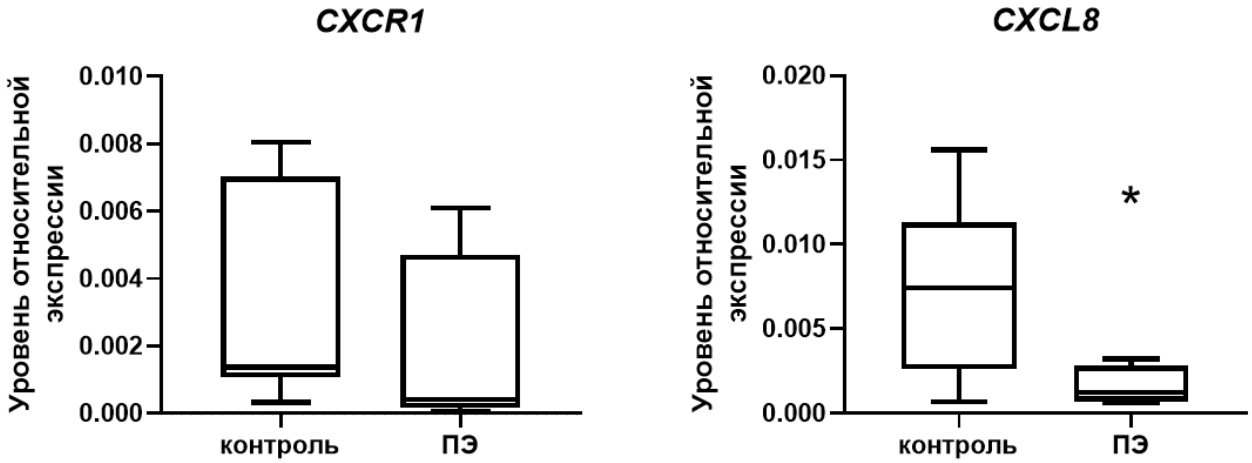

Рис. 3. Уровень относительной экспрессии генов *JUN* и *CXCL8* в классических CD14+ моноцитах от пациенток с физиологической беременностью (контроль) и пациенток с ПЭ. *p<0,05

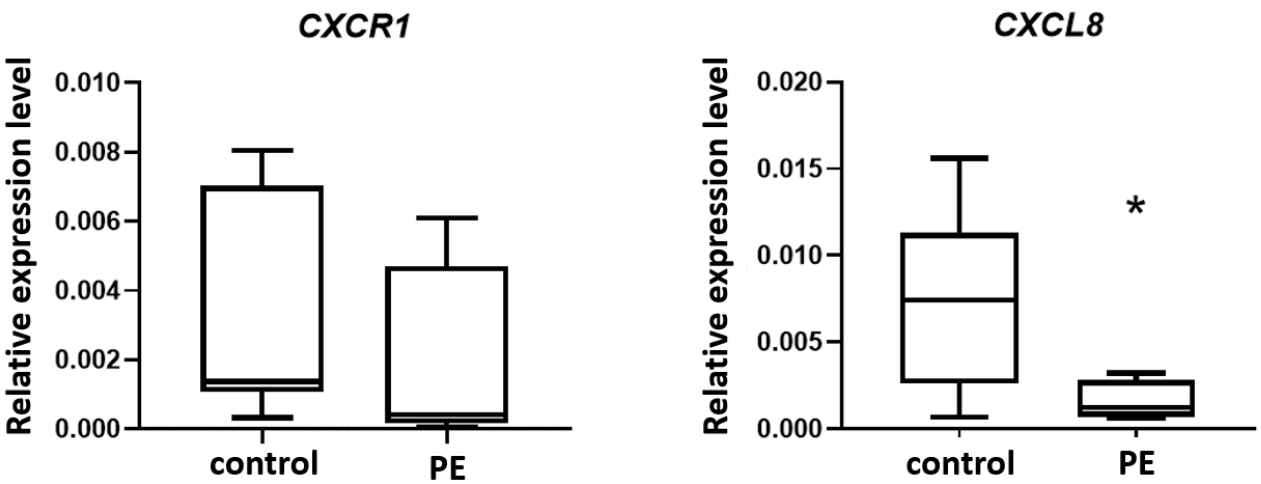

Fig. 3. Relative expression level of JUN and CXCL8 genes in classical CD14+ monocytes from patients with physiological pregnancy (control) and patients with PE. *p<0.05

Также нами было выявлено значимое повышение экспрессии гена *ADGRE4P* в группе с ПЭ (рис. 4). *ADGRE4P* — это псевдоген, который, как предполагается, является неактивной версией гена *ADGRE4*. *ADGRE4P* является членом семейства генов рецептора EGF-TM7, который, как полагают, играет роль в адгезии и миграции лейкоцитов [26].

Несмотря на некоторое снижение уровня относительной экспрессии *ARL17A* в той же группе, статистическая значимость не была достигнута. ARL17A относится к семейству малых GTPаз и предполагается, что он участвует в регуляции клеточной активности, включая взаимосвязь с клеточным цитоскелетом, изменениями в клеточной мембране и транспортом внутри клетки [29].

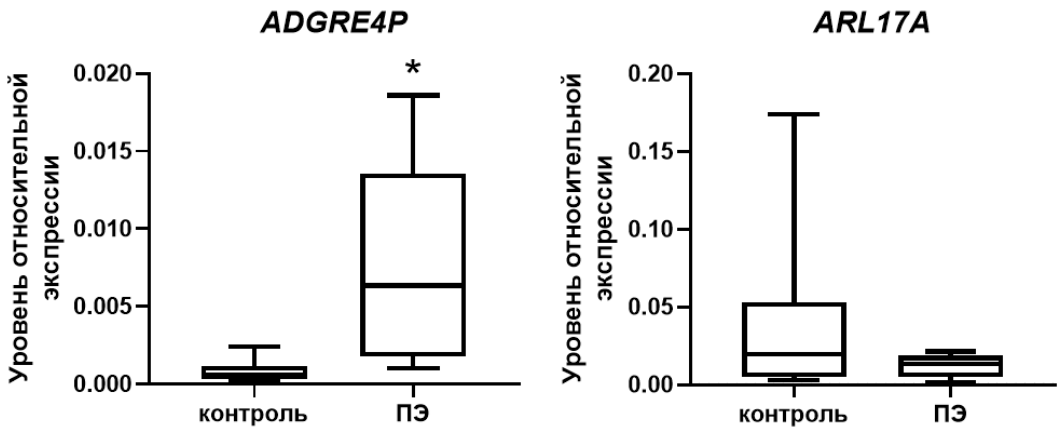

Рис. 4. Уровень относительной экспрессии генов *ADGRE4P* и *ARL17A* в классических CD14+ моноцитах от пациенток с физиологической беременностью (контроль) и пациенток с ПЭ. *p<0,05

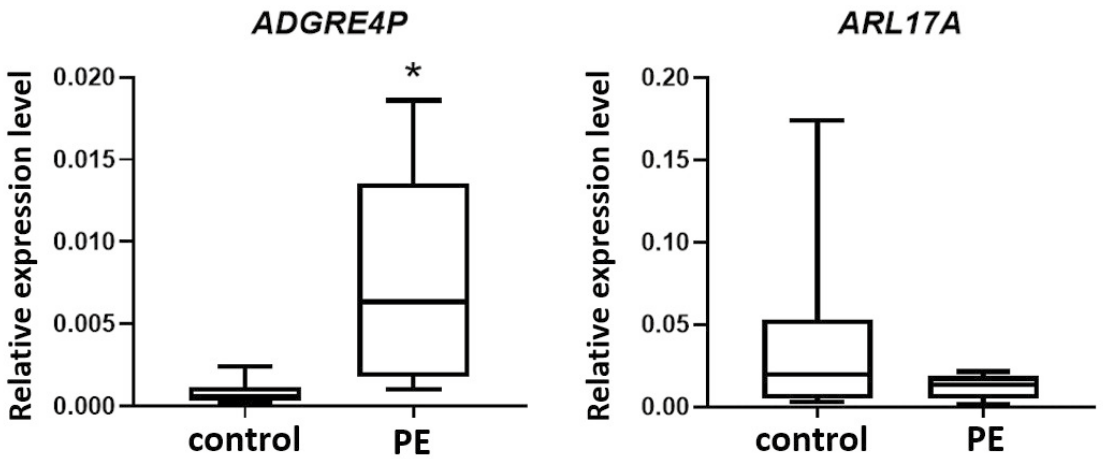

Fig. 4. Relative expression level of ADGRE4P and ARL17A genes in classical CD14+ monocytes from patients with physiological pregnancy (control) and patients with PE. *p < 0.05

Среди моноцитов периферической крови человека принято выделять три субпопуляции: классическую (CD14++CD16+), неклассическую (CD14-CD16++) и промежуточную (CD14+CD16++) на основании экспрессии на поверхности моноцитов паттерн- распознающего рецептора CD14 и Fc гамма III рецептора CD16 [30]. ПЭ, как тяжелое гестационное осложнение, опосредованное в том числе нарушениями иммунного взаимодействия мать-плод, представляет большой интерес в том числе с точки зрения участия моноцитов в этой патологии. Развитие технологий, в частности секвенирования, постепенно меняет наше понимание многообразия субпопуляций моноцитов и их роли при ПЭ. Четыре альтернативные субпопуляции моноцитов, циркулирующих в периферической крови, были выявлены при анализе на уровне единичной клетки в мононуклеарной фракции крови Zhou и коллегами [4].

Изменение субпопуляций моноцитов периферической крови при ранней и поздней ПЭ стало объектом исследования в работе Bernier [31]. Авторы показали, что уровень классических моноцитов был высоким как при ранней, так и при поздней ПЭ, то время как неклассические моноциты были снижены только в группе ранней ПЭ [31]. Также было доказано снижение количества регуляторных Т-клеток в обеих группах по сравнению с контрольной и уменьшение количества Th2 лимфоцитов при поздней ПЭ. Интересно, что повышение уровня цитокинов/хемокинов и факторов роста отмечались в случае поздней ПЭ в отличие от контрольной группы и ранней ПЭ. Также при поздней ПЭ авторы отмечали увеличение уровня моноцитов, продуцирующих IL-12, TNF-a и IL-1b, по сравнению с группой контроля.

Предпосылками к данному исследованию послужили раннее полученные нами данные microarray анализа выделенных из крови пациенток с ПЭ классических и неклассических моноцитов [14]. Нами были выбраны ключевые гены, задействованные в выявленных сигнальных путях и проведена оценка их экспрессии. Среди наиболее интересных результатов можно отметить изменения в экспрессии *CXCL8*, что согласуется с ранее опубликованными нами данными микрочипового анализа. При ПЭ происходило снижение относительного уровня экспрессии *CXCL8*. В работе Pinheiro и коллег анализ цитокинов в плазме крови показал, что уровень CXCL8 был значительно выше у женщин с ПЭ по сравнению с небеременными женщинами [32]. В другом исследовании также были обнаружены более высокие концентрации CXCL8 в сыворотке у пациенток с ПЭ, что подчеркивает роль CXCL8 в ее патогенезе [33]. Вероятно, наблюдаемые нами результаты являются компенсаторным эффектом, призванным снизить продукцию CXCL8 моноцитами при ПЭ.

В ходе многоэтапного биоинформатического анализа ген *IL7R* был идентифицирован как один из hub-генов, который может быть использован в качестве диагностического биомаркера ПЭ [34]. Для проверки этого результата был проведен метод ПЦР в реальном времени, результаты которого показали повышенный уровень экспрессии гена *IL7R* в тканях плаценты пациенток с ПЭ в сравнении с контролем. В нашем исследовании, однако, экспрессия *IL7R*, равно как и *JUN* и *ARL17A* в классических моноцитах, не изменялась.

Интересное находкой явилось значимое повышение экспрессии псевдогена adhesion G protein-coupled receptor E4 (*ADGRE4P)* при ПЭ. ADGRE4P — представитель класса Б (адгезионный, Adhesion GPCRs) суперсемейства рецепторов, сопряженных с G-белком, распознающих различные лиганды (гормоны, нейротрансмиттеры), и таким образом опосредующие регуляцию ключевых физиологических процессов. Роль отдельных представителей семейства Adhesion GPCRs показана при патологиях беременности, таких как невынашивание [35] и гипоксия плода [36]. Особенностью рецепторов подсемейства E является наличие Epidermal Growth Factor-like домена. Наиболее описанным представителем является ADGRE5/CD97. Для CD97 показано участие в процессе инвазии трофобласта через PI3K/Akt/mTOR сигнальный путь, а его низкий уровень экспрессии в плаценте ассоциирован с ПЭ [37]. Функции рецептора ADGRE4 и его псевдогена слабо описаны. Предполагают, что ADGRE4P может опосредовать клеточное взаимодействие между миелоидными клетками и B-клетками [38]. При анализе данных транскриптома лейкоцитов крови и моноцитов женщин со спонтанными преждевременными родами было выявлено значимое снижение уровня экспрессии гена *ADGRE4P* как в моноцитах, так и в лейкоцитах [39]. Также значимо низкий уровень экспрессии этого гена был выявлен при RNA-seq плацент при нормальной беременности и внутриутробной задержке развития плода [40].

Полученные в данной работе результаты являются дополнением к уже имеющимся данным других исследователей ввиду того, что описывают изменения, происходящие на уровне экспрессии генов в изолированной субпопуляции классических моноцитов, а не цельной крови или ее мононуклеарной фракции, как в упомянутых работах коллег [4, 31].

Ограничения исследования

Ограничением данного исследования является малый размер выборок, обусловленный сложностью взятия биоматериала.

Выводы

В заключение стоит отметить, что несмотря на малый размер выборок, результаты проделанной работы вносят весомый вклад в понимание роли отдельных субпопуляций моноцитов в развитие ПЭ. Очевидно, что моноциты могут изменять цитокиновый профиль плазмы крови пациенток с ПЭ, усиливать реакции врожденного иммунитета, в том числе воспаление. Будучи костномозговыми предшественниками в том числе плацентарных макрофагов, моноциты вовлечены в течение нормальной беременности, начиная с успешной имплантации эмбриона. Полученные нами данные указывают на то, что экспрессия CXCL8 (IL-8) претерпевает серьезные изменения в классических моноцитах при ПЭ.

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Development of a prognostic scale for assessing the risk of cervicitis based on extracellular microscopy data in Pap tests

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Abstract. *Relevance*. Cervicitis remains a major health problem worldwide with a global prevalence ranging from 20% to 40% among women attending reproductive health clinics. In Russia, this disease affects approximately 15% to 30% of women of reproductive age. It's a significant problem requiring a revision of existing medical screening protocols for this population. The high prevalence of cervicitis indicates the need for a more systematic approach to diagnosis and treatment to reduce incidence and prevent possible complications. *Materials and Methods*. We analyzed data from 2991 studies from the archive of the Laboratory Diagnostics Center of the Medical Complex of the Far Eastern Federal University in Vladivostok for the period 2014–2023. Data analysis included statistical processing, searching for correlation dependencies between numerical and categorical indicators, and building a logistic regression model. The data were checked and validated on a test sample to ensure the representativeness of the results and their application in clinical practice. *Results and Discussion*. During the study, a mathematical predictive model of logistic regression was developed in the form of a scale for preliminary assessment of the presence of inflammatory processes in the cervix based on parameters including the presence of mucus and key cells, as well as the calculated indicator of the total microbiota. The resulting model demonstrated moderate accuracy in recognizing cervicitis (AUC = 72%), allowing it to be effectively used in practice for the early diagnosis of cervicitis. *Conclusion*. Mathematical analysis of extracellular elements data can be used as a diagnostic tool to assess the presence of changes associated with an increased risk of cervical inflammation. The use of this scale in clinical practice can significantly improve the quality of diagnosis and treatment of cervicitis, helping to reduce morbidity and improve women's reproductive health.

Keywords: Pap test, cervicitis, extracellular elements, mathematical model, prognostic scale

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Introduction

Cervicitis, or inflammation of the cervix, is a condition particularly common among sexually active women [1–3]. Studies estimate that the prevalence of cervicitis in women worldwide ranges from 20% to 40%, with higher rates in developing countries due to limited screening and treatment options [1, 3]. In Russia, cervicitis is also a major public health problem: recent epidemiological data indicate that it affects approximately 15% to 30% of women of reproductive age [1–4]. The variability in prevalence both globally and within Russia highlights the need for improved screening protocols and available treatment options.

A variety of factors may contribute to the development of cervicitis in women [2–4]. These factors include estrogen deficiency, cervical trauma that occurs during childbirth, abortion, or diagnostic curettage. Also, the use of intrauterine contraceptives (IUD) disrupts the integrity of the cervix and its protective mechanisms, facilitating the penetration of infection into the genital tract and causing inflammation, including exo- and endocervicitis. Additional provoking factors may include benign tumors of the cervix, decreased immunity, prolapse of the cervix and vaginal walls, as well as practices such as sexual intercourse during menstruation, acid douching, and improper use of spermicides. Cervical pathology may also be caused by vaginal dysbiosis, since a deviation in the pH of the environment from the norm changes the composition of the vaginal microflora, creating conditions for infection [2, 4]. Women who have previously had cervicitis, suffer from concomitant inflammatory diseases of the genitourinary system, have had sexually transmitted infections (STIs), have had early sexual intercourse, have more than one partner, or have promiscuous sex without contraception are at increased risk of developing this pathology.

Cervicitis diagnostics include a few methods, each of which has its own advantages and disadvantages [3, 4]. Inflammation of the cervix is most often caused by infectious agents such as Chlamydia trachomatis and Neisseria gonorrhoeae, or non-infectious physicochemical factors listed above. Diagnostic tests usually

include a gynecological examination using speculums, colposcopy, ultrasound examination of the pelvic organs, nucleic acid amplification tests with polymerase chain reaction (PCR), culturing methods, microscopic examination, and serological tests. A pelvic examination with a speculum provides a basic visual assessment of the cervix, allowing for the detection of obvious signs of inflammation, discharge, or lesions. This method is a fundamental part of the pelvic examination and is usually the first step in the evaluation of a patient with symptoms of cervicitis [5–6]. However, its accuracy is limited because it relies solely on visual inspection, meaning that it cannot detect specific pathogens or cellular changes that may indicate infection.

Colposcopy offers a more detailed examination of the cervix using a specialized microscope — a colposcope. This method improves visual examination by magnifying the tissues of the cervix, allowing for the detection of abnormalities that are not visible during a standard gynecological examination [7, 8]. Colposcopy can detect precancerous changes, lesions caused by the human papillomavirus (HPV), and other structural changes, thereby increasing the accuracy of diagnosing conditions that may accompany cervicitis. However, since this method is invasive, it is contraindicated in acute inflammatory conditions (including acute vaginitis and cervicitis) [7, 8]. This method can also cause complications in the form of heavy bloody discharge, exacerbation of local inflammatory processes, discomfort in the genital area and lower abdomen, and an increase in temperature when taking biopsy material from altered areas. Pelvic ultrasound uses ultrasound waves to create images of the internal structures of the pelvis based on the physical principles of echolocation. This noninvasive imaging technique can identify associated macromorphologic complications of cervicitis such as abscesses, pelvic inflammatory disease, or other pelvic pathologies [9–11]. Ultrasound facilitates a comprehensive assessment, revealing abnormalities that cannot be detected by physical examination or laboratory testing alone. PCR is the gold standard for diagnosing infectious causes of cervicitis due to its high sensitivity and specificity. This test can detect the genetic material of pathogens with a sensitivity exceeding 90% and a specificity often exceeding 95%, making them highly accurate for identifying Chlamydia trachomatis and Neisseria gonorrhoeae and viruses such as human papillomavirus (HPV) strains and herpes virus. The ability to detect low levels of bacterial and viral DNA in clinical specimens such as endocervical swabs or urine provides a significant advantage over traditional methods [12–14, 17, 20, 21]. However, the major drawback of PCR is its high cost and the need for specialized equipment, which limits its availability in resource-limited settings.

Culture methods, although historically central to the diagnosis of bacterial infections, have fallen into disuse due to their lower sensitivity compared with PCR. Culture sensitivities for N. gonorrhoeae and C. trachomatis range from 50% to 85%, depending on the pathogen and specimen quality [3, 4, 14, 15]. Cultures are useful for antibiotic susceptibility testing, which helps to select appropriate treatment. However, they are time-consuming, typically requiring several days to obtain results, and require strict specimen handling and transportation conditions. Serologic tests, although less commonly used in the routine diagnosis of cervicitis, may be useful in certain circumstances, such as in the diagnosis of herpes simplex virus (HSV) infections, which may present with cervicitis [1, 3, 4, 14]. These tests measure the presence of antibodies and may indicate past or current infections. The main disadvantage of serologic testing is the potential for cross-reactivity and the inability to differentiate acute from chronic infections.

Microscopic cytomorphological screening examination of Pap tests, including Gram, Romanovsky-Giemsa and Papanicolaou staining, provides rapid information on the presence of infection and the state of the cells [3, 4, 17–19]. However, these methods, despite their effectiveness in obtaining rapid results, have limitations in sensitivity and specificity compared with molecular methods, making them an additional tool in modern diagnostics.

Gram staining is used to detect typical bacteria such as Neisseria gonorrhoeae with a sensitivity of 50% to 70%, by detecting characteristic Gram-negative diplococci [16, 18, 19]. However, this method is less

effective in detecting Chlamydia trachomatis, which stains poorly with Gram.

Wet microscopy of unfixed tissue is useful for identifying Trichomonas vaginalis and assessing for the presence of clue cells indicative of bacterial vaginosis. This method allows direct observation of the characteristic flagella of Trichomonas vaginalis, which makes it informative for the diagnosis of trichomoniasis [16, 18, 19]. The presence of clue cells, which are epithelial cells coated with bacteria, indicates bacterial vaginosis. However, wet microscopy is less informative for other causes of cervicitis.

Papanicolaou staining (Pap test) is used to assess not only the morphology of epithelial cells, but also to detect infections [17–19]. The method allows identification of *Chlamydia trachomatis* by the presence of cytoplasmic inclusions in epithelial cells. For more accurate detection, additional use of immunocytochemical methods is often required. In addition, the Pap test helps to detect viral infections, such as human papillomavirus (HPV) infection, by detecting koilocytes, epithelial cells with characteristic changes in the nucleus and cytoplasm, as well as precancerous and cancerous changes in the cervical epithelium. Smear analysis for purity (or bacterioscopic analysis) with Romanovsky-Giemsa staining expands diagnostic capabilities, allowing observation of a wide range of microorganisms such as *Candida, Gonococci, Gardnerella*, and assesses the general condition of the vaginal, urethral and cervical flora [16–19]. This method allows identification of *Trichomonas vaginalis, Gardnerella vaginalis* and other bacteria associated with bacterial vaginosis, as well as detection of *Candida spp.* by the presence of pseudomycelium and fungal spores. Romanovsky-Giemsa staining is also useful for assessing vaginal microflora and diagnosing inflammatory processes. This method also allows detection of signs of cytolysis, which indicates cell breakdown and may be a sign of infection or other pathological processes. Although this analysis provides valuable information about secondary infections and the state of the vaginal environment, it cannot provide a complete diagnosis of cervicitis and is often used in combination with other diagnostic methods.

There is evidence that the presence and gradation of extracellular elements of bacterial and fungal flora, mucus, is most often associated with urogenital inflammatory changes [17, 20–22].

The extracellular elements in question are assessed by laboratory diagnostic specialists during bacterioscopic analysis by indicating the range of values in the field of view (for example, from 5 to 15 units in the field of view) or by categorical gradations (absent, few, moderate, many, abundant, etc.) of various localizations: in the vagina (label V in bacterioscopic analysis), urethra (label U) and cervix (label C) in the research protocol. However, a literature review revealed that the topic of quantitative assessment of extracellular structures in the field of view during microscopic examination of gynaecological material has been poorly studied and requires further research. This would allow establishing objective boundary factors and developing scales that would allow medical professionals to associate quantitative parameters of extracellular elements with the presence of cervicitis [17, 20, 26–28]. This information could be used to create prognoses for the risk of developing inflammation in the cervix.

The aim of this study is to investigate the relationship between the quantitative assessment of extracellular structures in the field of view during microscopic examination of gynaecological material and the presence of cervicitis in patients.

Materials and methods

The study retrospectively analysed the archival data of the Laboratory and Diagnostic Centre of the Medical Complex of FEFU in Vladivostok. The study was conducted in compliance with the standards of the Helsinki Declaration (2000, 2013) and with the permission of the local Ethics Committee of FEFU. The data set included the results of 2991 Pap tests performed between 2014 and the first half of 2023 using the ALIS laboratory system, as well as the corresponding 1080 medical records of female patients aged 36.01 [22.79; 49.75] years [29]. Information on the primary diagnosis was obtained from the medical information system (MIS) 1C Hospital by matching

the full name and date of birth of the patients [6]. The main clinical diagnosis associated with changes in the cervix, according to ICD-10 categories (N72-N74), was revealed in 31.7% of patients aged 30.37 [21.12, 39.61] years, who underwent 1633 tests. In 1358 tests in patients aged 42.0 [28.92, 56.68] years, the main disease corresponded to the diagnoses of ICD-10 group Z. Mathematical and statistical analysis of the data included descriptive statistics, statistical tests (Mann-Whitney and assessment of correlation dependencies for quantitative data and Chi-square for categorical data). As a result, a predictive logistic regression model was developed to assess the relationship between the parameters of quantitative microscopy of extracellular elements observed in the field of vision with the presence of the main disease of the cervix. The modelling was carried out by dividing the data into training and test samples in a ratio of 80% to 20%, respectively, and evaluating the model hyperparameters using the K-Folding algorithm with the calculation of averaged model quality metrics over 30 cycles and the selection of maximum values. Calculations and data visualization were carried out using the high-level Python programming language and the Loginom analytical system.

Results and discussion

During the study, the integral indicator was determined, equal to the total number of elements in the vagina, urethra and cervix (1):

$$\sum V = \sum V_V + \sum V_U + \sum V_C \quad (1)$$

where ΣV_U is the sum of elements in the urethra (designated in bacterioscopic analysis as U), ΣV_C is the sum of elements in the cervix (label C), ΣV_V is the sum of elements in the vagina (label V).

Statistical analysis of the data set revealed several significant predictors associated with the presence of cervical inflammation. Continuous predictors were age at the time of examination and calculated total microbiota index in the visual field, identified using the Mann-Whitney test (p-value < 0.05) according to the data in Table 1.

Table 1

Statistical indicators when assessing continuous data using the Mann-Whitney test

Parameter	Number of tests in patients with cervicitis (*n* = 1633)	Number of tests in patients without cervicitis (*n* = 1358)	p-value
Age at the time of testing, years	30.37 [21.12, 39.61]	42.0 [28.92, 56.68]	<0.0001
Integral indicator V, number	4.0 [3.83, 4.17]	5.0 [4.82, 5.18]	<0.05

The categorical predictors, whose association with the presence of pathology was assessed using the Chi-square criterion, were the presence of key cells and the presence of mucus in the cervix according to the data in Table 2. In this case, the categorical values “absent”, “little”, “moderate”, “many”, “all” were pre-coded into the corresponding numerical values 0, 1, 2, 3 and 4 to enable statistical evaluation.

Additionally, an analysis of correlation interactions between the model predictors was performed, presented in Table 3.

Table 2

Statistical indicators when assessing categorical data

Parameter	Chi² statistics	p-value by Chi² test	CI by Chi² test
Presence of key cells in the field of view, category	24.38	<0.0001	[18.8; 30.0]
Presence of mucus in the field of view, category	37.14	<0.0001	[31.2; 43.1]

Table 3

Correlation matrix between predictors

Parameters	Age at the time of the test, years	Presence of key cells in the cervix, number	Presence of mucus in the cervix, number	Integral indicator, number
Age at the time of the test, years	1.00	-0.05	0.09	-0.01
Presence of key cells in the cervix, number	-0.05	1.00	-0.06	0.23
Presence of mucus in the cervix, number	0.09	-0.06	1.00	0.43
Integral indicator, number	-0.01	0.23	0.43	1.00

Most predictors do not correlate with each other. There is a moderate direct relationship between the integral indicator and the presence of key cells and mucus in the cervix, based on equation (1). The obtained result of the analysis indicates a weak influence of multicollinearity in constructing a logistic regression model. For each predictor, averaged logistic regression model coefficients were calculated over 30 cycles and are shown in Table 4.

Table 4

Coefficients of the developed model

Attribute	Coefficient
Constant, β_0	-3.534
Age of the patient at the time of the study, years	0.087
Presence of key cells in the cervix, number	-0.785
Presence of mucus in the cervix, number	0.158
Integral indicator, number	0.018

The developed logistic regression model achieved an average area under the curve (AUC) of 72%, indicating moderate prediction accuracy (Figure). The specificity and sensitivity values corresponded to the calculated optimal cutoff threshold within 67–75%. Based on the obtained coefficients, the developed scale takes the form of a logistic regression equation (2):

$$S = \beta_0 + Age \times \beta_1 + PKC \times \beta_2 + PM \times \beta_3 + PM \times \beta_4 \quad (2)$$

Where S is the calculated value of the logistic regression equation, Age is the patient's age at the time of the study, PKC is the number of key cells in the cervix, PM is the amount of mucus in the cervix, and TM is the total microbiota as an integral indicator.

Based on the calculated value of the logistic regression equation, the risk of having cervical cancer is assessed using the logit activation function (3):

$$p = \frac{1}{1+e^{-S}} \quad (3)$$

Where p is the probability of the patient having cervical cancer, e is the Euler constant.

The probability p obtained during the calculation can be dichotomized as follows (4):

$$\begin{cases} p \leq 0.5 is low rate of cervititis \\ p > 0.5 is high risk of cervicitis \end{cases} \quad (4)$$

Modern methods of cervicitis diagnostics, including visual examination, instrumental, molecular, microscopic and serological tests have their advantages and limitations

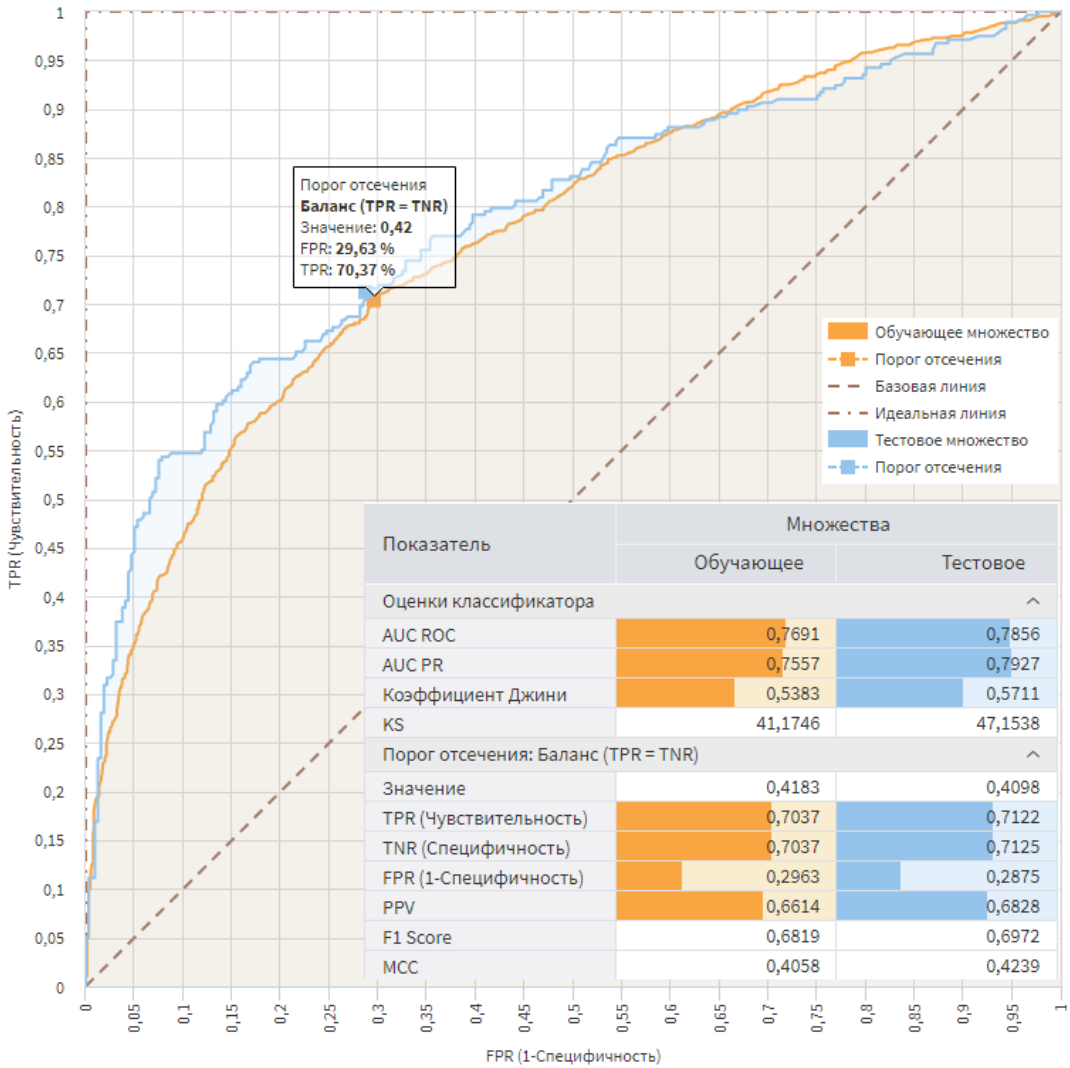

Fig. Quality metrics of the developed scale on training and test samples

in application. Visual examination using a gynaecological speculum provides only a basic assessment of changes in the mucosa condition without the ability to assess cellular changes [5–6]. Examination using a colposcope, despite the ability to assess altered tissues and take them for biopsy, has a significant limitation in the form of a contraindication to its implementation in acute inflammatory processes and the risk of developing post-diagnostic complications [7–8]. Ultrasound examinations, despite their non-invasiveness, allow you to see only macromorphological structures associated with inflammation and complications, without the ability to assess cellular processes occurring in tissues [9–11]. Nucleic acid amplification tests (PCR) have high sensitivity and specificity, making them the "gold standard" in the diagnosis of infectious causes of cervicitis [12–14, 17, 20, 21]. However, their high cost and the need for specialized equipment limit the availability of such tests in resource-limited healthcare settings. Cultivation methods, although less sensitive and more time-consuming, are useful for antibiotic susceptibility testing [16, 18, 19]. Microscopic methods such as bacterioscopic analysis and the cytomorphological Pap test provide information on the presence of infection and the state of cells, but are

inferior to molecular methods in sensitivity and specificity [17–19]. At the same time, it is known that cervicitis is associated in most cases with infectious and non-infectious agents [1–4]. When performing cytomorphological and bacterioscopic analysis, cytologists focus on studying the morphology of cells and assessing the amount of mucus and searching for bacterial agents similar to coccal, gonococcal and fungal flora, which are associated with a high risk of the presence of an inflammatory process [3, 4, 16–19]. However, other parameters of quantitative bacterioscopic analysis are included only in the protocol part without their interpretation and possible connection with the clinical picture with certain numerical values that would allow them to be associated with various diseases, in particular, with cervicitis. Due to the fact that the scientific literature provides little information on the influence of extracellular elements on the risk of developing gynecological diseases, an analysis was conducted and a mathematical model was developed to describe their connection with the risk of inflammation of the cervix [29].

The developed logistic regression model is a modernization of the existing method of microscopic screening study and uses quantitative data of extracellular elements obtained during microscopic bacterioscopic examination of gynecological material to predict inflammatory processes in the cervix. The main predictors of the model include the patient's age, the presence of clue cells and mucus in the cervix, as well as the integral indicator V, which is the total number of elements in the urethra, cervix and vagina. These predictors were selected based on their significant correlation with the presence of inflammation revealed during statistical analysis of the data. The patient's age affects the hormonal status and the state of local immune homeostasis (LIH). An increase in the amount of mucus in the cervix and the integral indicator V reflects the overall level of extracellular activity and is associated with an increased risk of an infectious process. At the same time, an increase in clue cells in the cervix is associated with a reduced risk of an inflammatory process. The advantage of this model is its ability to link data obtained during routine microscopic bacterioscopic examination with the presence of a clinical diagnosis of cervicitis. Presented in a simplified form as a logistic regression equation and a logit function, it will allow medical professionals to independently or automatically calculate and assess the risk of cervicitis in medical information systems. This will make it possible to conduct a preliminary assessment of the risk of cervicitis during screening studies, especially in resource-limited settings where access to expensive molecular methods may be difficult or in cases where inflammatory processes may not be associated with infectious agents. Assessing the odds of the risk of having an inflammatory process in the cervix with an assessment of such predictors as age, key cells, and the integral V index in routine diagnostic protocols can significantly improve the accuracy of diagnosis and contribute to a more targeted approach to treatment. The results of the study demonstrate the importance of extracellular elements in the diagnosis of cervicitis and offer a new tool for medical professionals. However, since the obtained results were obtained on the basis of a single medical institution, further studies are needed aimed at validation and adaptation of this model in other clinical settings and populations to improve screening protocols and diagnosis of cervicitis during screening microscopic examinations of gynecological smears.

Conclusion

The study presents the results and demonstrates the potential of quantitative microscopic analysis of extracellular elements in the field of view during smear microscopy as a method for additional detection of cervicitis. The identified patterns make it possible to improve the screening protocols for material from the cervical canal and increase the accuracy of detection of inflammatory processes in the cervix. However, further studies are needed to verify and clarify the parameters of prognostic models and integrate them into routine clinical diagnostic practice.

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Разработка прогностической шкалы оценки риска наличия цервицита на основе данных внеклеточной микроскопии в Пап-тестах

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Аннотация. *Актуальность*. Цервицит, глобальная распространенность которого колеблется от 20% до 40% среди женщин, посещающих клиники репродуктивного здоровья, остается серьезной проблемой здравоохранения во всем мире. В России этим заболеванием страдают примерно от 15% до 30% женщин репродуктивного возраста. Это является значительной проблемой, требующей пересмотра существующих протоколов медицинского скрининга для данной

категории населения. Высокая распространенность цервицита указывает на необходимость более системного подхода к диагностике и лечению для снижения заболеваемости и предотвращения возможных осложнений. Цель — разработать шкалу для оценки влияния количественных показателей внеклеточных элементов на риск наличия цервицита, основываясь на данных количественной оценки внеклеточных структур в полях зрения при микроскопическом исследовании гинекологического материала. *Материалы и методы*. Для разработки шкалы использовались данные 2991 исследований из архива Центра лабораторной диагностики Медицинского комплекса Дальневосточного федерального университета в г. Владивостоке за период 2014–2023 гг. Анализ данных включал статистическую обработку, поиск корреляционных зависимостей между числовыми и категориальными показателями и построение модели логистической регрессии. Данные были проверены и валидированы на тестовой выборке для обеспечения репрезентативности результатов и их применения в клинической практике. *Результаты и обсуждение*. В ходе исследования была разработана математическая прогностическая модель логистической регрессии в виде шкалы для предварительной оценки наличия воспалительных процессов в шейке матки на основе параметров, включающих наличие слизи и ключевых клеток, а также расчетного показателя суммарной микробиоты. Полученная модель продемонстрировала умеренную точность в распознавании цервицита (AUC = 72 %), позволяя эффективно использовать её в практике для ранней диагностики цервицита. *Выводы*. Математический анализ данных внеклеточных элементов может быть использован как диагностический инструмент для оценки наличия изменений, ассоциированных с повышенным риском воспалительного процесса в шейке матки. Применение данной шкалы в клинической практике может значительно улучшить качество диагностики и лечения цервицита, способствуя снижению заболеваемости и улучшению репродуктивного здоровья женщин.

Ключевые слова: тест Папаниколау, цервицит, внеклеточные элементы, математическая модель, прогностическая шкала

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REVIEW
ОБЗОР

The role of type 2 inflammation in the pathogenesis of atopic dermatitis

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Abstract. *Relevance.* Atopic dermatitis (AD) is classified as a chronic immune-mediated disease, with its pathogenesis rooted in genetic predisposition and immune response dysregulation, predominantly driven by T2-inflammatory reactions. This review highlights key aspects of the immunopathogenesis of AD, emphasizing its systemic inflammatory nature linked to T2-immune dysregulation. This leads to the activation of cytokines such as IL-4, IL-5, IL-13, and IL-31. The article analyzes modern treatment approaches, including targeted therapy aimed at blocking T2 cytokines, stressing the importance of early intervention to prevent complications and the development of the atopic march. Understanding T2-inflammation mechanisms opens new opportunities for developing effective personalized therapies for AD. *Conclusion.* Type 2 inflammation plays a pivotal role in the pathogenesis of AD, driving chronic inflammation, skin barrier dysfunction, and the clinical manifestations of the disease. Key mediators of T2 inflammation-including IL-4, IL-5, IL-13, and IL-31-regulate the activation of various immune-competent cells, not only amplifying inflammation but also contributing to the development of pruritus. This, in turn, establishes the self-perpetuating "itch-scratch" cycle, which exacerbates skin damage and further stimulates inflammatory processes. Impaired skin barrier function also facilitates the penetration of allergens and microbial agents, further activating the immune response and worsening disease severity. Studying type 2 inflammation as a central mechanism in AD pathogenesis not only advances our understanding of the disease but also facilitates the development of new therapeutic strategies to control AD and improve patients' quality of life, which remains a priority in contemporary immunology, allergology, and dermatology.

Keywords: atopic dermatitis, T2-inflammation, cytokines, biomarkers, target therapy

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by genetic predisposition, epidermal barrier dysfunction, and dysregulated type 2 immune responses [1, 2]. Immune-mediated inflammatory diseases are classified into three main types based on the predominant immune response driving their pathogenesis.

Type 1 inflammatory diseases are associated with excessive activation of Th1 lymphocytes and innate immune cells, leading to increased production of cytokines such as interferon-γ (IFN-γ), interleukin (IL)-12, and tumor necrosis factor (TNF). These cytokines provide protection against intracellular pathogens, but their overproduction triggers chronic inflammation and tissue damage. Examples of such diseases include rheumatoid arthritis, sarcoidosis, and Crohn's disease.

Type 2 inflammatory diseases are characterized by the predominance of Th2 lymphocytes, type 2 innate lymphoid cells (ILC2s), and cytokines such as IL-4, IL-5, and IL-13, which are associated with allergic inflammation, eosinophil activation, IgE production, and impaired skin and mucosal barrier function. Examples include AD, asthma, allergic rhinitis (AR), and related conditions.

Type 3 inflammatory diseases are driven by Th17 cell activation and the production of IL-17 and IL-22, which promote neutrophilic inflammation. This immune response targets extracellular bacteria and fungi, but when dysregulated, it contributes to tissue damage and chronic inflammation in diseases such as psoriasis, ankylosing spondylitis, and ulcerative colitis [3, 4]. This classification of chronic immune-mediated inflammatory diseases has become particularly relevant with the advent of targeted therapies directed at specific biological pathways.

According to global epidemiological studies, the prevalence of AD is 15–20% in children and up to 10% in adults [5]. One in five children with AD shows no detectable allergen-specific IgE to food or airborne allergens [6]. In 20–40% of patients, AD manifests as moderate-to-severe disease and is considered a systemic disorder with multi-organ involvement [7–9]. The pathogenesis of AD involves genetic predisposition, impaired

epidermal barrier function, predominant type 2 immune responses, skin microbiome alterations, IgE-mediated sensitization to allergens, and autoimmune mechanisms, which collectively determine the disease phenotype and endotype [10].

The immune response in AD involves various immune cells, including T lymphocytes, dendritic cells, ILC2s, keratinocytes, monocytes, and eosinophils. These cells are activated by allergens and microbial agents penetrating the compromised skin barrier and produce pro-inflammatory cytokines such as IL-4, IL-5, IL-13, IL-31, and others.

Investigation of the immunological mechanisms underlying AD has become particularly crucial with the emergence of novel targeted biologic therapies. This review synthesizes current understanding of type 2 inflammation in AD pathogenesis and evaluates contemporary therapeutic approaches for disease management.

Key characteristics of type 2 inflammation

The type 2 immune response normally provides protection against parasitic and helminthic invasions and supports the barrier functions of the skin and mucous membranes. However, its dysregulation can lead to the development of type 2 inflammation. This type of immune response is characterized by the activation of Th2 cells, ILC2s, and an increased production of cytokines such as IL-4, IL-5, IL-9, IL-10, IL-13, IL-31, certain chemokines, as well as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which are mainly secreted by non-immune cells. The main biological functions of these cytokines are presented in Table 1 [3, 11].

Table 1

The main biological functions of T2 cytokines

Cytokine/ References	Main biological functions
IL-4/ [11–13]	Stimulation of Th2 cell differentiation.Maintenance of survival, long-term persistence, and activity of Th2 cells under inflammatory conditions.Regulation of antibody production: stimulation of B cell isotype switching from IgM to IgE; enhancement of IgG4 production.Stimulation of eosinophils via activation of IL-5 and other mediators.Epidermal barrier dysfunction: downregulation of structural barrier proteins (filaggrin, involucrin, loricrin).Impaired antimicrobial defense: reduced synthesis of skin lipids and antimicrobial peptides.Modulation of inflammation through activation of other immune cells, including mast cells, basophils, and macrophages, and maintenance of pro-inflammatory cytokine production (IL-13).Tissue remodeling via stimulation AAMs, which participate in tissue repair and remodeling.
IL-13/ [11–13]	Stimulation of the production of other Th2 cytokines: IL-4 and IL-5.Maintenance of eosinophilic inflammation through interactions with other cytokines, including IL-5.Activation of AAMs, supporting chronic inflammation.Epidermal barrier dysfunction: downregulation of structural barrier proteins (filaggrin, involucrin, loricrin).Impaired antimicrobial defense: reduced synthesis of skin lipids and antimicrobial peptides (cathelicidins and beta-defensins).Enhancement of collagen and polyamine synthesis, contributing to tissue remodeling and repair.Goblet cell hyperplasia and increased mucus production, especially in the airways.Activation of sensory neurons, amplifying itch perception and pruritogenic responses.Stimulation of B cells isotype switching to IgE, thereby intensifying allergic reactions.
IL-5/ [11,14]	Regulation of eosinophils: stimulation of proliferation, maturation, and survival of eosinophils in the bone marrow; enhancement of eosinophil migration from the bloodstream to inflamed tissues.Activation of eosinophils: increased capacity of eosinophils to secrete granule contents (major basic protein, peroxidase, etc.) for the destruction of parasites and pathogens.Increased accumulation of eosinophils at sites of inflammation, contributing to the chronicity of inflammatory processes, especially in allergic diseases.Interaction with other Th2 cytokines (IL-4, IL-13), supporting allergic inflammation.Participation in the elimination of large extracellular pathogens, such as helminths, through activation of eosinophils and basophils.Maintenance of basophil survival, their activation, and migration into tissues.Induction of angiogenesis: stimulation of new blood vessel growth, which is associated with the maintenance of inflammatory processes
IL-31/ [15,16]	Pruritogenic function: activation of sensory neurons via IL-31 receptor alpha (IL-31RA) and oncostatin M-specific receptor beta (OSMRβ); IL-31 is a key mediator of itch in AD, chronic nodular prurigo, and other inflammatory skin diseases.Epidermal barrier dysfunction: downregulation of structural barrier proteins (filaggrin, involucrin, loricrin). Stimulation of keratinocytes to produce pro-inflammatory cytokines and chemokines CCL17 and CCL22.Amplification of skin inflammation by recruiting additional immune cells, including eosinophils and Th2 cells.Tissue remodeling: stimulation of cell proliferation and growth factor production.Interaction with other type 2 inflammation mediators IL-4 and IL-13.Involvement in itch mechanisms in systemic diseases such as Hodgkin lymphoma.Influence on the skin microbiome, creating conditions favorable for the growth of pathogenic microorganisms like *Staphylococcus aureus*.Interaction of IL-31 with skin and immune cells contributes to the transition from acute to chronic inflammation.

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IL-9/[17]	Proliferation, survival, and activation of mast cells, promoting the release of histamine and other mediators. Maintenance of type 2 inflammation: stimulation of IL-4 and IL-13 production.Participation in the immune response against helminths by stimulating mast cells, mucus secretion, and recruitment of immune cells to affected tissues. Stimulation of eosinophils.Enhancement of mucus secretion in the airways, contributing to parasite clearance but also causing hypersecretion in bronchial asthma.Stimulation of fibroblasts to produce collagen, potentially contributing to tissue fibrosis in chronic inflammation.Activation of ILC2s, which produce type 2 cytokines.Stimulation of B cells isotype switching to IgE, thereby intensifying allergic reactions.
IL-10/[18–20]	Suppression of inflammation: inhibition of the production of pro-inflammatory cytokines IL-1, IL-6, IL-12, IFN-γ, and TNF-α.Reduction of macrophage and dendritic cell activation by suppressing their antigen-presenting capacity and release of pro-inflammatory mediators.Inhibition of activation and proliferation of Th1 cells, thereby limiting inflammation.Maintenance of survival and function of Tregs, which play a critical role in preventing autoimmune diseases.Stimulation of antibody production by B cells, especially IgG4 and Ig A.Decreased production of autoantibodies, which is important for preventing the development of autoimmune reactions.Limitation of the inflammatory activity of neutrophils and macrophages.Reduction in the production of reactive oxygen species and enzymes capable of causing oxidative stress.Stimulation of growth factor production that supports tissue repair.Maintenance of immune tolerance: prevents hyperactivation of the immune system, ensuring tolerance to self-antigens and promoting tolerance to commensal microbes in the gut and other barrier tissues.Regulation of the microbiome.Limitation of tissue damage during infections by reducing the intensity of the inflammatory response; however, excessive IL-10 production may weaken immune defense and contribute to infection chronicity.
IL-33/[16,21]	Activation of ILC2: IL-33 stimulates ILC2 to produce key type 2 cytokines IL-5 and IL-13.Enhancement of Th2 cells differentiation and increased production of IL-4, IL-5, and IL-13, contributing to the development of allergic reactions. Activation of mast cells, basophils, and eosinophils, and recruitment of immune cells to sites of inflammation. Maintenance of skin itch through activation of keratinocytes and impairment of barrier function, facilitating allergen penetration.Stimulation of macrophage and fibroblast activation, promoting tissue remodeling and repair after injury.Support of immune responses against helminths by enhancing mucus secretion and recruiting immune cells. Alarmin function: released upon tissue damage to trigger inflammatory responses.Increased vascular permeability. Influence on the microbiome composition, promoting growth of pathogenic microorganisms and thereby exacerbating inflammation.
IL-25/ [21,22]	Stimulation of differentiation and activation of Th2 lymphocytes and activation of ILC2s, which enhances the production of cytokines IL-4, IL-5, and IL-13.Enhancement of eosinophil migration and activation.Participation in immune defense against helminths by stimulating mucus production, recruiting immune cells to affected tissues, and promoting intestinal smooth muscle contraction, thereby facilitating parasite expulsion.Activation of dendritic cells and macrophages, which sustain the inflammatory response.Increased production of chemokines that attract additional immune cells to the site of inflammation, further amplifying the immune response.Supports epithelial repair after injury.Maintains a type 2 immune response while suppressing Th1 and Th17 responses, thus limiting inflammation associated with other immune pathways.Interacts synergistically with other alarmins such as IL-33 and TSLP, creating a potent signal for the activation of type 2 inflammation.
TSLP/ [23,24]	Activation of dendritic cells, promoting their migration and enhancing their antigen-presenting capacity; programs dendritic cells to stimulate Th2 lymphocyte differentiation, thereby amplifying the type 2 immune response.Stimulation of Th2 cells to produce IL-4, IL-5, and IL-13, which intensify the inflammatory process.Activation of ILC2.Induction of itch and skin inflammation through activation of sensory neurons, contributing to increased pruritus, especially in AD.Enhancement and maintenance of chronic skin inflammation.Regulation of barrier functions of the skin and mucous membranes.Stimulation of migration and activation of eosinophils, mast cells, and basophils.Maintenance of survival and activation of Th2 lymphocytes.Interaction with other alarmins such as IL-33 and IL-25, enhancing their effects and promoting robust activation of type 2 inflammation.Modulation of interactions between immune and nervous system cells, strengthening the link between inflammation and itch.

The functions of IL-4 and IL-13 are largely similar but not identical: IL-4 and, to a lesser extent, IL-13 regulates immune response switching and IgE synthesis by plasma cells. IL-4, but not IL-13, promotes differentiation of T-helper cells from Th0 to Th2 cells. They also recruit inflammatory effector cells, reduce expression of filaggrin and other skin structural proteins; in mouse models these cytokines increased *S. aureus* skin colonization. IL-4 and IL-13 play a key role in macrophage activation through interaction with the IL-4Rα receptor, which is a common receptor chain for both cytokines. This process leads to the formation of alternatively activated macrophages (AAMs), which differ from classically activated macrophages by their role in inflammation regulation, tissue repair, and parasite defense [13, 25]. Several studies have shown that IL-4 and IL-13 stimulate macrophages to produce mediators such as arginase-1 (Arg1) and Resistin-like

molecule α (RELMα) [26, 27]. Arg1 competes with nitric oxide synthase (iNOS) for the common substrate arginine and suppresses NO-mediated antimicrobial pathways in classically activated macrophages. A key function of Arg1 is inflammation suppression, achieved not only through iNOS inhibition but also via direct effects on T-cell function. T-cells are sensitive to arginine concentration, and its depletion through arginase activation impairs their function. Ornithine, in turn, is used for polyamine and proline synthesis, which support cell proliferation and collagen production. These processes may underlie fibrosis development and pathological tissue remodeling in asthma [28]. Furthermore, studies demonstrate Arg1's ability to participate in tissue repair via L-ornithine and exert effector activity against nematodes by limiting parasite mobility and promoting macrophage uptake [29]. Macrophages also secrete RELMα, which can disrupt parasite metabolism and reduce their motility [30]. Macrophage activation through the IL-4Rα receptor, shared by IL-4 and IL-13 cytokines, leads to their alternative activation, significantly enhancing their ability to interact with antibody-coated parasites. This process involves several key mechanisms: increased Fc receptor expression, improved adhesion and interaction, and secretion of Arg1 and polyamines. Through IL-4Rα activation, macrophages alter their metabolism, switching to aerobic glycolysis, which enhances their capacity for active uptake and processing of opsonized particles. Thus, IL-4Rα-mediated macrophage activation makes them more efficient at recognizing antibody-coated parasites, enhancing their phagocytic capacity and providing significant immune defense against parasitic infections. AAMs also participate in recruiting other immune cells, such as eosinophils, which contribute to parasite destruction through toxic granule proteins. A key biological function of IL-4 is stimulating naive T-lymphocytes (Th0) and their differentiation into Th2 cells [3]. IL-4 and IL-13 promote immunoglobulin class switching in B-lymphocytes [31] and enhance IgE production [11]. One of the most important functions of IL-4 and IL-13 is their ability to activate sensory neurons (itch receptors) in the skin and participate in the pathological "itch-scratch" cycle, which on one hand aims to eliminate pathogens from the skin surface, but on the other exacerbates skin damage and inflammation [32, 33].

IL-5 plays a key role in eosinophil activation, mobilization, and parasite-killing capacity. This process involves several stages ensuring effective parasite elimination and inflammatory response regulation. IL-5 stimulates eosinophil differentiation and maturation in bone marrow, acting on eosinophil precursors through the IL-5 receptor (IL-5R), enhancing their proliferation, and after cell maturation, promotes eosinophil release from bone marrow into bloodstream and migration to inflammation sites [11, 14, 34, 35]. IL-5 increases adhesion molecule expression on eosinophils, enabling their interaction with endothelial cells and tissue migration through vascular walls [34]. IL-5 activates eosinophils, enhancing their ability to release toxic granules upon parasite contact.

IL-9 is an important cytokine in Th2 response, supporting mast cell, basophil and eosinophil activation. It enhances IL-4, IL-5 and IL-13 production, promoting development and maintenance of allergic inflammation. IL-9 plays a key role in parasite defense by stimulating mucus secretion and recruiting immune cells to affected tissues [36]. IL-9 participates in both protective mechanisms and pathological processes associated with allergic diseases and chronic inflammation [37].

IL-10 plays a crucial role in immune response regulation and homeostasis maintenance. On one hand, IL-10 suppresses proinflammatory cytokine production (IL-1, IL-6, IL-12, TNF-α, IFN-γ) by acting on macrophages, dendritic cells and other innate immune effector cells [19, 38, 39]. IL-10 reduces antigen presentation and inflammatory mediator release by macrophages and dendritic cells, limiting excessive inflammation and protecting tissues from damage [40]. On the other hand, IL-10 supports regulatory T-cells (Tregs), enhancing their role in suppressing inflammatory responses and preventing autoimmune reactions [41]. IL-10 stimulates antibody production by B-cells, particularly IgA, important for maintaining mucosal barrier function in gut and airways [42]. Moreover, IL-10 plays a key role in establishing immune tolerance to commensal microbiota, preventing excessive inflammation in

barrier tissues [43]. Thus, IL-10 has multifunctional roles, restraining inflammation and protecting against autoimmune reactions, but under certain conditions may weaken pathogen defense.

IL-31 is a key mediator of skin itching, inflammation and tissue remodeling. It activates sensory neurons causing itch, enhances skin inflammation through keratinocyte activation and proinflammatory cytokine production [44], and impairs skin barrier function by reducing expression of key structural proteins including filaggrin [45].

Alarmins (IL-25, IL-33 and TSLP)

Damaged epithelial cells release alarmins that play an important role in activating innate immunity and signaling threats to the body. Their function is to rapidly recruit immune cells to sites of injury and infection.

IL-25 plays a key role in activating type 2 inflammation by stimulating production of IL-4, IL-5 and IL-13 by Th2 cells and ILC2s [46]. Studies show elevated levels of this cytokine in patients with AD and asthma [47]. IL-25 also enhances protection against parasites and amplifies allergic inflammation by increasing migration and activation of immune cells [48]. IL-33 is a key mediator of type 2 inflammation that activates ILC2s, basophils and mast cells, boosting production of IL-5 and IL-13. It plays an important role in development of asthma and AD, where its levels are elevated in affected tissues [49]. IL-33 receptors are found on memory Th2 cells, suggesting its role in activating adaptive immune responses [50]. IL-33 is also involved in tissue remodeling processes and exacerbates chronic inflammation, particularly in allergic and inflammatory diseases. TSLP plays a crucial role in initiating and maintaining type 2 inflammation. It activates dendritic cells which stimulate Th2 cell differentiation and production of IL-4, IL-5 and IL-13 [51,52]. TSLP also enhances inflammatory responses through OX40 ligand expression, increasing activity of Th2 cells and ILC2s [53]. Its elevated expression in skin correlates with severity of AD and induces itching by acting on sensory neurons [54].

Thus, type 2 inflammation plays an important biological role in protecting against infections including parasitic infections and maintaining skin and mucosal barrier functions. Type 2 inflammation is characterized by activation of Th2 lymphocytes, ILCs and production of key cytokines including IL-4, IL-5, IL-13 and IL-31. These cytokines regulate eosinophils, mast cells and basophils which secrete inflammatory mediators and toxic proteins to eliminate parasites. Type 2 inflammation also activates IgE production. However, beyond its protective role, type 2 inflammation contributes to pathogenesis of chronic inflammatory and allergic diseases. It disrupts skin and mucosal barriers by suppressing structural protein synthesis and increasing permeability to allergens, pathogens and nonspecific irritants. Simultaneously, type 2 inflammation maintains chronic inflammation by recruiting immune cells to affected tissues, stimulating mucus secretion and provoking itch through activation of sensory neurons by alarmins IL-31 and TSLP. Interaction with microbiome further exacerbates inflammation, creating favorable conditions for growth of pathogenic microorganisms like *S. aureus.* Mechanisms of type 2 inflammation are involved in pathophysiology of multiple diseases: AD, prurigo nodularis, chronic spontaneous urticaria, bullous pemphigoid, eosinophilic esophagitis, chronic rhinosinusitis with nasal polyps, asthma, and eosinophilic chronic obstructive pulmonary disease [11, 55–57].

Pathogenetic mechanisms of atopic dermatitis

AD is a common chronic type 2 inflammatory systemic disease characterized by a chronic relapsing course, based on genetic predisposition to allergy, immune dysregulation, and skin barrier dysfunction [1, 10, 58].

Impairment of skin barrier function

Disruption of the epidermal barrier is a key link in AD pathogenesis, determining both predisposition to the disease and clinical features. These changes lead to increased skin permeability to various antigens and

nonspecific irritants and elevated transepidermal water loss. The main aspects of epidermal barrier dysfunction involve defects in epidermal structural proteins (filaggrin, involucrin, loricrin) [59, 60], changes in skin lipid layer composition (reduced ceramides, free fatty acids, and cholesterol) [61], increased transepidermal water loss, and decreased synthesis of antimicrobial peptides [62].

Filaggrin, the most important structural skin protein responsible for keratinization, hydration, and antimicrobial defense, is the main component of keratohyalin granules [63, 64]. Filaggrin deficiency caused by genetic disorders can lead to development of AD in early childhood, severe disease course, higher likelihood of concomitant respiratory allergic diseases, and predisposition to recurrent microbial and viral skin infections [65]. However, approximately 40% of filaggrin gene mutation carriers do not develop AD, and filaggrin mutations are found in only 15–50% of AD patients [64]. In a recently published study by Sahlén P. et al., the influence of single nucleotide polymorphisms (SNPs) identified through genome-wide association studies (GWAS) on epidermal barrier dysfunction was investigated using chromosome conformation capture [66]. It was shown that many GWAS-identified SNPs can affect distant genes, with only 35% of target genes being closest to known GWAS variants. In a GWAS-based study by DeVore et al., caspase recruitment domain family member 14 (CARD14) was shown to regulate filaggrin expression in the skin of children with AD [67], with CARD14 regulating filaggrin homeostasis depending on the rs11652075 variant in the CARD14 gene, which is also associated with psoriasis. Genetic filaggrin abnormalities do not explain all skin barrier dysfunctions in AD, but patients without such genetic defects may later show secondarily reduced filaggrin levels [68]. AD also features decreased levels of other terminal differentiation proteins of keratinocytes, such as loricrin and involucrin [69], as well as tight junction proteins [70].

AD patients also show reduced ceramide levels in both affected and unaffected skin, as well as disturbances in ceramide-to-cholesterol ratios [71]. The stratum corneum of AD patients shows elevated pH levels, leading to increased serine protease activity and contributing to inactivation and degradation of acid sphingomyelinase and glucocerebrosidase enzymes necessary for ceramide synthesis. Increased serine protease activity reduces lamellar body secretion through the protease-activated receptor 2 (PAR2) signaling pathway, leading to decreased stratum corneum thickness in AD patients.

Activation of type 2 inflammation

AD features dysregulation of type 2 immune response, leading to development of local and systemic inflammation characterized by activation and proliferation of Th2 lymphocytes, ILCs) and involvement of proinflammatory type 2 cytokines — IL-4, IL-5, IL-13 in response to allergens penetrating the impaired epidermal barrier [3, 4] (Figure). Although many immune signaling pathways involved in AD pathogenesis may underlie different disease subtypes, activation of type 2-mediated immune mechanisms is the dominant mechanism in disease pathogenesis [1, 72, 73].

Type 2 inflammation activation is a multi-stage process beginning with epidermal barrier damage, which can be caused by genetic defects such as filaggrin gene mutations [60, 71, 74], or external factors such as allergens [75], environmental pollution [76], and microbial toxins [77]. In response, skin epithelial cells release alarmins, including TSLP, IL-25 and IL-33, which activate innate and adaptive immune mechanisms. A recently published systematic review and meta-analysis included original articles examining TSLP levels in serum of AD patients [52]. The meta-analysis included 14 studies with 1032 AD patients and 416 controls. It showed that TSLP levels were significantly higher in AD patients compared to controls, with stratification by region, age, disease severity, TSLP detection method, sample size and study quality revealing significantly increased TSLP levels in adult AD patients living in Europe. TSLP elevation was found at all severity levels compared to controls, with higher levels in adults than children, and increasing with disease severity. The biological role of alarmins is described in Table 1, importantly, they play a key role in initiating type 2 inflammation

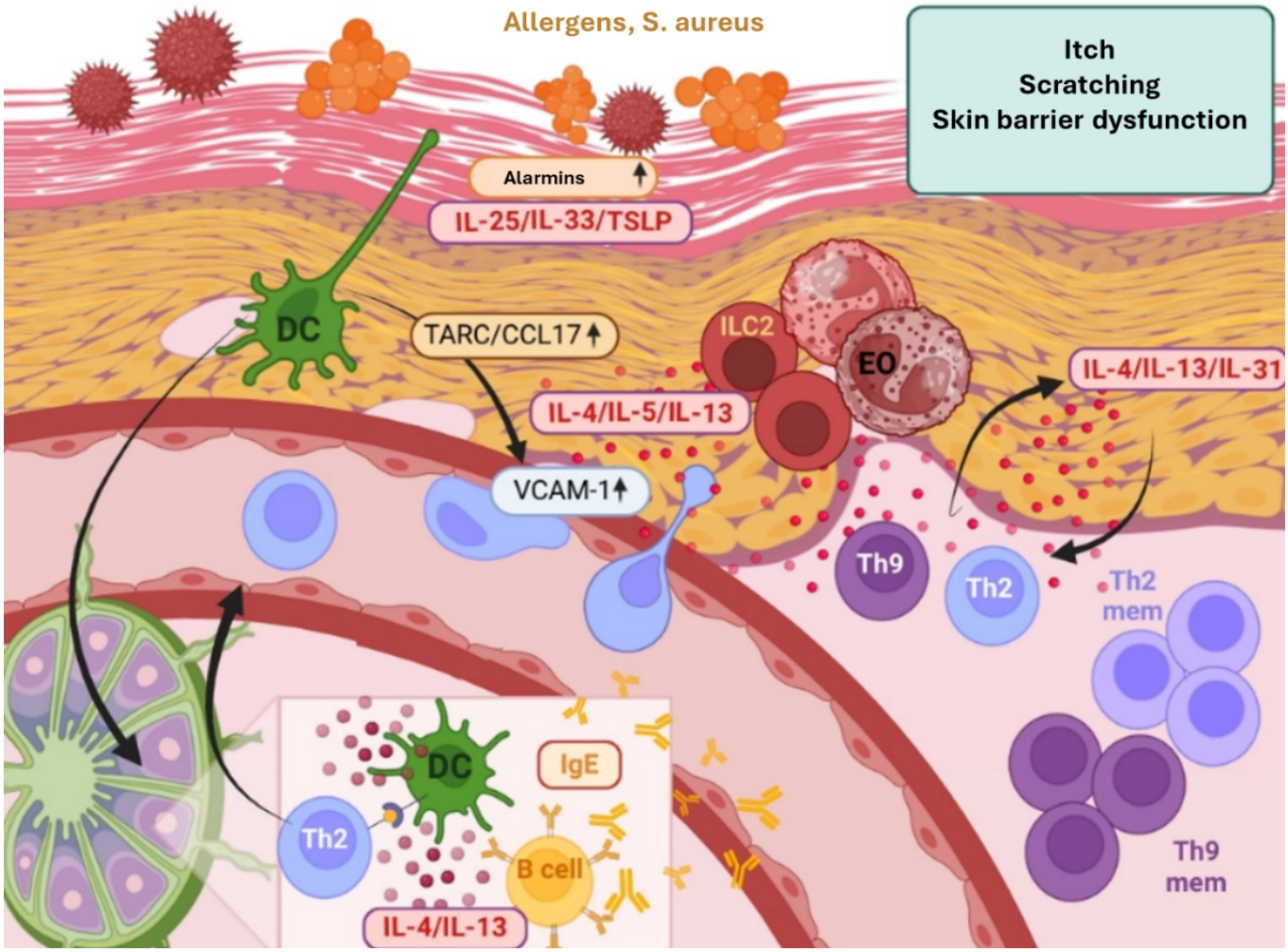

Fig. The main pathogenetic mechanisms of T2 inflammation in AD

by activating ILC2, mast cells, basophils and dendritic cells. TSLP-stimulated dendritic cells migrate to lymph nodes where they activate naive T cells and stimulate their differentiation into Th2 cells. These Th2 cells secrete key type 2 inflammation cytokines such as IL-4, IL-5, IL-13 and IL-31. IL-4 and IL-13 stimulate antibody isotype switching to IgE by plasma cells, maintaining allergic sensitization. Additionally, IL-4 plays a key role in differentiation of Th0 cells into Th2 cells, enhancing type 2 immune response (Figure).

IL-4 and IL-13 suppress synthesis of epidermal structural proteins such as filaggrin, involucrin and loricrin, which impairs skin barrier function and promotes colonization by pathogenic microorganisms such as *S. aureus*. IL-5 stimulates recruitment and activation of eosinophils, which release cytotoxic granules that damage tissues and enhance inflammation. IL-31 acts on sensory neurons, causing itch that contributes to the “itch-scratch” cycle [44]. This cycle exacerbates mechanical skin damage, worsens inflammation and maintains the chronic nature of the disease. Subsequently, inflammation may transition to a chronic phase when Th1- and Th17-mediated immune responses join type 2 inflammation. These mechanisms contribute to tissue remodeling, epidermal thickening and increased inflammation, making AD course more severe.

Relationship between inflammation and skin microbiome disruption

Microbial factors such as *S. aureus* toxins and superantigens further stimulate immune response by increasing proinflammatory cytokine production and exacerbating barrier dysfunction. The skin microbiome state depends on severity of epidermal barrier impairment, climatic factors, hygiene product use, and topical therapy. In AD patients, *S. aureus* colonization is particularly significant as it not only triggers exacerbations but also maintains pathological immune response. *S. aureus* attaches to corneocytes by binding to the N-terminal region of corneodesmosin [78], and also forms biofilms closely associated with AD severity [79]. *S. aureus* has been shown to not only be an exacerbation factor and cause of secondary bacterial infections, but also to initiate immediate hypersensitivity-type immune responses [80–82]. Moreover, *S. aureus* exacerbates epidermal barrier dysfunction in AD and stimulates expression of proinflammatory cytokines [83, 84]. AD features reduced skin microbiome diversity due to staphylococcal dominance, with *S. aureus* contamination being significantly higher in affected versus unaffected skin areas [84,85]. A prospective skin microbiome study assessing relationship between skin microbiota and disease progression in children aged 2–15 years with AD at different disease stages showed decreased microbiome diversity during exacerbations [86]. With impaired epidermal barrier, *S. aureus* can penetrate deep skin layers where it may interact with immune cells and stimulate production of type 2 cytokines: IL-4, IL-13 and IL-22 and TSLP.

Not only skin microbiome but also respiratory and gastrointestinal microbiomes may play roles in AD pathogenesis. In a prospective cohort study by Lehtimäki J. et al. [87] involving 700 children from urban and rural areas, respiratory and gut microbiota were studied for potential associations with asthma and AD development. Risk of asthma and IgE sensitization to respiratory allergens was higher in urban-reared children, with respiratory and gut microbiota composition differing between urban and rural infants.

AD patients also show increased susceptibility to fungal infections caused by *Candida* and *spp*. TLR2 receptors play an important role in this process by mediating interaction between immunogenic proteins and keratinocytes, stimulating production of antimicrobial peptides α- and β-defensins and chemokine CXCL8. Additionally, *Malassezia* antigens can induce specific IgE production through T cell-mediated B cell activation [88].

Thus, type 2 inflammation activation in AD represents a complex interaction between innate and adaptive immune mechanisms, epithelial cells, nervous system and microbial factors. This interaction underlies AD clinical manifestations including itch, chronic inflammation, skin barrier dysfunction and increased allergen sensitivity. Understanding these processes opens possibilities for targeted therapy aimed at blocking key type 2 inflammation cytokines such as IL-4, IL-13 and IL-31, as well as restoring skin barrier function.

Therapeutic approaches to control type 2 inflammation

Early intervention aimed at reducing the impact of systemic type 2 inflammation in AD may not only achieve disease control or remission but also reduce the likelihood of developing atopic march, i.e., the addition of comorbid allergic diseases such as asthma, allergic rhinitis, food allergies, as well as normalize skin structural changes and alter disease course [89]. The main goals of AD therapy are inflammation control, prevention of exacerbations, and improvement of patient quality of life. AD treatment depends on disease severity but always includes the use of emollients, identification and elimination of allergens and triggers. For mild cases, low-potency topical corticosteroids or calcineurin inhibitors are used, along with antihistamines to reduce itching. For moderate cases, moderate or high-potency corticosteroids are applied, with antibacterial agents prescribed when necessary to treat secondary infection. For severe AD, systemic therapy is prescribed: cyclosporine, methotrexate or targeted biologics, such as dupilumab, which blocks key type 2 inflammation cytokines IL-4 and IL-13, or selective JAK inhibitors (abrocitinib, baricitinib, upadacitinib) [2, 57].

Anti-cytokine targeted therapy for AD

Targeted immunotherapy for AD is aimed at specifically affecting key molecules and signaling pathways involved in inflammation development and pathological immune response in this disease. Unlike traditional systemic therapy using systemic corticosteroids or immunosuppressants, targeted therapy selectively acts on cytokines, receptors or other molecules, reducing side effect risks and increasing treatment effectiveness. The first approved targeted drug for moderate-to-severe AD was dupilumab, which inhibits IL-4 and IL-13, key mediators of type 2 inflammation [90–92]. In some countries, various biologics targeting type 2 cytokines are already registered or undergoing clinical trials for efficacy and safety in AD treatment: anti-IL-13 (lebrikizumab and tralokinumab), anti-IL-5 (mepolizumab and reslizumab); drugs blocking type 2 cytokine receptors (benralizumab (IL-5Rα), nemolizumab (IL-31RAα); anti-IgE (omalizumab and ligelizumab). The efficacy and safety of other drugs targeting other type 2 inflammation mediators such as alarmins IL-33 (astegolimab, etokimab, itepekimab, MEDI-3506), IL-33 receptor (melrilimab) and TSLP (tezepelumab) are also being studied. Table 2 presents the main targeted biologics acting on key type 2 inflammation cytokines, their biological targets and indications.

Table 2

Targeted biologic therapies for type 2 inflammation

Targeted biologic drug / References	Biological targets and effects	Therapeutic indications
Dupilumab / [91–96]	IL-4 (IL-4Rα, IL-13Rα)	AD, asthma, CRSwNP, EoE, prurigo nodularis, COPD (approved) Bullous pemphigoid, CSU, CIU, allergic fungal rhinosinusitis, ABPA (phase 3) Food allergy, pollen allergy (phase 2)
Tralokinumab / [97, 98]	IL-13(IL-13Rα2)	AD (approved in EU)
Cendakimab /[99, 100]	IL-13 (IL-13Rα2)	AD (phase 2)EoE (phase 3)
Lebrikizumab /[101–103]	IL-13 (IL-13Rα1)	AD (phase 3)
Nemolizumab /[104–106]	IL-31 (IL-31Rα)	AD (phase 3)Prurigo nodularis (phase 3)Chronic itch (phase 2)
Mepolizumab /[14, 35,107–110]	IL-5	Asthma, EGPA, HES (approved)COPD, nasal polyposis (phase 3) EoE (phase 3)
Reslizumab /[14, 111–113]	IL-5	Asthma (approved)Sinusitis (phase 3)EGPA
Depemokimab / [114]	IL-5	Asthma (phase 3)
Benralizumab /[112, 115–119]	IL-5 (IL-5Rα)	Asthma (approved)Bullous pemphigoid, COPD, EoE, EGPA, HES, Nasal polyposis (phase 3)AD, CSU, Rhinosinusitis, Eosinophilic gastroenteritis (phase 2)
Tezepelumab /[120–122]	TSLP	Asthma (approved), CRSwNP (phase 3)CSU, COPD (phase 2)
Astegolimab / [123,124]	IL-33 (IL-33R)	Asthma, COPD (phase 2)
Itepekimab /[125]	IL-33	COPD (phase 3)
Tozorakimab /[126]	IL-33	Asthma, AD, COPD, COVID-19 (phase 2)
Omalizumab /[127–132]	IgE	Asthma, CSU, nasal polyposis, seasonal AR (approved)Food allergy (phase 3)
Ligelizumab /[133,134]	IgE	CSU, Food allergy (phase 3)
Fezakinumab /[135]	IL-22	AD (phase 2)

Note: CRSwNP — Chronic rhinosinusitis with nasal polyps; EoE — Eosinophilic esophagitis; COPD — Chronic obstructive pulmonary disease; ABPA — Allergic bronchopulmonary aspergillosis; CSU — Chronic spontaneous urticaria; CIU — Chronic inducible urticaria; EGPA — Eosinophilic granulomatosis with polyangiitis; HES — Hypereosinophilic syndrome; AR — Allergic rhinitis.

Interestingly, the clinical efficacy of targeted drugs against type 2 cytokines has provided deeper insights into their role not only in AD but also in other diseases such as asthma, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis. The lack of efficacy of some targeted drugs in clinical trials has proven highly valuable for understanding the precise mechanisms underlying type 2 inflammatory diseases and their treatment. For instance, the limited effectiveness of mepolizumab [107], omalizumab [130], and ligelizumab [136] in AD suggested that IL-5-mediated peripheral blood eosinophilia is not the primary source of the inflammatory cascade in AD, and that extremely high IgE levels do not play a dominant role in disease symptom development. On the other hand, the use of certain biologic targeted drugs, such as anti-TNF [137], anti-IL-17 [138], and anti-IL-12/23 [139], demonstrated moderate clinical efficacy but was associated with an increased risk of opportunistic and/or serious bacterial, fungal, or viral infections.

JAK inhibitors

The JAK-STAT signaling system (Janus Kinases — signal transducer and activator of transcription) is a pathway consisting of Janus kinase (JAK) and signal transducer and activator of transcription (STAT) proteins, which transmits information from extracellular polypeptide signals through transmembrane receptors directly to target gene promoters in the nucleus. In AD, this signaling system plays a critical role in activating type 2 immune responses via IL-4, eosinophil activation, and B-cell differentiation. JAK inhibitors were initially approved for rheumatoid arthritis, psoriasis, and alopecia. The JAK1/JAK3 inhibitor tofacitinib is approved for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis; pilot studies have also explored its efficacy in AD. Results from oral tofacitinib use in a small group (six AD patients) for 8–29 weeks showed a 66.6% reduction in SCORAD index, with no adverse events reported [140]. A study of topical 2% tofacitinib ointment in 69 adult AD patients confirmed its clinical efficacy compared to placebo [141]. Another JAK inhibitor, delgocitinib, has broad-spectrum activity, suppressing Th1, Th2, and Th17 responses by inhibiting JAK1, JAK2, JAK3, and TYK2. Its topical form is approved in Japan for AD treatment [142], with efficacy demonstrated over 28 and 52 weeks [143, 144]. A study in 22 children aged 6–24 months applied 0.25% or 0.5% delgocitinib ointment twice daily for 52 weeks, showing a –73.5% reduction in modified Eczema Area and Severity Index (mEASI) by week 4, –81.7% by week 28, and –81.9% by week 52, with no treatment-related adverse events [145].

The JAK1/JAK2 inhibitor ruxolitinib carries high immunosuppression and infection risks when administered orally. Its topical form is approved in the U.S. for short-term, intermittent treatment of mild-to-moderate AD in patients ≥12 years without immunosuppression, when other topical therapies are inadequate or contraindicated. Two Phase III trials (TRuE-AD1 and TRuE-AD2) demonstrated the efficacy and safety of 0.75% and 1.5% ruxolitinib cream in adolescents/adults with mild-to-moderate AD [146].

Baricitinib, a selective JAK1/JAK2 inhibitor, is approved in the EU and Russia for moderate-to-severe AD in adults. Short- and long-term studies showed improved skin condition, reduced itch, better sleep, and enhanced quality of life with 4 mg/day over 16 weeks [147], sustained efficacy at 68 weeks [148].

Next-generation JAK1-selective inhibitors upadacitinib and abrocitinib are approved in Russia, the EU, U.S., and Japan for AD. Upadacitinib is also approved for six other indications in Russia (rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, non-radiographic axial spondyloarthritis, ulcerative colitis, Crohn's disease). Its AD profile was evaluated in five trials involving >4,000 patients [149–152]. Abrocitinib is approved for moderate-to-severe AD in adults/adolescents, showing rapid symptom reduction by week 12 versus placebo [153, 154].

A recent network meta-analysis compared abrocitinib, baricitinib, and upadacitinib in moderate-to-severe AD [155]. Analysis of 10 trials revealed all three significantly improved Investigator's Global Assessment (IGA) and EASI scores. Upadacitinib 30 mg outperformed other doses/drugs in efficacy but had higher adverse event rates; upadacitinib 15 mg and abrocitinib 200 mg showed comparable high efficacy. However,

upadacitinib 30 mg may be optimal for short-term use due to its superior efficacy despite higher side effects. JAK inhibitors rapidly reduce itch and AD symptoms by targeting cytokine pathways, but their selectivity *in vivo* is dose-dependent. Rare adverse effects (cytopenia, gastrointestinal perforation, malignancies) occur more frequently than with biologics, underscoring the need for further optimization in type 2 inflammatory diseases.

Conclusion

Type 2 inflammation plays a pivotal role in the pathogenesis of AD, driving chronic inflammation, skin barrier dysfunction, and the clinical manifestations of the disease. Key mediators of T2 inflammation-including IL-4, IL-5, IL-13, and IL-31-regulate the activation of various immune-competent cells, not only amplifying inflammation but also contributing to the development of pruritus. This, in turn, establishes the self-perpetuating "itch-scratch" cycle, which exacerbates skin damage and further stimulates inflammatory processes. Impaired skin barrier function also facilitates the penetration of allergens and microbial agents, further activating the immune response and worsening disease severity. The advent of targeted biologic therapies, such as dupilumab, lebrikizumab, and tralokinumab, has opened new avenues for AD treatment by specifically blocking key type 2 cytokines. These targeted approaches have already demonstrated efficacy in reducing inflammation, alleviating pruritus, and restoring skin barrier function. However, not all biologics have proven equally effective, highlighting the need for further research into disease mechanisms. For example, the lack of significant clinical benefit from IL-5 inhibition underscores the complexity of the inflammatory cascade and points to the importance of other mechanisms, including microbiome disturbances and autoimmune processes. Future research should focus on deepening our understanding of the interactions between the immune system, epidermal barrier, and environmental, genetic, and epigenetic factors that may influence disease severity and treatment response. Additionally, it is important to consider ethnic and geographic differences in the clinical presentation and pathogenesis of AD to enable the development of personalized treatment approaches.

In summary, studying type 2 inflammation as a central mechanism in AD pathogenesis not only advances our understanding of the disease but also facilitates the development of new therapeutic strategies to control AD and improve patients' quality of life, which remains a priority in contemporary immunology, allergology, and dermatology.

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Роль Т2-воспаления в патогенезе атопического дерматита

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Аннотация. *Актуальность.* Атопический дерматит (АтД) относится к иммуноопосредованным хроническим заболеваниям, в основе патогенеза которого лежат генетические факторы и нарушения иммунного ответа, с преобладанием Т2-воспалительных реакций. В обзоре рассмотрены ключевые аспекты иммунопатогенеза заболевания, АтД рассматривается как системное воспалительное заболевание, связанное с дисрегуляцией Т2-иммунного ответа, который активируется при нарушении барьерной функции кожи и приводит к активации ряда цитокинов, таких как ИЛ-4, ИЛ-5, ИЛ-13, ИЛ-31 и др. В статье представлен анализ современных подходов к лечению АтД, включая таргетную терапию, направленную на блокировку Т2-цитокинов, с учетом важности раннего терапевтического вмешательства для предотвращения осложнений и развития атопического марша. Понимание механизмов Т2-воспаления открывает новые перспективы в разработке эффективных методов персонифицированной терапии Ат Д. *Выводы.* Т2-воспаление играет ключевую роль в патогенезе АтД, определяя хроническое воспаление, нарушения барьерной функции кожи и клинические проявления заболевания. Основные медиаторы Т2-воспаления, включая ИЛ-4, ИЛ-5, ИЛ-13 и ИЛ-31, регулируют активацию различных иммунокомпетентных клеток, не только усиливая воспаление, но и способствуя развитию зуда, который формирует порочный цикл «зуд-расчесывание», усугубляющий повреждение кожи и стимулирующий дальнейшую активацию воспалительных процессов. Нарушение барьерной функции кожи также облегчает проникновение аллергенов и микробных агентов, что дополнительно активирует иммунный ответ и усугубляет течение заболевания. Изучение Т2-воспаления как ключевого механизма патогенеза АтД не только углубляет наше понимание заболевания, но и открывает перспективы для разработки новых терапевтических стратегий, которые позволят контролировать течение АтД и улучшить качество жизни пациентов, что является приоритетной задачей современной иммунологии, аллергологии и дерматологии.

Ключевые слова: атопический дерматит, Т2-воспаление, цитокины, биомаркеры, таргетная терапия

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Effect of mydriasis degree on intraoperative complications in patients with complicated cataract associated with pseudoexfoliative syndrome

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Abstract. *Relevance.* Cataract is one of the causes of blindness and low vision among the pathology of the organ of vision. Medication to cure cataracts is extremely ineffective. According to statistics, over the past year, there are about a million patients diagnosed with cataracts. The main method of surgical treatment of cataracts is phacoemulsification. The main cause of a narrow pupil with lens opacities is pseudoexfoliative syndrome, which affects the development of the disease, both in the intraoperative and postoperative periods. The aim of this study is to evaluate the effect of mydriasis on intraoperative complications in patients with complicated cataract in PES. *Materials and Methods.* The study involved 176 patients of varying severity of PES and a control group without signs of PES. Patients underwent ophthalmological diagnostics (visometry, biomicroscopy, ophthalmoscopy, CCFM, ruler for measuring pupil diameter, pneumotonometry, IOP according to A.N. Maklakov, 10g weight, OST of the anterior segment). In addition to ophthalmological examinations, all patients underwent anamnesis and laboratory tests before surgery according to generally accepted methods. Preoperative preparation of the patient included both drug therapy and a psychological aspect. Particular importance was attached to premedication. All patients in all study groups were prescribed a sedative (*per os*) 1 hour before surgery. In all observation groups, in order to achieve the cycloplegia required during the operation, instillations of mydriatics were performed according to the scheme. *Results and Discussion.* Evaluation of the results revealed that the degree of mydriasis is a statistically significant risk factor for the development of all complications except "conjunctiva". For the

conjunctiva, no statistically significant risk factors were found among the selected parameters. AUC for ROC curves are in the range of 0.7–0.9 for all complications, which indicates a good and satisfactory choice of model parameters. In the "photophobia" regression, the risk of developing complications is 6 higher with mydriasis up to 5 mm in the postoperative period, and 26 times higher to get a complication with mydriasis less than 4 mm. In the regression of "chamber moisture" — the moisture of the anterior and posterior chambers, the risk of developing turbid fluid is 353 times higher with mydriasis less than 4 mm, and 27 times higher with mydriasis up to 5 mm. *Conclusion.* The characteristic signs of pseudoexfoliation syndrome undoubtedly complicate the surgeon's work: rigid narrow pupil, ciliary muscle weakness, iridodonesis, phacodonesis. When planning cataract surgery, special attention should be paid to diagnosis, history taking in terms of general somatic features, and the choice of mydriatics. This work showed how much the degree of mydriasis can influence complications in the intraoperative period.

Keywords: complicated cataract, pseudoexfoliation syndrome, mydriatics, cycloplegia, rigid pupil, complications

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Introduction

More than 300 thousand cataract surgeries are performed annually in the Russian Federation. The leading position in cataract surgery is occupied by phacoemulsification [1]. The main cause of narrow pupil in case of lens opacities is pseudoexfoliative syndrome (PES), which is directly related to the development of the disease, both in intraoperative and postoperative periods. PES is an age-related systemic dystrophic disease with a characteristic lesion of the visual organ, mainly of the anterior segment of the eye [2]. The pupil in PES is stiffer than in the fellow eye and doesn't respond well to medication cycloplegia.

Spraying on the anterior capsule of the lens, in the iris stroma — on the anterior segment of the eye, causes atrophy of the iris sphincter and iris dilator, this is the cause of pupil stiffness, this condition leads to mechanical obstruction preventing the achievement of cycloplegia [3]. Non-medicamentous mydriasis of the pupil can be caused by heterogeneous condensed bodies at their molecular contact of exfoliative material to the iris pigment epithelium and the anterior capsule of the lens [4].

The authors noted that after medication cycloplegia, intraocular pressure rises, which may cause an abundant pigment release from the posterior chamber into the anterior chamber, which positively correlates with the

intensity of pigment dispersion [5]. Scientists have noted localization of exfoliative material, according to different sources, at the pupil margin, within 33–95% of patients, but there is also data on the detection of characteristic dustings at the pupil margin even with complete preservation of the iris pigment border [6]. WuDunn D. on the basis of his observations and work with clinical material considers the weakness of cinnamon ligaments and possible complications in the form of lens subluxation as a result of friction of iris and lens capsule covered with exfoliations [7].

The ways to achieve mydriasis are not only mechanical, and also medication too. Authors attempt to use antioxidants, vasoactive drugs, disaggregants, antihypoxants in the prevention of complications of this syndrome, but the effectiveness of actions needs further clarification [8]. Currently, to achieve a wide pupil in preparation of the patient for surgery, there is a choice of mydriatics, both in combination and in monotherapy. The most frequently used groups of drugs are adrenomimetics — phenylephrine, and M-cholinoreceptor blockers — cyclopentolate and tropicamide. Authors in various observations have repeatedly noted a pronounced enhancing effect of the use of mydriatics with such non-steroidal anti-inflammatory drugs as diclofenac sodium, flurbiprofen, ketorolac trometamol [9]. Dube P. (1990) in his works compared instillation of mydriatics according to the conventional method in combination with 1% indomethacin and 1% prednisolone. The results of the study showed that the strongest synergy, when comparing the two drugs, was observed in 1% indomethacin [10]. Other authors Guzinska M. and Dimitrakos S.A. conducted similar work, using diclofenac sodium with indomethacin. The results showed, more pronounced effect in diclofenac [11, 12]. Au M.K. and Singh P. noted the relationship between the use of mydriatics and antiprostoglandin piroxicam, but there is no information about the effectiveness of these drugs [13]. Allaire C. et al. found no significant difference when comparing 0.1% indomethacin and 0.03% flurbiprofen [14]. Psilas K. et al. noted opposite findings of a pronounced weak synergism in prolonged cycloplegia of 0.1% diclofenac compared to 1% indomethacin and 0.03% flurbiprofen [15]. Using non-steroidal anti-inflammatory drugs of choice, the author Solomon K.D. showed persistent mydriasis with 0.05% ketorolac, noting a pronounced effect than with 0.03% flurbiprofen, while the interval and frequency of instillation are important [16]. The authors Chaudhary K.P., Sofat B K. and Stewart R. suggested using 1 drop of instillation with an interval of 30 minutes 2 hours before the planned operation. Other authors suggested 60 minutes before the planned surgery with a 15 minute interval [17]. The third authors suggested instillation of 5-fold mydriatics every 30 minutes [11]. In the available sources there are data on the use of intracameral injection of adrenaline (epinephrine) to additionally achieve cycloplegia. Authors Corbett M.C. and Liou S.W. used epinephrine in irrigation solution at a concentration of 1:1.000.00. No data on the condition of patients with hypertension were noted [18]. Chen C.C. observed the possibility of restoring intraoperative cycloplegia by injecting 0.1 ml of adrenaline into the anterior segment of the eye, namely into the anterior chamber, but no data on systemic side effects were found [19]. Another scientist, when comparing alpha-adrenostimulant and adrenaline injected into the anterior chamber, noted less toxic effect on the body and adequate cycloplegia predominantly in alpha-adrenostimulant [20]. The author Schlichtenbrede F.C. compared instillations of alpha-adrenomimetics 5% and 10% phenylephrine, with concomitant pathologies of CHD, however, systemic cardiovascular effects were not found, but cycloplegia was achieved mainly with 10% instillation [21]. Kumar Vinod et al proposed the following regimen: 3-fold instillation 1 hour before the planned surgery with a 5-minute interval of M-choline blocker (tropicamide 1%) and 2-fold alpha-adrenomimetic (10% phenylephrine) [22]. Another author suggested another instillation scheme for persistent mydriasis: combination of mydriatics with NSAIDs by 3-fold injection into the conjunctival cavity of a solution of tropicamide, diclofenac sodium and phenylephrine in the ratio of 1%-0.1%-10% with simultaneous injection of a mixture of 0.1 ml of atropine and mesaton (in the ratio of 0.1%-1%) [23]. Authors Postupayeva N.V. and colleagues proposed an interesting scheme to achieve

mydriasis, a prepared drug mixture of 0.05 ml, which includes arenalin, mesaton, lidocaine (1% — 1% — 2% respectively), to inject localized at 12, 4 and 8 o'clock into the limbus region at the border of opaque and transparent parts of the cornea, using a 27G injection needle (ratio of solutions 0.02:0.02:0.01 respectively) [24].

The aim of this work was to determine the influence of the degree of mydriasis on intraoperative complications in patients with complicated cataract on the background of pseudoexfoliative syndrome.

Materials and methods

This scientific work was carried out at the Department of Eye Diseases of RUDN University, namely at the clinical base of the ophthalmologic department of the V.M. Buyanov State Clinical Hospital, and short-stay hospital unit. Patients (176 subjects) were divided into 3 groups according to severity and a control group without clinical manifestations of PES.

Group 1 n=40 (40 eyes) — the median age was 74.53 (IQR: 56–89 years), 75% were female, and 25% were male. Group 2 n=44 (45 eyes) — the median age was 74.25 (IQR: 59–91 years), 63.6% were female, and 36.4% were male.

Group 3n=47 (49 eyes) — the median age was 73.62 (IQR: 49–93 years), 61.7% were female, 38.3% were male. Control group n=45 (45 eyes) the median age was 70.93 (IQR: 54–82 years), 68.9% were female, 31.1% were male in Table 1.

The patients underwent ophthalmologic diagnostics (visometry, biomicroscopy, ophthalmoscopy, critical frequence of merge of flickers, ruler for pupil diameter measurement, pneumotonometry, intraocular pressure (IOP) according to A.N. Maklakov — 10g weight, OCT of the anterior segment). In addition to ophthalmologic examinations, anamnesis collection and laboratory tests were performed before the operation according to the generally accepted methodology. Preoperative preparation of the patient included both drug therapy and psychological aspect.

Special importance was given to premedication. 1 hour before surgery all patients in all studied groups were given a sedative drug (*per os*).

Inclusion criteria were:

– Presence of cataract in one eye (visual acuity not more than 0.4, with visual acuity of the other eye not less than 0.8).

– compensated IOP

Exclusion criteria were:

– Infectious — inflammatory diseases of the eye, oncologic diseases of the eyeball, appendicular apparatus of the eye, decompensated glaucoma, lack of light perception, decompensated somatic diseases.

Voluntary written consent was obtained from the patients for the investigation and publication of relevant medical information according to WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013.

Statistical processing of the data was performed in the development environment of R-4.1.3. When analyzing quantitative parameters, each parameter was pre-tested for normality of distribution using the Shapiro-Wilk test. In case of normal distribution the parameter is presented as M ± SD, in case of deviation from normal distribution the parameter is presented as Me (Q1; Q3). Four-group analysis of variance (ANOVA) was used when comparing groups for continuous parameters. Comparisons of conjugation tables for categorical parameters were performed using Fisher's exact test.

Graphical representation of the results was performed using span diagrams.

Regression analysis for generalized linear models (GLM) was used to analyze the relationships between the parameters. To analyze the probability of complications and factors that influence this probability, a multivariate logistic regression (MLR) model was used, for which ROC analysis was performed. The quality of the model was assessed by the AUC value for the ROC- curve.

Results and discussion

The comparison of the groups by age and gender showed that the studied groups had no statistically significant differences (p=0.152 and p=0.564, respectively) in Table 1.

Preoperative vision in the groups had no statistically significant difference (p=0.37) in Table 2.

Table 1

Demography

Parameter	Control	1- Group	2- Group	3- Group	P- value
Age (years)	70.93±7.45	74.53±8.16	74.25±7.51	73.62±9.42	0.152
GenderFemale	31 (68.9%)	30 (75%)	28 (63.6%)	29 (61.7%)	0.564
Male	14 (31,1%)	10 (25%)	16 (36.4%)	18 (38.3%)	

Table 2

Visual functions

Parameter	Control	1-Group	2-Group	3-Group	P-value
Vision before surgery	0.03(0.01;0.05)	0.03(0.02;0.052)	0.05(0.02;0.1)	0.02 (0;0.08)	0.37

In all observation groups, to achieve mydriasis required during surgery, mydriatic instillations were performed. M-cholinoblocker instillations (tropicamide 1%, 0.5% and cyclopentolate 1%) were used in 65%, 54.5% and 44.7% of groups 1, 2 and 3, respectively. Group 1 used cyclopentolate 1% once 40 min before the planned surgery, group 2 used cyclopentolate 1% instillations 30 and 15 min before surgery, and group 3 used 1% tropicamide solution 30, 20, and 10 min before surgery. Combined-action midriatics (tropicamide+phenylephrine) in 20%, 20.5% and 19.1%, respectively. Alpha-adrenomimetics (phenylephrine hydrochloride 2.5%) in 20%, 25% and 38.3%, respectively. In group 1 30 min before surgery, in group 2 30, 15 min, in group 3 1 hour, 30 min, 15 min. In all the observation groups, in addition to mydriatics, in the preoperative period, predominantly diclofenac sodium 100 mg, followed by nimesulide and indomethacin 1% were used.

From the preoperative instillation it is worth noting a statistically significant difference in the frequencies of M-choline blockers (p=0.006).

According to the results of mydriatic instillation we obtained the following data in Table 3. There were statistically significant differences between the groups ($p < 0.05$). In group 1, 67.5% of medial mydriasis was up to 6.5 mm, in group 2, 72.7% up to 5.5 mm., and in group 3 of observations, 70.2% of medial mydriasis was less than 4 mm.

Table 3

Degrees of medication-induced mydriasis

Parameter	Control	1-Group	2-Group	3-Group	P-value
Up to 8 mm	45(100%)	0(0%)	0(0%)	0 (0%)	0
Up to 6.5 mm	0 (0%)	27 (67.5%)	3 (6.8%)	0(0%)	0
Up to 5.0 mm	0 (0%)	13 (32.5%)	32 (72.7%)	14 (29.8%)	0
Less than 4.0 mm	0 (0%)	0 (0%)	9 (20.5%)	33 (70.2%)	0

To achieve our aim, we additionally studied the patients' general medical pathologies.

Statistical analysis of the history of concomitant comorbid pathologies showed that the groups had statistically significant differences in the frequencies of cardiologic, pulmonologic, and neurologic pathologies in Table 4. There was no statistically significant difference in the frequencies of endocrinologic pathologies between the groups (p=0.243). As follows from the results, all mentioned pathologies have a negative statistically significant effect on mydriasis. The associated pathologies worsen the process of mydriasis. The statistical significance of the remaining parameters has not been established.

Table 4

Associated pathologies

Parameter		Control	1-Group	2-Group	3-Group	P-value
Cardiology	No Yes	30 (66.7%) 15 (33.3%)	25(62.5%) 15(37.5%)	20(45.5%) 24(54.5%)	18 (38.3%) 29 (61.7%)	0.02
Endocrinology	No Yes	26 (57.8%) 19 (42.2%)	24 (60%) 16 (40%)	24(54.5%) 20(45.5%)	19 (40.4%) 28 (59.6%)	0.243
Pulmonology	No Yes	36 (80%) 9 (20%)	27(67.5%) 13(32.5%)	21(47.7%) 23(52.3%)	13 (27.7%) 34 (72.3%)	00
Neurology	No Yes	20 (44.4%) 25 (55.6%)	13(32.5%) 27(67.5%)	20(45.5%) 24(54.5%)	2 (4.3%) 45 (95.7%)	00

In the OLM for MIDRIAZ *Demography*, * Vision before surgery*, *Presence of associated pathologies* and use of preoperative instillations were selected as independent factors. The result estimation of OLM parameter estimation and their statistical significance are summarized in Table 5. As it follows from the results, all mentioned pathologies have a negative statistically significant effect on mydriasis.

Table 5

Group comparison

Parameter	Coefficient estimated	Standard error	P-value
Visual acuity on admission	0.542	1.158	0.64
Age	-0.001	0.011	0.963
Gender (m)	0.18	0.157	0.254
Cardiology	0.397	0.177	0.026
Endocrinology	0.319	0.148	0.033
Pulmonology	0.78	0.153	0
Neurology	0.612	0.163	0
Comb Mydriat	-0.089	0.515	0.863
M-cholinoblok	0.188	0.506	0.711
A-Adrenomim	-0.067	0.501	0.894

For the complications “conjunctiva”, “photophobia”, “anterior chamber fluid” MLR models were built, for which the following factors were selected: degree of mydriasis, gender, age, type of surgery and IOL model. The evaluation results of the estimated MLR models are summarized in Tables 6–8. Evaluation of the results revealed that the degree of mydriasis is a statistically significant risk factor for the development of all complications except “conjunctiva”. For conjunctiva, no statistically significant risk factors were found among the selected parameters (Table 6).

Table 6

Logistic regression — conjunctiva

Parameter	Estimation of LR coefficient	Standard error	P-value	Odds ratio	2.5% limit 95% DI	97.5% limit 95% DI
Mydriasisup to 6.5 mm	-1.036	0.509	0.042	0.355	0.128	0.947
Up to 5.0 mm	0.336	0.466	0.47	1.4	0.562	3.52
Less than 4.0 mm	1.071	0.687	0.119	2.918	0.794	12.001
Gender (m)	0.073	0.376	0.846	1.076	0.517	2.276
Ages	-0.01	0.023	0.665	0.99	0.945	1.036
Phaco+IOL+ periph. irid.	0.837	0.657	0.203	2.308	0.681	9.419
Phaco+IOL+ basal coloboma	-0.226	0.633	0.721	0.798	0.233	2.877
ECCE+IOL	-0.399	0.398	0.316	0.671	0.306	1.465
AFY	-0.28	0.463	0.546	0.756	0.303	1.877
HQ Acrylic IOL	-0.21	0.632	0.739	0.81	0.233	2.855
RPR, T-19, Miol	-0.129	0.732	0.86	0.879	0.215	3.999
Acryfold	0.564	0.483	0.246	1.758	0.69	4.646

Note: AFY- American type of intraocular lens; HQ Acrylic intraocular lens- German lens type; RPR, T-19, Miol- Russian lens type; Acryfold- Indian lens type. Abbreviations: Phaco+IOL+periph. irid.: Phacoemulsification+intraocular lens+peripheral iridectomy; ECCE+IOL: Extracapsular cataract extraction+ intraocular lens.

In the regression of "photophobia" the risk of complications is 6 times higher with mydriasis up to 5 mm, in the postoperative period, and 26 times higher to get a complication with mydriasis less than 4 mm (Table 7).

Table 7

Logistic regression — photophobia

Parameter	Estimation of LR coefficient	Standard error	P-value	Odds ratio	2.5% limit 95% DI	97.5% limit 95% DI
Mydriasisup to 6.5 mm	0.044	0.604	0.942	1.045	0.311	3.405
Up to 5.0 mm	1.855	0.534	0.001	6.393	2.333	19.203
Less than 4.0 mm	3.25	0.793	0	25.789	5.991	138.823
Gender (m)	-0.505	0.429	0.239	0.604	0.255	1.386
Ages	-0.042	0.028	0.136	0.959	0.907	1.012
Phaco+IOL+ periph. irid.	1.009	0.678	0.137	2.744	0.77	11.593
Phaco+IOL+ basal. coloboma	1.24	0.805	0.123	3.457	0.789	19.893
ECCE+IOL	-0.409	0.454	0.369	0.665	0.267	1.601
AFY	-0.089	0.526	0.866	0.915	0.324	2.575
HQ Acrylic IOL	-0.721	0.707	0.308	2.056	0.526	8.722
RPR, T-19, Miol	0.634	0.842	0.451	1.885	0.377	11.077
Acryfold	0.815	0.529	0.124	2.258	0.813	6.572

Note: AFY- American type of intraocular lens; HQ Acrylic intraocular lens- German lens type; RPR, T-19, Miol- Russian lens type; Acryfold- Indian lens type. Abbreviations: Phaco+IOL+perif. irid.: Phacoemulsification+intraocular lens+peripheral iridectomy; ECCE+IOL: Extracapsular cataract extraction+ intraocular lens.

In the regression of "anterior chamber fluid" — anterior and posterior chamber moisture, the risk of developing turbid fluid is 353 times higher with mydriasis less than 4 mm, and 27 times higher with mydriasis up to 5 mm (Table 8).

Table 8

Logistic regression- anterior chamber fluid

Parameter	Estimation of LR coefficient	Standard error	P-value	Odds ratio	2.5% limit 95% DI	97.5% limit 95% DI
Mydriasisup to 6.5 mm	1.77	0.667	0.008	5.871	1.683	24.243
Up to 5.0 mm	3.31	0.657	0.	27.379	8.285	113.521
Less than 4.0 mm	5.869	1.243	0	353.731	43.94	8176.802
Gender (m)	-0.272	0.479	0.57	0.762	0.295	1.953
Ages	-0.003	0.031	0.927	0.997	0.938	1.06
Phaco+IOL+ periph. irid.	0.199	0.687	0.773	1.22	0.32	4.943
Phaco+IOL+ basal. coloboma	0.664	0.826	0.422	1.942	0.409	11.305
ECCE+IOL	0.574	0.521	0.27	1.776	0.643	5.052
AFY	0.401	0.576	0.486	1.493	0.485	4.721
HQ Acrylic IOL	0.822	0.807	0.308	2.275	0.499	12.761
RPR, T-19, Miol	0.888	1.091	0.416	2.43	0.339	28.526
Acryfold	0.775	0.581	0.182	2.17	0.708	7.044

Note: AFY- American type of intraocular lens; HQ Acrylic intraocular lens- German lens type; RPR, T-19, Miol- Russian lens type; Acryfold- Indian lens type. Abbreviations: Phaco+IOL+perif. irid.: Phacoemulsification+intraocular lens+peripheral iridectomy; ECCE+IOL: Extracapsular cataract extraction+ intraocular lens.

AUC for ROC curves lie in the range of 0.7–0.9 for all complications, which indicates a good and satisfactory choice of model parameters shown in Figures 1, 2, 3.

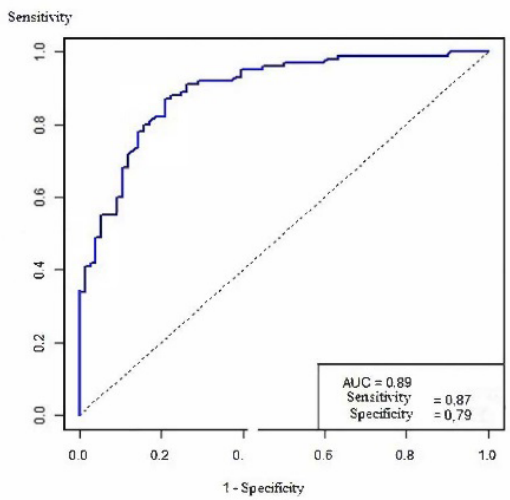

Fig 1. AUC: area under the ROC curve "anterior chamber fluid"

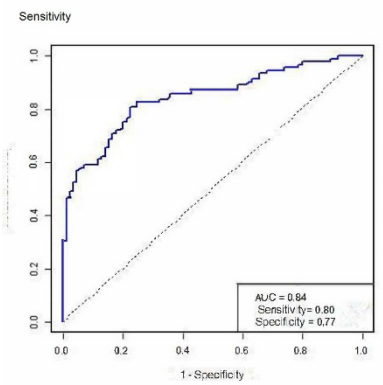

Fig 2. AUC: area under the ROC curve "photophobia"

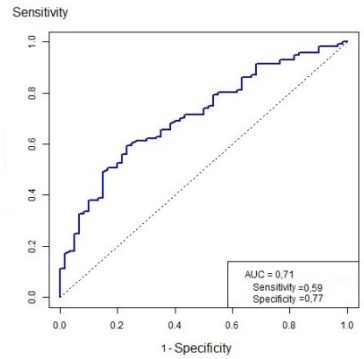

Fig 3. AUC area under the ROC curve "conjunctiva"

Conclusion

Undoubtedly, a narrow, rigid pupil causes complications in the intraoperative period, and negatively affects the postoperative period in the distant period, with the risk of complications, including IOP elevation. When planning cataract surgery, special attention should be paid to diagnosis, history taking in terms of general medical features, and most importantly, the choice of mydriatics. As the literature review shows there is no consensus on the choice, dosage, time intervals of mydriatic instillation to achieve persistent mydriasis, but to enhance the action of mydriatics, the authors undertake the prescription of drugs both NSAIDs and hormonal therapy intravenously and per os. Proceeding from the purpose of our work, we have shown what are the risks of complications in the intraoperative period in patients based on the development of our mydriatic instillation patterns.

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Влияние степени мидриаза на интраоперационные осложнения у пациентов с осложненной катарактой на фоне псевдоэксфолиативного синдрома

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Аннотация. *Актуальность.* Одна из причин слепоты и слабовидения среди патологии органа зрения является катаракта. Медикаментозно вылечить катаракту крайне малоэффективно. По данным статистики, за последний год больных с диагнозом «катаракта» составляет около миллиона. Основной способ хирургического лечения катаракты является

факоэмульсификация. Основные причины узкого зрачка при помутнений хрусталика является псевдоэксфолиативный синдром, который влияет на развитие заболевания как в интраоперационном, так и в послеоперационном периодах. Цель настоящего исследования – оценить влияние степени мидриаза на интраоперационные осложнения у пациентов с осложненной катарактой на фоне ПЭС. Материалы и методы. В исследовании принимали участие 176 пациентов различной степени тяжести ПЭС и контрольная группа без признаков ПЭС. Пациентам проводили офтальмологическую диагностику (визометрия, биомикроскопия, офтальмоскопия, КЧСМ, линейка для измерения диаметра зрачка, пневмотонометрию, ВГД по А.Н. Маклакову, грузом 10 г, ОСТ переднего отрезка). Всем пациентам помимо офтальмологических исследований, перед операцией проводили сбор анамнеза, лабораторные исследования по общепринятой методике. Предоперационная подготовка пациента включала в себя как медикаментозную терапию, так и психологический аспект. Особое значение придавалось премедикации. За 1 час до операции всем пациентам во всех исследуемых группах назначали седативный препарат (*per os*). Во всех группах наблюдения, для достижения необходимого в ходе операции циклоплегии, проводили инстилляции мидриатиков по схеме. *Результаты и обсуждение*. Оценка результатов выявила, что степень мидриаза является статистически значимым фактором риска для развития всех осложнений кроме «конъюнктива». Для конъюнктивы статистически значимых факторов риска среди выбранных параметров не обнаружено. AUC для ROC-кривых лежат в диапазоне 0,7–0,9 по всем осложнениям, что говорит о хорошем и удовлетворительном выборе параметров модели. В регрессии «светобоязни» риск развития осложнений в 6 раз выше при мидриазе до 5 мм, в послеоперационном периоде, и в 26 раз выше шанс получить осложнение при мидриазе менее 4 мм. В регрессии «камерной влаги» — влага передней и задней камеры — риск развития мутной жидкости в 353 раза выше при мидриазе менее 4 мм, и в 27 раз выше при мидриазе до 5 мм. *Выводы*. Характерные признаки псевдоэксфолиативного синдрома, несомненно, усложняют работу хирурга: ригидный узкий зрачок, слабость циллиарной мыщцы, иридодонез, факодонез. Особое внимание при планировании хирургии катаракты следует уделять внимание диагностике, сбору анамнеза в плане общесоматических особенностей и выбору мидриатиков. В данной работе показано, насколько сильно может повлиять степень мидриаза на осложнения в интраоперационном периоде.

Ключевые слова: осложненная катаракта, псевдоксфолиативный синдром, мидриатики, циклоплегия, ригидный зрачок, осложнения

Информация о финансировании — неприменимо

Вклад авторов: Б.Б. Бекмирова **—** сбор и обработка материалов, анализ полученных данных, написание текста, М.А. Фролов — концепция и дизайн исследования, редактирование рукописи. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Информация о конфликте интересов**.** Авторы заявляют об отсутствии конфликтов интересов.

Этическое утверждение — неприменимо.

Благодарности — неприменимо.

Информированное согласие на публикацию. У всех пациентов было получено добровольное информированное согласие на участие в исследовании согласно Хельсинкской декларации Всемирной медицинской ассоциации (WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013), обработку персональных данных и согласие на публикацию.

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Effectiveness of sensorimotor training in different social conditions of men's and women's activities in mono-gender dyads

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Abstract. *Relevance.* Investigation the features of human achievement of the results of purposeful activity in different conditions of social interactions is relevant and of high significance. The importance of this issue is underscored by the need to equip businesses with skilled professionals who possess the necessary competencies, including social abilities, in line with the evolving demands of the modern world, and also to increase the effectiveness of the educational process. Furthermore, it is crucial to safeguard the psychosomatic health of the general public, which is heavily influenced by societal factors throughout their lives and work relationships. The aim of the study was to examine changes in performance measures of sensorimotor training in different social contexts of activity in same-sex male and female pairs. *Materials and Methods:* Sixty-five pairs of men and 63 pairs of women (age 19 years 7 months ± 3 months) were examined, using the sensorimotor training "Columns" of the hardware-software complex "BOS-Kinesis" (Neurotech LLC, Taganrog, Russia). The research protocol included performing the tasks in different social contexts: individually, competitively, and collaboratively with a partner in conditions with and without feedback from participants' actions. *Results and Discussion*. Three groups of subjects were identified according to the indicator of maximum performance in three individual trainings: high-, medium-, and low-performers. In competition, an increase in productivity was observed in the latter two groups. Sex differences were found in the proportion of subjects with initially low performance who improved performance in competition: their % was significantly lower among men than in the sample of women. In interpersonal sensorimotor coordination with feedback from partners' actions, males had a significant decrease in personal performance and pair integral outcome measures, in contrast to female dyads. In cooperation without feedback

from participants' actions, a decrease in personal and integral performance was found for all pairs of subjects, but it was more significant in male dyads. *Conclusion.* Changes in result indicators in the joint contexts in dyads of subjects were determined by their initial individual performance levels and differed significantly between male and female pairs.

Keywords: performance, sensorimotor activity, social context, competition, cooperation, dyads

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Introduction

The study of the effectiveness of joint activities of people in various social conditions is an important problem of modern psychophysiology, which requires an interdisciplinary study of social, psychological and neurobiological mechanisms for achieving the results of purposeful human behavior in society [1, 2]. Work in this area has high practical significance in terms of increasing the efficiency of the educational process for schoolchildren and students [3], and providing enterprises with qualified personnel who meet modern professional requirements. In many professional fields, employees must have, in addition to special skills, so-called "non-technical" skills, which include the ability to establish optimal production relationships with colleagues and effectively interact with them to achieve a collective result. For example, such skills are necessary in the work of medical and rescue teams, for the coordinated activities of civil and military aviation crews [4, 5]. The development of measures to improve the social well-being of enterprise employees, young and elderly people helps to maintain psychosomatic health, increase the life expectancy of the population and improve labor productivity. In addition, understanding the characteristics of human interaction during sensorimotor activity, including interaction using technical devices in controlled movement processes, will contribute to the development of social and rehabilitation robotics and the development of software and hardware systems with artificial intelligence [6].

Competition and cooperation are the main forms of interaction in both interpersonal and professional rela-

tionships. In recent years, many studies have compared the performance of individual motor activity and that performed in various types of group interactions [7, 8]. The authors of studies that note an improvement in the effectiveness of joint activities compared to individual ones explain these positive effects by an increase in people's motivation [9], the ability to compare personal movements with the collective result of actions [10], the summation of physical efforts and the ability of partners to communicate and take specialized roles to solve assigned tasks [11].

It is known that cooperation facilitates the processes of motor learning and the development of motor skills by increasing the levels of internal motivation of participants and establishing positive interpersonal relationships [12]. Competitive conditions, on the other hand, reduce the perceived similarity between participants, which lead to attempts by one person to hinder the actions of another and reduce performance.

Studies have found inconsistent results when assessing the performance of participants in competitive and cooperative contexts in sport [13]. According to this study, the highest performance indicators of athletes were associated with dominance motivation, as opposed to the affiliative motive of belonging to a group. The observed decrease in a person's personal performance in team activities in a number of cases is also explained by "social laziness" that occurs when the actions of participants are anonymous, work is unevenly distributed among group members, and in other conditions that reduce the level of personal responsibility to the team [14].

Thus, studies of performance in the contexts of competition and cooperation are relevant; however, their results are contradictory and ambiguous, which is probably determined to some extent by the gender of the interacting subjects. During the evolution of human communities, as a result of intra-family and group interactions, different adaptive strategies and social roles of male and female individuals were formed, which influenced the levels of expression of different inter-gender socio-psychological characteristics of personality. It has been shown that men have a greater tendency to dominance and aggression in a social context; they are characterized by a more pronounced motivation for competition and a positive perception of the competitive conditions of interactions [15]. Women typically play a leading role in caring for offspring, not only their own, but also those of other family members or groups. During the evolution of species, women have developed empathy and compassion, the ability to recognize the emotional states of others, and a tendency to cooperate to a greater extent than men. It has been shown that adaptive social strategies under stressful conditions also depend on gender: in men, such forms of behavior as "fight or flight" predominate, selfishness and competitiveness increase; for women, behavior of the "tend and befriend" type is more typical, with a focus on perceiving the feelings of others and a desire for mutual assistance [16].

Gender differences in performance were also identified in conditions of individual activity; for example, in a task of recognizing visual images with a fixed time and feedback from the results of one's own actions, the quality of task performance was also higher in men compared to women [17]. This study also shows the influence of the personal characteristics of the subjects on the success of goal-directed activity and the correlation of performance with the characteristics of physiological support, in particular, indicators of heart rate variability.

The main interrelated factors contributing to sex differences are thought to be hormonal, contextual (e.g. parental roles in the family), and sexual selection (e.g. mating patterns of the species) influences. Despite the results of the above studies, the author of a recent meta-analysis of long-term studies of the gender aspects of cooperation in social dilemma choice tasks came to the conclusion that there is no absolute evidence of differences in cooperative behavior between men and women [18].

Thus, the data from the scientific literature indicate a significant influence of social contexts of activity on its effectiveness, the efficiency of learning and the quality of interpersonal relationships. However, a lot of contradictory data is found, depending on the type and models of activity, the initial individual psychophysiological characteristics of people, personal qualities,

abilities and skills of a person, as well as the gender of the interacting subjects. Despite the large number of studies of joint activities, the influence of social contexts on personal and integral sensorimotor performance of the same subject's remains insufficiently studied. In connection with the above, further study of this problem is necessary; the study of the characteristics of achieving results of activities by the same people in different contexts of social interactions is relevant and has high fundamental and applied significance. The aim is to study changes in performance measures of sensorimotor training in different social contexts of activity in same-sex dyads of men and women.

Materials and methods

Objects of the study

256 healthy subjects, university students (65 pairs of men and 63 pairs of women, average age 19 years, 7 months ± 3 months), without uncorrected visual impairment, neurological and cardiovascular diseases in the anamnesis. Subjects who knew each other participated in the study in pairs on an unpaid basis. All subjects gave voluntary informed consent to participate in the study and consent to the processing of personal data in accordance with the Declaration of Helsinki of the World Medical Association (WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013).

Activity model

The "Columns" training was used as a model of sensorimotor activity, based on biological feedback from electromyographic signals (EMG) recorded from the flexor muscles of the hand of the subjects' leading hand using the "Kolibri" telemetry sensors of the "BOS-Kinesis" hardware-software complex ("Neurotech" LLC, Russian Federation, Taganrog). During sensorimotor training (SMT), a column with a dynamically changing height corresponding to the current amplitude characteristics of the EMG is displayed on the computer monitor. The subjects were required to maintain a level of muscle tension to keep the column height within the highlighted target range (50±10% of the maximum muscle tension recorded during EMG signal calibration), with the column colored green. When the height of the column is outside the target area (< 30%) its color changes to yellow, and if it is more than 30% high, it becomes red. Performance of the SMT was evaluated as a percentage of the duration of holding the column height in the target range of the total training time.

Study design

Subjects performed the SMT sitting at computer monitors at a distance of 80 cm at separate, side-by-side desks. The social contexts of the activity were set through changes in the task environment and additional instructions from the experimenter. In the individual SMT sessions, participants were separated by partitions and performed the training 3 times for 2 min with 20–30 sec rest pauses. Then, during the joint activity stages, the partitions were removed and subjects performed SMT at a common computer monitor.

During the competition, two separate resultant columns from the EMG signals of both participants were displayed on the screen, with a training duration of 3 min. The position of the personal columns corresponded to the seating of the subjects, and the competitors could see the color and height of both columns, allowing them to evaluate their own and others' current performance. Before this training participants were instructed to try to keep their bar height in the target range longer than their opponent. Cooperation conditions were created by presenting one common column on the monitor, the height of which corresponded to the integral resultant calculated from two personal columns of the participants in the software "BOS-Kinesis". In the first cooperative training (Coop+), subjects saw a personal contribution to the pair's overall performance, i.e., the height and color of their columns. In the second cooperative task (Coop-), subjects were shown a dynamic representation of the overall resultant column only. The durations of SMT in the cooperative context were also 3 min.

Statistical analysis

The data were analyzed for normality of distribution using the Shapiro-Wilcoxon, D'Agostino-Pearson and Kolmogorov-Smirnov methods. Non-parametric statis-

tical methods were used because the data distributions differed from normal. Changes in performance measures between different contexts were analyzed using the Wilcoxon criterion (Wil) and the Friedman method (Fr) with correction for multiple comparisons. Differences in performance between independent groups of subjects were tested using the Mann-Whitney (MU) test and the Kraskell-Wallis (KW) method with corrections for multiple pairwise comparisons. Chi-square method (Chi^2) was used to assess the significance of differences between the distributions of the number of subjects in different subgroups of samples of men and women, and between activity contexts. Relationships between variables were analyzed using Spearman's rank correlation coefficient (r).

Results and discussion

Each subject's maximum initial performance (Rmax-i) was defined as the result of the most successful attempt of the three individual SMTs. Three modes on the histogram of the distribution of the Rmax-i index for the whole sample were identified (97.5%, 87.5% and 77.5%). Based on this polymodal distribution, boundaries were defined to separate groups of subjects with different levels of individual performance: low-performers (Rmax-i < 83.75%), medium-performers (83.75%≤Rmax-i < 91.25%), and high-performers (Rmax-i≥91.25%).

The following distributions of participants in these groups during individual SMT were identified: the majority of subjects fell into the high-performance group (56.9% of males, 59.5% of females); 17.7% of males and 19.8% of females were medium performers, and 25.4% of males and 20.6% of females were low performers. These differences in the proportions of subjects between the groups of males and females in the individual activity stage are not reliable.

A significant correlation was found between Rmax-i and performance in competition (Rcomp) in the samples of all male ($r = 0.50$, $p < 0.0001$) and all female ($r = 0.52$, $p < 0.0001$) subjects. A comparative analysis of the dynamics of SMT performance in competition (Rcomp) in comparison with performance in individual stages (Rmax-i) for samples of all subjects and separately for men and women did not reveal any reliable changes. However, sex differences were found between the ratios of the shares of subjects in groups with different levels of performance in competitive activities compared to those in the individual stage. In the male sample, the percentage of high-performing participants decreased (53.8%), the percentage of medium performers did not change, and the percentage of low performers increased (28.4%). For women, there was a different pattern of change in the distribution of these groups: the proportions of high-performing (61.1%) and low-performing (23.0%) participants increased, while the proportions of medium-performing participants decreased (15.9%).

Differential analysis of the dynamics of performance in the competition compared to the performance of the individual stage in groups with different initial levels of success revealed the following reliable changes (Figure 1). In the group of initially high-performing subjects in the competitive context, Rcomp decreased significantly in both male ($p(Wil) = 0.0005$) and female ($p(Wil) = 0.0042$) samples. In the groups of initially average-performing subjects, changes in performance during competition are not reliable. Initially low-performing subjects had an increase in Rcomp during competition compared to Rmax-i, significant only for this group of women ($p(Wil) = 0.0024$).

Personal values of relative performance differences between competitive and individual performance contexts $\Delta R = (Rcomp-Rmax-i)$ were also analyzed. A significantly higher percentage of participants with an increase in performance in the competition condition was found in initially medium-performing (males, 43.5%, $p(Chi^2) = 0.0018$; females, 56.0%, $p(Chi^2) = 0.0001$) and low-performing (males, 54.6%, $p(Chi^2) = 0.0001$; females, 76.9%, $p(Chi^2) = 0.0001$) subjects, compared to initially high-performing participants (10.8% males and 12.0% females). Significant differences were found in the distributions of the proportions of participants with different directions of change in performance during the competition compared to the individual activity stage between initially low-performing men and women ($p(Chi^2) = 0.093$). This category of subjects showed a significantly higher percentage of female participants

with an increase in performance in competition (76.9%) compared to the same group of males (54.5%). In 36.4% of initially low-performing men, performance decreased further in competitive conditions and only 11.5% of initially low-performing women showed a similar dynamic.

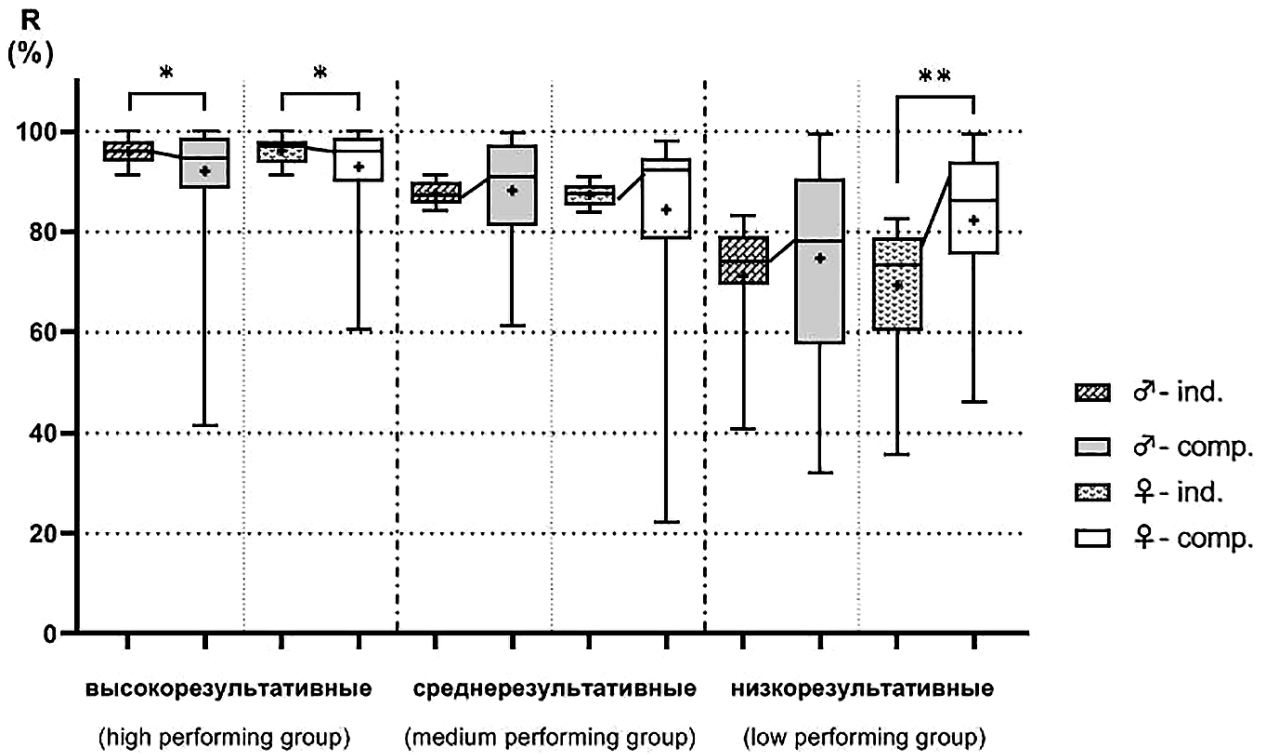

Fig. 1. Dynamics of the SMT performance in individual (ind., shaded boxes) and competitive (comp., unshaded boxes) contexts of activity in groups of young men (♂, gray boxes) and young women (♀, white boxes). The abscissa axis shows groups of high-, medium- and low-performance subjects. The ordinate axis shows the performance indicator (% of maintaining the column in the target range). Levels of reliable differences * — $p < 0.05$, ** — $p < 0.01$

The results of the comparative analysis of personal performance in individual, competitive and cooperative activity conditions are shown in Figure 2. Changes in SMT performance in the different activity contexts were significant in the samples of males (stat(Fr) = 172, p(Fr) < 0.0001) and females (stat(Fr) = 182, p(Fr) < 0.0001). A pairwise comparison of performance between samples of males and females in different social contexts of SMT revealed an overall reliability of differences (stat(KW) = 392, p(KW) < 0.0001).

Significant sex differences were found in both cooperative activity conditions. The performance of SMT in conditions of cooperation in a sample of men significantly decreased compared to individual and competitive contexts: with feedback from the partners' contribution (p(Wil) < 0.05) and without feedback (p(Wil) < 0.0001). The performance of SMT in a sample of women did not change in conditions of cooperation with feedback from the participants' contribution and was significantly higher than that of men (p(MU) = 0.0002). In the conditions of cooperation without feedback, women also showed a decrease in performance compared to previous contexts (p(Wil) < 0.0001), but the level of performance was significantly higher than that of men (p(MU) = 0.021).

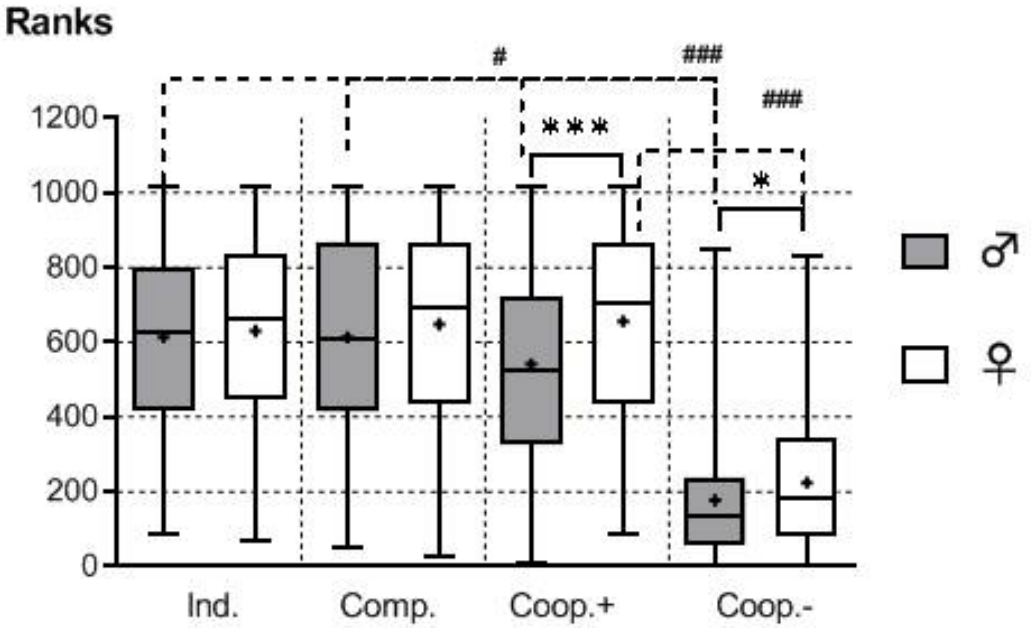

Fig. 2. Performance indicators in groups of men (♂, grey boxes) and women (♀, white boxes) in different contexts of sensorimotor activity: individual (Ind.), competitive (Comp.), cooperative with feedback (Coop.+) and without feedback (Coop.-) from the partners' actions. Abscissa axis — contexts, ordinate axis — performance ranks. Designations: box boundaries — upper and lower quartiles, lines in boxes — medians, crosses in boxes — means, whiskers of boxes — minima and maxima. Reliability of differences: asterisks — between samples of boys and girls * — p(MU) < 0.05, *** — p(MU) < 0.0001; hashes — between contexts # — p(Fr, Wil) < 0.05, ### — p(Fr, Wil) < 0.001

Based on the values of personal performance of the SMT in conditions of cooperation with feedback from the contribution of partners, all subjects were divided into high-, medium- and low-performance participants, similar to the division of participants at the individual and competitive stages. The ratios of the proportions of subjects with different levels of success in three activity contexts are presented in Figure 3.

In cooperation, the percentage of high-performing men decreased (to 40.8%), and the percentage of medium- and low-performing men increased (to 23.1% and 36.2%, respectively), which was significantly different from the distribution of subjects at the individual stage of training ($p(Chi^2) = 0.033$). In cooperation, the proportion of women participants with personal high performance increased (66.1%), while the percentage of of medium- and low-performance women decreased. Reliable differences ($p(Chi^2) < 0.001$) were found in these ratios of the proportions of subjects with different levels of performance in cooperation between samples of men and women.

Correlation analysis revealed significant correlations between personal performance in cooperation with feedback from partner contributions and performance in individual activity conditions in both male (r=0.36, p<0.0001) and female (r=0.40, p<0.000001) samples. An even stronger correlation was found between performance in this cooperative context and competitive performance in both males (r=0.46, p<0.0001) and females (r=0.60, p<0.00001). Women's personal performance in cooperation without feedback from participant contribution was also significantly correlated with individual (r=0.23, p=0.009) and competitive (r=0.42, p<0.0001) performance, whereas these correlations were absent in the male sample. Performance between the two cooperative contexts was significantly correlated in

females (r=0.37, p=0.0002) and more weakly correlated in males (r=0.20, p=0.02).

Next, we analyzed the values of the integral performance of pairs during cooperation (Ri,%), which corresponds to the percentages of the duration of holding the common column in the target range from the SMT time (Figure 4). The distributions of the Ri index differed significantly between samples of dyads of males and females ($p(\text{Chi}^2) = 0.0039$) during cooperative activity in the condition of presenting feedback from partners' actions. This difference indicates a shift in the mode of the distribution of the integral performance of male pairs towards lower values compared to female pairs, with the mode of the Ri index ranging from 90–100% in 60% of female dyads. This fact is also supported by the result of non-parametric comparison of Ri values of two independent samples of male and female dyads ($p(\text{MU}) = 0.0002$).

Integral performance Ri in cooperative conditions without feedback from the personal contribution of partners was significantly reduced in both male and female dyads. However, it remained significantly higher in female pairs than in male dyads ($p(\text{MU}) = 0.0216$), and 40% of female pairs had Ri over 75%. Thus, the integral result of pairs in cooperation was higher in female dyads compared to male dyads because it was determined by the more successful personal contributions of female participants.

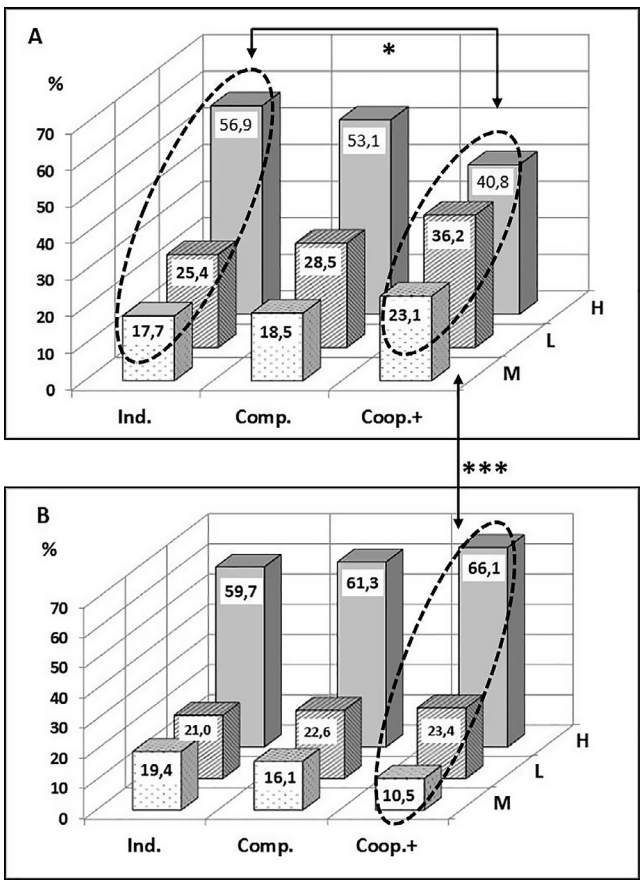

Fig. 3. Distributions of subjects in groups with different performance levels (H – high, M – medium and L – low) among men (A) and women (B) in different contexts of sensorimotor activity. The abscissa axis shows the contexts: individual (Ind.), competitive (Comp.) and cooperative with feedback from the contribution of partners (Coop.+). The ordinate axis shows the% of subjects in groups. Asterisks indicate reliable differences between the distributions highlighted by dotted ovals:
* – $p(\text{Chi}^2) < 0.05$, *** – $p(\text{Chi}^2) < 0.001$

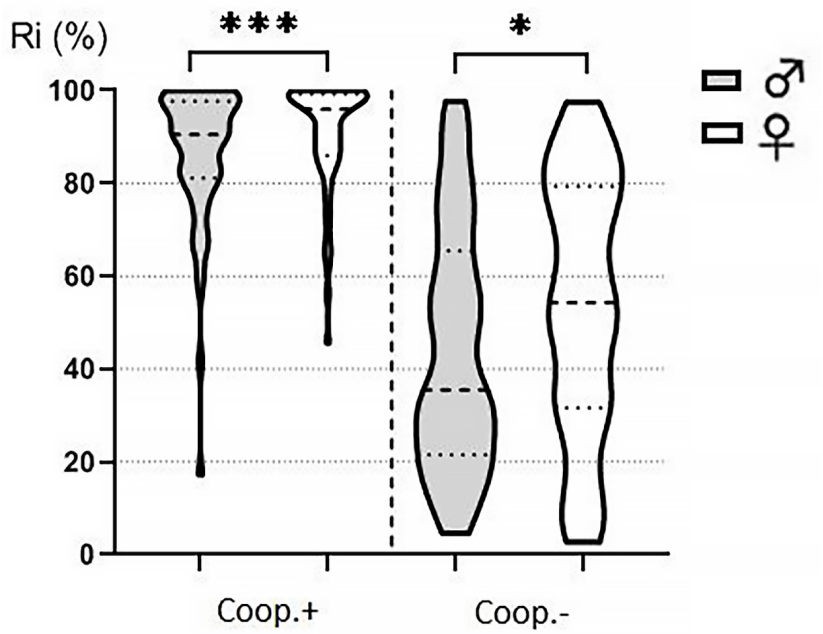

Fig. 4. Violin diagrams of distribution of integral performance of cooperative activity in pairs of men (♂) and women (♀) with feedback (Coop.+) and without feedback (Coop.-) from partners' actions. Significance of differences: * – p(MU) < 0.05, *** – p(MU) < 0.001

All subjects (both male and female) were divided into three groups according to their individual SMT performance: high-, medium-, and low-performers. In sensorimotor tasks of the static type, subjects are required to have a high level of motor self-control of behavior, which depends on the degree of emotional arousal, impulsiveness and characteristics of motor activity of individuals. The absolute values of the subjects' performance in the competitive context of the trainings and its relative changes were related to the initial level of performance achieved in the individual activity conditions. Gender differences were found between males and females with initially low SMT performance: a higher proportion of these female participants had increased performance compared to the corresponding group of males.

It has been shown that in competitive activity conditions, dominance motivation and the desire to compete are the leading factors of performance, especially in men [13, 15]. In these conditions, the level of attention and control over one's own and others' actions increases. It has been shown that men, compared to women, have more pronounced changes in EEG parameters and characteristics of evoked potentials of cortical structures of subjects during competition, reflecting neurophysiological mechanisms of greater sensitivity to errors made by both the subject and his opponent [19]. In addition, the subject's observation of the behavior and activity tactics of the more successful opponent in the dyad during the competition may also contribute to improving his or her performance of the SMT. However, in the sample of initially low-performing men, a rather high percentage of subjects were found who further reduced their performance in the competitive context. It is likely that these young men were exposed to social stressors in a competitive context related to comparing their own and others' current performance and errors, which led to increased psycho-emotional arousal and negatively affected subjects' performance through negative feedback [20]. A more reliable prediction of a person's competitive success requires an assessment of baseline personality characteristics, impulsivity and self-control of behavior, as well as the degree of dominance of individuals' behavioral inhibition or activation systems in situations of stress.

Analysis of the personal performance of subjects in dyadic cooperative conditions revealed significant differences between samples of men and women. In cooperative conditions with feedback from participants' contributions, performance did not change in the female group and was accompanied by an increase in the proportion of high-performing participants, higher than in the male group. Reduced performance was found in the female sample only in co-operative conditions without feedback from personal contributions, while remaining significantly higher than in the male sample. The findings of women's higher performance in cooperative settings compared to men are consistent with studies [15, 16] that have demonstrated women's greater propensity for empathy and cooperation.

The data of correlation analysis of performance indicators in different contexts of SMT show their greater conjugation in the sample of women than in men. It is shown that conditions of cooperative activity without feedback from partners' actions cause disorganization of sensorimotor activity in men with a significant decrease in performance, independent of the results of previous training in other contexts.

Monitoring one's own and others' performance during cooperative interactions is crucial for effective mutual behavioral adaptation and interpersonal coordination. In the process of performing a common task, when participants assign roles and do complementary parts of the work, each of them has a holistic perception and integrated representation of their own and other participants' actions, as if the whole activity were being performed by him/herself [21]. This phenomenon is called the social Simon's effect, after the test in which it was discovered. It has been shown that common representations arise predominantly in the process of interpersonal coordination, while competitive conditions of activity reduce such integration [22]. It was found that the indicators of motor coordination of a person with another subject demonstrating movements on the screen depended on the gender and emotions of the presented avatar [23]. The Simon's effect has been shown to be more pronounced in women than in men, and the female participants were also more strongly influenced by environmental factors not directly related to the activity [24]. The same study found that women's response speed was slower than men's, although there was no difference in accuracy. It has also been found that reaction times after one's own mistakes and the accuracy of task performance after observing the erroneous actions of others are modulated by the social context and depend on the gender of the subjects [20]. In men, changes in indicators of decision-making processes, including characteristics of evoked potentials of the brain, were more pronounced in a competitive context, while in women — in conditions of cooperation.

Some authors explain gender differences in the level of empathy, behavioral and neurophysiological indicators in the process of social interactions by neuroanatomical features of the functioning of the mirror neuron system, which plays a key role in ensuring the processes of interpersonal coordination [25, 26]. There is also evidence that gender differences in performance and decision-making characteristics in competitive and cooperative conditions of activity can be determined by the different sensitivity of men and women to positive and negative reinforcement factors [27].

Conclusion

Thus, the results of the study of the levels and dynamics of the effectiveness of subjects' performance of sensorimotor training in individual and joint conditions indicate gender differences associated with the different influence of social factors on the success of competitive and cooperative activities in dyads. In cooperation, women have significantly higher indicators of both personal and integral dyadic performance compared to men. In a sample of men, joint conditions of activity, especially cooperative ones, cause a decrease in personal and integral performance, as well as a decrease in the number of high-performing and an increase in the number of low-performing subjects.

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Результативность сенсомоторных тренингов в различных социальных условиях деятельности мужчин и женщин в моногендерных парах

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Аннотация. *Актуальность*. Исследование особенностей достижения человеком результатов целенаправленной деятельности в разных условиях социальных взаимодействий актуально и имеет высокую научно-практическую значимость. Высокая практическая значимость обусловлена необходимостью обеспечения предприятий квалифицированными кадрами, соответствующими нарастающим современным требованиям к компетенциям и навыкам, включая социальные, а также для повышения эффективности образовательного процесса школьников и студентов. Кроме того, актуально поддержание психосоматического здоровья населения, которое существенно зависит от влияния социальных факторов в процессе жизнедеятельности и характера производственных отношений. Цель исследования — изучить изменения показателей результативности выполнения сенсомоторных тренингов в разных социальных контекстах деятельности в однополых парах мужчин и женщин. Материалы и методы. Обследовано 65 пар мужчин и 63 пары женщин (19 лет 7 мес ± 3 мес), с использованием сенсомоторного тренинга «Столбики» программно-аппаратного комплекса «БОС-Кинезис» (ООО «Нейротех», Таганрог, РФ). Протокол исследования включал выполнение задания в разных социальных контекстах: индивидуально, конкурентно и в сотрудничестве с партнером в условиях с обратной связи от действий участников и без нее. *Результаты и обсуждение.* По показателю максимальной результативности за три индивидуальных тренинга определились три группы испытуемых: высоко-, средне- и низкорезультативные. При соревновании увеличение результативности наблюдалось в двух последних группах. Обнаружены половые различия в доле испытуемых с исходно низкой результативностью, которые улучшали показатели результативности деятельности в конкурентных условиях: их % был достоверно ниже среди мужчин, чем в выборке женщин. При межличностной сенсомоторной координации с обратной связью от действий партнеров у мужчин происходило достоверное уменьшение персональной результативности и показателей интегрального результата пар, в отличие от женских диад. При сотрудничестве без обратной связи от действий участников выявлено снижение персональной и интегральной результативности всех пар испытуемых, но более значимо в мужских диадах. *Выводы*. Изменения показателей результативности в совместных контекстах деятельности в диадах испытуемых определялись их исходными уровнями и достоверно различались между мужскими и женскими парами.

Ключевые слова: результативность, сенсомоторная деятельность, социальный контекст, соревнование, кооперация, диады

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