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ОБЗОР
REVIEW

Deciphering the role of angiotensin converting enzyme2 in health and diseases

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Abstract. *Relevance.* Angiotensin converting enzyme 2 (ACE 2) is recognised as a significant regulator of cardiovascular and pulmonary homeostasis owing to its involvement in the renin-angiotensin system (RAAS). This extensive review addresses ACE 2's conventional role in converting Angiotensin II (Ang II) to the Angiotensin-(1–7) to its broader implications in cardiovascular illness, pulmonary pathology, metabolic diseases, and cancers. *Conclusion.* Recent research has shed light on ACE2's significance beyond its enzymatic capabilities, specifically as a cellular receptor of various pathogens. Furthermore, recent evidence shows that ACE2 is involved in inflammation, glucose metabolism, and gut microbiome modulation. The tissue distribution patterns, regulatory mechanisms, and therapeutic possibilities show its dual role as a protective factor in and a possible entryway for the viral infections. Understanding these multiple processes in health and disease state serves to be essential in establishing tailored treatments for the diseases. This review outlines the existing understanding of ACE 2 and emphasizes areas for further research, notably its potential as a therapeutic target. Furthermore, we have discussed the challenges and future directions in ACE2-based therapeutics.

Keywords: ACE2, angiotensin converting enzyme 2, health, ailments, physiology, CVS, pulmonary, renal, cancer, immuno, skin, gut, neuro, ocular

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Significance/review highlights

- ACE2 regulates the Renin-Angiotensin System (RAAS), influencing cardiovascular, pulmonary, renal, and metabolic health.
- ACE2 serves as both a protective enzyme and a viral receptor, playing a crucial role in COVID-19 pathophysiology.
- ACE2 exhibits neuroprotective and endocrine regulatory functions, impacting brain health, insulin metabolism, and reproduction.
- ACE2 plays a dual role in cancer biology, with potential implications for tumour progression and therapeutic interventions.
- Therapeutic targeting of ACE2, including recombinant ACE2 and gene therapy, holds promise for multiple diseases.

Introduction

ACE 2 perform crucial role in the RAAS, that is essential for blood pressure regulation, electrolyte balance, fluid, along with systemic vascular resistance [1].The discovery of ACE 2 and the axis of ACE2/Ang (1–7)/Mas receptor has broadened our awareness of the RAAS's wider significance in health and illness, although it has traditionally been known for its function in cardiovascular physiology and pathophysiology. The global SARS-CoV and SARS-CoV-2 coronavirus outbreaks, along with the plethora of research findings as a response to subsequent COVID-19 pandemic, have revealed a fresh element of ACE 2's effects on living tissues and organs.

Donoghue et al. (2000) first characterized ACE 2 as a homolog of ACE (angiotensin-converting enzyme), highlighting its unique enzymatic properties [2]. Subsequent studies provided detailed crystallographic evidence of its molecular structure, revealing critical zinc-binding sites essential for its catalytic activity. A zinc-containing metalloenzyme is ACE 2 which is a membrane protein that occupies various organs that include the heart, gut, lungs, along with kidneys.

ACE 2 is extensively expressed in heart, kidneys, lungs, along with intestines, indicating its significant role in the cardiovascular, renal, respiratory, and gastrointestinal systems [3, 4]. ACE 2 is a transmembrane glycoprotein consisting of 805 amino acids that is a monocarboxypeptidase type I. It was identified in 2000 and shares sequence similarities with two other proteins,

collectrin and ACE. The highly polymorphic ACE 2 gene is found on Xp22 [5]. ACE 2 functions as a regulator for the RAAS system (Figure 1) to maintain homeostasis in addition to serving as an anchoring tool for SARS CoVs to attach to host cell membranes for fusion.

ACE 2 acts as a counterbalance to ACE, comprising an N-terminal peptidase domain (PD) along with a CLD (C-terminal collectrin-like domain), which terminates with a single transmembrane helix and an approximately 40 residue intracellular region, that makes up the full-length ACE 2. Through the PD, ACE2 cleaves Ang II to produce Ang-(1–7). Additionally, ACE 2 can cleave Ang I to create Ang-(1–9), that is subsequently transformed into Ang-(1–7) by other enzymes. This action not only minimizes levels of Ang II but also enhances levels of Ang (1–7), contributing to the balance of vasodilation and vasoconstriction [6].

ACE 2/Ang (1–7) axis exerts its physiological impact primarily through Mas receptor, a G protein-coupled receptor. This interaction promotes anti-fibrotic, vasodilation, anti-inflammatory, as well as anti-proliferative impact, which contrasts with the actions mediated by Ang II through AT1 receptor, causing vasoconstriction, inflammation, fibrosis, and cell proliferation. ACE 2/Ang (1–7) axis is also intricate in metabolic regulation, contributing to glucose and lipid metabolism [6–10].

ACE 2 being the RAAS regulator, we should be able to better understand how drugs like ACE inhibitors (ACEIs) along with ARBs (angiotensin receptor blockers) work. This would further deepen our comprehension of the pathophysiology connected to this biological system, like RAAS. In addition, the pandemic has increased the significance of immunohistochemistry-based morphological studies to pinpoint the location of ACE 2 positive cells and alterations in their distribution. Given the protective roles of ACE 2, there is significant interest in developing therapeutic strategies that enhance their functions. These include Ang (1–7) mimetics, ACE 2 activators, as well as Mas receptor agonists.

Thus, we undertook a review to provide a deep knowledge of ACE 2 that represents a vital counter-regulatory arm of the RAAS, with significant implications on health and diseases. And hence understanding the mechanisms and effects of

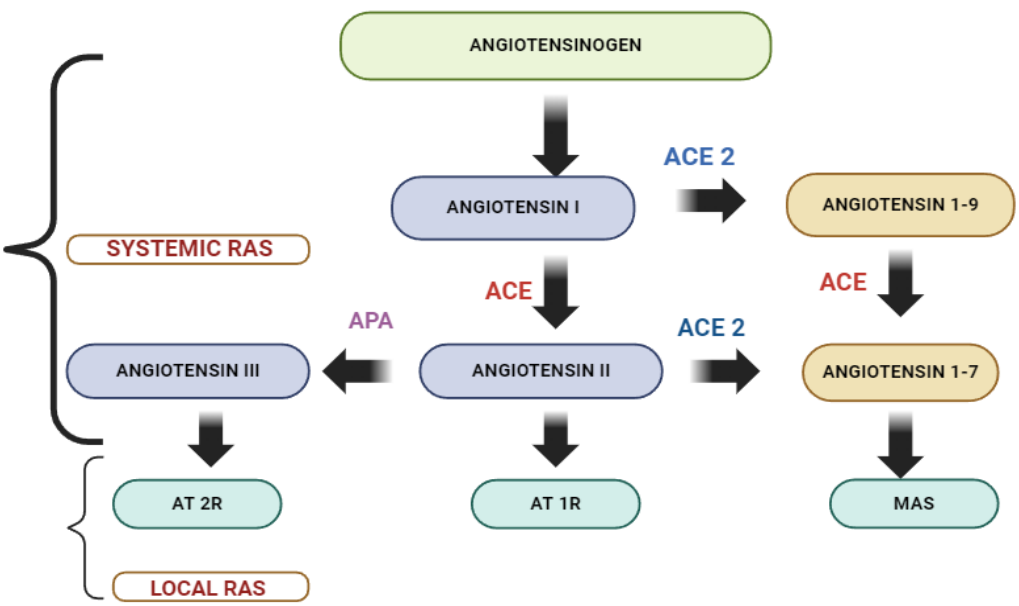

Fig.1. Cascade of Renin Angiotensin System (RAS)

ACE 2/Ang (1–7) axis continues to be an area of active research, with potential for developing new therapeutic strategies for range of diseases.

Cardiovascular functions of ACE 2 and linked diseases

As a component of the RAAS, ACE 2 is essential to cardiovascular physiology. The structural chimeric protein known as ACE 2 is the result of the 2 gene duplication: homology with ACE at the carboxypeptidase domain along with homology with Collectrin at the transmembrane C-terminal domain. ACE 2 is extremely expressed in heart [11], particularly in cardiomyocytes and fibroblasts. ACE 2 metabolises angiotensin II into Ang (1–7), shifting the balance from vasoconstriction and sodium retention (mediated by angiotensin II) towards vasodilation and natriuresis (Figure 2). This shift performs a vital role in blood pressure regulation, fluid balance, essential for both cardiovascular and renal health. ACE 2 undergoes three processes that contribute to ACE 2's protective benefits: (i) Ang I to Ang 1–9 degradation, which reduces amount of substrate available for the ACE activity; (ii) Ang II degradation, which lessens its harmful impact; and (iii) Ang 1–7 production that actually produces cardioprotective effects. The Ang II/AT1R axis is activated by decreased ACE 2 activity, which accelerates the progression of heart disease. Activation of ACE 2/Ang 1–9 and ACE 2/Ang 1–7 axes result from elevated ACE 2 level and activity, which protects against heart disease [12].

Significant roles are performed by the ACE 2 enzyme along with its product, the angiotensin (1–7) [Ang (1–7)], in the pathophysiology along with potential management of hypertension, a significant risk factor for cardiovascular diseases [13].Their actions provide a counter-regulatory mechanism to classical RAAS, which is recognized for controlling blood pressure through vasoconstriction, sodium retention, and aldosterone secretion. ACE 2 is extensively distributed in addition to other members of the systemic RAAS. Localised regions of ischemia/reperfusion (RAAS) are seen in cardiovascular tissues, and ACE 2 mRNA is expressed in diversity of cell types, such as coronary microcirculation.

Common mechanisms of ACE 2 in hypertension include *Vasodilation* where Ang (1–7) primarily exerts vasodilatory effects by the Mas receptor [13]. This action counters the vasoconstriction mediated by angiotensin

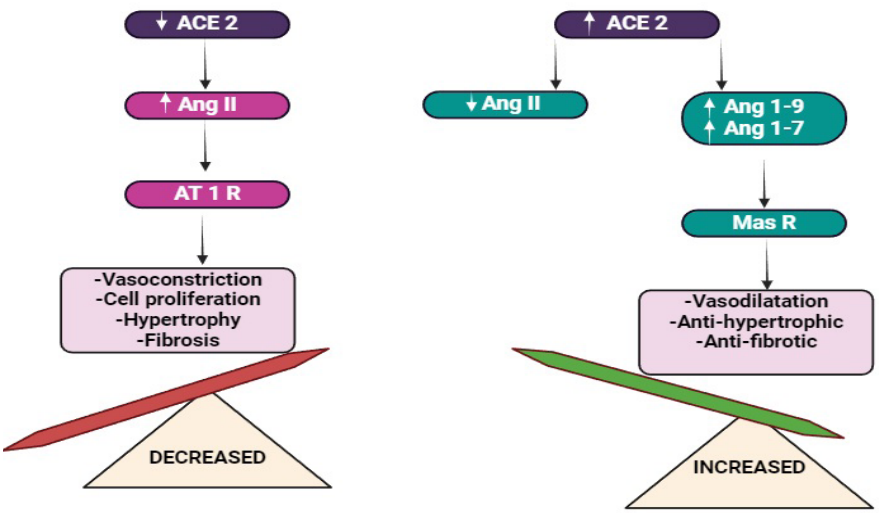

Fig. 2. ACE 2 shift paradigm. Decreased ACE 2 increases disease progression. Increased ACE 2 leads to protection from diseases

II (Ang II), thus contributing to blood pressure reduction [9, 13]; furthermore, Ang (1–7) reduces aldosterone secretion, which in turn decreases sodium and water retention, lowering blood pressure. The RAAS inhibition's impact on the renal sodium along with potassium excretion can be explained by the synergistic effects of Ang II and aldosterone on sodium along with potassium transport in distal nephron. Moreover, anti-fibrotic and anti-inflammatory effects of the Ang (1–7) reduce inflammation and fibrosis in cardiovascular system, which are pathophysiological mechanisms involved in hypertension and its complications [14] and in addition to all these mechanisms Ang (1–7) enhances endothelial function by promoting release of nitric oxide (NO), an effective endothelium-derived relaxing factor. Improved endothelial function is connected with better vasodilation and blood pressure regulation [14] Apelin, a crucial modulator of blood pressure and myocardium contractility, is one of the other vasoactive peptides that ACE 2 affects. ACE 2 mitigates myocardial remodelling and fibrosis by declining Ang II levels and rising Ang-(1–7), that acts through Mas receptor to inhibit hypertrophy and inflammation.

Given their roles in regulating blood pressure and vascular function, ACE 2 along with Ang (1–7) have therapeutic potential in hypertension management. ACE 2 Activators strategies to increase ACE 2 activity could enhance Ang II to the Ang (1–7) conversion, thus counteracting Ang II-mediated inflammation, protecting against oxidative stress along with endothelial dysfunction, shifting the balance towards vasodilation, reducing blood pressure both of which are implicated in conditions like hypertension and atherosclerosis. Ang (1–7) mimetics or Agonists can directly administer Ang (1–7) or drugs that mimic its action can be a therapeutic approach to harness its antihypertensive effects. Studies show that ACE2 prevents plaque instability by reducing inflammation in coronary vessels, offering potential therapeutic benefits for ischemic heart disease. Hence, circulating ACE2 levels may serve as biomarkers for early detection of cardiovascular dysfunctions, including heart failure and atherosclerosis.

Interestingly, Ang (1–9), a significant byproduct of ACE 2-mediated Ang I degradation, has newly demonstrated encouraging cardioprotective benefits [15] in the animal models of hypertension, myocardial infarction.

ACE 2 in pulmonary homeostasis and respiratory diseases

Over the years, the ACE2 has emerged as a critical molecular player in understanding lung physiology, inflammatory processes, and respiratory pathogenesis. The olfactory bulbs in the respiratory tract have the highest levels of ACE 2 gene expression, followed by the nasal respiratory epithelium, the bronchioles, and the alveoli. Research demonstrates that ACE2 expression in the lungs can be weakly detected at the protein level. By effects mediated through the Mas oncogene and the Ang (1–7) receptor, ACE-2 has been shown to have an established protective role in lung disease [16] Research shows that ACE2 protects against ALI (acute lung injury) and ARDS (acute respiratory distress syndrome) [17]. Experimental models of ALI demonstrate that downregulation of ACE 2 exacerbates lung damage, while its overexpression reduces oedema, inflammation, and oxidative stress. While ACE2/Ang-(1–7)/Mas axis, that inhibits the ACE/AngII/AT1R axis' activity, has been demonstrated to protect against the pulmonary fibrosis (PF), upregulation of the ACE/AngII/AngII type 1 receptor (AT1R) axis aggravates PF [17, 18]. Through balancing proapoptotic Ang II in addition to its antiapoptotic degradation product Ang 1–7 by its impact on Ang 1–7 and the MAS receptor, ACE-2 controls the survival of alveolar epithelial cells.

ACE 2 and SARS CoV infection: Ever since COVID-19 pandemic, the role of ACE2 has attracted a lot of attention and research. For virus that causes SARS CoV infections, ACE 2 serves as primary cellular receptor for the SARS-CoV-2 [19].Hence modulating ACE2/Ang (1–7) axis may have therapeutic benefits in ailment of illness.

Viral entry mechanism: The virus's spike S protein has a high affinity for ACE 2, facilitating its entry into cells (Figure 3). The interaction between the virus and ACE 2 performs a vital role in viral entry as well as subsequent infection. SARS-CoV-2's spike (S) protein

has a strong affinity for ACE 2. On host cell surface, S protein's RBD (receptor-binding domain) selectively binds with ACE 2 [20]. The SPIKE protein S is broken down into its S1, S2 subunits through host protease TMPRSS2 (transmembrane protease serine 2), this permits the virus to fuse its membrane with host cell's membrane [21].In order for the viral RNA to replicate in host cell's cytoplasm, this step is necessary.

It is demonstrated that interaction between SARS-CoV-2 and ACE 2 reduces ACE2 expression on cell surfaces. Although S2 subunit and ACE2 are responsible for membrane fusion and virus internalisation, the S1 subunit aids the virus in attaching to target cells in the epithelium. The expression of ACE 2 on the cell surface is significantly decreased when the extracellular juxta region of ACE 2 is cleaved, leading to internalisation and shedding [22, 23].The Ang II conversion into the protective Ang is slowed down by the reduction of ACE 2 expression at the cell surface brought on by ACE 2 internalisation (1–7). A rise in the Ang II to Ang (1–7) ratio exacerbates lung damage caused by SARS-CoV-2. Ang II causes tissue inflammation through the action of T-cells, mesangial cells, macrophages, dendritic cells, along with vascular smooth muscle cells. A deficit of ACE 2 has been identified in persons with several clinical disorders. Furthermore, the advancement of inflammation and thrombosis is favoured by the COVID-19 viruses binding to ACE2 receptors, membrane fusion, viral entrance into the cell, and subsequent downregulation of these receptors. This reduction in ACE2 can exacerbate imbalance among ACE/Ang II/AT1 receptor axis in addition to the ACE2/Ang (1–7)/Mas receptor axis, leading to increased inflammation, vascular permeability, and lung injury that include ARDS [24] hallmarks of severe COVID-19. Thus, interplay between ACE 2 and SARS viruses highlights its dual role in viral entry and disease progression, making it a crucial target for therapeutic interventions.

Renal functions and kidney diseases of ACE 2

Given its significant functions in RAAS balance, function of ACE2 in renal physiology and pathology has drawn interest, particularly in conditions for example CKD (chronic kidney disease), diabetic nephropathy, and hypertension-related kidney dysfunction [25]. Enzymatically ACE 2 converts Angiotensin II to the Ang (1–7) and is predominantly distributed in proximal tubular cells, glomerular endothelial cells, podocytes and

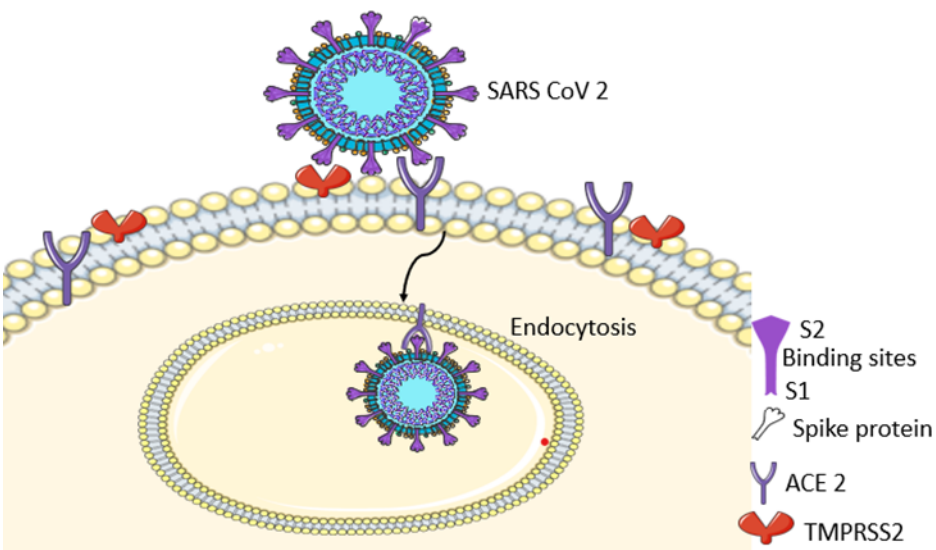

Fig. 3. Viral entry mechanism

in renal vasculature ACE 2 mitigates the impact of Ang II through reducing its concentration, thus preventing Ang II-mediated vasoconstriction of renal arterioles and promoting renal blood flow. Angiotensin-(1–7), the product of ACE2 activity, promotes natriuresis, diuresis, and vasodilation, all of which are protective for renal function [26].In renal tubular cells, ACE 2 modulates sodium and water reabsorption. This activity indirectly influences blood pressure regulation and fluid balance.

ACE 2 in Kidney Disease Pathology

Evidence shows that in healthy kidneys, high constitutive levels of ACE 2 and an increased ACE 2/ACE ratio are associated with a mechanism that is more important for breaking down Ang II than for producing it. This system is critical for maintaining the usual physiological and biological effects of Ang II [27]. The underlying causes of renal fibrosis and CKD progression are associated with abnormalities in RAAS, particularly ACE2/Ang (1–7) axis. A major contributor to the pathophysiology of CKD is ACE 2, which proposes potential therapeutic targets for condition's management and treatment. The characteristic of CKD is a steady decline in kidney function over time, which elevates blood pressure, causes waste products to build up in the body, and ultimately increases the chance of renal failure. Reduced ACE 2 expression exacerbates Ang II-mediated renal damage, contributing to inflammation, fibrosis, and glomerular hypertension. Animal studies have demonstrated that ACE 2 overexpression or supplementation with Ang-(1–7) can attenuate CKD progression [28].

Angiotensin II (Ang II), that stimulates vasoconstriction, fibrosis, inflammation, along with brine retention, is among the primary ways that the RAAS makes a contribution to CKD development [29].Angiotensin-(1–7), a product of ACE 2 (Figure 4) counteracts inflammation and fibrosis within the kidney, processes that are exacerbated by excessive Ang II activity in pathological conditions.ACE 2 functions as a counter-regulatory enzyme inside the RAAS. Through doing this, the detrimental impacts of Ang II on the kidneys are mitigated and renal function continues to improve.

Fibrosis, a condition where the kidneys' excessive connective tissue accumulates and impairs their function, is a defining feature of CKD. ACE 2 can reduce fibrosis through declining Ang II levels along with increasing Ang (1–7), that directly opposes fibrotic processes [30]. Inflammation contributes significantly to the progression of CKD. By declining Ang II levels whereas increasing Ang (1–7), ACE2 helps to dampen inflammatory responses in the kidney. Low expression of ACE2 might have contributed to the CKD progression, through

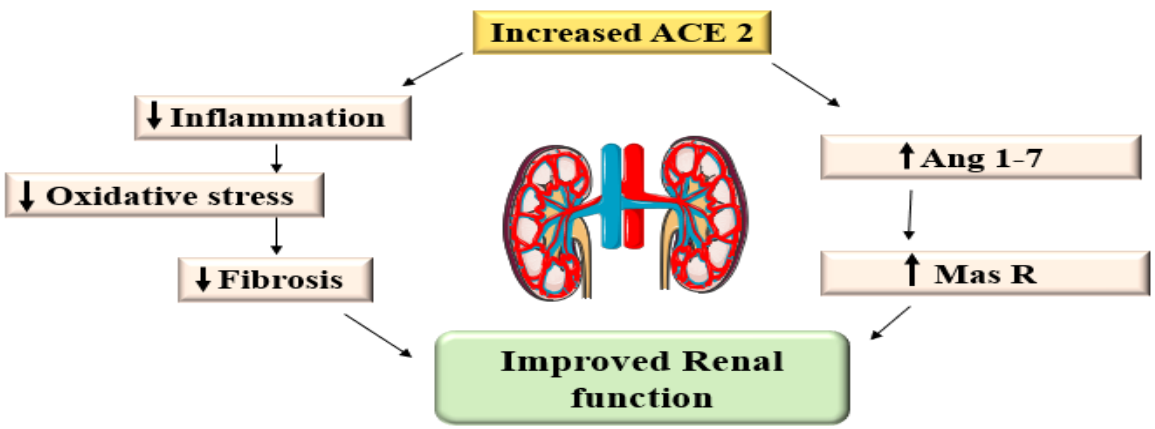

Fig. 4. Increased ACE 2's activity in renal wellness

improving early inflammation as well as contributing to the long-term fibrosis [29].High blood pressure is a cause while a consequence of the CKD. Dysregulated RAAS, with low ACE2 and high Ang II levels, made a contribution to the hypertension-induced renal injury development. ACE 2 improves kidney function by influencing glomerular hemodynamic, reducing glomerular hypertension, and thereby mitigating one of the key factors that contribute to CKD progression.

Furthermore, males had lower levels of ACE2 expression in both renal compartments than females [31]. ACE2 gene is situated on X chromosome; nonetheless, X inactivation is expected to mitigate any influence on ACE2 expression.One risk factor for CKD development is male sex. Though primarily linked to impact of the sex hormones on the kidney cells, variations in expression of ACE2 might also be partially responsible for this uneven risk [30].Acute Kidney Injury (AKI) is associated with a loss of ACE2 activity, leading to heightened Ang II activity and inflammatory responses. Experimental data suggest that restoring ACE 2 expression or activity may provide renal protection in AKI. The kidney-protective function of the ACE2/Ang (1–7)/MAS axis is supported by animal studies that demonstrate that vascular ACE 2-overexpression protects the kidney against ageing-induced decline in the kidney function [32].

ACE 2 in hormonal regulation

The ACE 2 has emerged as a crucial molecular mediator with profound implications across multiple endocrine systems. Originally characterized as a major component of the RAAS, recent research has unveiled its complex roles in hormonal regulation, metabolic homeostasis, and systemic physiology [33,34].The enzymatic activity of ACE 2 serves as a critical regulatory mechanism across multiple endocrine axes, demonstrating sophisticated molecular plasticity. Furthermore, ACE 2 performs complex interplay between hormonal systems and their variables between the individuals.

Aldosterone mechanism

Angiotensin-converting enzyme 2 has revealed complex regulatory mechanisms that significantly impact aldosterone secretion beyond traditional RAAS (renin-angiotensin-aldosterone system) paradigms. Traditionally, aldosterone secretion is mediated through: Angiotensin II (Ang II) stimulation, activation of AT1R (angiotensin II type 1 receptor), direct stimulation of zona glomerulosa cells in adrenal cortex. Whereas ACE 2 performs a critical role in modulating this classical pathway by enzymatic conversion of Ang II to the Ang (1–7), declining available Ang II for aldosterone stimulation creates a competitive inhibition and serves as a counter-regulatory mechanism. ACE 2 introduces numerous nuanced control mechanisms through Complex Regulatory Signalling. Acting as a molecular rheostat in aldosterone secretion ACE 2 provides dynamic, context-dependent regulation of zona glomerulosa cell responsiveness. Low tissue levels of the ACE-2 are not enough to generate enough Ang-(1–7) to regulate the release of cortisol and aldosterone, according to a study [35].Rodriguez, M., et al. discovered that ACE2 reduces pro-inflammatory signals in adrenal tissues thereby causing inflammatory modulation of Aldosterone secretion resulting in protective mechanisms against hyperaldosteronism [36].Precise molecular mechanisms of ACE 2 in aldosterone mechanism are currently uncertain.

Metabolic syndrome

Current investigation has offered more nuanced insights into metabolic implications of ACE2/Ang (1–7) signalling in insulin resistance. Chen et al. demonstrated that Ang (1–7) supplementation in animal models of metabolic syndrome significantly improved insulin sensitivity by enhancing mitochondrial function in adipose tissue, reduction in inflammatory markers associated with insulin resistance and modulating adipokine secretion [37].

Endocrine disruption and ACE 2 signalling

Emerging research has highlighted the vulnerability of the ACE2 axis to endocrine hormonal axis. Studies are investigating the impact of endocrine-disrupting chemicals on ACE 2 expression. Specific environmental toxins that downregulate ACE 2 activity demonstrated

potential mechanisms of hormonal axis disruption suggesting long-term metabolic consequences of chronic exposure [38].

Hypothalamus and pituitary system

Current investigations have highlighted ACE2's sophisticated interactions with the hypothalamic-pituitary system. Oliveira's animal model study demonstrates that corticotropin-releasing hormone cells exhibiting elevated ACE 2 expression were protected against hypoxia-induced pulmonary hypertension. Given that the majority of CRH expression takes place in brain nuclei for example the PVN (paraventricular nucleus of the hypothalamus) or else central nucleus of the amygdala (CeA), these findings imply that the protective effects of ACE 2 may be somewhat centrally mediated [39]. ACE 2 controls CRH (corticotropin-releasing hormone) release, that subsequently controls stress response mechanism and affects the neuroinflammatory processes in the hypothalamus. Evidences shows that increased expression of ACE 2 in the brain increases nitric oxide and antioxidant signalling, decreases oxidative stress as well as COX-mediated neuro-inflammation, slows the onset of neurogenic hypertension [40,41]. A number of investigations are currently underway to explore the molecular processes behind ACE2's potential in buffering hypothalamic inflammatory responses mediated by neuroendocrine stress adaptations.

Pancreatic Endocrine function and Insulin Resistance

Metabolic studies have revealed intricate ACE 2 connections in pancreatic endocrine regulation. ACE 2 is expressed by the islet microvasculature, pericytes, acinar, ductal, along with beta cells in the pancreas. Through essential enzymes, for example, ACE 2 and angiotensin, local RAAS in the pancreatic islet controls glucose homeostasis (1–7). Various physiological and endocrine roles of ACE 2 include upregulation of mitochondrial genes, mitochondrial metabolism in beta cells, secretion of insulin in existence of ROS, declines NADPH oxidase properties and ROS production, regulates rise in beta cell mass as well as adaptive hyperinsulinemia response to high-fat diet, enhance total insulin content in the islets, improves proliferation of beta cell along with prevents apoptosis[42,43,44]. ACE 2 /Ang (1–7)/Mas axis modulates Insulin secretion, protects from the oxidative stress thereby playing a pivotal in glucose homoeostasis [42]. Reduced ACE2 expression, which is prevalent in diabetes, increases RAAS activity and exacerbates fibrosis and inflammation [43]. A meta-analysis revealed that ACE 2 genetic variants correlate with increased risk of type 2 diabetes showing altered glucose metabolism and differential response to metabolic interventions.

Reproductive health

Preliminary studies and recent investigations have expanded our understanding of ACE2's role in reproductive physiology. ACE 2 is expressed in the testes and ovaries, and its activity influences the production of sex hormones such as testosterone and oestrogen [46,47,48,49].Decreased ACE2 expression correlates with age-related reproductive decline and also observed for potential protective mechanisms in ovarian aging and Implications of ACE 2 expression for fertility preservation strategies [48].

Growth Hormone regulation

Growth Hormone Regulation of ACE 2, while direct evidence is limited, the general influence of the RAAS on growth hormone (GH) secretion and the counter-regulatory effects of ACE 2 might suggest a role in modulating GH release.

Thyroid function and Inflammatory modulation

RAAS components, encompassing ACE2 and Ang (1–7), are expressed in thyroid gland, indicating potential roles in thyroid hormone synthesis and secretion [50]. Thyroid hormones are crucial for regulating metabolism, growth, and development. The precise impact of ACE2 and Ang (1–7) on thyroid function remains an area of active research. Advanced research has provided deeper insights into ACE2's inflammatory regulatory mechanisms. Studies demonstrate mechanistic links between RAAS components and thyroid inflammation. Study by Narayan et al examined the Thyroid tissue

ACE 2 expression and its potential utilization as a biomarker for the detection of thyroid cancer. ACE 2 were significantly increased in goitres, follicular adenomas, follicular thyroid carcinomas, papillary thyroid carcinomas, undifferentiated thyroid carcinomas [51]. ACE2 is regulated within thyroid benign and malignant tissues. The differentiation grade of thyroid cancer is correlated with increase in ACE 2. These complex mechanisms of ACE 2 suggest promising potential therapeutic implications for autoimmune thyroid diseases.

Immunomodulation

The role of ACE 2 extends by encompassing significant immunomodulatory effects. ACE 2 works on the MAS receptor, produces Ang (1–7) and declines the synthesis of pro-inflammatory cytokines and chemokines to produce anti-inflammatory effects. This modulation of the inflammatory response can be beneficial in conditions characterised by excessive inflammation [52]. ACE 2 regulates immune cell function through Ang (1–7) by modulating the function of various immune cells, that include neutrophils, macrophages, T cells. Macrophages perform a crucial role in the innate immunity, inflammation, and tissue repair. They exist in a spectrum of activation states, from pro-inflammatory (M 1) to the anti-inflammatory (M 2), depending on the cytokine environment and other signals [53]. Ang II tends to promote the M1 phenotype, which is characterized by the release of pro-inflammatory cytokines that include TNF-α, IL-6, and IL-1β, via acting on the AT1 receptor [54–56]. In contRAASt, ACE 2, has been shown to promote the M 2 phenotype [57], which is involved in tissue repair and inflammation resolution. This suggests that the balance among pro-inflammatory and anti-inflammatory macrophage phenotypes is modulated by ACE 2, thereby influencing the course of inflammatory responses. This aligns with the finding that monocyte/macrophage overreactions contribute to the hyperinflammation or cytokine storm observed in severe COVID-19 cases [58, 59].

T cells are central to adaptive immunity, with various subsets playing roles in immune regulation, cytotoxic responses, and help for B cells in antibody production. The RAAS, particularly through Ang II, has been shown to influence T cell function directly. Ang II can promote T cell proliferation and the cytokines production. ACE 2, by reducing Ang II levels, may indirectly modulate T cell responses, promoting a shift towards less inflammatory states [60].Additionally, Ang (1–7) can have direct effects on T cells, though this area requires further research to fully understand the mechanisms and implications. Key participants in the early stages of the inflammatory response are neutrophils, capable of rapid deployment to sites of infection or injury. While the direct effects of ACE 2 on neutrophils are less well characterised than those on macrophages and T cells, the overall anti-inflammatory milieu promoted by ACE 2 activity could lead to a modulatory effect on neutrophil recruitment and function [61]. For instance, reducing Ang II levels may decrease vascular permeability and adhesion molecule expression, potentially modulating neutrophil extravasation to inflamed tissues.

Beyond macrophages, T cells, and neutrophils, ACE 2 may also influence the function of other immune cells, for example, B cells, dendritic cells, along with NK (natural killer) cells [62].The overall anti-inflammatory and immunomodulatory effects of ACE 2 suggest that it could perform a role in shaping activities of an extensive variety of immune cells.

The relevance of ACE 2 in infectious diseases became prominently recognized during the COVID-19 pandemic, as ACE 2 is entry receptor for the SARS-CoV-2 [63].When SARS CoV-2 is present, the immunological responses of ACE 2 cause tissue and organ damage, coagulopathy, along with ARDS. These conditions then trigger the production of further proinflammatory cytokines and chemokines, causing an uncontrollable loop of inflammation and damage [64].While the interaction of the virus with ACE 2 can lead to downregulation of ACE 2 expression and enhanced lung injury, the immunomodulatory role of ACE 2 suggests that enhancing this pathway could potentially mitigate severe inflammatory responses associated with infections [65].

Deregulation of ACE 2 may enhance kinin activity while resulting in angioedema [66].Systemic kallikrein-kinin system activation can cause a "kinin storm," which can lead to vascular permeability, enhanced inflammation, effusion, along with eventual damage to organs [67].One of the main causes of endothelial damage, microthrombi development, and the ischemic symptoms that follow COVID-19 is RAAS dysregulation [68].

ACE2/Ang (1–7)/Mas axis may perform a role in modulating autoimmunity. Its anti-inflammatory properties suggest potential therapeutic benefits in autoimmune diseases by dampening inappropriate immune responses against self-tissues [69,70]. Through declining Ang II levels and improving Ang (1–7) levels, ACE 2 can reduce the inflammatory milieu that fosters autoimmune reactions, potentially mitigating the severity of autoimmune diseases. The exact impact of ACE 2 on specific autoimmune diseases that include, multiple sclerosis, rheumatoid arthritis, type 1 diabetes, requires further research. However, the potential for ACE 2 to modulate immune responses suggests that enhancing ACE 2 activity or Ang (1–7) signalling could be a promising therapeutic strategy in autoimmunity.

ACE 2 in central nervous system

With all of its parts found in CNS (central nervous system), the brain has its own intrinsic RAAS [71]. Originally identified as a regulator of blood pressure along with cardiovascular homeostasis, ACE 2 also modulates brain function through its effects on neurovascular health, oxidative stress, and inflammatory pathways. The brainstem, hypothalamus, and cortex are among the areas of the brain where ACE 2 is expressed [72]. It performs a crucial role in neurovascular regulation by counteracting the effects of angiotensin II (Ang II), a peptide known for its pro-inflammatory and vasoconstrictive properties. ACE 2 boosts vasodilation, anti-inflammatory effects, along with neuroprotection by converting Ang II to angiotensin-1–7 (Figure 5) [73].

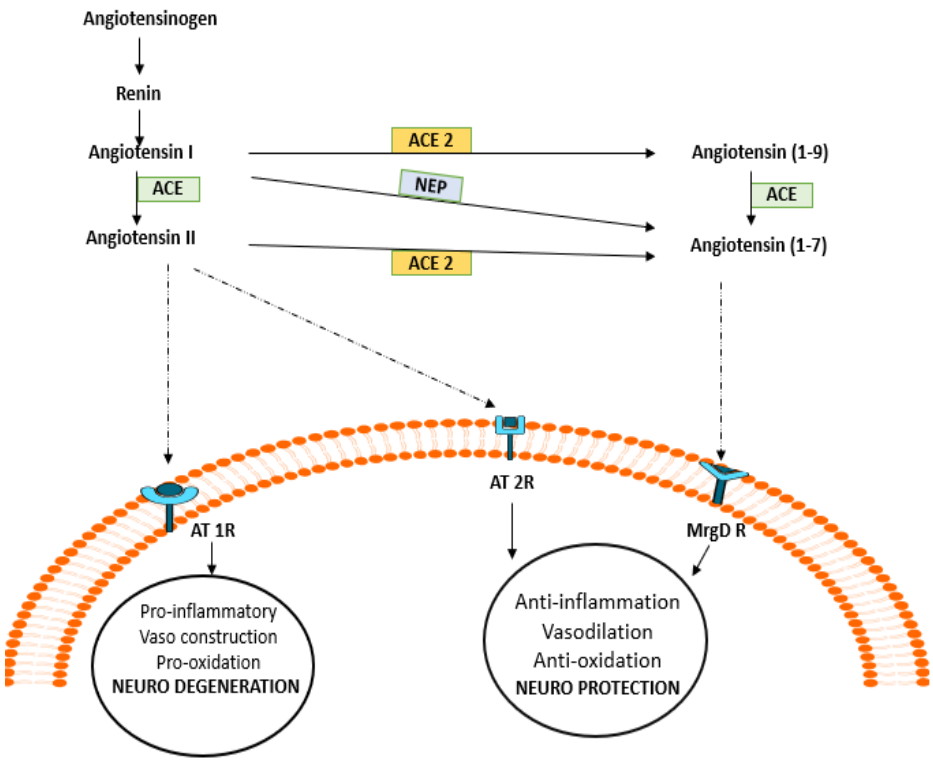

Fig. 5. Role of Renin Angiotensin System on the neurosystem

Along with these traditional RAAS pathways, few other channels are recognized that aid in the synthesis of various angiotensin and angiotensin fragments. Renin and pro-renin receptors have even been demonstrated to exhibit biological activity. In addition to Ang-(1–7), ACE 2 also generates alamandine, a peptide similar to Ang-(1–7) that selectively activates the MrgD receptor. These interactions are critical for maintaining neurovascular integrity and counteracting the detrimental impact of Ang II in the brain [74].

Neuroinflammation and oxidative stress are central to pathology of many neurodegenerative diseases (NDD), that include PD (Parkinson's disease), MS (multiple sclerosis), along with AD (Alzheimer's disease) [75]. ACE 2 reduces neuroinflammation by modulating the balance among pro-inflammatory along with anti-inflammatory pathways in the RAAS [76]. According to research on animals, ACE 2 activation can lower microglial activation and the generation of pro-inflammatory cytokines that include TNF-α, IL-6. MrgD activation decreases the pro-inflammatory cytokines production that includes, IL-6, TNF-α, whereas promoting anti-inflammatory cytokines that include IL-10. This modulation helps counteract neuroinflammatory effects of Ang II [77].

Overexpression of ACE 2 in the CNS has been shown in recent years to enhance GABA release in the presynapse, altering its neurotransmission and function to enhance mice's anxiety [78].The amygdala, paraventricular hypothalamic nucleus, nucleus of the solitary tract, along with ventrolateral medulla are among the brain regions that endogenously express both ACE 2 and MrgD (Figure 6). These regions regulate behavioral and physiological reactions to stress and anxiety [79]. The amygdala, a part of the brain that regulates the behavioural expressions of fear and anxiety, had more MasR mRNA when ACE2 was overexpression.Kehoe et al and his colleagues have found reduced ACE2 expression in brains of AD patients, causes increased Ang II activity and exacerbation of neuroinflammatory and neurotoxic pathways [78]. Angiotensin(1–7) has been shown to boost memory as well as decline amyloid-beta accumulation in the animal models of AD. On the same hand, ACE 2 protects dopaminergic neurons by reducing oxidative stress and inflammation. Studies suggest that enhancing ACE 2 activity may offer neuroprotective benefits in PD [77]. The MrgD receptor, through ACE2-derived peptides, reduces oxidative stress by enhancing antioxidant defense and lowering reactive oxygen species (ROS) levels. This mechanism is predominantly relevant in NDD for example AD and PD. In relation to ischaemic stroke, ACE2 has been extensively studied. Its activation lessens cerebral ischemia-reperfusion injury by lowering disruption of the BBB (blood-brain barrier), attenuating neuroinflammation, and triggering angiogenesis [79].

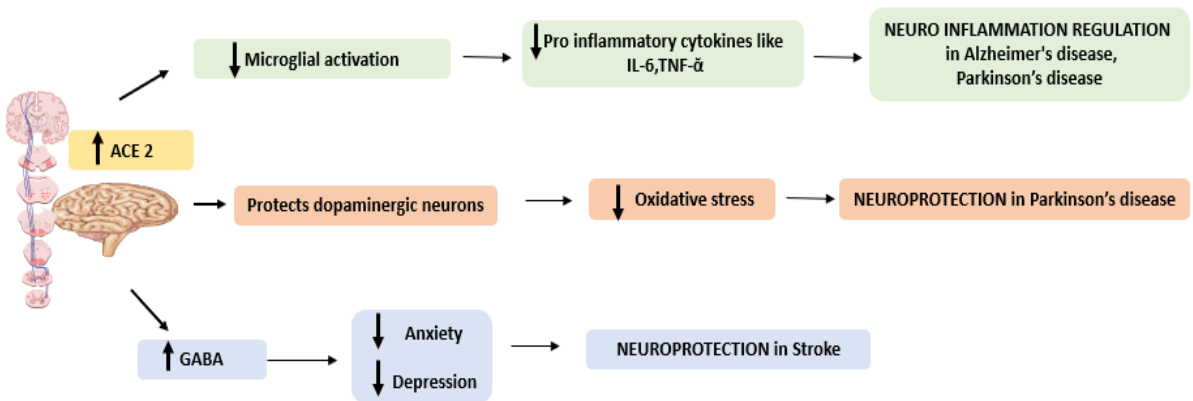

Fig. 6. Physiological process of ACE 2 -neuroprotection, neuroinflammation regulation plays an important role in AD, Parkinson's disease, stroke, anxiety and depression

ACE2 and gut

ACE2/Angiotensin-(1–7)/Mas receptor axis, as the renin–angiotensin–aldosterone system's (RAAS) non-canonical arm, plays a very important role for gastrointestinal homeostasis [80]. ACE2 controls the gut microbial balance and the nutrient absorption plus the immune responses and epithelial integrity, and ACE2 is expressed mainly on the enterocytes' luminal surface and on the intestinal epithelial cells' apical surface inside the intestinal tract. ACE2 presence within Paneth cells and within goblet cells implies secretory with immunological roles inside of the gastrointestinal tract.

ACE2 eases in a physiological way the uptake of neutral amino acids by way of transporter B^0AT1 plus particularly tryptophan (Figure 7). ACE2 greatly helps nutrient absorption within the healthy gut. Its control over the neutral amino acid transporter B^0AT1 (SLC6A19) stands out most [81]. For mucosal immunity along with gut-brain axis regulation, bioactive molecules from tryptophan metabolism are needed in epithelial regeneration. Tryptophan levels that are adequate secrete mucins with antimicrobial peptides, so they maintain intestinal epithelial defence as well as supporting gut mucosal immunity. For regulation of pancreatic insulin-producing β cells, amino acid Tryptophan activates enteroendocrine L cells so that they release GLP-1 and GIP. The GLP-1 and GIP do also inhibit glucagon-producing α cells with this having an effect upon plasma glucose levels [82, 83].

In addition, ACE2 converts pro-inflammatory angiotensin II into angiotensin-(1–7), through the Mas receptor exerting vasodilatory, anti-inflammatory, and cytoprotective effects within the gut. This conversion decreases the epithelial damage by helping tight junction protein expression and reducing intestinal permeability, thereby preserving the mucosal barrier. Angiotensin-(1–7) also promotes mucosal blood flow and attenuates the production of pro-inflammatory cytokines such as TNF-α and IL-6, while supporting the release of anti-inflammatory mediators. Through these mechanisms, the ACE2/Ang-(1–7)/Mas axis suppresses intestinal inflammation and supports tissue repair. This signalling pathway indirectly modulates the overall

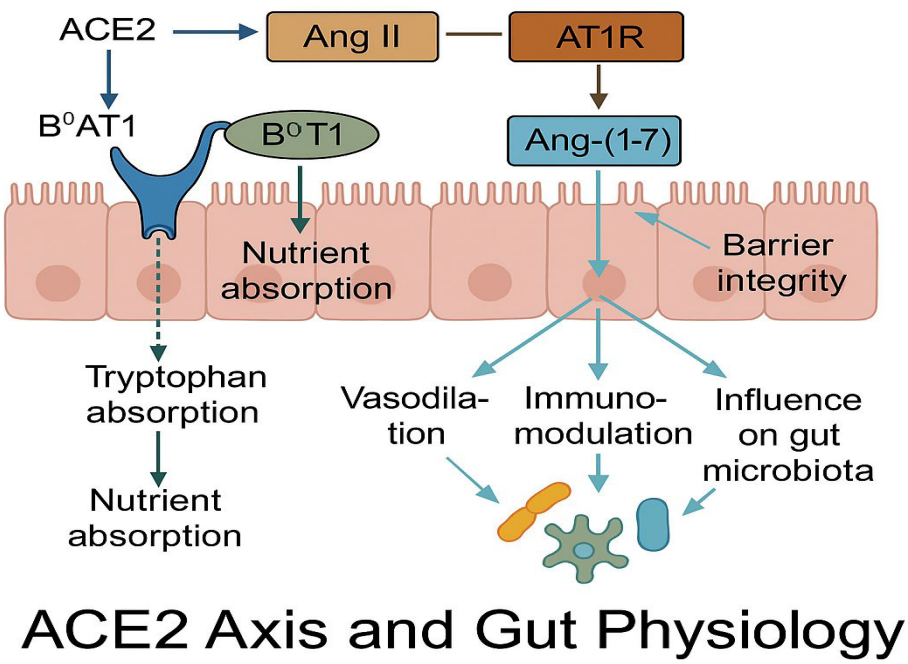

Fig. 7. ACE2 axis and gut physiology

composition and function of the gut microbiota by maintaining a favourable immune environment and controlling nutrient availability.

Reduced ACE2 expression causes dysregulation of this axis leading to excessive angiotensin II activity resulting in impaired barrier function, microbial dysbiosis, and chronic inflammation. Such disruptions have been implicated in a range of gastrointestinal disorders, including inflammatory bowel disease, ischemic colitis, and infection-associated enteropathies.

ACE2 in Gastrointestinal Disorders

Altered ACE2 expression is implicated in a spectrum of gastrointestinal diseases. In inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis [84, 85]. ACE2 dysregulation has been associated with increased inflammation and this intestinal inflammation is induced by epithelial damage disrupted barrier function, and altered cytokine profiles.

In Crohn's disease, ACE2 expression in the inflamed ileum was 60% lower than in healthy patients [86].However, colonic ACE2 expression was shown to be elevated in Crohn's disease patients. In Patients examined with inflammatory bowel disease (IBD), ACE2 and TMPRSS2 were found to be highly expressed in the ileum and colon. However, inflammation is associated with a considerable downregulation of epithelial ACE2 [86, 87].

Systemic infections like SARS-CoV-2, viral binding to the ACE2 receptor causes subsequent downregulation of ACE2 on gut epithelial surfaces. Symptoms such as diarrhoea, nausea, and intestinal inflammation have been reported during SARS CoV2 infections. These gastrointestinal symptoms were correlated with more severe pulmonary disease as patients required ventilatory support [86]. Altering ACE2 axis through genetic deletion, pharmacological inhibition, or disruptions by viral interactions such as SARS-CoV-2-mediated ACE2 internalization have been associated with increased intestinal inflammation, epithelial damage, and microbial imbalance [86].

ACE2 and the Gut Microbiome

The influence of ACE2 on the gut microbiome and metabolome profiles is now a higher concern. ACE2 regulates the microbial environment of the intestine through regulation of amino acid transport and immune mediators. Experimental models have demonstrated that ACE2 deficiency leads to microbial dysbiosis, characterized by a shift toward pathogenic species and a reduction in beneficial commensals. Studies have proved that upregulation of ACE2 may reverse these effects by improving stress state, mitochondrial dysfunction, and IRS-1/Akt/AMPK signalling [87]. Experimental study shows that ACE2 deficiency affects the microbiota and gut-vascular integrity by decreasing angiogenic bone marrow components in diabetes, perhaps inducing bacterial translocation [88].These findings collectively underscore the ACE2/Ang-(1–7)/Mas pathway as a critical regulator of gut physiology and a promising therapeutic target for inflammatory and infection-related gastrointestinal disorders.

ACE 2 in cancer biology

A growing understanding of the RAAS role in cancer biology has led to focus extensively on the role of ACE 2 in carcinogenesis. Although ACE 2 has been shown to be inhibitory, diminishing angiogenesis during tumour growth by preventing cell division and causing cell death, evidence also indicates that ACE 2 dysregulation may promote growth of tumour [89]. ACE 2 in cancer is complex and appears to be context-dependent, varying across different types of cancer. ACE 2 counter-regulates the impact of classical RAAS pathway, which is known to promote cell proliferation, angiogenesis, inflammation, and fibrosis [90].It seems that ACE 2 protects against the development of cancer; its up-regulation implies a favourable prognosis, and it is negatively linked to several important tumour development pathways, particularly proliferation and mismatch repair.

Research supporting the tumour-suppressive role of ACE 2 includes studies across several cancer types, that include lung, colorectal, breast, along with pancreatic cancers [91]. Higher expression levels of ACE 2 have

been associated with better survival outcomes in certain cancers. Conversely, a decline in ACE2 expression or activity, causing an unchecked angiotensin II signalling pathway, has been correlated with tumour growth, metastasis, and poor prognosis. Research has shown that ACE2 is down-regulated in a number of tumours, that include breast tumours [92], non-small cell lung cancer (NSCLC) [93], pancreatic ductal adenocarcinoma (PDAC) [94] along with gallbladder cancer [95]. Declined *ACE 2* expression had been also stated in Hepatocellular carcinoma.

RAAS pathway is inhibited through ACE 2 converting angiotensin II, a peptide that promotes proliferation and angiogenesis, into Ang (1–7), which has both antiproliferative and antiangiogenic properties. This switch shifts the balance from a pro-tumorigenic to a tumour-suppressive environment; Ang (1–7), a product of ACE 2 activity, inhibits cancer cell proliferation via the Mas receptor. This signalling pathway can promote apoptosis- programmed cell death, cause cell cycle arrest, and limit cancer cell proliferation, all of which contribute to tumour suppression [96].

Angiogenic factors often mediate tumour angiogenesis. ACE 2 also inhibits angiogenesis, that is new blood vessel formation, that tumours need for oxygen and nutrients to grow and metastasize [97]. The VEGFa/VEGFR2/ERK pathway may be involved in the mechanism through which ACE 2 inhibits the angiogenesis of cancer. By preventing phosphorylation of ERK1/2, ACE 2 reduces the production of VEGFa in the cancer cells, indicating that ERK signaling pathway controlled by ACE 2 was involved in the regulation of VEGFa [97]. It was established by research that VEGFa in tumour cells would attach to VEGFR2 on the nearby endothelial cells' membrane. This speeds up the phosphorylation and activation of VEGFR2, which in turn causes the ERK signaling pathway to becoming phosphorylated and activated. Following this, MEK1/2 is phosphorylated and activated by a cascade reaction from the ERK pathway, which in turn promotes phosphorylation and activation of ERK1/2. Consequently, nuclear translocation speeds up migration, differentiation, and proliferation, all of which support angiogenesis [98]. By limiting angiogenesis, ACE 2 activity can restrict tumour growth and spread. Through its anti-inflammatory and immunomodulatory effects, ACE 2/ang (1–7) axis might create a less favourable environment for tumour progression.

Beyond direct effects on tumour cells, ACE 2 also influences the tumour microenvironment, which includes extracellular matrix, immune cells, along with signalling molecules [99].The TME (tumour microenvironment), which affects growth, metastasis, along with response to treatment, is an essential factor in progression of cancer. It consists of various components, including stromal cells, cancer cells, signalling molecules, immune cells, n addition with extracellular matrix. Nature of ACE 2 influence is influenced by the specific tumour type and the balance of the RAAS components within tumour microenvironment [100, 101].

Understanding ACE 2's role in the TME involves examining its effects on cellular signalling, inflammation, angiogenesis, and the interplay between different cells within the tumour and its surroundings. ACE 2 influences the balance of angiotensin peptides in the TME, which can modulate inflammation — a key driver of tumour progression. ACE 2 acts by effect decreasing Ang II levels, thereby potentially limiting angiogenesis within the TME.

Several cancers, that include NSCLC, PDAC, clear cell renal carcinomas, thyroid carcinomas, colorectal adenocarcinoma, gastric adenocarcinoma, Oral Squamous cell carcinoma [102] shows decreased expression of ACE 2. This implies low levels of ACE 2 as the cancer progresses. In contrast, RT-PCR research revealed higher ACE2 mRNA expression levels in OSCC samples. These findings point to probable post-transcriptional regulation, protein degradation, or translational inhibitory mechanisms impacting ACE2 in oral squamous cell cancer.Invitro studies have shown that increased expression of ACE 2 may potentially suppress angiogenesis and invasion over the progression of cancer [103, 104].

Modulating ACE 2 activity levels could provide novel approaches for inhibiting tumour growth, reducing metastasis, and enhancing anti-tumour immunity [104]. However, developing such therapies

requires a nuanced understanding of the ACE 2 diverse roles in different cancers and their complexity.

ACE2 in ocular physiology

RAS components including ACE, ACE2 and Ang 1–7 has been shown to have significant levels of in several structures of the eye. Two key enzymes ACE and ACE2 being hot spots [105] in the renin-angiotensin system are highly expressed in epidermal basal cells and also detected in suprabasal and granular cells of the human aqueous humor [106]. ACE2 expression has also been detected in conjunctival cells and pterygium [107], an overgrowth of the subconjunctival tissue onto the corneal epithelium, multiple nonvascular neuroretinal cells, including the retinal ganglion cell layer, inner plexiform layer, inner nuclear layer, and photoreceptor outer segments in both nondiabetic and diabetic retinopathy specimens [108]. Ang II and ACE2 have been identified in both human limbal and corneal tissues. ACE2 being expressed in multiple ocular tissues, including the cornea, conjunctiva, aqueous humor, retina, and choroid, it plays a pivotal role in maintaining ocular homeostasis.

ACE2 in the anterior segment of the eye impacts aqueous humor dynamics and trabecular meshwork function, which has an effect on regulating intraocular pressure and protects against glaucomatous damage. In the posterior segment, ACE2 is highly expressed in retinal pigment epithelial (RPE) cells, Müller glia, and vascular endothelial cells. ACE/Ang II arm of the RAS system has been identified as the pro-inflammatory, pro-proliferative and pro-fibrotic axis in ocular physiology whereas ACE2/Ang 1–7 acts as counter-regulatory role as the anti-inflammatory, anti-proliferative and anti-fibrotic arm [109].Hence, the ACE2/Ang-(1–7)/Mas receptor axis modulates intraocular pressure, retinal blood flow, oxidative stress, and inflammatory signalling, thereby contributing to the preservation of visual function.

ACE2 plays regulatory role by regulating inflammation in varied ocular tissues. These anti-inflammatory effects of ACE2 are associated with the inhibition of MAPK, NF-κB and STAT3 pathways. An animal study by Wang et al shows that loss of ACE2 in the mouse cornea delayed the healing of corneal epithelial and the study suggest that ACE2/Ang1–7 axis has a translational potential in corneal re-epithelialization and also in preventing fibrosis [110]. Recent studies have proven that imbalance in Ang II/ACE2, might lead to increased inflammatory response in corneal epithelial and stromal tissues. Decreased ACE2 increases Ang II levels that leads to anti-fibrotic function in the cornea. Evidence shows that reduction in ACE2 levels causes also cloudy corneal haze which is accompanied by chronic inflammation, corneal edema and neovascularization.

Intraocular Pressure and ACE2

Studies have shown that intraocular RAS is involved in the regulation of intraocular pressure (IOP). In a study where the intrinsic ACE2 is pharmacologically activated has significantly decreased the Intraocular Pressure in glaucomatous rats. Hence, activation of intrinsic ACE2 may act as a potential therapeutic strategy to treat glaucoma [111].

Diabetic retinopathy

Increased activity of the ACE/ (Ang II)/AT1 receptor axis of the renin–angiotensin system (RAS) is associated with the pathogenesis of diabetic retinopathy. Studies have evaluated the retinal RAS gene expression in diabetic retinopathy shows decreased ACE2 expression that resulted in worsened pathophysiology of Diabetic Retinopathy. A study by Verma and colleagues [112] on rodent models showed that intravitreal administration of adeno-associated virus (AAV)- mediated gene transfer vector expressing ACE2 or Ang-1–7 peptide in the retina reduced diabetes-induced retinal pathophysiology.

Age-related macular degeneration

In an in vitro model study by Fu et al, overexpression of ACE2 reduces the inflammatory response in age-related macular degeneration (AMD) via inhibiting overproduction of cytokines such as IL-1β and CCL-2. By stimulating the ACE2/Ang-(1–7)/Mas axis in human RPE cells, overexpression of ACE2 reduces the inflammatory response brought on by Aβ [113].

All together ACE2 serves as a critical regulator of ocular vascular tone, neuroprotection, and anti-inflammatory signalling [120].And thus, targeting modulation of the ACE2/Ang-(1–7)/Mas axis represents a promising target for managing ocular pathologies ranging from glaucoma and diabetic retinopathy to viral conjunctivitis and AMD.

ACE2 in skin physiology

Angiotensin-converting enzyme 2 (ACE2) is an integral component of the cutaneous renin–angiotensin system (RAS) is expressed in several cells of the skin in keratinocytes, endothelial cells, fibroblasts, hair follicles, immune cells, lymphatic endothelial cells, melanocytes, and sweat gland cells. Hamming et al. [114] first showed the presence of ACE2 using immunohistochemistry staining in the skin, particularly in the basal cell layer of the epidermis extending to the basal cell layer of hair follicles. Smooth muscle cells surrounding sebaceous glands also shows positive forACE2 staining. ACE2 was weakly observed in sebaceous glands. The eccrine glands exhibit strong granular staining pattern for ACE2.

Functionally, ACE2 plays a significant role in modulating oxidative stress, inflammation, collagen degradation, and overall skin damage. ACE2 prevents oxidative stress by converting Ang II into Ang-(1–7). ACE2 reduces inflammatory mediators by downregulating Ang II by activating AT1 receptor. And also, ACE2 inhibits the matrix metalloproteinases (MMPs) activity through Ang-(1–7), and reducing collagen degradation [115].ACE2 also functions as a mechanosensitive protein.

Divergent ACE2 expression and activity has been associated with various dermatological pathologies. ACE2 protein expression was substantially upregulated in the epidermis of psoriasis lesions, especially in basal keratinocytes [116]. Increased *ACE2* expression in skin plaques was identified in psoriasis patients due to IL-17-mediated inflammation. In fibrotic conditions, including systemic sclerosis and keloids, impaired ACE2 signalling may promote fibroblast overactivation and excessive extracellular matrix deposition. Alterations in ACE2 protein affects skin soft tissue expansion, by changing cutaneous Ang II metabolism resulting from ACE2 modulation influence cellular function [117].

COVID skin manifestations

Cutaneous manifestations were increasingly observed during COVID-19. These cutaneous reactions may arise from both direct viral effects via ACE2-expressing epidermal keratinocytes, dermal vascular endothelial cells, and eccrine glands, as well as from indirect immune-mediated and microvascular injury mechanisms. They include upregulated innate immune human response, hypercoagulable state, and non- structural proteins in SARS-CoV-2 [118].They were presented as different dermatologic manifestations, which are maculopapular rash, papulovesicular rash, and livedo reticularis. Asymmetrical lesions like pernio-like (chilblain-like) acral lesions, often associated with microangiopathy and type I interferon responses; vesicular eruptions resembling varicella, suggestive of viral cytopathic activity; maculopapular (morbilliform) rashes linked to cytokine-mediated inflammation; and urticarial lesions driven by mast cell activation [119] were presented in many cases.

Emerging evidence shows ACE2 modulation to pigmentary changes through RAS-mediated effects on melanocyte biology. Studies suggests suggest that ACE2 activators, Ang-(1–7) analogs, or Mas receptor agonists may influence inflammation, accelerate wound closure, and reduce dermal fibrosis. However, experimental and clinical validation is required for targeting ACE2 axis in management of skin diseases.

Future perspectives

The outbreak of COVID-19 further expanded interest in ACE 2, for its potential as therapeutics. Hence this has fuelled the novel ACE2-based therapeutic strategies development, not only for viral infections but also for a range of cardiovascular, pulmonary, renal, cancer, and metabolic disorders.

a) Recombinant human ACE 2 (rhACE2) has been investigated as a treatment for cardiac disease, ARDS, ALI, and COVID-19. It reduces viral entry and restores RAAS balance by serving as an intermediary receptor

for SARS-CoV-2. Recombinant ACE 2 have shown several positive effects, including reversing pathological hypertrophy, improving endothelial dysfunction, reducing tissue inflammation and myocardial fibrosis, and correcting metabolic dysfunction. Recombinant human ACE 2 effectiveness in various disorders is being assessed in ongoing animal studies and clinical trials.

b) Synthetic novel compounds known as ACE 2 peptidomimetics mimic the structure and activity of Angiotensin Converting Enzyme 2. These compounds are being investigated for their potential in pulmonary hypertension, heart failure, hypertension, and SARS-CoV virus entry inhibitors.

c) Gene therapy-based approaches are gaining attention as innovative strategies to restore ACE 2 function in various diseases. This method involves the introduction of a functional ACE 2 gene into target cells to restore its protective effects. These techniques aim to either upregulate ACE 2 expression or deliver functional ACE 2 to counteract pathological conditions such as hypertension, heart failure, ARDS, and COVID-19 related complications.

d) mRNA-based strategies involve delivering synthetic mRNA encoding ACE 2 to cells, allowing temporary but effective expression of functional ACE 2. This strategy has gained momentum due to the success of mRNA vaccines in COVID-19. Lipid nanoparticles (LNPs), polymeric nanoparticles, and exosome-based delivery methods are some of the effective ways to deliver mRNA-based ACE 2.

ACE 2-based strategies have limitations despite their potential for treatment. These include the short half-life of recombinant ACE 2, which necessitates frequent administration, the possibility of off-target effects and immune reactions, the difficulty of efficiently delivering ACE 2-based gene therapies, and anticipates about viral mutations that could reduce the effectiveness of ACE 2-targeting treatments.

Conclusion

The review summarises recent discoveries on ACE 2 function and pathogenesis in diverse illnesses. ACE 2 is a double-edged sword, acting as both a preventive factor in different diseases and a receptor for viral infections, prompting researchers to investigate its eccentric role. Besides, this overview looked into ACE 2's therapeutic potential and research possibilities. Future research should focus on improving drug delivery strategies, developing long-lasting ACE2 activators, and exploring combination therapy for increased efficacy.

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Расшифровка роли ангиотензинпревращающего фермента 2 в норме и при заболеваниях

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Аннотация. *Актуальность*. Ангиотензинпревращающий фермент 2 (АПФ 2) признан важным регулятором сердечно-сосудистого и легочного гомеостаза благодаря его участию в РААС (ренин-ангиотензиновой системе). В этом обширном обзоре рассматривается как традиционная роль АПФ 2 в превращении ангиотензина II (Ang II) в ангиотензин-(1–7), так и его более широкое значение в сердечно-сосудистых заболеваниях, легочной патологии, метаболических заболеваниях и раке. Выводы. Недавние исследования пролили свет на значение АПФ 2, выходящее за рамки его ферментативных возможностей, в частности, как клеточного рецептора различных патогенов. Кроме того, недавние исследования показывают, что ACE2 участвует в воспалении, метаболизме глюкозы и модуляции микробиома кишечника. Распределение в тканях, механизмы регуляции и терапевтические возможности демонстрируют его двойную роль: защитного фактора и возможного пути проникновения вирусных инфекций. Понимание этих множественных процессов в состоянии здоровья и болезни имеет важное значение для разработки персонализированных методов лечения заболеваний. В данном обзоре изложено существующее понимание ACE2 и выделены области для дальнейших исследований, в частности, его потенциал в качестве терапевтической мишени. Кроме того, обобщены проблемы и будущие направления в терапии на основе ACE2.

Ключевые слова: ACE2, ангиотензин превращающий фермент 2, здоровье, заболевания, физиология, сердечно-сосудистая система, легочная система, почечная система, рак, иммунология, кожа, кишечник, нейрофизиология

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Differences in the ratio of the peripheral blood phospholipid fractions among residents of different climatic and geographic territories

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Abstract. *Relevance.* A key element of human adaptation to the complex of extreme ecological factors is intensification of the energy metabolism. Mobilization of energy resources may lead to modification of the biological membranes and, as a consequence, to change their functional activity. Evaluation of the persistent imbalance degree on the level of phospholipid fractions may contribute to early diagnosis of the maladaptive states. *Aim:* an analysis of the levels of phosphatidylserine (PS), phosphatidylcholine (PC), phosphatidylethanolamine (PE) and sphingomyelin (SM) in the peripheral blood of the population in the Arctic and subarctic region of Russia, as well as the Southern Caucasus inhabitants. *Materials and Methods*. From 2010 to 2018, 687 people of both sexes aged 22 to 60 years were examined. The participants were divided into the following groups: 1) natives of the Russian Arctic region (AR); 2) residents of the subarctic region of Russia (SR); 3) residents of the South Caucasus (JUR). The level of the phospholipids was assessed using the thin-layer chromatography method. The results are presented in percentage terms. *Results and Discussion.* The residents of the AR revealed lower PS and higher PE levels compared to those of SR and JUR natives. At the same time, the AR individuals in the phospholipid spectrum reveal a relative decrease in the share of PC. Unlike the AR natives, the low PS content in the SR residents' peripheral blood did not affect the overall pool of the phospholipids, which is within similar variation limits regarding the natives of the JUR. The SM medians in the compared groups had no statistically significant differences. *Conclusion.* The complex of adaptive alterations in the human body under Arctic conditions is associated with mobilization of mechanisms aimed at increasing physical fluidity of the biological membranes, which may indicate a significant increase in their permeability and intensification of receptor and enzymatic activity in cells.

Keywords: phosphatidylethanolamine, phosphatidylcholine, sphingomyelin, phosphatidyletanolamine, Arctic region, subarctic region, South Caucasus

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Introduction

Assessing the impact of latitudinal factor on human health is an important eco-physiological task. The latitude-zone variations have a significant impact on the formation of physiological strategy of the adaptation. At the same time, prolonged exposure to sub-extreme and extremal natural and climatic conditions may lead to depletion of compensatory mechanisms, which contributes to the occurrence and development of the chronic diseases, which begin to manifest long before the onset of clinical symptoms [1].

As the living area expands towards higher latitudes, the negative effects (such as significant fluctuations in atmospheric pressure, cold weather, changes in daylight hours, geomagnetic activity) increase. It is established that such climatogeographic features, being to some extent extremal for the human life activity, initiate a characteristic set of adaptive changes at the level of the body's metabolic, morphological and regulatory systems [2]. However, the key element in the process of acquired adaptation is a shift in the energy homeostasis system, primarily driven by lipid metabolism components, which are inherently linked to cellular structural elements. This indicates that intensification of the lipid oxidation process may lead to the modification of biological membranes and, consequently, to changes in their functional activity. A system of such transformations can lead to increasing the degree of persistent metabolic imbalance which may involve other environmentally-related criteria for its assessment [3].

The phospholipids are a key element in ensuring the structural and functional integrity of the biological membranes. A number of critical physiologic processes depend on their dynamic equilibrium, including maintenance of cellular homeostasis, regulation of the cell cycle as well as adaptation of cells to changes in the environment [4].

Available empirical data, obtained during observational studies, provide convincing evidence of a specific phospholipid profile in Arctic residents [5–8]. However, there is a lack of information in the available scientific literature concerning the comparative assessment of the fractional composition of peripheral blood phospholipids in population at different climatic and geographical zones. Research in this area is fragmentary. In the available data, metabolic parameters of the population of the North are often analyzed in isolation from similar indicators of natives of southern

regions. We believe this approach distorts understanding of adaptive restructuring occurring within serum phospholipid fractions under extreme natural-climatic influences.

Mentioned aspects highlight the need to develop criteria for assessing the phospholipid profile in humans under contrasting extreme climatic and geographical conditions. This will not only enhance diagnostic capabilities for pre-pathological states but also help design rational preventive measures and correctional strategies addressing metabolic disorders associated with extreme environmental impacts. Therefore, it seems important to conduct a comparative analysis of ratios between phosphatidylserine, phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin in peripheral blood serum samples from Russian Arctic and subarctic Okrug populations compared to Southern Caucasus residents.

Materials and methods

The present study was conducted as part of a comprehensive expedition program that took place from 2010 to 2018. During the winter-spring season, 687 individuals were examined — men and women aged between 22 and 60 years. Separate groups were formed based on the location of birth and residence of the volunteers. The first group consisted of 264 persons — natives of the Arctic region of Russia (AR; 71-65°N) — villages: Gyda, Soyakha, Antipayuta, Krasnoselkup; Tazovskiy settlement and Nadym town in the Yamalo-Nenets Autonomous Okrug. The second group included 244 representatives of the local population of the subarctic region of Russia (SR; 64°N) — Pinega settlement of the Arkhangelsk region and Arkhangelsk city. The third group comprised 179 natives of South Caucasus (JUR; 42°N) — Tskhinvali city, Republic of South Ossetia. The average age of participants was as follows (mean ± SD): AR — 42.41 ± 11.06 years; SR — 42.56 ± 10.85 years; JUR — 39.40 ± 11.09 years.

The Arctic is a territory with harsh natural and climatic conditions that are unsuitable for permanent human habitation. The climate of the Arctic zone in the Yamalo-Nenets Autonomous region is highly uncomfortable. The unique climatic conditions are characterized by low temperatures and a combination of factors, including permafrost, Arctic air circulation, and the immediate proximity of the Kara Sea. The annual mean temperature: about –10 °C [9].

Climatic and geographical features of the subarctic regions, despite considerable mitigation of the extreme conditions inherent in the Arctic, still create a significant level of discomfort for the local population. (The city of Arkhangelsk and the Pinega settlement are situated in the Atlantic-Arctic sector of the temperate zone. The meteorological regime of these territories is determined by the complex interaction of advective processes, in particular — outgoing from the northern seas. The average annual temperature varies from 0,1 to 2,0 °C [10].

South Ossetia is characterized by a variety of ecological factors due to the complex topography of the region. The ecological and climatic situation of the city of Tskhinvali, where the study was conducted, can be described as physiologically favorable for human life. The region under consideration is located in the foothills of the Greater Caucasus, at an altitude of about 600 meters above sea level. The climatic conditions in this area are characterized as subtropical, with an average annual temperature fluctuating around 11,2 °C [11].

Within the framework of the study, a targeted sampling of the respondents was performed among the local residents, compliant with the criteria of health groups I and II. To reduce the likelihood of influencing of the pathological processes on the results of the analysis, all volunteers were in a state of remission from their chronic diseases. The examinations were conducted in strict accordance with the ethical standards regulated by the WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013. The studies were conducted based on the written consent of each participant, obtained after careful explanation of all aspects of the procedure, potential risks and expected benefits. The study protocols were approved by the Biomedical Ethics Commission of the IPNA UrB

RAS and the Ethics Committee of the FECIAR UrB RAS (dated February 2, 2009, February 4, 2023, and November 9, 2016).

The examination process included a questionnaire, designed to determine age, anthropometric data, the presence of chronic diseases, work experience, ethnicity, bad habits, level of physical activity, and diet. In the morning, between 08:00 and 10:00 local time, venous blood was collected from the cubital vein. The procedure was performed exclusively under fasting conditions, which implied observing a strict time interval of 10–12 hours from the last meal.

Lipids from blood serum were extracted and purified using the liquid extraction method [12]. To achieve optimal phospholipid separation, an eluent was used in the following proportions: 6.5 parts chloroform, 2.5 parts methanol, and 0.5 parts aqueous ammonia solution with a mass fraction of NH_3 of at least 25%. The total volume of the system was 3 cm^3. The identification of phosphatidylcholine (PC), sphingomyelin (SM), phosphatidylethanolamine (PE), and phosphatidylserine (PS) was performed by comparing with Rf values of standard samples provided by Sigma (USA). The densitometer «DenSkan» (Russia) was used as a tool for measuring the optical density of chromatographic spots. The analysis of chromatographic data was carried out using the peak area normalization method implemented using the «Dens» software version 14–12–03 beta (Russia).

The statistical analysis of the obtained material was carried out using the IBM SPSS Statistics 22.0 program (USA) [13]. The hypothesis of a normal distribution of a random variable was tested using the Shapiro-Wilk test. Due to the revealed anomalies in the distribution of the studied features, the median (Me) indicators were used as the central trend, and the values of the first (Q_1) and third (Q_3) quartiles were used to estimate the range of variability. The Kruskal-Wallis test (H-test) was used to assess the degree of differences between the compared groups. The Mann-Whitney test (U-test) was applied to a posteriori comparisons. In order to minimize the risk of false positives, the Bonferroni correction was applied when testing hypotheses. The found changes were considered statistically significant if the probability of error in accepting the null hypothesis was less than 5%.

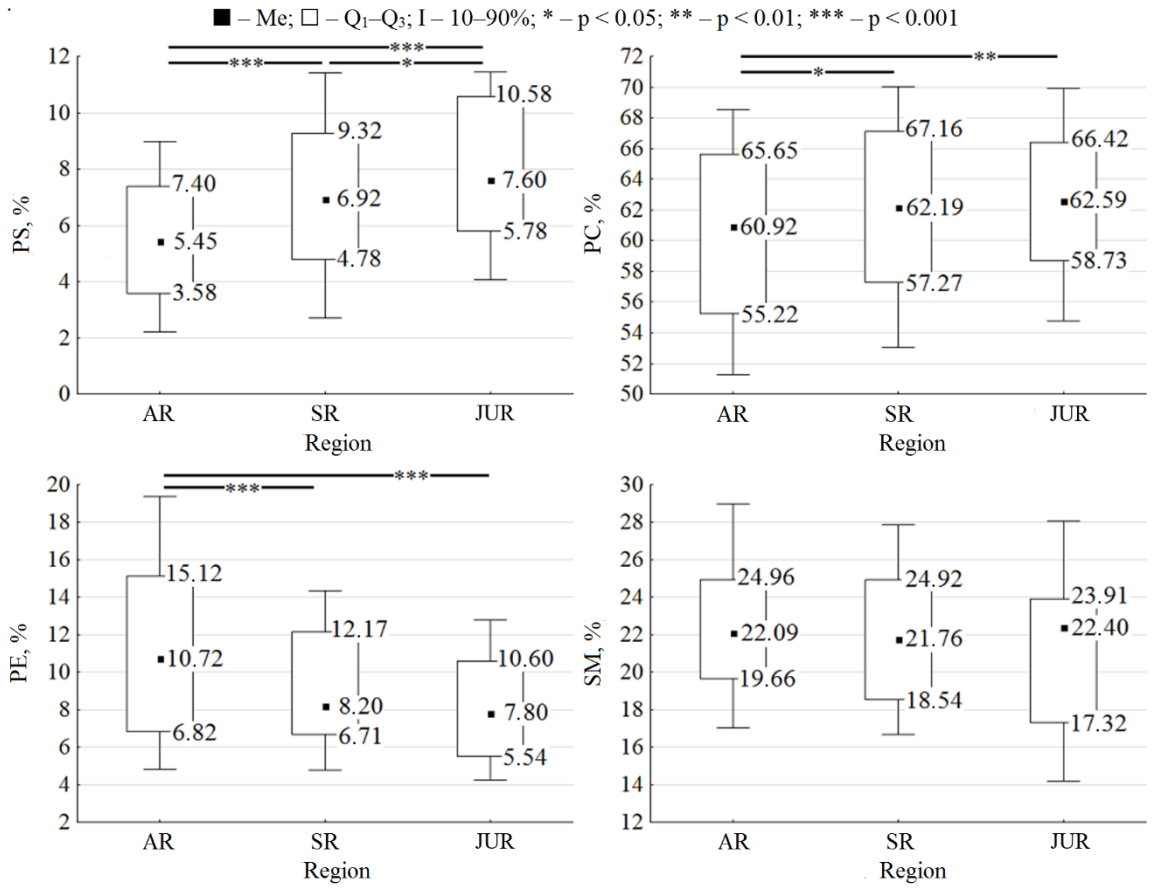
Results and discussion

The phospholipid composition of peripheral blood is largely determined by the intensity of synthesis as well as breakdown of these compounds in the tissues of the liver, kidneys, and lungs as well as in blood cells and in the vascular walls. Therefore, the ratio of the phospholipid fractions in blood serum not only reflects a generalized picture of their metabolism, but it can also serve as an indirect indicator of the structural and functional organization of the cell membranes of many organs and tissues [14].

A preliminary analysis of the data obtained during the comparison of three independent groups revealed statistically significant differences in the PS indicators ($H = 57.36$; $p = 3.50\times10^{-13}$), PE ($H = 36.48$; $p = 1.20\times10^{-8}$), PC ($H = 13.78$; $p = 1.02\times10^{-3}$), SM ($H = 6.45$; $p = 3.98\times10^{-2}$).

The subsequent calculation was performed using the method of a posteriori comparisons (Figure).

The analysis of the obtained results showed that the profile of phospholipid fractions in the peripheral circulation system of residents of the JUR region differs in a statistically significant high level of PS relative to individuals living in the SR and AR of Russia ($p = 4.58\times10^{-2}$; $p = 5.69\times10^{-13}$ accordingly). In the same time, in 90% of the subjects examined in the Arctic, the proportion of this fraction in the total pool of phospholipids did not exceed 9.0%, which is a statistically significant low content compared to SR natives ($p = 1.36\times10^{-6}$) and JUR natives. According to the data obtained on the PC, it was found that the level of this indicator is statistically significantly lower among the residents of AR than relative to the natives of SR and JUR ($p = 1.85\times10^{-2}$; $p = 1.50\times10^{-2}$, respectively). It is also important to note that the range of PC fluctuations in the total phospholipid spectrum of 80% of the individuals examined in the Arctic was between 51.3% and 68.6%. At the same time, the SR and JUR groups had statistically significantly lower concentrations of PE than the AR group ($p = 1.00\times10^{-4}$; $p = 4.75\times10^{-8}$, respectively), where 80% of the



Analysis of the fractional composition of phospholipids in peripheral blood serum of the population of natives of the Russian Arctic region (AR) and residents of the subarctic region of Russia (SR) regions of Russia, as well as residents of the South Caucasus (JUR)

participants had a relative value range of 4.82–19.46%. At the same time, the median value of SM did not differ statistically significantly between the compared groups. In particular, the residents of the AR and JUR the probability of differences in the obtained SM values in the statistical trend zone ($p = 5.55 \times 10^{-2}$).

It is believed that the metabolic pathways of the PS, PE and PC are closely related [15]. It has been established that the main metabolic pathway from PS to PE is the carbon dioxide elimination reaction catalyzed by phosphatidylserine decarboxylase. This enzyme is a transmembrane protein whose active site is located on the outer side of the inner mitochondrial membrane. In this regard, it plays a key role in the production of mitochondrial PE. It has been noted that PE synthesized in mitochondria is actively exported to other cellular organelles, including the plasma membrane. Alternatively, PE can be obtained by synthesis on the surface of the endoplasmic reticulum, which involves the phosphorylation and activation of exogenous ethanolamine, followed by the condensation of diacylglycerol [16]. Given that the human adaptation process is associated with the intensification of metabolic processes, it can be assumed that the identified changes in the residents of the AR represent an element of specific adaptive-compensatory reaction caused by increased enzymatic activity. This reaction may be typical for Arctic natives in response to prolonged and intense exposure to stressful environmental factors. On the other hand, this may be a consequence of the relationship between the substrate and the reaction

product, which is related to the exogenous supply of the substrate.

The next significant stage of the PE metabolic cycle is its methylation process involving S-adenosylmethionine. In this reaction, PE acts as a precursor to PC and can serve as a source for its synthesis [17]. In this regard, it is likely that the high level of PE in the population of the Arctic territories serves as a reserve that supports the synthetic capacity for producing PC. According to the data presented in the work by E.R. Boyko and co-authors [6], the decrease in the PC indicators in individuals, living in the climatic and geographical conditions of the North, may have several causes, among which the process of activating cholesterol esterification reactions is the main factor. According to the authors, the active use of PC in this process is an adaptive reaction of the body that helps to eliminate this atherogenic lipid from the vascular bed.

Another important factor that, in our opinion, may limit the synthesis of PC in high-latitude residents is the high degree of unsaturation of fatty acids in lipids. The current data indicates that the PS and PE fractions, unlike the PC esters, are directly associated with the polar transport form of fatty acids that have four or more double bonds in the hydrocarbon chain [18]. At the same time, the length and degree of unsaturation of the acyl components usually depend on the fatty acid composition of the food [19]. In addition, the content of fatty acids in the diet can exogenously affect the rate, balance, and direction of phospholipid metabolism [20, 21]. So, in a study aimed at studying the fatty acid composition of blood plasma lipids and erythrocytes among the population of the Chukotka Autonomous Okrug and the city of Moscow, it was revealed that the content of polyunsaturated fatty acids of the n-3 family in these media in representatives of Chukotka, especially in coastal areas, significantly exceeds similar indicators in Muscovites. At the same time, in the subfractions of high-density lipoproteins, residents of Chukotka have a lower proportion of PC and a higher percentage of SM and PE compared to Muscovites [22]. Concurrently, a decrease in the proportion of PS in the total pool of serum phospholipids in individuals in the AR compared to those in the SR and JUR leads to a corresponding relative increase the PE percentage. Their data demonstrate that the level of n-3 fatty acids in the PE fraction of Arctic residents significantly exceeds similar indicators in the control group formed from representatives living in Vancouver. Moreover, it was found that the occurrence of these fatty acids in PE is higher than in PC, which may also indicate their specific distribution and significance in the context of adaptation to a cold climate [23].

Based on the presented data, it is possible to make a reasonable assumption that the direction of metabolic processes occurring in the human body is not only associated with the qualitative characteristics of his diet, but is also largely determined by the climatic and geographical factors of the territory of his permanent residence. These parameters, in turn, have a complex effect on the dynamics and structural distribution of phospholipid fractions, both in the peripheral circulation system and in the organization of cellular membranes of organs and tissues. In particular, the results of the study indicate enrichment of the cell membranes of Arctic residents with phospholipid fractions characterized by a high degree of unsaturation of their acyl chains. On the one hand, this leads to a decrease in the antioxidant properties of membrane phospholipids, and on the other hand, it can contribute to an increase in the liquid properties of biological membranes, expanding the kinetic and thermodynamic characteristics of enzymes and receptors. As a result, such changes in the total pool of phospholipids in the peripheral blood of local residents can reflect the adaptive orientation of metabolic processes to the extreme environmental conditions of the Arctic, which occurs at the level of cell membranes.

Conclusion

The results of the study show that residents of the AR have the lowest level of PS in the peripheral blood phospholipid spectrum, while residents of the JUR have the highest concentration. At once, a decrease in the proportion of PS in the total pool of serum phospholipids in individuals in the AR compared to those in the SR

and JUR leads to a corresponding relative increase of the PE percentage. However, in volunteers examined in AR, the observed changes in the ratio of phospholipid fractions are accompanied by a relative decrease in the concentration of PC. At the same time, the concentration of SM in the groups under consideration did not differ statistically significantly.

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Оценка различий в соотношении фосфолипидных фракций периферической крови у жителей различных климатогеографических территорий

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Аннотация. *Актуальность.* Ключевой элемент адаптации человека к комплексу экстремальных экологических факторов — интенсификация энергетического обмена. Мобилизация энергетических ресурсов может приводить к модификации биологических мембран и, как следствие, изменять их функциональную активность. Оценка степени устойчивого метаболического дисбаланса на уровне фракций фосфолипидов может способствовать ранней диагностике дезадаптивных состояний. Цель работы заключалась в анализе фосфатидилсерина (ФС), фосфатидилхолина (ФХ), фосфатидилэтаноламина (ФЭА) и сфингомиелина (СФМ) в сыворотке периферической крови населения арктического и приарктического регионов России, а также жителей Южного Кавказа. Материалы и методы. С 2010 по 2018 год обследовано 687 лиц обоего пола в возрасте от 22 до 60 лет. Среди участников были сформированы следующие группы: 1) уроженцы арктического региона России (АР); 2) лица, проживающие в приарктическом регионе России (ПР); 3) жители Южного Кавказа (ЮР). Уровень фосфолипидов оценивался с помощью метода тонкослойной хроматографии. Результаты представлены в процентном соотношении. *Результаты и обсуждение*. У жителей АР по сравнению с уроженцами ПР и ЮР выявлено низкое содержание ФС и высокое — ФЭА. При этом у лиц из АР в фосфолипидном спектре отмечается относительное снижение доли ФХ. В отличие от уроженцев АР у жителей ПР низкое содержание ФС в периферической крови не оказывало влияние на общий пул сывороточных фосфолипидов, который находится в схожих лимитах варьирования относительно уроженцев ЮР. Медианы СФМ в сравниваемых группах не имели статистически значимых различий. *Выводы*. Сложный комплекс адаптационных изменений в организме человека в условиях Арктики ассоциирован с мобилизацией механизмов, направленных на повышение физической текучести биологических мембран, что может указывать на значительное увеличение их проницаемости, а также интенсификацию рецепторной и ферментативной активности в клетках.

Ключевые слова: фосфатидилсерин, фосфатидилхолин, сфингомиелин, фосфатидилэтаноламин, арктический регион, приарктический регион, Южный Кавказ

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Регуляция ритма сердца при постуральных изменениях у студенток с различной возбудимостью парасимпатических центров

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Аннотация. *Актуальность.* Изменения гормонального фона во время менструального цикла у женщин оказывает влияние не только на репродуктивную функцию организма, но и на функциональное состояние автономных механизмов регуляции физиологических систем. *Целью* настоящего исследования явилось изучение особенностей вариабельности сердечного ритма при постуральных изменениях у женщин в зависимости от возбудимости центров парасимпатической нервной системы и фазы менструального цикла. *Материалы и методы.* В исследовании участвовали 47 студенток Ивановского государственного медицинского университета. Средний возраст испытуемых составил 19,20 ± 0,16 лет. Обследование проведено в фолликулярную и лютеиновую фазу менструального цикла, средняя продолжительность которого составила 29,22 ± 0,32 дней. Особенности возбудимости парасимпатической нервной системы оценивали по величине коэффициента К30:15 при переходе в вертикальное положение тела. Регистрацию электрокардиограммы производили с использованием компьютерного электрокардиографа «Поли-спектр» компании Нейрософт (г. Иваново, Россия) в течение 5 минут в горизонтальном положении тела, а также в течение 5 минут при активном ортостазе, пассивном ортостазе и пассивном антиортостазе. *Результаты и обсуждение.* По результатам анализа динамики спектральных и временных показателей установлено, что переход в ортостатическое положение тела сопровождается уменьшением влияния блуждающего нерва на сердце. При активном ортостазе это не зависит от возбудимости парасимпатической системы и фазы менструального цикла, тогда как при пассивном ортостазе при сниженной возбудимости парасимпатических центров это проявляется в обе фазы цикла, а при нормальной возбудимости — только в фолликулярную фазу. Антиортостаз инициирует увеличение парасимпатической активности у женщин с нормальной возбудимостью в фолликулярную фазу цикла, тогда как у лиц со сниженной возбудимостью отмечается уменьшение влияния блуждающего нерва в обе фазы менструального цикла. *Выводы.* Характер реакции системы кровообращения на ортостатические и антиортостатические положения у женщин зависит не только от вида постурального воздействия, но и от особенностей возбудимости парасимпатической системы и фазы менструального цикла.

Ключевые слова: вариабельность сердечного ритма, постуральные изменения, возбудимость парасимпатической нервной системы, менструальный цикл

Информация о финансировании. Авторы заявляют об отсутствии внешнего финансирования настоящего исследования.

Вклад авторов. Скорлупкин Д.А. — сбор материала, статистическая обработка результатов, написание текста рукописи; Голубева Е.К. — концепция и дизайн исследования, интерпретация результатов, написание текста рукописи; Ярченкова Л.Л. — консультативная помощь в интерпретации результатов, редактирование текста рукописи. Все авторы настоящей работы внесли значительный вклад в разработку дизайна и концепции, проведение исследования и подготовку текста рукописи, прочитали и утвердили окончательную версию перед публикацией.

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Heart rhythm regulation during postural changes in female students depending on the parasympathetic centers excitability

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Abstract. *The aim* of this study was to investigate the features of heart rate variability during postural changes in women, depending on the excitability of parasympathetic centers and of the menstrual cycle phase. *Material and Methods.* 47 female students from Ivanovo State Medical University participated in the study. The average age of participants was 19.2±0.16 years. The study took place during the follicular and luteal phases of menstrual cycle, lasting an average of 29.3 ± 0.4 days. The features of parasymphathetic center excitability were assessed using the K30:15 ratio during the transition to an upright position. The electrocardiogram was recorded for 5 minutes using a computer electrocardiographic system Poly-spectrum (NeuroSoft, Ivanovo, Russia) both in the horizontal position and during active orthostasis, passive orthostasis and passive antiorthostasis. *Results and Discussion.* Based on the analysis of the dynamics of HRV indicators, it was found that the transition from a supine position to an upright body position was accompanied by a decrease in the influence of the vagus nerve on the heart. With active

orthostasis, this does not depend on the excitability of the parasympathetic system and the phase of the menstrual cycle. While with passive orthostasis and reduced excitability of the parasympathetic centers, this is manifested in both phases of the cycle, and with normal excitability — only in the follicular phase. Antiorthostasis initiates an increase in parasympathetic activity in women with normal excitability only in the follicular phase, whereas in women with reduced excitability, there is a decrease in the influence of the vagus nerve in both phases of the cycle. *Conclusion.* The nature of circulatory system responses to changes in body position in women depend not only on type of posture but also on excitatory characteristics of parasympathetic nerves and menstrual cycle phases.

Keywords: heart rate variability, postural changes, excitability of the parasympathetic system, menstrual cycle

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Введение

Состояние здоровья студентов высших учебных заведений является важной медико-биологической и социальной проблемой [1]. Высокий уровень интенсивности учебного процесса и малоподвижный образ жизни являются факторами развития сердечно-сосудистых заболеваний [2, 3]. Ортостатические и антиортостатические положения тела в настоящее время широко используются в практической медицине для оценки функционального состояния системы кровообращения, а также механизмов регуляции деятельности сердца и просвета сосудов [4, 5]. Реакция на постуральные воздействия проявляется изменением сердечного ритма, что в значительной мере определяется уровнем возбудимости центров вегетативной нервной системы. В связи с этим характер адаптивного ответа при орто- и антиортостатических воздействиях может различаться у разных людей [6].

У женщин репродуктивного возраста отмечаются циклические изменения гормонального статуса во время овариально-менструального цикла (ОМЦ). Фолликулярная фаза цикла характеризуется повышением уровня эстрогенов, лютеинизирующего и фолликулостимулирующего гормонов [7]. В лютеиновую фазу наблюдается увеличение концентрации прогестерона с вторичным, более низким, всплеском концентрации эстрогенов [8, 9]. Благодаря своей стероидной природе половые гормоны способны проникать через гематоэнцефалический барьер,

оказывая воздействие на структуры центральной нервной системы (ЦНС) [10].

В экспериментальных исследованиях разных авторов подтверждено наличие эстрогеновых и прогестероновых рецепторов в различных органах и тканях организма человека. Показана высокая плотность рецепторов к гормонам овариального происхождения в лимбической системе, таламусе, гипоталамусе, гиппокампе, миндалевидном теле, стволе мозга и других структурах ЦНС [11–13]. Гормоны яичников оказывают влияние на проявление эффекта нейромедиаторов, изменяют чувствительность постсинаптических рецепторов, модулируют интенсивность высвобождения нейромедиаторов в пресинаптических окончаниях. В частности показано влияние овариальных гормонов на функциональность глутаматергических, ГАМК-ергических, серотонинергических, дофаминергических и других синапсов. Также женские половые гормоны оказывают нейротрофическое и нейропротекторное действие [14, 15]. В связи с этим состояние автономных механизмов регуляции физиологических функций у женщин в значительной мере зависит не только от функциональной активности вегетативных центров, но и от фазы менструального цикла.

Цель исследования: изучить особенности вариабельности сердечного ритма при постуральных изменениях у женщин в зависимости от возбудимости парасимпатических центров и фазы менструального цикла.

Материалы и методы

Исследование выполнено с участием 47 студенток Ивановского государственного медицинского университета в возрасте 18–20 лет. Все участники исследования подписали добровольное информированное согласие. Протокол составлен с учётом положений Хельсинской декларации по проведению биомедицинских исследований на человеке и утвержден этическим комитетом Ивановского ГМУ. Обследование женщин выполнено на 5–6 день после начала ОМЦ (фолликулярная фаза) и за 5–6 дней до его окончания (лютеиновая фаза).

Особенности возбудимости центров парасимпатической нервной системы оценивали по коэффициенту К30:15 во время активной ортостатической пробы: К30:15 = 1,20–1,80 у.е. — нормальная возбудимость парасимпатических центров; К30:15 = 1,0–1,19 — сниженная возбудимость; К30:15 > 1,80 — повышенная возбудимость [16].

Вариабельность сердечного ритма оценивали по результатам регистрации электрокардиограммы (ЭКГ) с использованием компьютерного электрокардиографа «Поли-спектр» (Нейрософт, г. Иваново, Россия). Анализировали динамику следующих показателей: ЧСС (уд/мин) — частота сердечных сокращений, RRNN (мс) — средняя продолжительность R-R интервалов, RMSSD (мс) — квадратный корень из среднеквадратичного отклонения последовательных R-R интервалов, SDNN (мс) — стандартное отклонение R-R интервалов, pNN50 (%) — доля R-R интервалов, отличающихся на 50 и более мс, %LF (%) — доля низкочастотной составляющий спектра ВСР, %HF (%) — доля высокочастотной составляющей спектра ВСР, LF/HF (у.е.) — симпатико-парасимпатическое равновесие. После 10 минут адаптации к горизонтальному положению производили запись ЭКГ в течение 5 минут в положении лёжа на спине (контроль), затем 5 минут при активном ортостазе, пассивном ортостазе (угол подъема 25°) и пассивном антиортостазе (угол подъема 15°).

Статистический анализ производили в программах Microsoft Excel и Statistica. Результаты представлены в виде медианы (Me) и межквартильного размаха [Q_1; Q_3]. Нормальность распределения количественных переменных проверяли с использованием критерия Шапиро–Уилка (при объёме выборки ≤ 50). Статистическую значимость различий оценивали с помощью непараметрических критериев Манна–Уитни и Вилкоксона. Различия считали достоверными при $p \leq 0{,}05$.

Результаты и обсуждение

По результатам расчета коэффициента К30:15 во время активной ортостатической пробы все

испытуемые были разделены на две группы: с нормальной возбудимостью парасимпатических вегетативных центров (n = 31; К30:15 = 1,20–1,80 у. е.) и со сниженной возбудимостью — (n = 16; К30:15 = 1,0–1,19).

Результаты спектрального анализа при активном ортостазе позволили выявить прирост величины показателя %LF и снижение %HF в спектре ВСР, что сопровождается увеличением индекса LF/HF (Таблица 1). Описанные изменения отмечаются у всех обследованных студенток, независимо от уровня возбудимости центров парасимпатической нервной системы, как в фолликулярную, так и в лютеиновую фазу ОМЦ. На фоне отклонения спектральных показателей ВСР у всех испытуемых наблюдается прирост ЧСС, более выраженный у женщин со сниженной возбудимостью парасимпатической системы во время фолликулярной фазы цикла. Кроме того, независимо от фазы цикла и возбудимости парасимпатических центров, активный ортостаз вызывает снижение временных показателей RRNN, SDNN и RMSSD, что свидетельствует об уменьшении вариационного размаха значений интервалов R-R.

При пассивном ортостазе у женщин во время фолликулярной фазы ОМЦ отмечается увеличение показателя %LF и индекса LF/HF, что наблюдается независимо от особенностей возбудимости парасимпатических вегетативных центров (Таблица 2).

Таблица 1

ВСР при активном ортостазе у студенток, Me [Q_1; Q_3]

Параметр	Фолликулярная фаза (n = 47)		Лютеиновая фаза (n = 47)	
	Контроль	Ортостаз	Контроль	Ортостаз
Нормальная возбудимость парасимпатических центров (n = 31)				
ЧСС, уд/мин	69,8 [64,7; 77,0]	92,3 [84,1; 97,3] *p < 0,001	71,2 [66,3; 77,0]	93,2 [86,8; 100,1] *p < 0,001 #p = 0,031
RRNN, мс	860,0 [780,0; 928,0]	650,0 [617,0; 713,0] *p < 0,001	843,0 [779,0; 906,0]	644,00 [600,5; 691,0] *p < 0,001
RMSSD, мс	57,0 [45,0; 73,0]	20,0 [18,0; 27,0] *p < 0,001	59,0 [38,0; 81,0]	20,0 [16,0; 25,5] *p < 0,001
SDNN, мс	56,0 [48,0; 68,0]	43,0 [33,0; 48,0] *p < 0,001	61,0 [51,0; 79,0]	41,0 [32,5; 50,0] *p < 0,001
%LF, %	30,1 [21,2; 35,2]	44,9 [37,0; 52,7] *p < 0,001	29,8 [22,5; 35,3]	47,7 [38,7; 55,7] *p < 0,001
%HF, %	45,9 [30,2; 53,7]	14,50 [9,4; 20,9] *p < 0,001	36,6 [25,6; 42,7]	12,90 [8,5; 28,4] *p < 0,001
LF/HF, у. е.	0,6 [0,4; 1,1]	2,7 [1,8; 4,7] *p < 0,001	0,8 [0,6; 1,3]	3,6 [1,5; 6,1] *p < 0,001
Сниженная возбудимость парасимпатических центров (n = 16)				
ЧСС, уд/мин	72,9 [67,6; 79,4]	100,2 [89,9; 118,5] *p < 0,001	73,0 [70,1; 77,3]	97,9 [86,4; 105,7] *p < 0,001
RRNN, мс	823,0 [755,3; 888,3]	598,5 [506,8; 669,5] *p < 0,001	822,0 [776,0; 856,0]	613,0 [568,0; 694,0] *p < 0,001
RMSSD, мс	65,0 [42,5; 94,5]	24,50 [10,8; 29,0] *p < 0,001	54,0 [41,0; 74,0]	15,0 [10,0; 30,0] *p = 0,005
SDNN, мс	68,0 [46,5; 76,0]	37,5 [26,5; 53,3] *p = 0,006	59,0 [40,0; 71,0]	30,0 [26,0; 47,0] *p = 0,021
%LF, %	26,8 [15,7; 35,1]	37,5 [31,3; 45,7] *p < 0,001	25,0 [19,1; 30,5]	44,1 [32,6; 54,6] *p < 0,001
%HF, %	33,1 [17,9; 44,3]	12,8 [7,9; 18,9] *p = 0,003	30,6 [26,6; 51,6]	11,9 [6,6; 24,9] *p < 0,001
LF/HF, у. е.	0,7 [0,5; 1,1]	3,1 [2,1; 4,9] *p < 0,001	0,9 [0,3; 1,1]	3,3 [1,9; 6,0] *p < 0,001

Примечание: * — статистически значимые различия с контролем (p≤0,05), # — статистически значимые различия показателей у испытуемых с нормальной и низкой возбудимостью парасимпатических центров (p ≤ 0,05).

Table 1

HRV with active orthostasis in female students, Me [Q_1; Q_3]

Parameter	Follicular phase (n = 47)		Luteal phase (n = 47)	
	Control	Orthostasis	Control	Orthostasis
Normal excitability of parasympathetic centers (n = 31)				
HR, bpm	69.8 [64.7; 77.0]	92.3 [84.1; 97.3] *p < 0.001	71.2 [66.3; 77.0]	93.2 [86.8; 100.1] *p < 0.001 #p = 0.031
RRNN, ms	860.0 [780.0; 928.0]	650.0 [617.0; 713.0] *p < 0.001	843.0 [779.0; 906.0]	644.0 [600.5; 691.0] *p < 0.001
RMSSD, ms	57.0 [45.0; 73.0]	20.0 [18.0; 27.0] *p < 0.001	59.0 [38.0; 81.0]	20.0 [16.0; 25.5] *p < 0.001
SDNN, ms	56.0 [48.0; 68.0]	43.0 [33.0; 48.0] *p < 0.001	61.0 [51.0; 79.0]	41.0 [32.5; 50.0] *p < 0.001
%LF, %	30.1 [21.2; 35.2]	44.9 [37.0; 52.7] *p < 0.001	29.8 [22.5; 35.3]	47.7 [38.7; 55.7] *p < 0.001
%HF, %	45.9 [30.2; 53.7]	14.50 [9.4; 20.9]и*p < 0.001	36.6 [25.6; 42.7]	12.90 [8.5; 28.4] *p < 0.001
LF/HF, c.u.	0.6 [0.4; 1.1]	2.7 [1.8; 4.7] *p < 0.001	0.8 [0.6; 1.3]	3.6 [1.5; 6.1] *p < 0.001
Decreased excitability of parasympathetic centers (n = 16)				
HR, bpm	72.9 [67.6; 79.4]	100.2 [89.9; 118.5] *p < 0.001	73.0 [70.1; 77.3]	97.9 [86.4; 105.7] *p < 0.001
RRNN, ms	823.0 [755.3; 888.3]	598.5 [506.8; 669.5] *p < 0.001	822.0 [776.0; 856.0]	613.0 [568.0; 694.0] *p < 0.001
RMSSD, ms	65.0 [42.5; 94.5]	24.50 [10.8; 29.0] *p < 0.001	54.0 [41.0; 74.0]	15.0 [10.0; 30.0] *p = 0.005
SDNN, ms	68.0 [46.5; 76.0]	37.5 [26.5; 53.3] *p = 0.006	59.0 [40.0; 71.0]	30.0 [26.0; 47.0] *p = 0.021
%LF, %	26.8 [15.7; 35.1]	37.5 [31.3; 45.7] *p < 0.001	25.0 [19.1; 30.5]	44.1 [32.6; 54.6] *p < 0.001
%HF, %	33.1 [17.9; 44.3]	12.8 [7.9; 18.9] *p = 0.003	30.6 [26.6; 51.6]	11.9 [6.6; 24.9] *p < 0.001
LF/HF, c.u.	0.7 [0.5; 1.1]	3.1 [2.1; 4.9] *p < 0.001	0.9 [0.3; 1.1]	3.3 [1.9; 6.0] *p < 0.001

Note: * — statistically significant differences with the control (p < 0.05), # — statistically significant differences in indicators in subjects with normal and low excitability of parasympathetic centers (p < 0.05).

При нормальной возбудимости парасимпатической системы также отмечается укорочение RRNN. В лютеиновую фазу ОМЦ у студенток со сниженной возбудимостью уменьшается RRNN и доля кардиоинтервалов, отличающихся на 50 и более мс (pNN50). В горизонтальном положении контрольное значение показателя pNN50 у этой группы испытуемых составляет 44,4 [35,4; 49,6] %, тогда как при пассивном ортостазе — 24,1 [17,6; 39,8] % (p = 0,030). Следует отметить, что у женщин с нормальной парасимпатической возбудимостью контрольные величины LF-компонента и %LF

в лютеиновую фазу ОМЦ достоверно выше, чем в фолликулярную. Изменений ВСР при пассивном ортостазе у студенток с нормальной возбудимостью парасимпатической системы во время лютеиновой фазы не отмечается.

При пассивном антиортостазе у женщин с нормальной возбудимостью парасимпатических центров в фолликулярную фазу цикла происходит снижение ЧСС и увеличение показателя RRNN (Таблица 3). В то же время у лиц со сниженной парасимпатической возбудимостью в спектре ВСР отмечается увеличение %LF. Во время лютеиновой фазы менструального цикла у студенток со сниженной возбудимостью также отмечается уменьшение величины RMSSD, тогда как при нормальной возбудимости парасимпатической системы изменений ВСР в антиортостатическом положении тела не происходит.

Таблица 2

ВСР при пассивном ортостазе у студенток, Me [Q_1; Q_3]

Параметр	Фолликулярная фаза (n = 47)		Лютеиновая фаза (n = 47)	
	Контроль	Ортостаз	Контроль	Ортостаз
Нормальная возбудимость парасимпатических центров (n = 31)				
ЧСС, уд/мин	66,7 [63,0; 72,3]	66,9 [62,9; 71,7]	68,2 [64,4; 70,9]	68,3 [65,5; 72,1]
RRNN, мс	900,0 [830,0; 953,0]	837,0 [833,0; 953,0] *p = 0,041	880,0 [846,5; 931,5]	878,0 [831,0; 916,5]
RMSSD, мс	64,0 [47,0; 79,0]	61,0 [45,0; 74,0]	69,0 [55,0; 94,5]	63,0 [48,5; 87,0]
SDNN, мс	63,0 [49,0; 75,0]	58,0 [44,0; 68,0]	68,0 [57,5; 78,5]	62,0 [53,5; 80,0]
%LF, %	23,9 [17,7; 28,9]	27,7 [21,9; 37,5] *p = 0,012	30,9 [20,6; 34,3]	26,8 [19,7; 32,0]
%HF, %	47,1 [31,9; 53,5]	42,1 [31,0; 56,8]	42,7 [33,8; 53,4]	43,5 [27,9; 53,3]
LF/HF, у.е.	0,5 [0,4; 0,9]	0,7 [0,5; 1,3] *p = 0,011	0,7 [0,4; 0,9]	0,7 [0,4; 1,4]
Сниженная возбудимость парасимпатических центров (n = 16)				
ЧСС, уд/мин	69,7 [61,1; 73,5]	71,8 [63,4; 76,2]	68,3 [65,3; 71,6]	69,2 [64,8; 74,8]
RRNN, мс	861,0 [816,8; 981,8]	836,5 [788,3; 947,5]	880,5 [838,5; 921,5]	854,0 [798,3; 910,3] *p = 0,020
RMSSD, мс	66,5 [47,8; 75,3]	64,5 [46,8; 75,0]	62,0 [51,0; 75,0]	50,0 [38,0; 60,0]
SDNN, мс	65,5 [52,0; 70,0]	59,0 [47,8; 73,5]	58,0 [48,0; 68,0]	50,0 [46,0; 60,0]
%LF, %	24,1 [17,2; 29,8]	33,7 [27,1; 39,7] *p = 0,002	26,6 [18,7; 30,4]	21,2 [18,8; 31,2]
%HF, %	41,0 [27,4; 56,1]	39,3 [23,4; 45,9]	43,0 [27,3; 50,0]	37,7 [27,4; 49,9]
LF/HF, у.е.	0,5 [0,4; 1,0]	0,9 [0,6; 1,4] *p = 0,023	0,6 [0,4; 1,6]	0,6 [0,4; 1,2]

Примечание: * — статистически значимые различия с контролем (p ≤ 0,05).

Table 2

HRV in passive orthostasis in female students, Me [Q_1; Q_3]

Parameter	Follicular phase (n = 47)		Luteal phase (n = 47)	
	Control	Orthostasis	Control	Orthostasis
Normal excitability of parasympathetic centers (n = 31)				
HR, bpm	66.7 [63.0; 72.3]	66.9 [62.9; 71.7]	68.2 [64.4; 70.9]	68.3 [65.5; 72.1]
RRNN, ms	900.0 [830.0; 953.0]	837.0 [833.0; 953.0] *p = 0.041	880.0 [846.5; 931.5]	878.0 [831.0; 916.5]
RMSSD, ms	64.0 [47.0; 79.0]	61.0 [45.0; 74.0]	69.0 [55.0; 94.5]	63.0 [48.5; 87.0]
SDNN, ms	63.0 [49.0; 75.0]	58.0 [44.0; 68.0]	68.0 [57.5; 78.5]	62.0 [53.5; 80.0]
%LF, %	23.9 [17.7; 28.9]	27.7 [21.9; 37.5] *p = 0.012	30.9 [20.6; 34.3]	26.8 [19.7; 32.0]
%HF, %	47.1 [31.9; 53.5]	42.1 [31.0; 56.8]	42.7 [33.8; 53.4]	43.5 [27.9; 53.3]
LF/HF, c.u.	0.5 [0.4; 0.9]	0.7 [0.5; 1.3] * p = 0.011	0.7 [0.4; 0.9]	0.7 [0.4; 1.4]
Decreased excitability of parasympathetic centers (n = 16)				
HR, bpm	69.7 [61.1; 73.5]	71.8 [63.4; 76.2]	68.3 [65.3; 71.6]	69.2 [64.8; 74.8]
RRNN, ms	861.0 [816.8; 981.8]	836.5 [788.3; 947.5	880.5 [838.5; 921.5]	854.0 [798.3; 910.3] *p = 0.020
RMSSD, ms	66.5 [47.8; 75.3]	64.5 [46.8; 75.0]	62.0 [51.0; 75.0]	50.0 [38.0; 60.0]
SDNN, ms	65.5 [52.0; 70.0]	59.0 [47.8; 73.5]	58.0 [48.0; 68.0]	50.0 [46.0; 60.0]
%LF, %	24.1 [17.2; 29.8]	33.7 [27.1; 39.7] *p = 0.002	26.6 [18.7; 30.4]	21.2 [18.8; 31.2]
%HF, %	41.0 [27.4; 56.1]	39.3 [23.4; 45.9]	43.0 [27.3; 50.0]	37.7 [27.4; 49.9]
LF/HF, c.u.	0.5 [0.4; 1.0]	0.9 [0.6; 1.4] *p = 0.023	0.6 [0.4; 1.6]	0.6 [0.4; 1.2]

Note: * — statistically significant differences with the control (p<0.05).

Таблица 3

ВСР при пассивном антиортостазе у студенток, Me [Q_1; Q_3]

Параметр	Фолликулярная фаза (n = 47)		Лютеиновая фаза (n = 47)	
	Контроль	Антиортостаз	Контроль	Антиортостаз
Нормальная возбудимость парасимпатических центров (n=31)				
ЧСС, уд/мин	69,1 [65,1; 74,3]	66,1 [63,7; 74,6] *p=0,028	69,6 [65,1; 71,9]	68,9 [65,6; 72,9]
RRNN, мс	868,0 [808,0; 922,0]	907,0 [804,0; 942,0] *p=0,019	862,0 [835,0; 915,5]	871,0 [824,0; 915,0]
RMSSD, мс	64,0 [52,0; 79,0]	65,0 [50,0; 85,0]	66,0 [46,5; 85,0]	62,0 [42,5; 99,5]

Окончание табл. 3

Параметр	Фолликулярная фаза (n = 47)		Лютеиновая фаза (n = 47)	
	Контроль	Антиортостаз	Контроль	Антиортостаз
SDNN, мс	60,0 [51,0; 69,0]	60,0 [51,0; 74,0]	64,0 [51,0; 75,0]	68,0 [44,5; 80,0]
%LF, %	27,0 [19,7; 36,6]	27,5 [20,3; 34,9]	25,3 [20,8; 33,3]	27,4 [18,6; 35,3]
%HF, %	47,0 [33,2; 54,6]	46,9 [37,0; 56,0]	43,2 [34,3; 54,2]	42,4 [34,7; 58,8]
LF/HF, у. е.	0,7 [0,4; 1,0]	0,5 [0,4; 0,9]	0,6 [0,4; 0,9]	0,6 [0,4; 0,9]
Сниженная возбудимость парасимпатических центров (n = 16)				
ЧСС, уд/мин	67,9 [62,8; 79,4]	65,9 [62,2; 80,4]	70,3 [65,4; 73,4]	69,5 [64,8; 72,9]
RRNN, мс	882,5 [755,5; 955,0]	911,0 [746,0; 943,8]	854,0 [817,0; 917,0]	863,0 [823,0; 926,0]
RMSSD, мс	81,5 [55,5; 95,5]	81,5 [54,5; 86,8]	58,0 [48,0; 76,0]	53,0 [37,0; 61,0] *p=0,041
SDNN, мс	63,0 [52,3; 87,8]	64,0 [53,0; 82,3]	55,0 [46,0; 71,0]	55,0 [41,0; 64,0]
%LF, %	20,2 [14,3; 29,8]	26,9 [17,8; 32,4] *p = 0,030	24,2 [15,6; 33,1]	22,5 [16,5; 32,2]
%HF, %	39,2 [25,7; 52,6]	41,7 [31,6; 56,8]	45,1 [24,6; 55,4]	41,3 [23,5; 56,3]
LF/HF, у. е.	0,5 [0,3; 0,7]	0,6 [0,3; 0,9]	0,6 [0,3; 1,1]	0,6 [0,4; 1,5]

Примечание: * — статистически значимые различия с контролем (p ≤ 0,05).

Table 3

HRV in passive antiorthostasis in female students, Me [Q_1; Q_3]

Parameter	Follicular phase (n = 47)		Luteal phase (n = 47)	
	Control	Antiorthostasis	Control	Antiorthostasis
Normal excitability of parasympathetic centers (n = 31)				
HR, bpm	69.1 [65.1; 74.3]	66.1 [63.7; 74.6] *p=0.028	69.6 [65.1; 71.9]	68.9 [65.6; 72.9]
RRNN, ms	868.0 [808.0; 922.0]	907.0 [804.0; 942.0] *p=0.019	862.0 [835.0; 915.5]	871.0 [824.0; 915.0]
RMSSD, ms	64.0 [52.0; 79.0]	65.0 [50.0; 85.0]	66.0 [46.5; 85.0]	62.0 [42.5; 99.5]
SDNN, ms	60.0 [51.0; 69.0]	60.0 [51.0; 74.0]	64.0 [51.0; 75.0]	68.0 [44.5; 80.0]
% LF, %	27.0 [19.7; 36.6]	27.5 [20.3; 34.9]	25.3 [20.8; 33.3]	27.4 [18.6; 35.3]

Ending tabl. 3

Parameter	Follicular phase (n = 47)		Luteal phase (n = 47)	
	Control	Antiorthostasis	Control	Antiorthostasis
% HF, %	47.0 [33.2; 54.6]	46.9 [37.0; 56.0]	43.2 [34.3; 54.2]	42.4 [34.7; 58.8]
LF/HF, c.u.	0.7 [0.4; 1.0]	0.5 [0.4; 0.9]	0.6 [0.4; 0.9]	0.6 [0.4; 0.9]
Decreased excitability of parasympathetic centers (n=16)				
HR, bpm	67.9 [62.8; 79.4]	65.9 [62.2; 80.4]	70.3 [65.4; 73.4]	69.5 [64.8; 72.9]
RRNN, m	882.5 [755.5; 955.0]	911.0 [746.0; 943.8]	854.0 [817.0; 917.0]	863.0 [823.0; 926.0]
RMSSD, ms	81.5 [55.5; 95.5]	81.5 [54.5; 86.8]	58.0 [48.0; 76.0]	53.0 [37.0; 61.0] *p=0.041
SDNN, ms	63.0 [52.3; 87.8]	64.0 [53.0; 82.3]	55.0 [46.0; 71.0]	55.0 [41.0; 64.0]
% LF, %	20.2 [14.3; 29.8]	26.9 [17.8; 32.4] *p=0.030	24.2 [15.6; 33.1]	22.5 [16.5; 32.2]
% HF, %	39.2 [25.7; 52.6]	41.7 [31.6; 56.8]	45.1 [24.6; 55.4]	41.3 [23.5; 56.3]
LF/HF, c.u.	0.5 [0.3; 0.7]	0.6 [0.3; 0.9]	0.6 [0.3; 1.1]	0.6 [0.4; 1.5]

Note: * — statistically significant differences with the control ($p < 0.05$).

Результаты выполненного исследования показали, что у женщин проявление ответных реакций на изменение положения тела определяется не только характером постуральных воздействий, но и индивидуальными особенностями функциональной активности центров вегетативной нервной системы, а также состоянием гормонального фона.

Активный ортостаз сопровождается смещением вегетативного равновесия в сторону преобладания симпатических влияний. Это, вероятно, вызвано перераспределением кровотока в сосудистой системе и уменьшением импульсной активности барорецепторов рефлексогенных зон каротидного синуса и дуги аорты, что проявляется снижением степени возбуждения ядра блуждающего нерва и его тормозного влияния на деятельность сердца [17, 18]. В связи с этим барорецепторный рефлекс, являясь механизмом быстрого реагирования, обеспечивает поддержание адекватного уровня гемодинамики в сосудистой системе во время постуральных воздействий [19, 20]. При этом описанные изменения у женщин не зависят от фазы менструального цикла и возбудимости центров парасимпатической нервной системы.

Пассивный ортостаз также сопровождается уменьшением активности парасимпатических кардиальных центров, что наблюдается во всех группах испытуемых. Однако у женщин со сниженной возбудимостью парасимпатической системы уменьшение вагусных влияний на сердечный ритм отмечается в обе фазы ОМЦ, тогда как у студенток с нормальной возбудимостью — только в фолликулярную фазу. В лютеиновую фазу цикла у женщин с нормальной возбудимостью парасимпатической системы отмечается более высокий исходный уровень активности симпатических центров и отсутствие отклонения показателей ВСР при переходе в ортостатическое положение, что свидетельствует о меньшем функциональном резерве приспособительных механизмов у испытуемых этой группы.

Пассивный антиортостаз у женщин со сниженной возбудимостью парасимпатических центров приводит к увеличению степени участия симпатической нервной системы в регуляции сердечного

ритма, независимо от фазы ОМЦ. Это может быть обусловлено более высоким уровнем возбудимости симпатической нервной системы и концентрации катехоламинов у испытуемых в эту фазу [21, 22].

Увеличение диапазона значений кардиоинтервалов и снижение ЧСС при антиортостазе у женщин с нормальной возбудимостью в фолликулярную фазу цикла свидетельствует об увеличении влияния блуждающего нерва на миокард. Антиортостатическое положение способствует венозному возврату крови к сердцу, что приводит к повышению давления в магистральных сосудах и активации барорецепторного механизма регуляции сердечной деятельности, инициирующего активацию парасимпатического кардиального центра [23, 24]. В лютеиновую фазу цикла у испытуемых этой группы ВСР при антиортостазе не изменяется, что может быть обусловлено исходно более высокой активностью симпатических центров [25].

Выводы

Активный переход в вертикальное положение тела у студенток сопровождается уменьшением выраженности парасимпатического влияния на ритм сердца, что не зависит от фазы менструального цикла и возбудимости парасимпатических кардиальных центров. При пассивном ортостазе у женщин со сниженной возбудимостью парасимпатической системы также наблюдается уменьшение вагусного влияния на сердечную деятельность в обе фазы цикла. При нормальной парасимпатической реактивности аналогичные изменения проявляются только в фолликулярную фазу менструального цикла. Пассивный антиортостаз во время фолликулярной фазы у женщин с нормальной парасимпатической возбудимостью сопровождается увеличением вагусного эффекта на сердце, тогда как у студенток со сниженной реактивностью влияние парасимпатических центров при этом воздействии уменьшается в обе фазы цикла.

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Исследование экспрессии Ki-67 в трансплантированном жировом графте у крыс

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Аннотация. *Актуальность*. Аутотрансплантация жира применяется в пластической, реконструктивной и эстетической хирургии. В настоящее время нет исследований, направленных на изучение пролиферативной активности аутотрансплантатов жира после его различной предоперационной обработки. *Цель исследования:* оценить экспрессию Ki-67 в жировых аутотрансплантатах как маркера пролиферации на отдаленных сроках у крыс. *Материалы и методы:* исследована экспрессия белка Ki-67 в адипоцитах после аутотрансплантации жира у крыс через 30, 90 и 180 дней. Было применено три вида жировых аутотрансплантатов: солидный графт (3 группа), измельченный скальпелем графт (4 группа) и гомогенизированный жир в шприце Luer Lock (5 группа). Группу 1 составили интактные животные, а группу 2 — животные, которым однократно вводили в холку 0,9 % раствор хлорида натрия. *Результаты и обсуждение:* через 30 дней после операции количество Ki-67-позитивных клеток в жировом графте 3-й группы было значимо выше, чем в ПЖК реципиентного места 3-й группы и 5-й группы ($p<0,001$). Данный показатель был значимо выше в 4-й группе, по сравнению с ПЖК в месте аутотрансплантации жира 3-й группы ($p<0,001$) и 5-й группы ($p<0,001$), и ниже, по сравнению с солидным графтом 3-й группы ($p<0,05$). На 90-й день после проведения операции количество Ki-67-позитивных клеток в солидном графе 3-й группы было значимо выше, чем в ПЖК реципиентного места той же группы и 5-й группы ($p<0,001$), а также 4-й группы ($p<0,01$). В 4-й группе в ПЖК в месте введения жировых аутотрансплантатов количество Ki-67-позитивных клеток было значимо выше, чем в ПЖК 3-й группы ($p<0,001$) и 5-й группы ($p<0,01$). В группе гомогенизированного жира этот показатель был статистически выше, чем в подкожно-жировой клетчатке в области места аутотрансплантации солидного графта в 3-й группе ($p<0,05$). *Выводы.* Трансплантация солидного графта через 3 месяца провоцирует стимуляцию образования подкожно-жировой клетчатки в месте его введения, с высокой активность экспрессии белка Ki-67 клетками в самом жировом графте. При аутотрансплантации жировых графтов мелкого размера

(1×2×1 мм) и гомогенизированного жира через 30 и 90 дней отмечается прорастание соединительно-тканных тяжей, содержащих Ki-67-позитивные клетки и кровеносные сосуды.

Ключевые слова: трансплантация жира, Ki-67, липофилинг, пролиферация, адипоцит

Информация о финансировании. Авторы заявляют об отсутствии внешнего финансирования.

Вклад авторов. Ибадуллаева С.С. — проведение эксперимента, написание статьи. Кастыро И.В. — написание статьи, разработка дизайна исследования, Дьяченко Ю.Е. — редакция статьи, проведение эксперимента. Лаврентьева Э.А. — проведение эксперимента, статистическая обработка данных, работа с научной литературой. Хлысталов М.В. — проведение эксперимента, статистическая обработка данных, работа с научной литературой. Мороз С.Е. — проведение эксперимента, описание гистологических препаратов, корректура статьи, работа с научной литературой. Ганьшин И.Б. — разработка дизайна исследования, корректура статьи, работа с научной литературой. Попадюк В.И. — разработка дизайна исследования, Карташева А.Ф. — корректура статьи, работа с научной литературой. Королев А.Г. — проведение эксперимента, статистическая обработка данных. Баранник М.И. — корректура статьи, работа с научной литературой. Сарыгин П.В. — корректура статьи, работа с научной литературой. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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Study of Ki-67 expression in transplanted fat graft in rats

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Abstract. *Relevance.* Autotransplantation of fat is used in plastic, reconstructive and aesthetic surgery. Currently, there are no studies aimed at studying the proliferative activity of autotransplants of fat after its various preoperative treatment. *Aims.* To evaluate Ki-67 expression in fat autografts as a marker of proliferation at distant time points in rats. *Materials and Methods.* Ki-67 protein expression was examined in adipocytes after fat autografting in rats after 30, 90 and 180 days. Three types of fat

autografts were used: solid graft (group 3), scalpel-shredded graft (group 4) and homogenised fat in Luer Lock syringe (group 5). Group 1 consisted of intact animals and group 2 consisted of animals injected once in the withers with 0.9 % sodium chloride solution. *Results and Discussion.* The findings of the study indicated that, 30 days following the surgical procedure, the number of Ki-67-positive cells in the fat graft of group 3 was considerably higher than in the SCF of the recipient site of groups 3 and 5 ($p<0.001$). The same marker was found to be significantly higher in the 4th group when compared to the control group of the autotransplantation of fat in the 3rd and 5th groups ($p<0.001$), and to the 3rd group ($p<0.05$). On the 90th day following surgery, the number of Ki-67-positive cells in the solid graft of group 3 was significantly higher than in the subcutaneous fat of the recipient site of the same group and group 5 ($p<0.001$), as well as group 4 ($p<0.01$). In group 4, the number of Ki-67-positive cells in subcutaneous fat at the injection site of fat autografts was significantly higher than in subcutaneous fat in group 3 ($p<0.001$) and group 5 ($p<0.01$). In the group of homogenised fat, this indicator was found to be statistically higher than in subcutaneous fat in the area of the autotransplantation site of the solid graft in group 3 ($p<0.05$). *Conclusion.* The transplantation of a solid graft after a period of three months has been shown to stimulate the formation of subcutaneous fatty tissue at the site of its insertion. Furthermore, high activity of Ki-67 protein expression by cells in the fat graft itself has been observed. Moreover, at the time of autotransplantation of small-sized fat grafts (1×2×1 mm) and homogenised fat after 30 and 90 days, sprouting of connective-tissue strands containing Ki-67-positive cells and blood vessels was observed.

Key words: fat transplantation, Ki-67, fat grafting, proliferation, adipocyte

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Введение

Аутотрансплантация жира завоевала широкую популярность в пластической хирургии для коррекции контуров мягких тканей, восполнения потери ее объемов и омоложения кожи, однако проблема потери объема после трансплантации остается все еще актуальной. В последние годы были разработаны новые стратегии, которые несколько улучшили результаты липофилинга и трансплантации жировой ткани. Вопрос сохранения жирового трансплантата все еще требует дальнейших исследований. Это открывает новые возможности в изучении механизмов регенерации стволовых клеток жировой ткани в реципиентном месте после трансплантации

жира. Значение белка экспрессии Ki-67, апоптоза, макрофагов, которые тесно связаны с локальной микросредой и регенерацией тканей, становится все более важной в контексте пересадки жира [1–4].

Изучение активности стволовых клеток жировой ткани и стромально-васкулярной фракции может стать новым этапом в понимании методов улучшения приживаемости жировых трансплантатов и их последующей сохранности в месте пересадки [5]. Белок Ki-67 на протяжении десятилетий используется в качестве маркера пролиферации опухолевых клеток человека. В процессе митоза Ki-67 играет ключевую роль в формировании перихромосомного слоя — рибонуклеопротеиновой оболочки, которая покрывает конденсированные хромосомы. В этой структуре Ki-67 предотвращает агрегацию митотических хромосом, обеспечивая их правильное разделение [6].

Для лучшего понимания нормальных митотических и пролиферативных процессов в жировом аутотрансплантате при различных методах его обработки возможна оценка экспрессии белка Ki-67 в жировой ткани и тканях, окружающих жировой трансплантат.

Цель исследования. Оценить экспрессию Ki-67 в жировых аутотрансплантатах как маркера пролиферации на отдаленных сроках у крыс.

Материалы и методы

Дизайн исследования

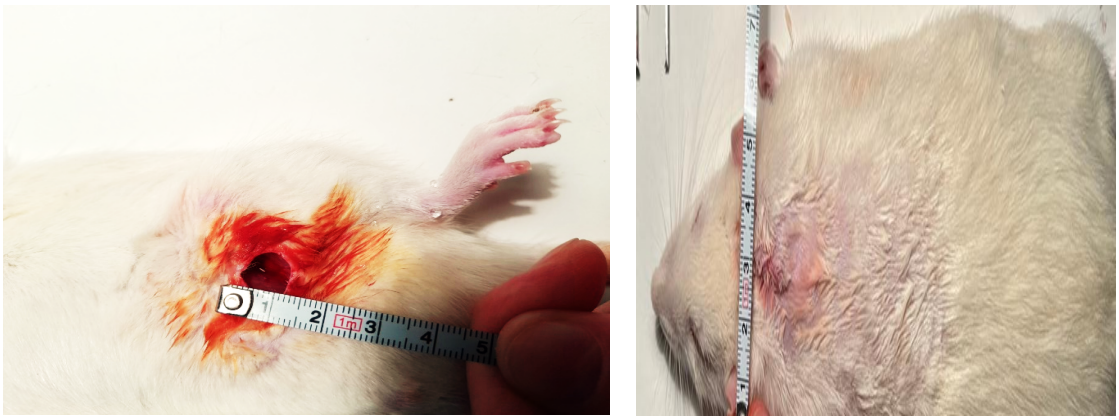
Исследование было проведено на 65 половозрелых крысах-самцах линии Wistar. Контрольнегативную группу интактных животных составили 5 крыс, которым не проводилось никаких манипуляций (1 группа, n = 5). Во 2-й группе (контрольпозитивная, n = 15) иглой 25G (D = 0.5 мм) в участок кожи на холке площадью 1 см^2 внутрикожно 6-кратно вводили 0,05 мл 0,9 % раствор хлорида натрия. В третьей группе (n = 15) вводился аутотрансплантат цельной необработанной жировой ткани размером 2×4×3 мм (1,2 ± 0,5 мг) в область холки через разрез длиной 5 мм. В четвертой группе (n=15) проводилась трансплантация предварительно измельченной скальпелем собственной жировой ткани 1×2×1 мм (1,33 ± 0,47 мг). Крысам данной группы в область холки через разрез 0,5 см вводили предварительно измельченную скальпелем жировую ткань. В пятой группе (n = 15) через иглу 20G (D=1 мм) в области холки внутрикожно вводили препарат собственной жировой ткани после предварительной ее обработке в шприце Луер Лок (2 мл) с последовательной сменой насадок с диаметром отверстий от 2,4 мм до 0,2 мм. Критерием готовности материала была его способность проходить через иглу шприца диаметром 0,6 мм. Объем одной инъекции составлял 0,05 мл посредством 6-ти инъекций на площадь 1 см^2. Жировая ткань у всех крыс извлекалась из паховой области (Рисунок 1) и промывалась охлажденным 0,9 % раствором хлорида натрия, после чего обрабатывалась одним из указанных методов. Оценивали количество клеток с экспрессией Ki-67 в месте трансплантированного жира и толщину жировых графтов.

Эксперименты выполнены в соответствии с требованиями Директивы 2010/63/EU. Исследование одобрено локальным Комитетом по этике медицинского института РУДН, протокол № 02–24 от 20.02.2023 г.

Всем крысам 2–5 групп манипуляции проводились под общей анестезией при помощи изофлуранового наркоза (6 %) в эксикаторе. После чего крысы проверялись на стандартные защитные рефлексы. Затем уменьшалась подача наркоза в испарителе до 0.6–1 %. После чего животные помещались на операционном столе и им надевали наркозную маску. После окончания процедур выключали испаритель и снимали наркозную маску.

Забор тканей и иимуногистохимическая окраска препаратов

Эвтаназию крысам 2–5 групп проводили через 30, 90 и 180 дней после проведения эксперимента при помощи внутрибрюшинного введения токсичных доз раствора Золетила 100. После этого проводилась вырезка тканей в области холки. Ткани после проведения их забора помещались в 10 %



а *б*

Рис. 1. Локализация места забора аутотрансплантата жировой ткани у крыс (*а*), определение координат для трансплантации жировой ткани у крыс в 3–5 группах (*б*). Стрелкой указано место трансплантации

Fig. 1. Localization of the site of autotransplantation of adipose tissue in rats (*а*), determination of coordinates for transplantation of adipose tissue in rats in 3–5 groups (*б*). The arrow indicates the place of transplantation

раствор забуференного формалина и фиксировались в течение 1 недели. Проводилась заливка тканей парафином и приготовление парафиновых блоков. Толщина всех срезов составляла 4 микрона. Срезы окрашивались моноклональными кроличьими антителами к белку Ki-67 (клон GM0010, Россия). Оценивали площадь сальных желез (ПСЖ) и долю Ki-67-позитивных клеток в них. Препараты сканировались на микроскопе KFBIO 400 (Konfoong Biotech International Co., Ltd., КНР). Сканированные срезы анализировались при помощи программного обеспечения Aperio ImageScope v12.2.2.5015 (Leica Microsystems, Франция).

Статистическая обработка данных

Данные обрабатывались в программном обеспечении Microsoft Exel, MATLAB, STATISTICA 12.6, JASP 0.14.0.0. При сопоставлении данных группы на различных сроках после введения препаратов применялся критерий Вилкоксона. При сравнении данных экспериментальных групп между собой и с данными контрольных групп применяли Краскела–Уоллиса или критерий Манна–Уитни. Для каждого сравнения в результате статистического анализа определялся свой уровень значимости ($p <$ от 0,001 до 0,05).

Результаты и обсуждение

Критерий Краскела–Уоллиса показал, что толщина имплантированного солидного жирового графта на всех сроках в 3-й группе была значимо выше, чем толщина подкожной жировой клетчатки (ПЖК) в той же группе и жировой ткани после аутотрансплантации мелких графтов (4-я группа) и введения гомогенизированного жира (5-я группа) ($p<0,001$). При этом его размеры значимо не менялись в течение всего срока анализа.

Критерий Манна–Уитни показал, что через 1 месяц после проведения эксперимента в 5-й группе подкожно-жировая клетчатка в реципиентной области была достоверно толще по сравнению с 3-й и 4-й группами ($p<0,001$). Через 3 месяца размер ПЖК был значимо выше в 4-й группе по сравнению с остальными экспериментальными группами ($p<0,01$). Через полгода сохранялась та же тенденция — толщина жировой ткани в гиподерме была выше в 4-й группе по сравнению с 3-й ($p<0,05$) и 5-й группами ($p<0,001$) (рис. 2, табл. 1).

Критерий Манна–Уитни выявил, что в группе крыс, которым имплантировали солидный графт, толщина образовавшейся ПЖК на 90-й день увеличилась по сравнению с 30-м днем ($p<0,05$). На 180-й день она также выросла по сравнению с 90-м днем

($p<0,001$). В 4-й группе толщина жира в гиподерме значимо возросла на 90-й день по сравнению с 30-м ($p<0,001$) и на 180-й день, по сравнению с 90-м днем ($p<0,001$) ($p<0,001$) ($p<0,001$) ($p<0,001$) ($p<0,01$). Увеличение толщины ПЖК в месте введения гомогенизированного жирового графта произошло лишь на 180-й день после проведения эксперимента ($p<0,05$) (Рисунок 2, Таблица 1).

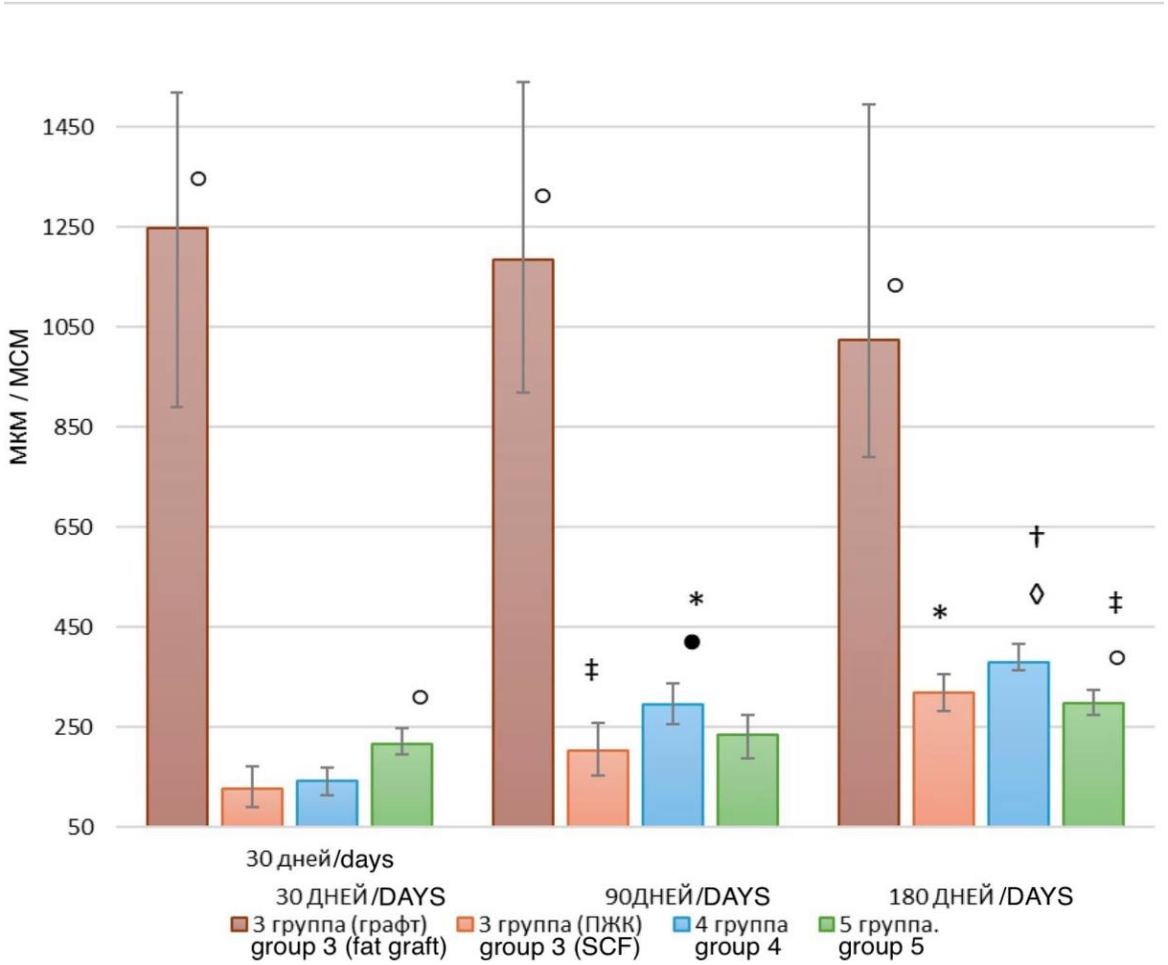


Рис. 2. Изменения толщины жировых графтов после различных видов липофилинга

Примечание: ⁎ — различия между сроками в экспериментальных группах ($p<0,001$); ✝ — различия между сроками в экспериментальных группах ($p<0,01$); ‡ — различия между сроками в экспериментальных группах ($p<0,05$); ○ — различия между экспериментальными группами на разных сроках ($p<0,001$); ● — различия между экспериментальными группами на разных сроках ($p<0,01$); ◊ — различия между экспериментальными группами на разных сроках ($p<0,05$).

Fig. 2. Changes in the thickness of fat grafts after various types of lipofilling.

Note: ⁎ — differences between the dates in the experimental groups ($p<0.001$); ✝ — differences between the dates in the experimental groups ($p<0.01$); ‡ — differences between the dates in the experimental groups ($p<0.05$); ○ — differences between the experimental groups at different dates ($p<0.001$); ● — differences between experimental groups at different dates ($p<0.01$); ◊ — differences between experimental groups at different dates ($p<0.05$).

Таблица 1

Значения толщины жировых графтов и ПЖК после трансплантации различных видов липофилинга

Толщина графта (мкм)		3 группа (графт)	3 группа (ПЖК)	4 группа	5 группа
30 дней	25 % перцентиль	357	45	25	31
	Медиана	1247	127	143	217
	75 % перцентиль	271	38	29	23
90 дней	25 % перцентиль	264	55	42	41
	Медиана	1184	204	295	234
	75 % перцентиль	356	51	39	47
180 дней	25 % перцентиль	233	38	38	26
	Медиана	1023	318	379	298
	75 % перцентиль	472	36	16	24

Table 1

Values of the thickness of fat grafts and subcutaneous fat tissue after transplantation of various types of lipofilling

Graft thickness (μm)		Group 3 (fat graft)	Group 3(SCF)	Group 4	Group 5
30 days	25% percentile	357	45	25	31
	median	1247	127	143	217
	75% percentile	271	38	29	23
90 days	25% percentile	264	55	42	41
	median	1184	204	295	234
	75% percentile	356	51	39	47
180 days	25% percentile	233	38	38	26
	median	1023	318	379	298
	75% percentile	472	36	16	24

Количество Ki-67-позитивных клеток в жировой ткани. Критерий Краскела–Уоллиса показал, что на 30-й день после операции в солидном графе 3-й группы количество Ki-67-позитивных клеток статистически значимо было выше, по сравнению с 90-м днем ($p < 0,001$). Это количество значимо уменьшилось на 180-й день по сравнению с 90-м днем ($p < 0,001$). Количество Ki-67-позитивных клеток в ПЖК 3-й группы по сравнению с 30-м послеоперационным днем на 90-й и 180-й дни достоверно снизилось ($p < 0,001$). Этот показатель снижался и в 4-й группе. Так, на 90-й день Ki-67-позитивных клеток было меньше, чем на 30-й день ($p < 0,001$), а на 180-й день эта величина снизилась по сравнению с 90-м днем ($p < 0,01$). Количество Ki-67-позитивных клеток в жировой ткани в месте введения гомогенизированного жира на 90-й день было значимо меньше, чем на 30-й день ($p < 0,001$). Через 6 месяцев этот показатель достоверно уменьшился по сравнению с тремя месяцами раннее ($p < 0,05$) (рис. 3, табл. 2). Критерий Манна–Уитни определил, что через 30 дней после операции количество Ki-67-позитивных клеток в жировом графте 3-й группы было значимо выше, чем в ПЖК реципиентного места 3-й группы и 5-й группы ($p < 0,001$). Данный показатель был значимо выше в 4-й группе по сравнению с ПЖК в месте аутотрансплантации жира 3-й группы ($p < 0,001$) и 5-й группы ($p < 0,001$) и ниже, по сравнению с солидным графтом 3-й группы ($p < 0,05$). Количество Ki-67-позитивных клеток

было достоверно выше в 5-й группе по сравнению с ПЖК 3-й группы ($p < 0,01$) (рис. 3, табл. 2). Согласно критерию Манна–Уитни, на 90-й день после проведения операции количество Ki-67-позитивных клеток в солидном графе 3-й группы было значимо выше, чем в ПЖК реципиентного места той же группы и 5-й группы ($p < 0,001$), а также 4-й группы ($p < 0,01$). В 4-й группе в ПЖК в месте введения жировых аутотрансплантатов количество Ki-67-позитивных клеток было значимо выше, чем в ПЖК 3-й группы ($p < 0,001$) и 5-й группы ($p < 0,01$). В группе гомогенизированного жира этот показатель был статистически выше, чем в подкожно-жировой клетчатке в области места аутотрансплантации солидного графта в 3-й группе ($p < 0,05$). Через 180 дней количество Ki-67-позитивных клеток было достоверно выше лишь в солидном графте 3-й группы по сравнению с ПЖК той же группы и остальных экспериментальных групп ($p < 0,001$) (рис. 3, табл. 2).

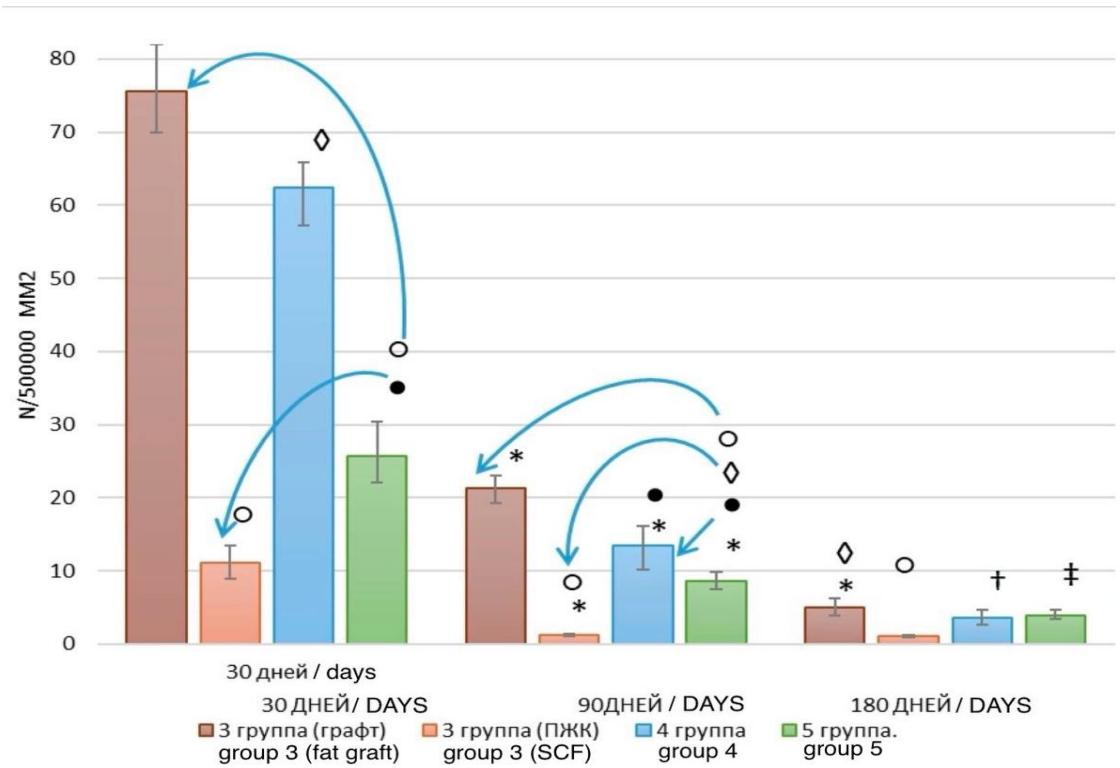


Рис. 3. Изменения содержания Ki-67-позитивных клеток в жировой ткани после различных видов липофилинга (описание в тексте)

Примечание: ∗ — различия между сроками в экспериментальных группах ($p < 0,001$); † — различия между сроками в экспериментальных группах ($p < 0,01$); ‡ — различия между сроками в экспериментальных группах ($p < 0,05$); ○ — различия между экспериментальными группами на разных сроках ($p < 0,001$); ● — различия между экспериментальными группами на разных сроках ($p < 0,01$); ◊ — различия между экспериментальными группами на разных сроках ($p < 0,05$).

Fig. 3. Changes in the content of Ki-67-positive cells in adipose tissue after various types of lipofilling (description in the text)

Note: ∗ — differences between the dates in the experimental groups ($p < 0.001$); † — differences between the dates in the experimental groups ($p < 0.01$); ‡ — differences between the dates in the experimental groups ($p < 0.05$); ○ — differences between the experimental groups at different dates ($p < 0.001$); ● — differences between experimental groups at different dates ($p < 0.01$); ◊ — differences between experimental groups at different dates ($p < 0.05$).

Таблица 2

Значения количества Ki-67-позитивных клеток после трансплантации различных видов жировых графтов

Ki-67-позитивные клетки (n/500000 μm²)		3 группа (графт)	3 группа (ПЖК)	4 группа	5 группа
30 дней	25 % перцентиль	5,67	2,33	3,53	4,78
	Медиана	75,61	11,18	62,37	25,64
	75 % перцентиль	6,33	2,27	5,09	3,49
90 дней	25 % перцентиль	2,08	0,17	2,64	1,24
	Медиана	21,33	1,26	13,55	8,57
	75 % перцентиль	1,72	0,13	3,41	1,01
180 дней	25 % перцентиль	1,07	0,21	1,01	0,67
	Медиана	4,97	1,08	3,67	3,95
	75 % перцентиль	1,34	0,09	0,99	0,44

Table 2

Values of the number of Ki-67-positive cells after transplantation of various types of fat grafts

Ki-67-positive cells (n/500000 μm²)		Group 3(fat graft)	Group 3(SCF)	Group 4	Group 5
30 days	25% percentile	5.67	2.33	3.53	4.78
	median	75.61	11.18	62.37	25.64
	75% percentile	6.33	2.27	5.09	3.49
90 days	25% percentile	2.08	0.17	2.64	1.24
	median	21.33	1.26	13.55	8.57
	75% percentile	1.72	0.13	3.41	1.01
180 days	25% percentile	1.07	0.21	1.01	0.67
	median	4.97	1.08	3.67	3.95
	75% percentile	1.34	0.09	0.99	0.44

Данное исследование является первым, в котором описана экспрессия белка Ki-67 в жировых графтах в зависимости от вида обработки пересаженного аутожира у крыс.

Обогащение жирового графта культивированными клетками СВФ и тромбоцитарным фактором роста представляет собой один из перспективных методов, активно исследуемых для улучшения выживаемости трансплантатов. Эти подходы могут способствовать выживанию трансплантата через несколько механизмов, включая усиление ангиогенеза, что, в свою очередь, улучшает кровоснабжение и доставку кислорода и питательных веществ к клеткам трансплантата. Кроме того, разбиение жирового трансплантата на более мелкие фрагменты также может способствовать улучшению выживаемости. Такой подход обеспечивает более эффективный доступ привитых клеток к оксигенации и питанию в донорской области. Уменьшая размер фрагментов, можно увеличить площадь поверхности, что позволяет улучшить диффузию кислорода и питательных веществ, а также способствует более равномерному распределению клеток в трансплантате. Таким образом, сочетание этих методов может создать оптимальные условия для выживания и интеграции жирового трансплантата, что имеет важное значение для успешного выполнения процедур пересадки жировой ткани в клинической практике [7]. В настоящем исследовании именно группа крыс, которой были пересажены мелкие жировые графты, показала

самую высокую экспрессию Ki-67 в графте через 1 и 3 месяца по сравнению с другими группами. Эти показатели схожи и с ростом толщины жира в гиподерме. Это связано, по-видимому, с тем, что солидный графт подвергается некрозу на ранних стадиях его приживаемости и с последующим его фиброзированием, а при пересадке гомогенизированного жира, вероятно, погибает достаточное количество стволовых клеток из стромально-васкулярной фракции [8]. Рост экспрессии белка Ki-67 в солидном графте, по сравнению с другими группами, по нашему мнению, свидетельствует о запуске процессов регенерации и фиброза, так как количество Ki-позитивных клеток было высоко в соединительной ткани [9], а не в жировой.

У интактных крыс и крыс, которым вводили 0,9 % раствор хлорида натрия, в гиподерме жировой ткани обнаружено не было. В связи с этим представляется интересным тот факт, что после трансплантации солидного графта между гиподермой и мышечным слоем в гиподерме у крыс была обнаружена новая жировая ткань. Это, скорее всего, связано с миграцией клеток стромально-васкулярной фракции из поверхностных слоев графта в соседние слои гиподермы или воздействием факторов дифференцировки из трансплантированных клеток на стволовые клетки мезенхимы в реципиентном месте. Это подтверждается исследованиями, в которых меченые стволовые клетки жировой ткани мышам вводили внутривенного после пересадки жировых графтов, в которых эти клетки активно накапливались [10]. В других исследованиях, направленных на изучение стволовых клеток жировой ткани в процессах ревитализации послеоперационных тканей, была подтверждена способность СТКЖ к миграции в области послеоперационной раны [11]. Тем не менее, толщина этого новообразованного жира с течением времени (на 90-й и 180-й дни) стала уменьшаться, что связано, по-видимому, со снижением активности клеток СВФ, которые в условиях гипоксии могут сохранять свою активность до 3 недель и запускать процессы регенерации уже через 3 дня после проведения липофилинга [12]. Подобные изменения новообразованной жировой клетчатки у крыс помогут объяснить исследования, направленные на изучение апоптоза после аутотрансплантации жира [13–19]. В клинической практике понимание этих механизмов поможет найти методику сохранения объемов имплантированного и новообразованного жира.

Выводы

На основании полученных результатов очевидно, что трансплантация солидного графта через 3 месяца провоцирует стимуляцию образования подкожно-жировой клетчатки в месте его введения, с высокой активностью экспрессии белка Ki-67 клетками в самом жировом графте. При аутотрансплантации жировых графтов мелкого размера (1x2x1 мм) и гомогенизированного жира через 30 и 90 дней отмечается прорастание соединительно-тканных тяжей, содержащих Ki-67-позитивные клетки и кровеносные сосуды. Различный размер адипоцитов при данных методах трансплантации косвенно свидетельствует о разных стадиях их роста и дифференцировки.

Размер жирового графта напрямую оказывает влияние на экспрессию белка Ki-67 в клетках аутотрансплантатов. Введение гомогенизированного жира провоцирует наименьшую активность экспрессии белка Ki-67 на всех сроках по сравнению с солидным и измельченными жировыми графтами.

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ОБЗОР
REVIEW

Highly differentiated cells in the therapy of acute respiratory distress syndrome

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Abstract. *Relevance.* Acute respiratory distress syndrome (ARDS) is a severe, life-threatening form of acute lung injury with a high mortality rate. In severe cases, pathological changes extend to the systemic level and manifest as cytokine storm syndrome. The lack of effective treatment options underscores the importance of exploring therapeutic approaches, including cell therapy. Interest in this treatment option increased during the SARS-CoV-2 pandemic, as evidenced by the numerous clinical trials registered for the use of cell preparations to treat ARDS. *The aim of the study:* Thus, this review summarizes preclinical and clinical studies on using highly differentiated cells, including immune system cells, to treat ARDS. To this end, we will describe key points in the pathogenesis of ARDS, including etiologic subtypes and stages, as well as the key cells involved and the results of their use in ARDS therapy. This review highlights the potential of using alveolar cells type 1 and type 2, as well as epithelial cells, for rapid lung regeneration after ARDS. Currently, there are no data describing the use of neutrophils, which trigger primary pathological changes in the lungs, for ARDS treatment. The use of macrophages, which play a key role in ARDS pathogenesis,

is limited by their ability to quickly repolarize. Natural killer cells (NK cells), regulatory T cells (Tregs), and invariant natural killer T (iNKT cells) have shown high efficacy in treating ARDS in preclinical and clinical studies. *Conclusion.* Thus, using NK cells, Tregs, and iNKT cells for ARDS cell therapy seems promising. However, the lack of standardized protocols for preparing and administering cell therapies, as well as small sample sizes, indicate the need for additional studies.

Keywords: ARDS, cell therapy, macrophage, iNKT cells, Treg, neutrophils, clinical trials

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Introduction

Acute respiratory distress syndrome (ARDS) is a critical form of acute lung injury (ALI). It is characterized by impaired gas exchange and reduced lung compliance [1]. According to the Berlin definition, ARDS requires meeting three key criteria. These include an acute onset, bilateral pulmonary infiltrates on imaging (chest X-ray or computer tomography) not caused by cardiac failure, and a PaO_2/FiO_2 ratio of less than 300 mmHg [2]. The mortality rate in ARDS varies depending on disease severity and population, with a reported weighted pooled mortality of approximately 40% [3].

Current management of ARDS is primarily supportive, aiming to sustain vital organ function while the lungs heal. The cornerstone of this approach is lung-protective ventilation, which minimizes further ventilator-induced lung injury. Adjunctive strategies include prone positioning to improve oxygenation, careful sedation, and fluid balance management, often utilizing diuretics. In the most severe cases, extracorporeal membrane oxygenation (ECMO) serves as a salvage therapy to provide gas exchange directly [4]. The lack of treatments that directly address the underlying pathophysiology of ARDS has significantly intensified the search for new disease-modifying interventions. Cell therapy has emerged as a particularly promising avenue, supported by its established therapeutic role in a variety of conditions, from accelerating wound healing to treating neurodegenerative diseases. Since the first FDA-approved cell therapy product in 2010 [5], the field of advanced treatments has rapidly evolved, with over 30 gene and cell therapies currently approved [6], including the landmark 2023 approval of the first

CRISPR/Cas-based treatment for sickle cell disease [7]. However, this remarkable innovation and the growing complexity of therapy have simultaneously raised significant concerns about prohibitive costs and the difficulty of ensuring equitable patient access to treatment [8].

Although "cell therapy" is often equated with mesenchymal stem cells (MSCs)—valued for their multipotency, availability, and suitability for allogeneic use — advances in biotechnology now enable the application of more differentiated cell types. Additionally, strategies aiming to modulate specific pathogenic cell populations in situ represent a growing direction in ARDS treatment.

Thus, the objective of this review is to synthesize recent findings on ARDS pathogenesis, with a focus on alterations in immune cell populations, and to evaluate their translational potential for novel therapeutic interventions.

Key points of acute respiratory distress syndrome pathogenesis

In the previous reviews, the pathogenesis of ARDS was revealed in detail [9]. We highlighted key points in the pathogenesis of ARDS and some interesting facts necessary to understand the points of impact for the use of immune cells in the therapy of this condition.

Etiological subtypes of ARDS

A key feature of ARDS is its polyetiological nature. Its primary risk factors are categorized into two distinct groups. The first group involves direct lung injury, leading to pulmonary ARDS. This includes etiologies such as aspiration, inhalation of toxic substances, pulmonary infection, and blunt chest trauma [10]. The second group encompasses indirect lung injuries that originate outside the lungs, causing extrapulmonary ARDS. Examples are shock, sepsis, trauma, major hemorrhage, blood transfusions, poisoning, and cardiopulmonary bypass. These two etiological subtypes lead to divergent pathophysiological and histological changes [11]. In pulmonary ARDS, direct damage to the bronchial and alveolar epithelium occurs. This damage, resulting from factors like infection or contusion, leads to bronchial obstruction, atelectasis, and alveolar edema. Histologically, alveolar edema and intra-alveolar fibrin deposition are predominant features. Advanced stages are further characterized by significant collagen fiber formation and the presence of apoptotic neutrophils. Single-cell sequencing analyses reveal that pulmonary ARDS lung tissue contains elevated levels of B cells, neutrophils, and T helper (Th) cells. Conversely, it shows relatively lower counts of basophils, macrophages, monocytes, and dendritic cells compared to the extrapulmonary subtype [12]. In the second case, the initial insult is systemic, leading to damage of the pulmonary capillary endothelium. This injury triggers metabolic and structural alterations, which increase the permeability of the alveolar-capillary barrier. Consequently, plasma and blood cells extravasate into the lung interstitium, causing a pronounced thickening of the interalveolar septa. The resulting pathological pattern in the lungs is more diffuse than in pulmonary ARDS and is predominantly characterized by alveolar collapse rather than consolidation.

Stages of the acute respiratory distress syndrome

The course of ARDS includes three sequential phases: exudative, proliferative, and fibrotic [13]. The exudative phase begins with activation of innate immunity via Toll-like receptors on alveolar macrophages and epithelium. This triggers the recruitment of neutrophils and their formation of neutrophil extracellular traps (NETs). Simultaneously, levels of thrombin, TNF-α, and VEGF increase, destabilizing the endothelial VE-cadherin and epithelial E-cadherin junctions. This leads to disruption of the alveolar-capillary barrier, impaired fluid clearance, and the development of alveolar oedema, which defines this stage.

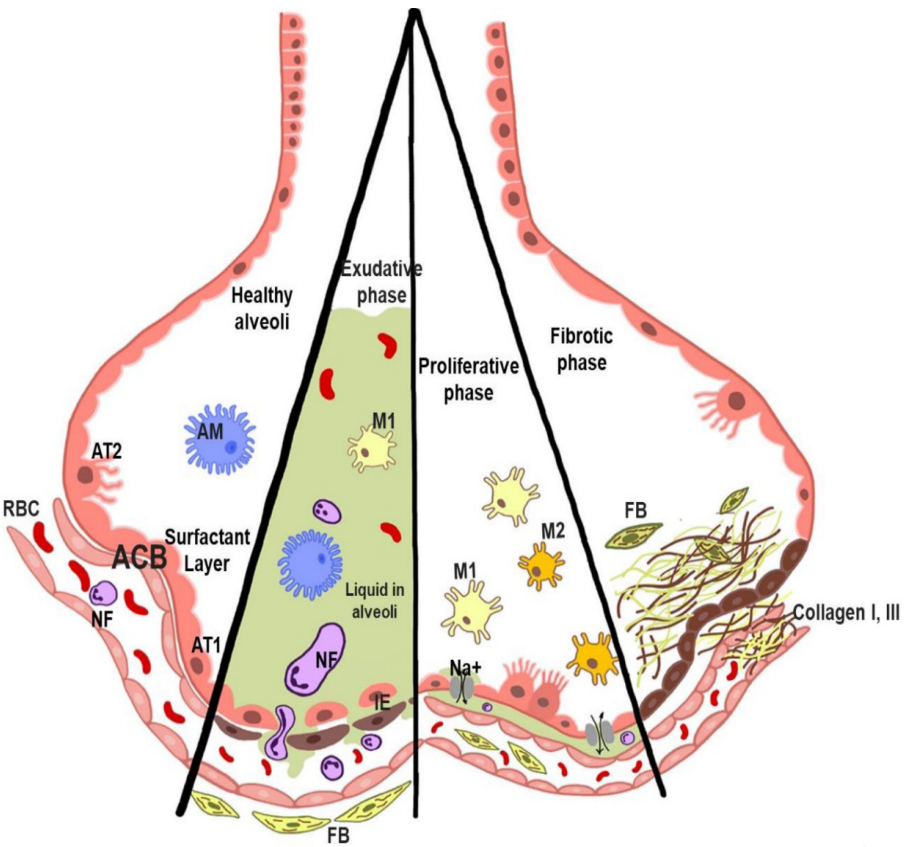
The proliferative phase focuses on inflammation resolution through three key processes: epithelial barrier repair, clearance of inflammatory cells, and restoration of alveolar fluid homeostasis. This stage involves proliferation of type II alveolar cells, fibroblasts, and myofibroblasts. Disease progression can then follow one of two paths. The first, favourable pathway leads to

normalized gas exchange via alveolar cell regeneration. The second, less favourable pathway involves fibroblast invasion into alveolar spaces through breaches in the basal lamina [14]. During this remodelling, hyaline membranes are cleared by macrophage phagocytosis or become infiltrated by fibroblasts. The interstitial space, rich in collagen and elastic fibers, hosts interstitial fibroblasts (IFs). Buechler et al. categorizes fibroblasts across organs into two principal subtypes: universal and specialized, the latter existing in either a steady-state or activated (perturbed) form [15]. Close crosstalk between alveolar macrophages (AMs) and IFs is essential for regulating extracellular matrix remodelling and driving fibroblast activation into contractile myofibroblasts, a process relevant in both health and disease [16, 17].

The final, fibrotic phase is marked by chronic scarring and vascular occlusion. As ARDS is a systemic condition, pulmonary recovery is contingent on overall clinical improvement. Activated fibroblasts proliferate and deposit collagen types I and III, forming fibrotic foci that lead to either slowly resolving or permanent architectural distortion. Notably, in influenza-associated ARDS, the fibroblast secretome can shift; for instance, production of ADAMTS4 protease by activated fibroblasts correlates with severe disease and increased mortality [18].

The main stages of ARDS pathogenesis are summarized in Figure.

In healthy lungs, endothelial and alveolar epithelial integrity is mediated by vascular endothelial cadherin (VE-cadherin) and E-cadherin respectively. Type I and type II alveolar epithelial cells are involved in maintaining an osmotic gradient for the removal of fluid from the alveoli into the interstitium of the lung. A key component necessary for the creation of the osmotic gradient is the sodium channel (ENaC). Initially, there



Pathogenesis of Acute respiratory distress syndrome. AT1 — type I alveolar cells, AT2 — type II alveolar cells, AM — alveolar macrophages, ACB — alveolar-capillary barrier, NF — neutrophils, RBC — red blood cells, FB — fibroblasts, IE — interstitial edema

is activation of the innate immune system via Toll-like receptors on pulmonary epithelium and alveolar macrophages. Recruitment of neutrophils to the lungs occurs and NETs are formed. Thrombin, tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF) are increased, leading to destabilization of VE-cadherin bonds. Neutrophils migrating to the focus of inflammation cause damage to the epithelium. Simultaneously with the disruption of the alveolar-capillary barrier, alveolar fluid clearance is impaired. As a result, the formation of pulmonary oedema occurs. Therefore, the first stage of the disease is called the exudative stage. Resolution of inflammation requires restoration of the alveolar epithelial barrier, removal of inflammatory cells and restoration of alveolar fluid clearance. Type II alveolar cells, fibroblast and myofibroblasts proliferate in this phase. The proliferative phase transitions smoothly into the fibrotic phase. There is an accumulation of collagen and fibrin with subsequent occlusion of vessels and loss of alveoli of their functions.

Key cells involved in acute respiratory distress syndrome pathogenesis and approaches to treating based on targeting these cells

The alveolar-capillary barrier, consisting of endothelial cells, type I alveolar epithelial cells (AEC1), type II alveolar epithelial cells (AEC2) and basement membranes, takes the main blow in developing ARDS. In addition, both innate (macrophages, neutrophils) and adaptive (T and B lymphocytes) immune cells are actively involved in the pathogenesis of ARDS. Currently, all of the cell types described are under close research scrutiny. The data obtained can be used both to deepen knowledge of the pathogenesis of ARDS and to develop new approaches to its therapy based on their use.

Endothelial cells

In physiological conditions endothelial cells (EC) are known to regulate the balance between the processes of coagulation and fibrinolysis. Normally, they inhibit coagulation by binding antithrombin III on the endothelial surface, endothelial production of tissue factor pathway inhibitor (TFPI), expression of thrombomodulin, activation of protein C and production of tissue plasminogen activator (t-PA) [19]. In inflammatory diseases, including ARDS, endothelial anticoagulant function is impaired by NF-kB-dependent mechanisms. It was experimentally shown that inhibition of NF-kB in the endothelium leads to increased barrier function of the vascular wall, decreased neutrophil infiltration in the lungs, liver, kidneys, heart and small intestine, as well as decreased thrombin-antithrombin complexes in the blood [20]. The glycocalyx of the endothelial lining, composed of glycosaminoglycans, proteoglycans, and glycoproteins, plays an important role in maintaining barrier function. Disruption of the glycocalyx leads to NO release, vasodilation, and increased vascular permeability [21]. In experimental models of LPS-induced endotoxemia and in patients with SARS-CoV-2, a thinning of the glycocalyx on the surface of the endothelium of pulmonary capillaries was observed. This facilitates the interaction of neutrophils with adhesion molecules on EC, their rolling and edge-standing [22]. Vascular endothelial cells of alveolar capillaries can be involved in regenerative processes. In [23] it was shown that the alveolar capillary endothelium, like the alveolar epithelium, consists of two intermixed cell types. The first cell type is the “aerocytes”. It is specialized for gas exchange and leukocyte transport and is unique to the lung. The other cell type, termed gCap (“general” capillary), is specialized to regulate vasomotor tone. It functions as a stem/progenitor cell in capillary homeostasis and repair. Aerocytes (aCap) may be particularly important in lung injury because they are the likely site of leukocyte trafficking, which is primarily a capillary function in the lung [24]. They specifically express adhesion and leukocyte sequestering genes. gCap cells function as specialized stem/progenitor cells that replenish the alveolar capillary endothelium during maintenance and repair. gCap cells express genes encoding MHC class II components, suggesting that they present antigens. In addition, gCap cells express a vasoconstrictor (Edn1) that can signal to the endothelin type A receptor

(Ednra) on pericytes; they also express endothelial nitric oxide synthase (Nos3) and prostaglandin I2 synthase (Ptgis), making them a source of vasodilators. In the experimental model of ARDS, robust apelin expression has been demonstrated in gCap, stem-like ECs that give rise to apelin receptor-positive, highly proliferative progenitor cells responsible for replenishing all depleted endothelial cell pools, including aCap that rebuild the air-blood barrier [25]. Other work [26] has identified macrovascular endothelium (maECs), microvascular endothelium (miECs), and a novel population of Car4-high ECs in the mouse lung. Car4-high ECs express a unique gene signature and ligand-receptor analysis indicates that they are primed to receive reparative signals from alveolar type I cells. After acute lung injury, they are preferentially localized in regenerating regions of the alveolus. Influenza infection reveals the emergence of a population of highly proliferative ECs, likely derived from multiple miEC populations, that contribute to alveolar revascularization after injury. These findings highlight the critical role of ECs cells in the regenerative process in ARDS mediating lung microvascular repair and provide insights for the development of novel regenerative strategies for the treatment of ALI and ARDS.

Type I alveolar epithelial cells

Alveolar epithelial cells (AEC1 or AT I) are large flat cells that cover more than 95% of the alveolar surface area and promote efficient gas exchange [27]. In healthy lung this cells maintain fluid and ion balance by expression aquaporin-5 (AQP5), which is crucial for water movement across the lung epithelium, helping maintain the optimal amount of alveolar lining fluid and amiloride-sensitive epithelial sodium channel (ENaC) and various potassium channels, which help regulate ion fluxes and maintain the electrochemical gradient necessary for fluid balance [28, 29]. They express receptors like TLR4 and RAGE, which can initiate inflammatory responses upon sensing microbial products [27]. Emerging evidence suggests that AEC1 cells are involved in protein transport and translocation via transcytosis, contributing to the regulation of macromolecules across the alveolar epithelium. The potency of this cell type in the therapy of ARDS remains to be explored.

Type II Alveolar Epithelial Cells (AEC2 or AT II)

The main functions of AEC2 in healthy lungs are surfactant production, secretion, and regeneration of alveolar epithelium [30]. It is shown that in humans, cell trapping in the transition state leads to the development of fibrosis. AEC2 cells regulate the immune response by synthesizing surfactant and other anti-inflammatory proteins and lipids as stated above. These cells help repair damaged lung tissue, rapidly proliferating and differentiating into AEC1 cells after epithelial cell injury. Therapy with freshly isolated enriched fraction of AEC2 cells from HCl-LPS-induced ARDS rats led to the effects similar to MSC therapy. A significant decrease in total protein and IgM in bronchoalveolar lavage (BAL) was shown, indicating a decrease in epithelial permeability. The results of counting the number of neutrophils in BAL fluid and myeloperoxidase (MPO) activity showed a decrease both during treatment with MSCs and during treatment with AEC2 cells. Thus, it can be assumed that AEC2 therapy has great potential [31].

Neutrophils

Normally, neutrophils are located in the lung microvasculature beyond the airspaces [10]. This pool of lung neutrophils exists in a dynamic equilibrium with circulating neutrophils, allowing for rapid response to infections or other stimuli [32]. The proinflammatory environment that forms in the alveoli during the development of ARDS promotes the recruitment of neutrophils. Here, neutrophils are activated and release reactive oxygen species, proteases, and proinflammatory lipid mediators such as prostaglandins and leukotrienes [33]. It is shown that in sepsis, a common complication of which is ARDS, neutrophils are marginalized in capillaries due to increased expression of adhesion factors — E-selectin, ICAM-1 and V–CAM-1 — on endothelial cells. Adhesion of activated neutrophils to the vascular wall and their transmigration into tissues leads to further activation of endothelial cells, completing the “vicious circle” [34]. As a result, exudate penetrates the pulmonary parenchyma and alveolar

airspace. Gas exchange is disrupted and hypoxia occurs [35]. In the sheep model of ARDS, it was shown that alteration of perfusion mechanisms leads to an increase in dead space, an early marker of mortalit [36]. Formation of NETs is another antimicrobial defense mechanism, hyperactivation of which can lead to tissue damage. NETs are composed of DNA, histones, and proteases and, when released into the airspace during the development of ARDS, can increase inflammation by activating the NRLP3 inflammasome, which initiates localized release of interleukin-1-β and interleukin-18 [37]. NETs hyperactivation can also promote thrombosis.

Thus, excessive neutrophil recruitment and their hyperactivation at the site of inflammation lead to tissue damage and progressing ARDS. Targeting these processes can be used as an approach to the therapy of ARDS. Molecules of most interest are chemokine receptor antagonists such as CXCR2 or CXCR4, the inhibition of which reduces neutrophil infiltration into the lung, and antibodies against CD11b/CD18 or ICAM-1 integrins, which limit the interaction of neutrophils with the endothelium [38–40]. The following approaches may lead to suppression of neutrophil hyperactivation: use of neutrophil elastase (NE) inhibitors (e.g., sivelestat), which reduce protease-mediated lung and alveolar damage, the use of NADPH-oxidase (NOX) inhibitors that reduce the production of reactive oxygen species (ROS) thus limiting oxidative stress in the lungs in ARDS and phosphodiesterase (PDE) inhibitors (e.g., pentoxifylline) that attenuate proinflammatory cytokine release and neutrophil priming [41]. The latter has even been the subject of a clinical trial. Undoubtedly, suppression of excess NETs formation is also an approach to therapy of ARDS DNase I degrades NET DNA, reducing alveolar obstruction and inflammation. Inhibitors of peptidyl arginine deiminase 4 (PAD4) which is a transcriptional coregulator and catalyzing the conversion of histone H3 arginine residues to citrulline residues prevent NET formation by inhibiting histone citrullination [42]. Considering the therapy of ARDS from the point of view of neutrophils represents a great opportunity and shows positi ve results, but a great limitation is the need for action in the early stages of the disease, when neutrophils are particularly active [43, 44].

Macrophages

Normally, AM in the lung have an anti-inflammatory phenotype, whereas macrophages recruited from blood monocytes have a pro-inflammatory phenotype [45, 46]. The outcome of ARDS is determined by the balance of pro- and anti-inflammatory macrophages [35]. In the exudative phase, cytokines and other proinflammatory substances are released in response to inflammation, which activate resident AM and circulating neutrophils. In this stage, proinflammatory macrophages dominate under anti-inflammatory cells. Activation of macrophage pattern- recognising receptors leads to the formation of an inflammasome in which caspase-1 promotes the maturation of interleukin (IL) 1 and IL18 [47]. Disease progression can be severe if the maturation process of the inflammasome is disrupted [48]. CXCL8, also known as IL8, secreted by macrophages and endothelial cells during the development of inflammation, leads to the recruitment of neutrophils to the site of inflammation [49]. In the proliferative phase of ARDS pro-inflammatory macrophages are succeeded by anti-inflomatory macrophages which remove cellular debris and release anti-inflammatory cytokines. It was shown that defective efferocytosis can lead to the prolonged inflammation observed in ARDS. Fine regulation of the macrophage's ratio in the last stage of the disease is essential for a favorable outcome at the fibrotic phase since high M2 activity can lead to fibrosis [35].

Given the peculiarities of ARDS and the potential role of macrophages in this process, it is reasonable to speculate that targeting macrophage phenotypes in an anti-inflammatory manner may improve the outcome or alleviate the course of the disease. To date, there are no reported clinical studies using adoptive macrophage transfer. In Kosyreva's pilot study in a mouse model of LPS-induced ARDS, infusion of chemically M2-polarized RAW 264.7 macrophages was shown to promote the movement of lymphocytes from their depots in immune organs to the lungs, as well as to reduce the pro-inflammatory marker CD38 in the lungs and to express the anti-inflammatory markers Arg1,

Vegfa and Tgfb. However, treatment of ARDS with M2-polarized macrophages did not change the number of neutrophils in the lungs, and Arg1 protein levels in the lungs decreased throughout the treatment period, suggesting the need for other polarization approaches to use macrophages as a therapeutic agent [50].

The use of genome modification strategies is of great interest in this case, for example, due to the possibility of creating cells that express a specific protein, as was shown in the work of Huiying Liu. In a mouse model of LPS-induced ARDS, the authors demonstrated a therapeutic effect and reduced mortality when using macrophages with stable expression of IL4 [51].

To date, one work has been presented on the use of Crispr/Cas technology to obtain anti-inflammatory macrophages [49]. Chi Liang and colleagues used electroporation to knock out tumor necrosis factor receptor 1 (TNFR1) and overexpress IL-4 using Cas9-ribonuclear proteins (Cas9-RNP). In a rat model of osteoarthritis, compared with macrophages and M2 exosomes, L–M2a macrophages demonstrated significantly better therapeutic effects, successfully resolving inflammation, restoring tissue homeostasis, and promoting cartilage regeneration [52].

An interesting approach using M2 macrophage-derived nanovesicles and lung-targeting liposomes coupled to fabricate hybrid liposomes-nanovesicles (LNVs) was proposed by researchers from China [53]. In a mouse model of ARDS, they showed that the integrated nanosystems lead to a reduction of inflammation through decreased inflammatory cell infiltration, curbed cytokine storms, and alleviation of oxidative stress.

The use of macrophages in cell therapy, including ARDS, has great potential. However, the ability to change phenotype depending on the microenvironment creates difficulties in their use in clinical practice and the long-term effects of genetically modified cells have not been studied. It should be noted that the use of these cells is limited by the relative complexity of their isolation and expansion, especially n humans. These limitations have favoured the study of macrophages as cellular drug targets for improving the outcome of ARDS. Potential drugs and targets are shown to reduce AM pyroptosis. The phytogromone Abscisic acid [54], a natural polysaccharide derived from the East Asian terrestrial orchid Bletilla striata (BSP), and the antioxidant luteolin contribute to the reduction of AM pyroptosis and a more favorable disease outcome [55, 56]. Among substances of non-plant origin, Dynasore (inhibits GTPase activity) has shown efficacy in reducing pyroptosis [54]. A transcription factor that is comprehensively involved in inflammation Basic helix-loop-helix family member e40 (Bhlhe40) has been shown to be a macrophage target that improves outcomes of ARDS [57].

NK cells

NK cells or granular lymphocytes play a crucial role in linking innate and adaptive immune system activity [58]. Lung NK cells are generally thought to originate and develop in the bone marrow, and then migrate to the lungs. In human lungs, NK cells, accounting for about 10–20% of the lymphocytes, are located in the parenchyma and are not detected outside of it. NK cells are categorized based on the level of expression of CD56 (bright (br) and dim) and CD16 and include two broad subsets: CD56br/dimCD16– and CD56dim CD16+. CD16– NK cells are less differentiated and have low cytolytic ability, but produce greater amounts of IFN-γ and TNFα than their CD16+ counterparts [59]. Conversely, CD16+ NK cells are more differentiated and has high cytolytic activity. Human lung NK cells are mostly composed of the CD56dimCD16+ subset. Despite the well-differentiated phenotype, both human and mouse lung NK cells are hypofunctional in homeostasis. Human lung NK cells are hyporesponsive to stimulation by target cells (irrespective of priming with IFN-α) compared with peripheral blood NK cells. This may be caused by suppressive effects of alveolar macrophages and soluble factors in the epithelial lining fluid of the lower respiratory tract [60]. NK cells are cytotoxic, but do not carry a lineage-specific receptor like T and B lymphocytes. NK cells recognize virus-infected or tumorigenic cells without the presence of antibodies or major histocompatibility complexes (MHC).

The use of NK cells as a cell therapy for ARDS was extensively studied in relation to Covid19 because they play an important role in the pathogenesis of Covid-associated ARDS due to the ability of activating receptors, such as NKG2D, to exhibit antiviral activity. There are 17 registered studies devoted to their use in Covid-19 [61]. NK cells' plasticity is provided by activating and inhibitory receptors on their surface. Killer Ig-like receptors (KIR) genotype has been shown to influence recovery from COVID-19 [62]. NK cells play a significant role in the pathogenesis of ARDS by promoting neutrophil recruitment through the regulation of CXCR2+, CCL2 и CCL7 [63,64]. It has been shown that NK cells and CD4 T cells were reduced in ARDS patients.

The advantages of NK-cell therapy include the absence of the risk of graft-versus-host disease (GVHD) or cytokine release syndrome, as well as direct antiviral activity. A variety of approaches are being developed for the use of NK in Covid19 therapy, from infusions of activated NK cells to CAR-NK technology (NCT04324996). Also, NK cells are administered both as maintenance (NCT04280224) and as a stand-alone therapeutic agent (NCT04900454) [65–68].

T Cells

T cells are cells of the adaptive immune system that have a large number of subtypes differing by the type of T cell receptor, coreceptor molecules, type of major histocompatibility complex (MHC) molecule recognized and, of course, by the production of effector molecules [69]. T helper and T killer cells are distinguished based on the expression of CD4 or CD8 coreceptor molecules.

Regulatory T cells

Regulatory T cells (Tregs) are the subtype of the CD4 cells and play important role in lung homeostasis. Tregs are mainly categorized into two groups, one is natural Tregs (nTreg) which develop in thymus, the other is named as induced Tregs (iTreg) which are converted from naïve CD4+ T cells and could be generated both in vivo and in vitro [69]. Based on the level of expression of Forkhead box P3 (Foxp3), Foxp3+ and Foxp3- populations are distinguished. FOXP3+ Tregs are responsible for keeping immune tolerance, which can prevent allergic and autoimmune diseases as well as inhibit the anti-tumor or anti-pathogen immune responses [70]. Treg cells exert immunosuppressive effects by secreting anti-inflammatory cytokines such as IL-10. Regulatory T-cells promote pulmonary repair by modulating T helper cell immune responses in lipopolysaccharide-induced acute respiratory distress syndrome [71]. In a model of sepsis-induced ARDS in PTENM-KO/β-cateninM-KO knockout mice, the involvement of HMGB1/PTEN/β-catenin signaling in regulating Treg development in ARDS was demonstrated [72]. The participation of Tregs in the restoration of the lung epithelium was shown in the work of Mock JR et al [73]. The close relationship of immune system components in the pathogenesis of ARDS was shown in the work of Cheng L et al. IL-6 and IL-23 secreted from IL-33-activated DCs leads to normalization of the Th17/Treg ratio [74]. Secreted phosphoprotein 1 (SPP1) increases the Th17/Treg and M1/M2 ratios by suppressing VHL expression and ubiquitination-dependent degradation of HIF-1α, thereby exacerbating ARDS [75].

In ARDS Tregs play a crucial role in controlling the immune response; they maintain the physiological level of other immune cells activation, proliferation and function thus ensuring autotolerance and balance of the whole immune system [76]. In severe cases of ARDS, CD4+ T cells may become exhausted due to chronic stimulation by persistent inflammatory signals. This exhaustion leads to impaired immune responses and increased susceptibility to secondary infections, further complicating the clinical course of ARDS. Adoptive transfer of CD4+CD25+Foxp3+ Tregs to LPS — induced Rag1-deficient (Rag1-/-) mice model with loss of functional activity of B and T lymphocytes resulted in decreased levels of pro-inflammatory cytokines and increased levels of TGF-beta [77]. These data formed the basis of the treatment strategy for two patients with COVID-19 — associated ARDS [78]. Patients with severe disease were administered 1×108 allogenic Tregs derived from cord blood per dose intravenously two or three times. After a few days of administration, a decrease in the level of inflammatory markers was

noted [78]. This study was further developed with the support of Cellenkos, Inc. A randomized, placebo controlled, multi-center trial was conducted with the participation of 45 patients who received different doses of allogeneic Tregs three times (NCT04468971). The absence of negative effects from the administration of non-HLA-matched cells and the effectiveness of therapy, expressed in the absence of the need for intubation after 28 days from the administration of the first dose of the drug, were shown [79, 80].

Natural killer T

Natural killer T (NKT) cells are innate-like T lymphocytes that share surface markers and functional characteristics with both NK cells and T cells. Invariant natural killer T (iNKT) cells are a unique subset of T cells with aβ T-cell receptor and cell surface molecules similar to ones on NK cells. Unlike other T cells, they recognize glycolipid antigens presented by CD1d [81]. Shortly upon activation, iNKT cells can rapidly secrete abundant amounts of cytokines, predominantly IFN-γ and IL4, which allows them to activate or regulate other immune cells, such as dendritic cells, B cells, NK cells, CD8+T cells, and CD4+T helper cells, through cytokine stimulation or cognate interaction. In the lungs iNKT-cells make up 5–10% of all lymphocytes and inhabit interstitial space and the vasculature [82]. In ARDS patients, the peripheral blood NKT cell fraction was reduced (median 0.02% versus 0.05% in controls) while activation marker CD69 was elevated (median 25.4% versus 9.55%) along with IL-17 production (median 24.1% versus 3.50%). Moreover, bronchoalveolar lavage fluid contained a higher NKT cell count than blood and was associated with proinflammatory cytokine release and enhanced extracellular matrix protein expression. Activation of the IL-33/ST2 axis in ARDS models leads to recruitment of iNKT cells, and blockade of the CD1d pathway reduces inflammation and injury. Clinical data show negative associations between NKT cell reduction and both the PaO2/FiO2 ratio and albumin levels, and a positive association with C-reactive protein. Park et al. found that NKT induced IL-17 production by NKT cells from ARDS patients, which could stimulate neutrophil recruitment and tissue damage, as well as ECM protein expression in fibroblasts, potentially contributing to fibrosis in later stages of ARDS.

Adoptive transfer of allogenic iNKT, named ‘agenT-797’, at different doses was used in an open-label clinical trial (NCT04582201) for Covid19 treatment and showed positive results. Safety of HLA-mismatched cells has been demonstrated in this research. Administration of ‘agenT-797’ resulted in increased levels of IL-1RA and decreased levels of proinflammatory cytokines. A high 30-day survival rate was shown (70% versus 10% in the control group) [83]. A limitation of the study is the small sample size. Also, its results cannot be easily extrapolated to ARDS caused by causes other than COVID-19.

The use of iNKT cells for the treatment of ARDS is limited by the high probability of fibrosis and inhibition of the functional activity of cells by a highly proinflammatory environment in the lungs in ARDS.

B cells

B cells are found in inducible bronchoassociated lymphoid tissue (iBALT) in the lungs. iBALT is a poorly organized, poorly expressed aggregate of lymphoid cells that develops rapidly in response to infection, chronic inflammation, or autoimmunity. The main functions of B cells in lungs are lung-specific immunity and tolerance. ARDS leds to imbalance in B cells which is confirmed by the results of single cell RNA-sequencing performed by Dan He and colleges. At the same time, high level of B cells correlated with a favourable prognosis. Zhun Sun and colleagues have shown an important anti-inflammatory role of B Cells in ARDS [84]. In a mouse model of LPS-induced ARDS, it was shown that IL-10 is produced predominantly by B cells during the recovery process after ALI. Mechanically, IL-10 produced by B cells suppresses the activation and recruitment of macrophages and reduces the production of keratinocyte chemoattractant (CXCL-1), which recruits neutrophils to the lungs. The presence of IL-10-producing B cells shortly after ARDS onset

has been associated with better survival rates. It can be suggested that the use of adoptive transfer of B cells highly expressing IL10 is a potential cell therapeutic drug.

Key immune cells involved in ARDS pathogenesis and their potential use for treatment this pathology summarize in Table.

Conclusion

Due to the heterogeneity of its pathogenesis, ARDS requires an individualized treatment approach. Cell therapy may be a promising treatment option, as shown in preclinical studies. In addition to stem cells, which have been shown to be safe in many studies, therapy using highly differentiated immune cells or aimed at altering their functional properties in vivo has great therapeutic potential in the resolution of ARDS. Genetic modification techniques open new horizons in the possibility of increasing the therapeutic efficacy when using cells in the treatment of ARDS. However, many aspects of cell therapy applications remain controversial, such as standardization of cell product preparation and processing, dose and number of administrations, etc., and multicenter studies are needed to improve the validity of preclinical results. Nevertheless, this review shows that both in vivo adoptive transfer of immune cells and in vivo targeting of immune cells have great potential in the field of ARDS therapy.

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Key cells involved in ARDS pathogenesis and their potential use for treatment this pathology

Function in normal lung	Involvement in the pathogenesis of ARDS	Strategies for use as potential therapy
Alveolar macrophages		
Immunological tolerance in alveoli and surfactant catabolism;Anti-inflammatory phenotype	The acute phase secretion of proinflammatory cytokinesThe proliferative-fibrotic phase efferocytosis and reorganizing the matrix.	Enhancing phagocytosis:Regulating macrophage polarizationInhibiting pyroptosisExosome therapy
Neutrophils		
First line of defense against pathogens by phagocytosis and NET fo rmation	Releasing reactive oxygen species (ROS), reactive nitrogen species (RNS), proteases, and pro-inflammatory cytokines like IL-6 and NET formation	Inhibition of Neutrophil Recruitment Suppression of Neutrophil Hyperactivation Targeting Neutrophil Extracellular Traps (NETs)
Invariant natural killer T cells (iNKT)		
Regulation of immune tolerance in lung and regulation of other immune cells through cytokine stimulation or cognate interaction	Participation in the development of inflammation in the acute phase	Adoptive transfer of inkt cells in clinical trial nct04582201
T Cells (Tregs)		
Maintain immune system homeostasis and preventing autoimmune diseases	Promote the clearance of neutrophils from the alveolar spaceSecrete anti-inflammatory cytokines such as il-10 and tgf-β	Adoptive transfer of tregThere is clinical trial nct04468971 with promising results
B cells		
lung-specific immunity and tolerance	Decreased quantity in ARDS	Introduction of B cells, highly producing IL-10

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Высокодифференцированные клетки в терапии острого респираторного дистресс-синдрома

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Аннотация. *Актуальность.* Острый респираторный дистресс-синдром (ОРДС) — это тяжелая, угрожающая жизни форма острого поражения легких с высоким уровнем смертности. В тяжелых случаях патологические изменения распространяются на системный уровень и проявляются в виде синдрома цитокинового шторма. Отсутствие эффективных вариантов лечения подчеркивает важность изучения терапевтических подходов, включая клеточную терапию. Интерес к этому варианту лечения возрос во время пандемии SARS-CoV-2, о чем свидетельствуют многочисленные клинические исследования, зарегистрированные для использования клеточных препаратов для лечения ОРДС. Целью исследования стало обобщение доклинических и клинических исследований по использованию высокодифференцированных клеток, включая клетки иммунной системы, для лечения ОРДС. В работе рассмотрены стадии развития ОРДС с точки зрения участвующих в них клеток иммунной системы, а также этиологические подтипы. Описаны существующие на настоящий момент доклинические и клинические исследования использования иммунных клеток в терапии ОРДС. В этом обзоре подчеркивается потенциал использования альвеолярных клеток 1-го и 2-го типов, а также эпителиальных клеток для быстрой регенерации легких после ОРДС. В настоящее время отсутствуют данные, описывающие применение нейтрофилов, вызывающих первичные патологические изменения в легких, для лечения ОРДС. Использование макрофагов, играющих ключевую роль в патогенезе ОРДС, ограничено их способностью к быстрой реполяризации. Естественные клетки-киллеры (NK-клетки), регуляторные Т-клетки (Treg) и инвариантные естественные клетки-киллеры (iNKT-клетки) показали высокую эффективность в лечении ОРДС в доклинических и клинических исследованиях. *Выводы.* Таким образом, использование NK-клеток, Treg и iNKT-клеток для клеточной терапии ОРДС представляется перспективным.

Однако отсутствие стандартизированных протоколов подготовки и введения клеточной терапии, а также небольшой размер выборки указывают на необходимость дополнительных исследований.

Ключевые слова: ОРДС, клеточная терапия, макрофаги, клетки iNKT, Treg, нейтрофилы, клинические испытания

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Association of *BAP1* polymorphisms with development of uveal melanoma

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Abstract. *Relevance.* Uveal melanoma is a rare form of cancer that originates in the eye, most frequently arises in the choroid (90%). *BAP1* is a tumor suppressor gene, mutations in this gene were found in 40–84% of primary UM. Given many investigators have proven the association of mutations in the *BAP1* gene with UM. *Aim*: our study aims to figure out UM associated polymorphisms by sequencing DNA in exon 10, exon 11, exon 15, exon 16, and exon 17 as well as to assess the role of *BRCA1* mutations in risk of UM development. *Materials and Methods*. A total of 95 individuals recruited in the study, out of them 42 as a patient group, 23 as a risk group, and 30 as a control group. The target regions of *BAP1* gene amplified by PCR were sequenced by Sanger method and *BRCA1* was genotyped by real-time PCR using commercially produced kits. *Results and Discussion*. This study did not demonstrate presence of any polymorphisms in the sequenced regions of the *BAP1* gene or the genotyped specific *BRCA1* sites that are correlated with an increased risk of uveal melanoma development. Our findings do not deny the published strong association between *BAP1* inactivating mutations and the UM disease. This study's findings instead propose that within this targeted population, the molecular mechanisms for BAP1 loss-function may include aberrations other than changes in the examined exons. *Conclusion*. Consequently, we recommend future research that includes sequencing the entire *BAP1* gene in larger sized samples and studying of other candidate genes.

Keywords: uveal melanoma, BAP1, BRCA1

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Introduction

Uveal melanoma (UM) is a rare and serious form of cancer that arises from melanocytes of the uvea. Uvea is the middle tissue layer in the wall of the eye, which compresses the iris, ciliary body, and choroid. It is molecularly distinct from cutaneous melanoma, primarily due to a different pattern of driver mutations. This subtype of melanoma is the most common primary intraocular cancer in adults. Roughly 50% of all UM patients will develop metastasis to other sites, including the liver (most common site), the lungs, and bones. The mean incidence rate of uveal melanoma is approximately 5.0 cases per million people per year. Males have a higher incidence rate of 5.9 per million in comparison to females with an average incidence rate of 4.5 per million [1]. Understanding UM aetiology carries unique challenges in comparison to cutaneous melanoma, which remains an area of active research. The aetiology of uveal melanoma is influenced by many factors that contribute to its development. Both genetic and environmental factors are included in UM aetiology, or can emerge from a complex interplay of genetic and environmental factors [2–6]. Genetic contribution occurs in approximately 80% of UM cases. A comprehensive investigation of UM genomes has revealed a total of 130 genetic mutations. Somatic and germline mutations in some genes; *BAP1*, *GNAQ*, *GNA11*, *SF3B1*, *SRSF2*, *EIF1AX*, *PLCB4*, *CYSLTR2*, and *TERT*, are being notably recurrent UM and thought to play a critical role in tumor initiation and progression [2, 3, 4]. Mutations in the TP53 gene are a common cause of p53 disruption in many cancers [7], but they occur only rarely in uveal melanoma (UM), despite p53's frequent involvement in cancer overall [8]. Additionally, chromosomal alterations are also significant in UM, where have been found a loss of chromosome 3, its short arm or other chromosomal regions, has been associated with a higher risk of metastasizing UM [9, 10].

BAP1 refers to the BRCA1 associated protein-1 gene located on chromosome 3 in the region p21.31-p21.2. The gene codes for an enzyme that consists of 729 amino acids. BAP1 is a nuclear-localized protein that belongs to the subfamily of deubiquitinase enzymes. It contains a ubiquitin C-terminal hydrolase (UCH) domain that gives it deubiquitinating activity involved in removal of ubiquitin molecules from target proteins. By removing ubiquitin tags, BAP1 can stabilize targeted proteins and prevent their degradation by the proteasome. Accordingly, BAP1 orchestrates the stability and function of several proteins involved in cell cycle control, DNA repair, transcription, tumor suppression, and chromatin dynamics. Loss of BAP1 function can lead to genome instability and contribute to the development of various malignancies [11,12].

It has been found, *BAP1* is deleted or mutated in diverse human cancers and its re-expression reversed their tumorigenicity. This is suggesting that BAP1 might function as a tumor suppressor protein that prevents uncontrolled cell growth and division [11]. Therefore, the enzyme probably exerts its function by tightly regulating various cellular processes through deubiquitination of its substrates. The processes regulated by BAP1 include; regulation of cell cycle, transcription growth, and cellular differentiation. It also responds to DNA damage and chromatin dynamics.

Three functional domains constitute BAP1 protein, two binding domains and one catalytic domain. The binding and catalytic domain (UCH) (approximately amino acid residues 1–240) located at the N-terminal, is responsible for binding to host cell factor-1 (HCF-1) and functions as ubiquitin carboxy-terminal hydrolase. The second domain (amino acid residues 182–365 encoded by multiple exons including exon 10) is a binding region also located at the N-terminal interacting with BARD1 and UCH37-Like domain (ULD), reported that a mutation in this region is associated with development of cancer [13]. The third one is also a binding domain (approximately amino acid residues 675–693 encoded by exons 15,16,17) located at the C-terminal interacting with BRCA1 and ASXL [14–16]. The BAP1 enzyme enhances the BRCA1 tumor suppressor activity through interaction with the RING finger domain of BRCA1 and BARD1 proteins and acts as a tumor suppressor [11, 17]. BAP1 interacts with BARD1 to inactivate the E3 ligase activity of BRCA1/BARD1. The E3 ligase is responsible for the addition of ubiquitin to specific proteins to regulate DNA repair, cell cycle, and chromatin remodeling [17].

BAP1 with high affinity interacts directly with ASXL1, ASXL2, and ASXL3 through the ASXH domain. The BAP1 binding to ASXL proteins is to form the active PR-DUB complex crucial for its proper function of tumor suppression. The interaction of BAP1 with the DEUBAD domain of ASXL proteins through the C-terminal ULD is mandatory for stimulating its activity. Consequently, ASXL binding is significantly enhancing BAP1 ability to deubiquitinate its main substrate, histone H2A at lysine 119 in humans [18]. It has been found that BAP1 promotes the ubiquitination of ASXL2 to stabilize it, in turn which stimulates its own deubiquitinase activity [19]. The deubiquitin hydrolase activity of BAP1 is strongly stimulated by the direct binding of the ASXL2 AB box to the BAP1-ULD domain. This interaction is obligatory for BAP1 enzymatic activity and that many *BAP1* mutations allosterically inhibit BAP1-ASXL2 binding [16].

The alteration in this gene takes a significant part in various cancers, including uveal melanoma. As well as *BAP1* mutations are identified at low prevalence in many cancer diseases including mesothelioma, bladder, breast, pancreatic, and colorectal cancers [11]. Several studies have reported that mutations in *BAP1* gene are strongly associated with poor prognosis and increased risk of metastasis in UM patients [2–4, 12]. Somatic *BAP1* mutations were recognized in roughly 84% of UM patients. Germline *BAP1* mutations were found in approximately 8% of metastatic tumors originated from metastasizing uveal melanoma [10,11,20]. According to statistical findings of published studies, human carriers of inherited inactivated *BAP1* gene are strongly at a high risk of developing at least one and often many cancers, in particular UM, during their lifetime. This guided to infer that inherited *BAP1*-inactivating mutations have a penetrance approaching 100% [11, 21].

In the context of significant predisposition of aberrant *BAP1* carriers to cancers in particular uveal melanoma, the ongoing study aims to detect new polymorphisms in the exome of *BAP1* gene. Thereby, our study focused on analysis of the sequence of coding regions including the exons 10, 11, 15, 16, and 17 in the candidate *BAP1* gene. The analysis of these regions may help recognize any pathogenic or likely pathogenic variants might be associated with a risk of developing uveal melanoma among Russians. Giving that ASXL is essential for the BAP1 ubiqutination activity, we have targeted these exons to sequence since they encode the BAP1 domains that bind to ASXL, BCRA1, and BARD1 proteins [13], this interaction is verry essential for the tumor suppression function of BAP1. Our expectation was that presence of polymorphisms at these exons can fail the interaction of BAP1 and ASXL and inhibits BAP1 activity. Additionally, since BRCA1 functions together with the BAP1 to

suppress tumor development, we genotyped the following *BRCA1* polymorphisms; 4153delA, 5382insC, 185delG, 3875del14, T300G, 2080delA (insA). The *BRCA1* genotyping aimed to assess whether the chosen mutations play roles in uveal melanoma formation. Recognition of pathogenic or likely pathogenic variants associated with a higher risk of developing uveal melanoma among Russians may provide novel insights into predictive biomarkers for diagnosis and managing hereditary UM risks within families.

Materials and methods

Participants and samples

The participants were classified into three groups: the case group consisted of 42 patients suffering from UM and choroidal nevus, with the mean age of 56.3 ± 9.8 years, the risk group composed of 23 patients with benign choroidal nevus, with the mean age of 47.5 ± 7.9 years, and the control group included 30 healthy volunteers with no history of intraocular neoplasms, with the mean age of 39.63 ± 12.07 years. The DNA sequences from the UM patients, individuals at risk of UM, and healthy individuals were compared to a reference DNA sequence in NCBI database to identify any nucleotide base pair abnormalities. The sequencing analysis targeted the exon 10, exon 11, exon 15, exon 16, and 17 as well as the introns between the exons 15–17 performed for the genomic DNA extracted from all the samples of studied groups. Genotyping for *BRCA1* polymorphisms was performed by real-time PCR.

DNA extraction, PCR and sequencing and genotyping of SNPs

Genomic DNA was isolated from leucocytes of peripheral blood samples of all the study participants by standard procedures using a commercially available kit (EX-509–100 DNA-extran-1 kit; Syntol, Russia). Extracted DNA was kept at –20 °C. DNA sequencing was performed using the Sanger method in Syntol Laboratory. Sequencing of *BAP1* included the coding regions of the 10th and 11th, 15th, 16th, 17th exons as well as the introns between 15th, 16th, and 17th exons. The PCR products were separated by gel electrophoresis on a 2% agarose gel, visualized by ethidium bromide under UV light, and then prepared for sequencing with a purification kit (Cleanup S-cap, Evrogen, Russia) following the manufacturer's protocol. The target regions were amplified using PCR according to the following thermocycling conditions. For exon 10 and exon 11: initial denaturation at 95 °C for 5 minutes and 40 cycles of amplification at 95 °C for 30 seconds, annealing at 60 °C (exon 11) or 65 °C (exon 10) for 30 seconds, extension at 72 °C for 30 seconds, and a final extension step at 72 °C for 5 minutes. For exon 15, exon 16, and exon 17: initial denaturation at 95 °C for 10 minutes and 40 cycles of amplification at 95 °C for 45 seconds, annealing at 58 °C for 40 seconds, extension at 72 °C for 60 seconds, and a final extension step at 72 °C for 10 minutes. The primers used for PCR amplification were designed using Primer-BLAST as presented in the table.

Primers, annealing temperature, and amplified fragment size for the analyzed exons of *BAP1* gene

Exons of *BAP1*gene	Primers	Length of PCR product	Annealing temperature
Exon10	F:5'-AGAGAATCCTGCAAGGGTGC-3' R:5'-CCCTGTCTCAGATGGTGCAG-3'	175bp	65 °C
Exon 11	F:5'-CCCCAGTACCTGTGTGGTT-3' R:5'-CCTGGATTCTGTTGTTAGCTGAT-3'	225bp	60 °C
Exons 15, 16, 17	F: 5'-AGGGGCCTTGATAGGCATGG-3' R:5'-TAATACTGGGAAAAGGGGAAGTGG-3'	789bp	58 °C

Genotyping for the *BRCA1* 4153delA, 5382insC, 185delG, 3875del14, T300G, 2080delA (insA) was performed by PCR using RealBEST-Genetics reagent kits from VectorBEST (Russia) according to the manufacturer's protocol.

Results and discussion

Our sequencing results for all the analyzed exons as well as the last two introns (between exons 15–16 and exons 16–17) have not revealed any polymorphisms relevant to the risk of uveal melanoma development. The DNA sequencing in our study did not detect any changes in the *BAP1* nucleotide sequence between the healthy volunteers and uveal melanoma patients in Russian population. To the best of knowledge, different studies indicate that mutations in *BAP1* frequently found in uveal melanomas are monosomy 3 (chromosome 3 loss) and large deletions including the *BAP1* locus itself [22]. Our study as well as results of other researchers necessitate a further investigation of whole *BAP1* gene sequencing, copy number variation assessment, and analysis of promoter or deep intronic regions in a larger sized-sample of people to fully elucidate the role of *BAP1* in uveal melanoma. Our findings coincide with the results of many investigators overall the world, so here we are shedding light on their explanations and conclusions about correlation of *BAP1* mutations with uveal melanoma. Truncating mutations (nonsense, frameshift) lead to a complete loss of BAP1 function, severely impairing both homologous recombination and nucleotide excision repair pathways. As a result, cells exhibit increased sensitivity to DNA-damaging agents and a higher accumulation of genetic defects, contributing to cancer progression [23]. While these mutations may alter BAP1 function, they often do not completely abolish its activity. The impact of missense mutations on DNA repair can vary, but they are generally associated with less severe consequences than truncating mutations [23].

Pathogenic *BAP1* mutations are predominantly found in the ubiquitin C-terminal hydrolase domain of the BAP1 protein, which is essential for its deubiquitinating activity. This suggests that the loss of this function plays a crucial role in UM progression and the metastatic process. Other mutations occur in binding domains for BARD1, BRCA1, ASXL, and HCF-1 proteins, which may impair their functional stability so that affecting cellular functions related to tumor suppression.

The absence of *BAP1* nucleotide sequence changes in our study contrasts with the well-established role of BAP1 inactivation, often through large deletions on chromosome 3. It is possible that the changes were in the non-analyzed regions of the gene targeted by our study or the predisposition to UM is caused by polymorphisms of other genes. On this point of view, our findings and those of other literatures could extract that the fundamental mechanism of BAP1 inactivation in UM is mostly not due to point mutations in the coding sequence but rather due to large-scale deletions that comprise the entire BAP1 locus. As well as it could arise due to mutations in regions that silence the gene transcription, such as promoter, deep intronic regions, which could hinder mRNA splicing and the other exons not covered by our study or other previous sequencing studies.

There were no significant changes between the experimental group, the risk group, and the control group when the frequency of different alleles of loci 4153delA, 5382insC, 185delG, 3875del14, T300G, 2080delA (insA) of *BRCA1* was examined. In every group, the normal allele was found in 100% of cases, except for the *BRCA1 4153delA*. All patients in the risk group were homozygous for the normal allele, except for one patient (4.34%) who was heterozygous for the *BRCA1 4153delA* mutation. Our findings coincide with the published findings that failed to reveal a significant association between *BRCA1* mutations and uveal melanoma.

Additionally, as indicated in a previously published study, our results detected that uveal melanoma development has a strong association with *BARD1* gene inactivation mutation [24]. This indirectly supports our hypothesis in currently study that uveal melanoma may correlate with damages in different components of nucleotide excision repair pathways.

Conclusion

In summary, our sequencing analysis of the examined exons of the *BAP1* gene and genotyping of specific sites in the *BRCA1* gene within the Russian population did not recognize polymorphisms associated with an increased predisposition to development of uveal melanoma. Consequently, our results do not disprove the strong association between aberrant BAP1 (loss-of-function) and uveal melanoma development demonstrated by published studies. Instead, they postulate that in the Russian population, the mechanisms of *BAP1* inactivation may differ from simple point mutations in the sequenced exons. This leads us to recommend sequencing the whole gene in a larger sample size in different populations and studying for other candidate genes. The complete lack of association with the tested *BRCA1* mutations proves the absence of correlation with UM as reported in previous studies.

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Ассоциация полиморфизмов гена *BAP1* с развитием увеальной меланомы

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Аннотация. *Актуальность*. Увеальная меланома (УМ) представляет собой редкую форму онкопатологии, которая развивается в глазу и наиболее часто возникает в хориоидее (90 %). *BAP1* является геном-супрессором опухолей; мутации в этом гене обнаруживаются в 40–84 % случаев первичной УМ. Учитывая, что многие исследователи показали связь мутаций в гене *BAP1* с УМ. Цель: целью нашей работы стало выявить ассоциированные с УМ полиморфные варианты в экзонах 10, 11, 15, 16 и 17, а также оценить роль мутаций гена *BRCA1* в развитии УМ. *Материалы и методы*. Всего в исследовании приняли участие 95 человек, включая 42 пациента с УМ, 23 пациента из группы риска и 30 добровольцев контрольной группы. Целевые участки гена *BAP1*, амплифицированные с помощью ПЦР, были секвенированы методом Сэнгера; генотипирование по гену *BRCA1* проводилось методом ПЦР в реальном времени. *Результаты и обсуждение*. Настоящее исследование не выявило полиморфных вариантов в секвенированных последовательностях гена *BAP1* и мутаций гена *BRCA1*, которые были бы ассоциированы с повышенным риском развития УМ. Наши результаты не опровергают литературные данные о связи между инактивирующими мутациями *BAP1* и увеальной меланомой, но позволяют предполагать, что молекулярные механизмы потери функции *BAP1* могут включать нарушения за пределами исследованных экзонов. *Выводы*. Таким образом, целесообразны дальнейшие исследования с секвенированием всего гена *BAP1* в выборках большего объёма и изучением других кандидатных генов.

Ключевые слова: увеальная меланома, BAP1, BRCA1

Информация о финансировании. Авторы заявляют об отсутствии финансирования

Вклад авторов. Мухана Л. — генотипирование пациентов, участие в подготовке рукописи; Ахмед А.А.М. — анализ результатов исследования, участие в подготовке рукописи; Гигани О.О. — участие в подготовке рукописи; Саакян С.В. — анализ клинических данных и подбор пациентов; Цыганков А.Ю. — анализ клинических данных и сбор биологического материала; Азова М.М. — дизайн исследования. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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ВНУТРЕННИЕ БОЛЕЗНИ
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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Место сердечно-сосудистой патологии в структуре коморбидности и смертности больных ревматоидным артритом

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Аннотация. *Актуальность*. Получение надежных данных об уровнях сердечно-сосудистой заболеваемости и смертности среди пациентов с ревматоидным артритом остается актуальным. Эти аспекты ведения пациента очень важны, они определяют дальнейшую терапевтическую тактику и направлены на снижение рисков развития осложнений. *Цель* — провести анализ сердечно-сосудистой патологии в структуре коморбидности и смертности больных РА в когорте пациентов ООО «Центр ответственной ревматологии "Индукция"» (далее – Центр) в период 2015–2022 гг. *Материалы и методы*. Произведена выборка 1020 больных с достоверным диагнозом РА, установленным согласно классификационным критериям (ACR/EULAR, 2010 г.), проходивших лечение в Центре «Индукция». Средний возраст 55,3±1,8 лет, преобладали женщины (88,8 %). Коморбидный статус оценивался на основе прижизненных консультаций и анализа медицинской документации обследуемых пациентов по разработанной карте, включающей уточненное сердечно-сосудистое заболевание, а также факт наступления смертельного исхода. Проводился систематизированный обзор научных работ (2019–2024 гг.) по ревматоидному артриту в аспекте кардиоваскулярной патологии. *Результаты и обсуждение*. Частота встречаемости кардиоваскулярных патологий у пациентов с РА согласно сведениям многочисленных исследований (2019–2024) колеблется в широком диапазоне. Ведущее место по распространенности занимают ГБ, ИБС, сердечная недостаточность, нарушения ритма и проводимости сердца, атеросклеротические сердечно-сосудистые заболевания. Пациенты с РА исследуемой когорты характеризовались сложной структурой коморбидности. Сердечно-сосудистая патология выступает наиболее распространенной (42,29 %). За ней следуют респираторные заболевания (23,07 %), COVID-19 (11,53 %), «Бластоматоз» (7,69 %). Острый панкреатит, осложненный панкреонекрозом, бронхиальная астма,

лимфолейкоз, гипотиреоз, аутоиммунный тиреоидит, сахарный диабет регистрировались не более чем у 3,85 % когорты. Сердечно-сосудистые нарушения составляли ИБС (30,76 %) и ГБ (11,53 %). *Выводы.* Проведен анализ новых данных о месте сердечно-сосудистых заболеваний в структуре коморбидности и смертности пациентов Ставропольского края когорты ООО «Центр ответственной ревматологии ″Индукция″» с установленным диагнозом РА. В тройку основных причин смерти пациентов с РА вошли сердечно-сосудистые, респираторные заболевания, сепсис. Лидирующую позицию занимали сердечно-сосудистые события (47,83 %), преимущественно острый инфаркт миокарда (30,43 %). Полученные сведения полезны для лучшего понимания клинического портрета больных РА с сердечно-сосудистой патологией, и могут учитываться ревматологами для оптимизации тактики управления РА и риском сердечно-сосудистых событий.

Ключевые слова: ревматоидный артрит, коморбидность, кардиоваскулярная патология, смертность

Информация о финансировании. Авторы заявляют об отсутствии внешнего финансирования.

Вклад авторов. Щендригин И.Н. — концепция и дизайн исследования, написание текста. Лила А.М. — редактирование, утверждение окончательного варианта статьи. Писков С.И. — сбор, обработка материалов, написание текста. Димитриади А.И. — сбор материала. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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Cardiovascular pathology in the structure of comorbidity and mortality of patients with rheumatoid arthritis

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Abstract. *Relevance.* Obtaining reliable data on the levels of cardiovascular morbidity and mortality among patients with rheumatoid arthritis remains important. These aspects of patient management are very important; they determine further therapeutic tactics and are aimed at reducing the risks of complications. Target — to analyze cardiovascular pathology in the structure of comorbidity and mortality of patients with RA in the cohort of patients of the Center for Responsible

Rheumatology ″Induction″ LLC in the period 2015–2022. *Materials and Methods.* A sample of 1020 patients with a reliable diagnosis of RA, established according to the classification criteria (ACR/EULAR, 2010), who were treated at the LLC Center for Responsible Rheumatology ″Induction″, was made. The average age was 55.3 ± 1.8 years, women predominated (88.8%). Comorbid status was assessed on the basis of lifetime consultations and analysis of medical documentation of the examined patients according to a developed chart, including a specified cardiovascular disease, as well as the fact of death. A systematic review of scientific works (2019–2024) on rheumatoid arthritis in the aspect of cardiovascular pathology was carried out. *Results and Discussion.* The incidence of cardiovascular pathologies in patients with RA, according to numerous studies (2019–2024), varies widely. Hypertension, coronary artery disease, heart failure, cardiac rhythm and conduction disorders, and atherosclerotic cardiovascular diseases occupy the leading place in prevalence. Patients with RA in the study cohort were characterized by a complex comorbidity structure. Cardiovascular pathology is the most common (42.29%). Respiratory diseases (23.07%), COVID-19 (11.53%), and Blastomatosis (7.69%) follow it. Acute pancreatitis complicated by pancreatic necrosis, bronchial asthma, lymphocytic leukemia, hypothyroidism, autoimmune thyroiditis, diabetes mellitus were recorded in no more than 3.85% of the cohort. Cardiovascular disorders included ischemic heart disease (30.76%) and hypertension (11.53%). The three main causes of death in patients with RA included cardiovascular, respiratory diseases, and sepsis. The leading position was occupied by cardiovascular events (47.83%), predominantly acute myocardial infarction (30.43%). *Conclusion.* An analysis of new data on the place of cardiovascular diseases in the structure of comorbidity and mortality of patients in the Stavropol Territory of the LLC “Center for Responsible Rheumatology ″Induction″ cohort with an established diagnosis of RA was carried out. The information obtained is useful for a better understanding of the clinical portrait of RA patients with cardiovascular pathology, and can be taken into account by rheumatologists to optimize management tactics for RA and the risk of cardiovascular events.

Keywords: rheumatoid arthritis, comorbidity, cardiovascular pathology, mortality

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Lila A.M. — research concept and design, text writing, editing, approval of the final version of the article. Piskov S.I. — research concept and design, collection and processing of materials, text writing. Dimitriadi A.I. — research concept and design, data collection, text writing. All authors made significant contributions to the concept development, conduct of the study, and preparation of the article; they read and approved the final version before publication.

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Ethics approval. The study was conducted in accordance with the decision of the Ethical committee of the Central Clinical Hospital of the V.A. Nasonova Research Institute of Rheumatology, Moscow.

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Введение

Ревматоидный артрит (РА) является наиболее распространенным аутоиммунным заболеванием, характеризующимся хроническим системным воспалением с вовлечением синовии и внесуставными проявлениями. В общей популяции РА поражает до 1 % населения, приводит к снижению качества жизни, ранней инвалидизации и преждевременной смертности [1].

Особо дискутируемой темой для ревматологов сегодня выступает проблема коморбидности при РА. Профессиональный интерес к коморбидным

состояниям при РА обусловлен их влиянием на течение и прогноз самого заболевания, постановку диагноза, выбор лечебной тактики и качество жизни больного. Недостаточная оценка коморбидных составляющих и неэффективная терапия таких пациентов делает невозможным достижение основной цели в лечении РА и приводит к быстрому прогрессированию развития сопутствующих заболеваний и их осложнений [2, 3]. Вместе с тем коморбидные состояния при РА часто недооцениваются, несмотря на их влияние на активность заболевания и исходы лечения, а также на осознание большинством ревматологов ответственности за их лечение. Соблюдение рекомендаций по выявлению и лечению сопутствующих заболеваний при РА сегодня еще далеко от оптимального и варьируется в зависимости от страны, возможностей и бюджета региональной системы здравоохранения [4].

Особое место среди коморбидных состояний у пациентов с РА занимают сердечно-сосудистые заболевания (ССЗ) [5]. РА выступает независимым фактором риска ишемической болезни сердца (ИБС), а гипертоническая болезнь (ГБ) ассоциирована с неблагоприятным прогнозом в отношении смерти от кардиоваскулярных событий [6]. Контроль активности РА может снизить риск ССЗ [7]. При этом важно, что кардиоваскулярная патология может появиться до развития или на ранней стадии РА, в период обострения или ремиссии, а также являться осложнением хронического аутоиммунного воспаления и/или его терапии [8]. В патологический процесс могут быть вовлечены перикард, миокард, клапаны сердца, проводящая система, крупные и мелкие коронарные сосуды [9]. Поэтому основной задачей ревматологов сегодня выступает своевременная диагностика не только ревматического заболевания, но и оценка рисков развития коморбидных состояний, профиля причин смертности и выбор эффективной терапии.

Недостаточная масштабность и продолжительность наблюдения за доступными когортами остаются препятствием для точной количественной оценки сердечно-сосудистого риска при конкретных ревматических заболеваниях. Надежных данных об уровнях сердечно-сосудистой заболеваемости и смертности среди пациентов с РА недостаточно. При этом вопросы о том, о том, следует ли и когда начинать терапию по профилактике ССЗ, являются ли определенные классы препаратов более эффективными, чем другие, или их следует избегать у пациентов с факторами риска ССЗ, остаются открытыми [10, 11]. Правильное управление установленными факторами риска кардиоваскулярной патологии может предотвратить опасные для жизни осложнения [4]. Эти аспекты ведения пациента очень важны, они определяют дальнейшую терапевтическую тактику и направлены на снижение рисков развития осложнений коморбидных состояний.

В этом контексте целью настоящей работы выступил анализ кардиоваскулярной патологии в структуре коморбидности и смертности больных РА когорты пациентов ООО «Центр ответственной ревматологии ″Индукция″» в период 2015–2022 гг.

Материалы и методы

Для достижения цели исследования была произведена выборка 1020 больных ревматоидным артритом (средний возраст 55,3±1,8 лет, преобладали женщины 88,8 %), сформированная в соответствии с диагностическими критериями ACR/EULAR (2010) [12]. Пациенты проходили амбулаторное лечение в ООО «Центр ответственной ревматологии ″Индукция″» (далее Индукция).

Согласно Хельсинкской декларации Всемирной медицинской ассоциации (WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013) каждый пациент подписал добровольное информированное согласие на обработку персональных данных и участие в исследовании.

Коморбидный статус пациентов устанавливался согласно сведениям медицинской документации. Летальные исходы больных РА изучались на основании протоколов вскрытий

за 2015–2022 гг. При проведении статистического анализа использована программа Biostat 4.0. Все результаты носили качественные данные и представлялись виде относительных частот (%).

Проводился систематизированный обзор научных работ (2019–2024 гг.) по ревматоидному артриту в аспекте кардиоваскулярной патологии. Поиск документов проводился в базах: Mendeley; Scopus; Pubmed; ScienceDirect; Elibrary с использованием терминов: ревматоидный артрит, коморбидность, кардиоваскулярная патология, смертность.

Результаты и обсуждения

Данные анализа частоты сердечно-сосудистой патологии в структуре коморбидных состояний больных РА, проведенного на основе систематизированного обзора литературных источников (2019–2024 гг.) приведены в таблице.

Представительство кардиоваскулярных нарушений в структуре коморбидности больных ревматоидным артритом (данные литературы)

Representation of cardiovascular disorders in the structure of comorbidity in patients with rheumatoid arthritis (literature data)

Ссылка/Link	Тип исследования/ Type of research	ИБС/ IHD	ГБ/ HT	ХСН/ CHF	НРПРС/ DCRC	АССЗ/ ASCVD
Абишева С.Т. с соавт., 2019 [13]	ретроспективное/ retrospective	–	32,1 %	–	–	–
Batko B. et.al., 2019 [14]	ретроспективное/ retrospective	14,8 %	46,9 %	–	–	–
Ramos A.L. et al., 2019 [15]	когортное/cohort	15,3 %	62,5 %	10,3 %	18,9 %	–
Mochizuki T. et al., 2019 [16]	лонгитудинальное/ longitudinal	–	37,2 %	–	–	–
Насырова В.В. с соавт., 2020 [17]	ретроспективное и проспективное/ retrospective and prospective	8,2 %	27,2 %	–	–	–
Agca R. et al., 2020 [18]	лонгитудинальное/ longitudinal	–	61,0 %	–	–	–
Daniel C.M. et.al., 2020 [19]	систематический обзор/ systematic review	–	–	–	–	46,9 %
Skielta M. et.al., 2020 [20]	ретроспективное и проспективное/ retrospective and prospective	–	47,8 %	–	18,7 %	–
Хусаинова М.А., 2021 [21]	клиническое/ clinical	–	–	33,0 %	–	–
Юдин В.А. с соавт., 2021 [2]	клиническое/ clinical	8,0 %	54,0 %	4,0 %	9,0 %	18,0 %
Taylor P.C. et.al., 2021 [22]	систематический обзор/ systematic review	19,00 %	–	–	–	30,0–47,0 %
Tekaya A.B. et al., 2021 [23]	ретроспективное/ retrospective	–	31,4 %	–	–	–
Hill J. et al., 2022 [24]	систематический обзор и метаанализ/ systematic review and meta-analysis	–	37,7 %	–	–	–
Miura T. et al., 2022 [25]	ретроспективное/ retrospective	–	37,3 %	–	–	–
Varela D.C. et al., 2022 [26]	ретроспективное когортное/ retrospective, cohort	–	27,7 %	–	–	–

Окончание табл.
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Ссылка/Link	Тип исследования/ Type of research	ИБС/ IHD	ГБ/ HT	ХСН/ CHF	НРПРС/ DCRC	ССЗ/ ASCVD
Zikiryayeva S.G. et al., 2022 [27]	аналитическое одномоментное (поперечное)/ analytical single-stage (transverse)	45,9 %	–	–	22,1 %	–
Lee E.E. et al., 2022 [28]	ретроспективное когортное/ retrospective cohort	11,1 %	44,7 %	5,6 %	–	–
Khusainova M.A. et al., 2023 [29]	клиническое/ clinical	–	–	–	65,7 %	–
Kodishala C. et al., 2023 [30]	ретроспективное когортное	–	62,6 %	3,7 %	–	–
Koster F. et al., 2023 [31]	ретроспективное когортное/ retrospective cohort	–	4,6 %	2,2 %	6,1 %	–
Mena-Vázquez N. et al., 2023 [32]	когортное/cohort	–	26,0 %	5,8 %	–	–
Adelowo O. et al., 2024 [33]	ретроспективное/ retrospective	–	22,3 %	–	–	–
Duruöz M.T. et al., 2024 [34]	многоцентровое перекрестное исследование/ multicenter crossover	3,7 %	27,2 %	–	–	–

Примечание: ИБС –ишемическая болезнь сердца; ГБ — гипертоническая болезнь; ХСН — хроническая сердечная недостаточность; НРПРС — нарушения ритма и проводимости сердца; ССЗ — атеросклеротические сердечно-сосудистые заболевания; — значение признака не определялось.

Note: IHD — ischemic heart disease; HT — hypertension; CHF — chronic heart failure; DCRC — disorders of cardiac rhythm and conduction; ASCVD — atherosclerotic cardiovascular diseases; — the value of the feature was not determined.

Частота встречаемости ССЗ у пациентов с РА согласно сведениям многочисленных исследований (2019–2024) колеблется в широком диапазоне. В основной массе литературных источников ведущее место по распространенности занимают ГБ, ИБС, сердечная недостаточность, нарушения ритма и проводимости сердца, атеросклеротические сердечно-сосудистые заболевания. При этом разброс данных по встречаемости этих состояний весьма значителен и, полагаем, обусловлен не только применяемой тактикой ведения больных РА, но и участием генетических, регионально-экологических, социально-культурных факторов риска как в тяжести течения РА [35, 36], так и в развитии ССЗ [37, 38]. Расхождения данных в разных исследованиях могут объясняться также гетерогенностью течения РА и различиями в активности заболевания, сравнением амбулаторных и стационарных пациентов, применением разных методов для выявления сердечно-сосудистых событий [39, 40]. Кроме того, не исключен фактор приходящейся на эти годы заболеваемости COVID-19. Пандемия и изоляция повлияли на пациентов с ревматическими заболеваниями не только по характеристикам, связанным с заболеванием [41, 42], но и по распространенности сопутствующих патологий, предрасполагая их к развитию новых осложнений и, следовательно, к увеличению сердечно-сосудистого риска [41]. Это в очередной раз подтверждает важность периодических когортных исследований и определения возможных популяционных рисков развития кардиоваскулярных патологий у больных РА.

Пациенты с РА исследуемой нами когорты Индукции характеризовались сложной структурой коморбидности. Встречаемость ССЗ в спектре коморбидных состояний наглядно представлены в виде диаграммы на рисунке 1.

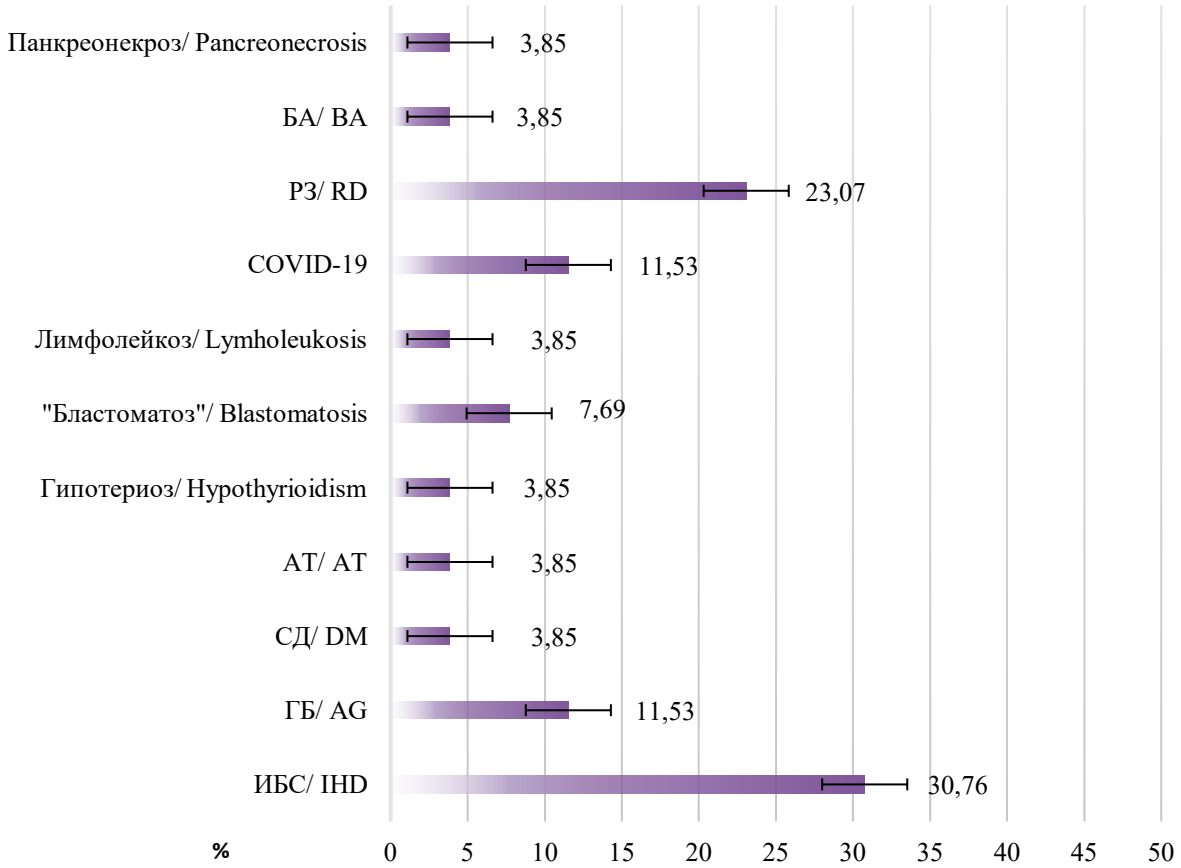

Рис. 1. Доля кардиоваскулярных патологий в структуре коморбидного профиля больных РА

Примечание: БА — бронхиальная астма; РЗ — респираторные заболевания; АТ — аутоиммунный тиреоидит; СД — сахарный диабет; ГБ — гипертоническая болезнь; ИБС — ишемическая болезнь сердца.

Fig. 1. The share of cardiovascular pathologies in the structure of the comorbid profile of patients with RA

Note: BA — bronchial asthma; RD — respiratory diseases; AT — autoimmune thyroiditis; DM — diabetes mellitus; HT — hypertension; IHD — ischemic heart disease.

Сердечно-сосудистая патология выступает наиболее распространенной (42,29 %). За ней следуют респираторные заболевания (23,07 %), COVID-19 (11,53 %), «Бластоматоз» (7,69 %). Острый панкреатит, осложненный панкреонекрозом, бронхиальная астма, лимфолейкоз, гипотиреоз, аутоиммунный тиреоидит, сахарный диабет регистрировались не более чем у 3,85 % когорты.

Наше исследование не включало контрольную группу и при анализе результатов ориентировались на опубликованные популяционные данные заболеваемости болезнями системы кровообращения в Ставропольском крае с учетом возрастного и гендерного распределения [44].

Кардиоваскулярные нарушения в исследуемой нами когорте включали ИБС (30,76 %) и ГБ (11,53 %). Приведенные значения встречаемости ИБС у пациентов с РА на 8,76 % превышали общие популяционные данные.

Известно, что специфическими для РА факторами риска коронарных синдромов могут выступать системное воспаление, эндотелиальная дисфункция, а также вносящие вклад в патогенез РА Т-клетки, участвующие в нестабильности атеро-

склеротической бляшки [1, 45]. Имеются сведения о взаимосвязи хронического воспаления с повышением артериального давления и впоследствии развитием ГБ у пациентов с РА. Возможными причинами артериальной гипертензии при РА считаются аутоиммунные и метаболические нарушения [9, 46], генетические факторы, а также применение противоревматических препаратов с потенциально гипертензивными свойствами [47]. Однако если по большинству современных литературных данных ГБ превалирует в структуре сердечно-сосудистых патологий при РА [14, 33], для исследуемой нами когорты пациентов лидирующая позиция оказалась за ИБС.

Во-первых, это может объясняться незарегистрированными случаями впервые возникшей артериальной гипертензии в исследуемой нами выборке пациентов, что логично перекликается с данными [40, 48] по длительному наблюдению за пациентами с РА, согласно которым около половины пациентов, характеризуются развитием у них ГБ уже на фоне имеющегося РА и не всегда на ранней стадии его развития. Во-вторых, выявленный факт может быть связан с общей популяционной тенденцией роста заболеваемости ИБС за последние несколько лет в исследуемом нами регионе. Так, по сведениям Савиной А.А. и Фейгиновой С.И. [49], из субъектов РФ Ставропольский край выделялся ростом заболеваемости ИБС в динамике 2007–2019 гг. в 4 раза. Это логично перекликается с результатами проведенного нами анализа медицинской документации, согласно которым зарегистрированное в Ставропольском крае общее число заболеваний РА и ИБС и взятых под диспансерное наблюдение за недавние несколько лет значительно возросло (рис. 2).

Кроме того, согласно некоторым данным [34] на структуре кардиоваскулярной патологии при РА исследуемой нами когорты могли отразиться особенности демографических, поведенческих, клинических факторов и диагностических подходов. Так в ряду доступных литературных источников мы нашли исследование [27], тоже демонстрирующее относительно высокую долю ИБС (45,9 %), установленную у больных РА за счет расширения спектра использованных дополнительных диагностических тестов.

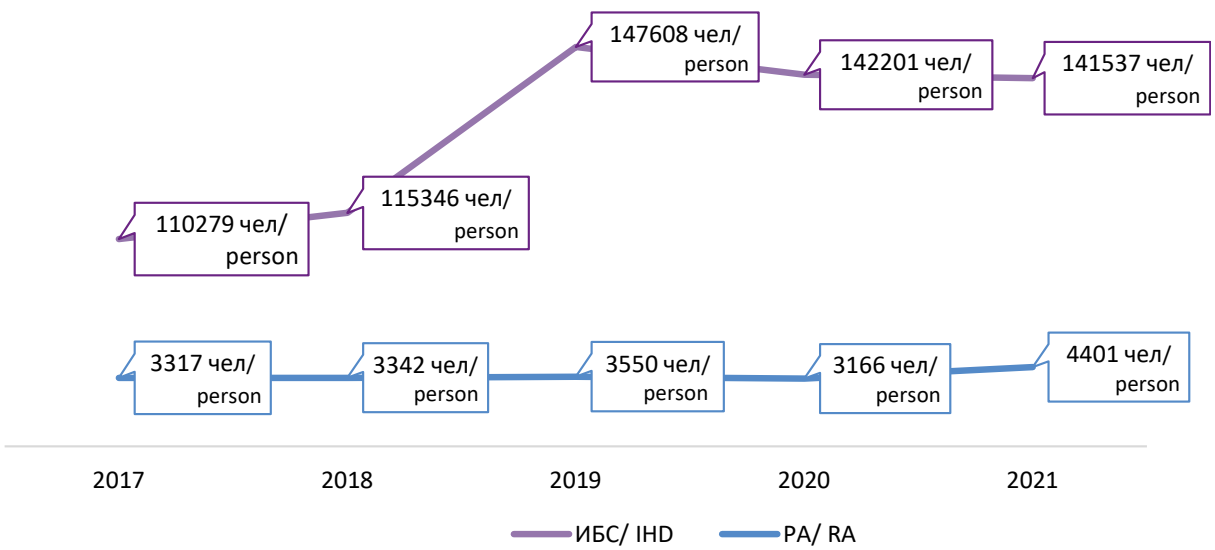

Рис. 2. Динамика зарегистрированных заболеваний ишемической болезнью сердца (ИБС) и ревматоидным артритом (РА) за 2017–2021 гг. в Ставропольском крае

Fig. 2. Dynamics of registered diseases of coronary heart disease (IHD) and rheumatoid arthritis (RA) for 2017–2021 in the Stavropol region

Больные РА остаются проблемой с точки зрения, не только заболеваемости, но и смертности. При этом важно отметить, что риск летальности, связанный с РА, может быть не напрямую связан с самим РА, а опосредованно через другие сопутствующие заболевания, возникающие у пациентов с РА [50]. Уже определена значительная связь между РА и смертностью от ССЗ [51]. Имеется целый ряд данных [52, 53], указывающих на более высокую частоту коронарных атеросклеротических событий, сердечной недостаточности и нарушений мозгового кровообращения у больных РА. В целом риск сердечно-сосудистой смерти при РА примерно на 50 % выше общего популяционного [54].

Увеличение риска развития фатальных кардиоваскулярных осложнений (инфаркт миокарда, инсульт, внезапная сердечная смерть) при РА обусловлено рядом причин. К ним относятся традиционные модифицируемые (дислипидемия; сахарный диабет; курение; ожирение; стресс) и немодифицированные (возраст, мужской пол, отягощенная наследственность). Кроме того, из-за повреждения суставов снижение физической активности может способствовать повышению уровня свертываемости крови и увеличению риска кардиоваскулярных заболеваний и смертности.

Важно отметить, что величина рисков сердечно-сосудистой смерти при РА различается в отдельных исследованиях. Это может быть связано с особен-

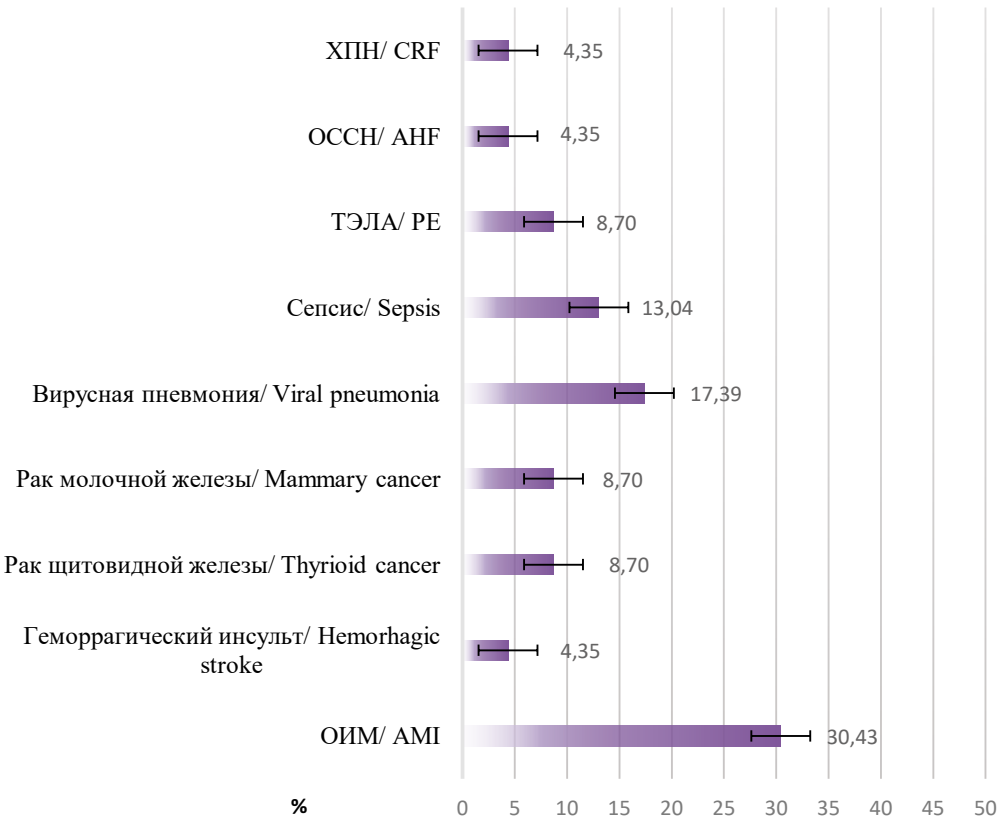

Рис. 3. Диаграмма ряда заключительных клинических диагнозов пациентов Индукции с РА, установленных посмертно, со вскрытием

Примечание: ХПН — хроническая почечная недостаточность; ОССН — острая сердечно-сосудистая недостаточность; ТЭЛА — тромбоэмболия легочной артерии; ОИМ — острый инфаркт миокарда.

Fig. 3. Diagram of a number of final clinical diagnoses of patients (Induction) with RA, established posthumously, with autopsy

Note: CRF — chronic renal failure; AHF — acute heart failure PE — acute pulmonary embolism; AMI — acute myocardial infarction.

ностями обследуемых когорт пациентов и спецификой терапевтических подходов в разных странах, с эффективностью достижения или не достижения цели лечения [10, 27].

В исследуемой нами когорте в тройку основных причин смерти пациентов с РА вошли сердечно-сосудистые, респираторные заболевания, сепсис (рис. 3).

Лидирующую позицию занимали сердечно-сосудистые события (47,83 %), преимущественно инфаркт миокарда (30,43 %). Полученные данные согласуются с доступными результатами других исследований [55, 56] и, полагаем, связаны с ускоренным процессом атеротромбоза, вероятность развития которого при РА даже после исключения всех традиционных факторов риска остается довольно высокой [57]. Это не только в очередной раз подтверждает взаимосвязь патогенетических механизмов РА и ИБС, прослеживаемую рядом авторов [58], но и выставляет ИБС ведущей причиной сердечно-сосудистых осложнений у пациентов с РА.

Новые стратегии терапии воспаления и сердечно-сосудистой патологии положительно отражаются на снижении смертности больных РА. В исследованиях отмечается снижение риска смерти больных РА от ССЗ [59]. Полученные нами результаты идут несколько в разрез с этими данными. ССЗ в структуре состояний, приведших к смертности пациентов с РА, стоят на первом месте со сравнительно высокой встречаемостью. Тенденция к снижению летальности больных РА Ставропольского края когорты Индукции еще не проявляется и позволяет полагать, что коррекция и обновление методических рекомендаций по контролю и управлению сердечно-сосудистыми рисками в этом аспекте, может оказаться весьма полезным.

Выводы

В настоящей работе проведен анализ новых данных о месте сердечно-сосудистой патологии в структуре коморбидности и смертности пациентов Ставропольского края когорты «Индукции» с установленным диагнозом РА.

Ретроспективный дизайн проведенного исследования явился некоторым ограничением возможности определения временной последовательности между началом кардиоваскулярных заболеваний и диагнозом РА. При этом сильной стороной работы выступало то, что в исследовании использовались точные данные медицинских баз и документаций и включались пациенты с достоверно установленным диагнозом.

Полученные сведения полезны для лучшего понимания клинического портрета больных РА с кардиоваскулярной патологией и могут учитываться ревматологами для оптимизации тактики управления РА и риском кардиоваскулярных событий.

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ORIGINAL RESEARCH
ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Relationships between linear-quadratic parameters for cells irradiated in the presence and absence of cisplatin

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Abstract. *Relevance*. According to experimental data, administration of the drug cisplatin into the tumor during radiation therapy can increase its effectiveness. To date, there is no model that can predict the effectiveness of such therapy. The development of such a model is an important task for planning therapy. The goal of this work is to find analytical relationships for the survival of cells exposed to the combined effect of radiation and cisplatin in vitro. *Materials and methods*. Based on digitized experimental data on cell survival from a number of publicly published works, the corresponding linear-quadratic (LQ) approximation coefficients for survival were found for irradiation without the drug α_R, β_R, and for combined exposure to radiation and cisplatin α_{RC}, β_{RC}. Next, a regression analysis of the resulting set of coefficients and cell survival when exposed to cisplatin alone S_C was performed. *Results and Discussion*. α_{RC} was found to be statistically dependent on α_R, β_R and S_C. This dependence could be described by several models, the best of which in terms of a number of indicators was $\alpha_{RC} = \alpha_R + a\beta_R \ln S_C$, where $a = -4.27 \pm 0.57$ is a parameter that is the same for all cell types and experimental conditions. It was found that β_{RC} is statistically dependent on β_R. No signs of dependence of β_{RC} on α_R and S_C were found. The best model for β_{RC} was $\beta_{RC} = \beta_R$. These models are simple, but they allow predicting the value of cell survival under the combined effect of radiation and cisplatin S_{RC} from the values α_R, β_R and S_C only approximately. The obtained models are collated with kinetic equations and a mechanistic interpretation is given, which is based on the hypothesis of a decrease in the rate of recovery of cells from potentially lethal lesions r_+ with an increase in the radiation dose and cisplatin concentration. *Conclusion*. The type of statistical dependence of LQ coefficients α_{RC} and β_{RC} on α_R, β_R and S_C has been found. In the case of high toxicity of cisplatin (low values of S_C), the combination of the above-mentioned models for α_{RC} and β_{RC} allows to make a useful for practical application prediction of cell survival S_{RC}.

The results of this work will help for the future construction of more complex models of the combined effects of radiation and cisplatin, and may also have practical application in the case mentioned above.

Keywords: cisplatin, LQ approximation of cell survival, photon beam therapy, regression analysis, kinetic models of cell survival

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Introduction

For several decades, cisplatin has been used to treat various cancers [1, 2]. The presence of side effects during treatment [3] leads to the need of developing complex therapy that would increase the effectiveness of the drug and reduce the dose required for treatment. One of the options for such therapy may be the use of the drug in combination with radiation. A large number of *in vitro* experiments have shown the potential effectiveness of this method, revealing that cisplatin can serve as a radiosensitizer (see, for example, [4–6]).

To plan therapy with the combined effects of radiation and cisplatin, a model is needed that can predict the fraction of surviving cells after exposure to a given dose of drug and radiation [7]. To date, such a model does not exist. In our opinion, the first step towards its construction is to obtain simple empirical relationships for cell survival *in vitro*. In the future, based on them, it will be possible to build more complex models that take into account in more detail the conditions of the experiment. Further, if necessary, on the basis of such models it will be possible to build mechanistic models of cell survival that contain the most relevant scientific knowledge about the internal processes occurring in cells during therapy.

The purpose of this work is to find analytical relationships for the survival of cells exposed to the combined effects of radiation and cisplatin *in vitro*.

Materials and methods

The main idea of the work

It is known that, over a wide range of doses, experimental data on cell survival during irradiation *in vitro* are almost always well described by a linear-quadratic (LQ) function of the form:

$$S_R = e^{-\alpha_R D - \beta_R D^2}, \quad (1)$$

where S_R — cell survival, D — deposited dose, α_R and β_R — coefficients selected using regression analysis methods [8, 9]. α_R and β_R depend on cell type, type of radiation and a number of additional experimental conditions. A more general form of expression (1) is applicable to describe cell survival in the presence of cisplatin:

$$\frac{S_{RC}}{S_C} = e^{-\alpha_{RC}D-\beta_{RC}D^2}, \quad (2)$$

where S_{RC} — cell survival under combined exposure to cisplatin and radiation; S_C — cell survival in the presence of cisplatin but without irradiation; α_{RC} and β_{RC} — coefficients similar in meaning to α_R and β_R. Experimental conditions for S_C and S_{RC} must be equivalent, including the use of the same concentration of cisplatin and time of incubation with cells.

Thus, α_R and β_R characterize the response of cells to radiation, and S_C — to the presence of cisplatin. It is logical to assume that, knowing the response of cells to radiation and cisplatin separately, it is possible to predict it for the case of their combined action, that is, knowing α_R, β_R and S_C, to predict α_{RC} and β_{RC}. Mathematically, this hypothesis can be written in the form of relations:

$$\alpha_{RC} = f_{\alpha_{RC}}\left(\alpha_R, \beta_R, S_C, \vec{a}_{\alpha_{RC}}\right) + \varepsilon_{\alpha_{RC}}, \quad (3)$$

$$\beta_{RC} = f_{\beta_{RC}}\left(\alpha_R, \beta_R, S_C, \vec{a}_{\beta_{RC}}\right) + \varepsilon_{\beta_{RC}}, \quad (4)$$

where $f_{\alpha_{RC}}$ and $f_{\beta_{RC}}$ — unknown functions of variables α_R, β_R and S_C; $\vec{a}_{\alpha_{RC}}$ and $\vec{a}_{\beta_{RC}}$ — vectors with parameters that are the same for all cell types, types of photon sources, cisplatin concentrations, times of incubation of cells with cisplatin and other factors; $\varepsilon_{\alpha_{RC}}$ and $\varepsilon_{\beta_{RC}}$ — Gaussian errors. To date, experimental data on the combined effect of radiation and cisplatin are quite small, which is why it is possible to consider only the simplest types of functions $f_{\alpha_{RC}}$ and $f_{\beta_{RC}}$, containing no more than two parameters each. In view of this, we will consider functions of a simpler form:

$$\alpha_{RC} = \alpha_R + f_{\alpha_{RC}}\left(\beta_R, S_C, \vec{a}_{\alpha_{RC}}\right) + \varepsilon_{\alpha_{RC}}, \quad (5)$$

$$\beta_{RC} = \beta_R + f_{\beta_{RC}}\left(\alpha_R, S_C, \vec{a}_{\beta_{RC}}\right) + \varepsilon_{\beta_{RC}}, \quad (6)$$

where we have redefined functions $f_{\alpha_{RC}}$ and $f_{\beta_{RC}}$ and errors $\varepsilon_{\alpha_{RC}}$ and $\varepsilon_{\beta_{RC}}$ from expressions (3) and (4) so as not to introduce too much notation; expressions (3) and (4) will not be used further.

Finding functions $f_{\alpha_{RC}}$ and $f_{\beta_{RC}}$ and their inaccuracies is a regression analysis problem in which expressions (5) and (6) are regression models.

The parameters of models (5) and (6) can be interpreted mechanistically by proposing a new kinetic model of the dynamics of lethal and potentially lethal events occurring in cells during irradiation and administration of cisplatin.

Selection of experimental data

Experimental data were extracted from published articles mainly by digitizing the graphs presented in them. We only used articles that met a number of requirements:

— the article must explicitly indicate: photon source (for example, ^{60}Co or 200 kV), cell type, incubation times of cells with cisplatin during measurement of S_C and S_{RC} (these times must match);

— the dose rate should not significantly exceed the range of usual values used in this kind of experiments (approximately from 0.5 to 5 Gy / min);

— cells should not be exposed to obviously extreme conditions such as hypoxia or hyperthermia;

— the experiment must not involve manipulation of the cell cycle.

A sufficient amount of data was extracted from articles [10–15] to find the parameters of regression models of simple form (5) and (6), containing no more than two parameters, with satisfactory accuracy, namely 25 sets of values $\hat{\alpha}_R$, $\hat{\beta}_R$, $\hat{S}_C$, $\hat{\alpha}_{RC}$, $\hat{\beta}_{RC}$, where the cap above the value means that it represents an estimate based on the experimental data of the article (that is, based on a sample), rather than its true value (within the framework of the frequentist approach to mathematical statistics). Thus, we did not consider all the existing experimental data, but only part of it, due to the fact that a larger amount of data would not significantly

improve the quality of the regression analysis results for their practical application.

In the experimental data retrieved from articles, the dose rates ranged from approximately 0.6 to 1.5 Gy/ min. The incubation times of cells with cisplatin varied from 1 to 24 hours. Cells were irradiated either before incubation with the drug or after it (differently in different experiments). 11 types of cells were irradiated with 5 types of photon sources.

Data on the SCC-25 cell line from the article [14] were excluded from consideration as outliers: at a dose of 1 Gy in the presence of cisplatin, an increase in cell survival was observed in them, which did not occur in other experiments.

Regression analysis of experimental data

Unfortunately, we were unable to extract standard errors for all measurements from the articles, so they were not used in our calculations.

If the article did not explicitly indicate the values of $\hat{S}_C$, then they were found by interpolating the presented data. First, we tried interpolation with the Hill function [16]:

$$S_C = \frac{1}{1+\left(\frac{C}{IC_{50}}\right)^n}, \quad (7)$$

where C — drug concentration, IC_{50} and n — parameters. However, in a number of cases it turned out to be unsatisfactory, which is why linear interpolation between the nearest values was used to obtain values of $\hat{S}_C$.

LQ parameter values $\hat{\alpha}_R$, $\hat{\beta}_R$, $\hat{\alpha}_{RC}$ and $\hat{\beta}_{RC}$ were found using the least squares method (LS) for the functions:

$$f_R = -\frac{\ln \hat{S}_R}{D} = \hat{\alpha}_R + \hat{\beta}_R D, \quad (8)$$

$$f_{RC} = -\frac{\ln \frac{\hat{S}_{RC}}{\hat{S}_C}}{D} = \hat{\alpha}_{RC} + \hat{\beta}_{RC} D, \quad (9)$$

where $\hat{S}_R$ and $\hat{S}_{RC}$ — estimations of functions (1) and (2) based on experimental samples. It should be noted that the obtained parameter values cannot be considered the result of solving a standard linear regression problem

$$f'_R = -\frac{\ln S_R}{D} = \alpha_R + \beta_R D + \varepsilon_R, \quad (10)$$

$$f'_{RC} = -\frac{\ln \frac{S_{RC}}{S_C}}{D} = \alpha_{RC} + \beta_{RC} D + \varepsilon_{RC}, \quad (11)$$

where ε_R and ε_{RC} — Gaussian errors. The point is that the sizes of the samples relevant to $\hat{S}_R$ and $\hat{S}_{RC}$ are too small (in some cases they have only one degree of freedom) to provide meaningful arguments about the validity of the models (10) and (11). In other words, it cannot be stated that the quantities ε_R and ε_{RC} are random variables having a normal distribution. In view of this, in order to avoid gross errors in further calculations, we assumed that the values of $\hat{\alpha}_R$, $\hat{\beta}_R$, $\hat{\alpha}_{RC}$ and $\hat{\beta}_{RC}$ obtained by this method represent single measurements of the corresponding quantities.

Since it is known that the LQ approximation (1) is not applicable for low doses [17], when selecting parameters, points with a dose value of less than 0.9 Gy were excluded from consideration.

The resulting set of values of $\hat{\alpha}_R$, $\hat{\beta}_R$, $\hat{\alpha}_{RC}$ and $\hat{\beta}_{RC}$ was used to solve regression problems (5) and (6), that is, finding model parameters, their inaccuracies and accompanying statistical criteria.

In total, more than 100 types of functions $f_{\alpha_{RC}}$ and $f_{\beta_{RC}}$ were considered, containing no more than two parameters, from the simplest type to the more complex. Consideration of such a large number of functions was necessary because we were not based on any already published model, so the type of functions was not known in advance and had to be found by enumerating options.

The amount of experimental data was too small to prove the validity of models (5) and (6), but it was possible to provide significant arguments in favor of this based on statistical criteria. To do this, we used the Shapiro-Wilk test, which is considered one of the most powerful tests for testing data for normality [18]

and the one-sample t-test for the mean [19]. Based on these criteria, we drew conclusions about the possibility of considering that the quantities $\varepsilon_{\alpha_{RC}}$ and $\varepsilon_{\beta_{RC}}$ have a normal distribution with zero mathematical expectation. It should be noted that for samples of finite size, the use of these criteria is an approximation and assumes that the functions $f_{\alpha_{RC}}$ и $f_{\beta_{RC}}$ with true parameter values are not far from their sample estimates. Despite this rough approximation, this method allows one to track models with highly non-Gaussian errors.

The values of the model parameters and their uncertainties were found in two ways, depending on the type of $f_{\alpha_{RC}}$ and $f_{\beta_{RC}}$. For functions linear in parameters, analytical relations were used [20]. For non-linear functions, one of the bootstrapping methods was used [21]: regression residuals were modeled randomly and for each case the parameter values were found using LS. For each function, a set of one million parameter values was calculated. With such an amount, the inaccuracy of this method was less than 1%, and in the problem under consideration it could be neglected. This method could also be used for linear functions, since it gives the same results as analytical relations, but the calculation required much more time, which is why it was applied only to non-linear cases.

Results and discussion

Figure 1 shows examples of approximation of experimental data by functions (1) and (2), whose parameters were found using (8) and (9), as described in materials and methods. The approximation described the data well in all 25 cases of combined exposure to radiation and cisplatin and, thus, the validity of (2) was not in doubt. The mean value of the coefficient of variation for function (9) was 0.127.

Diamonds indicate experimental data, a solid line of the same color indicates their approximation. Cisplatin concentrations are shown in the legend. a) Data from [10] for CHO cells irradiated with photons from a ^{137}Cs source at a cell incubation time with cisplatin of 1 hour. At a concentration of 8 μg / ml, the authors of the work examined separately the case of cell irradiation after incubation with

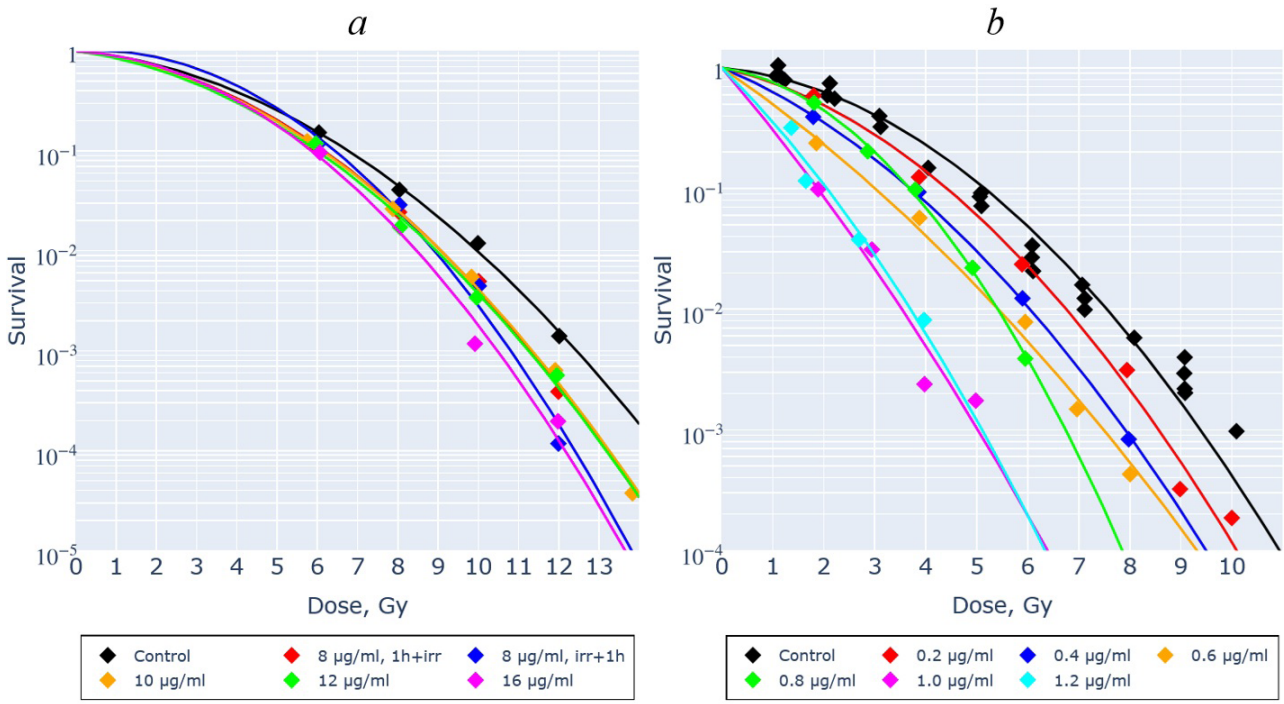

Fig. 1. Examples of approximation of experimental data by LQ functions (1) and (2)

cisplatin (1h + irr) and before incubation (irr + 1h), without finding a significant difference between the data. b) Data from [11] for RIF1 cells irradiated with 200 kV photons at a cell incubation time with cisplatin of 1 hour.

In Table 1 and Table 2 the resulting models (5) and (6) for α_{RC} and β_{RC} are presented, which are most worthy of mention (there are more than 100 models in total). For α_{RC}, by the latter, we mean several of the best models in terms of statistical indicators and simplicity, as well as several models that characterize the methods and results of regression analysis of this work. For β_{RC}, models are presented that have the same form as models for α_{RC}. We found that α_{RC} is statistically dependent on α_R, β_R and S_C, and β_{RC} is dependent on β_R. We found no evidence of a statistical dependence of β_{RC} on α_R and S_C. The results of the regression analysis did not allow us to clearly identify the best model for α_{RC}. Thus, based on statistical indicators, several models could be used as such. In such a situation, we conditionally chose model number 8 as the best one, since among the models with the best performance it had the simplest form. The approximation of experimental data by this model is shown in Figure 2. Unlike α_{RC}, the best model for β_{RC} could be chosen unambiguously and this was model number 2.

Table 1

Models of LQ coefficient α_{RC} for combined exposure to radiation and cisplatin

		α_{RC}, Gy^{-1}					
#	Model	a	b	RSD	Shapiro-Wilk p-value	One-sample t-testp-value	R^2
1	a	0.234 ±0.062	-	0.312	4.49×10^{-5}	1.00	-
2	α_R	-	-	0.288	7.31×10^{-6}	0.0166	-
3	$\alpha_R + a$	0.148 ±0.058	-	0.288	7.31×10^{-6}	1.00	-
4	$\alpha_R + a\beta_R{}^2$	99.0 ±17.6	-	0.214	0.190	0.835	0.569
5	$\alpha_R + a \ln S_C$	-0.237 ±0.040	-	0.206	0.799	0.515	0.599
6	$\alpha_R + a \ln^2 S_C$	0.118 ±0.018	-	0.195	0.0803	0.602	0.642
7	$\alpha_R + a\left(-\ln S_C\right)^b$	0.118 ±0.063	2.00 ±0.85	0.199	0.0845	0.592	-
8	$\alpha_R + a\beta_R \ln S_C$	-4.27 ±0.57	-	0.177	0.119	0.844	0.703
9	$\alpha_R + a\beta_R \ln^2 S_C$	1.91 ±0.26	-	0.178	0.0573	0.415	0.699
10	$\alpha_R + a\beta_R\left(-\ln S_C\right)^b$	3.43 ±1.22	1.30 ±0.54	0.180	0.0343	0.867	-

Note: α_R is expressed in Gy^{-1}, β_R in Gy^{-2}, S_C is dimensionless. The table shows sample parameter estimates and their standard errors, separated from the former by ±. Parameter a has different dimensions depending on the model, and parameter b is dimensionless. RSD — residual standard deviation. The p-value for Shapiro-Wilk test is indicated for the null hypothesis that the sample is drawn from a population with a normal distribution. The p- value for one-sample t-test for the mean is indicated for the null hypothesis that the sample is drawn from a population with an expected value of zero (see "Materials and methods" section). Coefficient of determination R^2 is indicated only for cases of linear regression, where it can be interpreted in a standard way.

Table 2

Models of LQ coefficient β_{RC} for combined exposure to radiation and cisplatin

		β_{RC}, Gy^{-2}					
№	Model	$a \times 10^2$	b	RSD×10^2	Shapiro -Wilk p-value×10^2	One -sample t-testp-value	R^2×10^2
1	a	3.25 ± 0.65	-	3.25	0.577	1.00	-
2	β_R	-	-	1.94	6.44	0.786	-
3	$\beta_R + a$	0.106 ± 0.387	-	1.94	6.44	1.00	-
4	$\beta_R + a\alpha_R^2$	-8.0 ± 16.5	-	1.93	4.51	0.590	0.984
5	$\beta_R + a \ln S_C$	-0.229 ± 0.370	-	1.92	8.32	0.872	1.57
6	$\beta_R + a \ln^2 S_C$	0.137 ± 0.178	-	1.92	9.19	0.915	2.41
7	$\beta_R + a(-\ln S_C)^b$	0.125 ± 0.409	-0.10 ±1.45	1.98	6.22	0.937	-
8	$\beta_R + a\alpha_R \ln S_C$	0.20 ± 3.65	-	1.94	6.13	0.757	0.0129
9	$\beta_R + a\alpha_R \ln^2 S_C$	0.92 ± 1.93	-	1.93	8.08	0.978	0.939
10	$\beta_R + a\alpha_R(-\ln S_C)^b$	-1.37 ± 3.71	0.33 ±1.53	1.98	4.80	0.591	-

Note: The table data format is similar to Table 1.

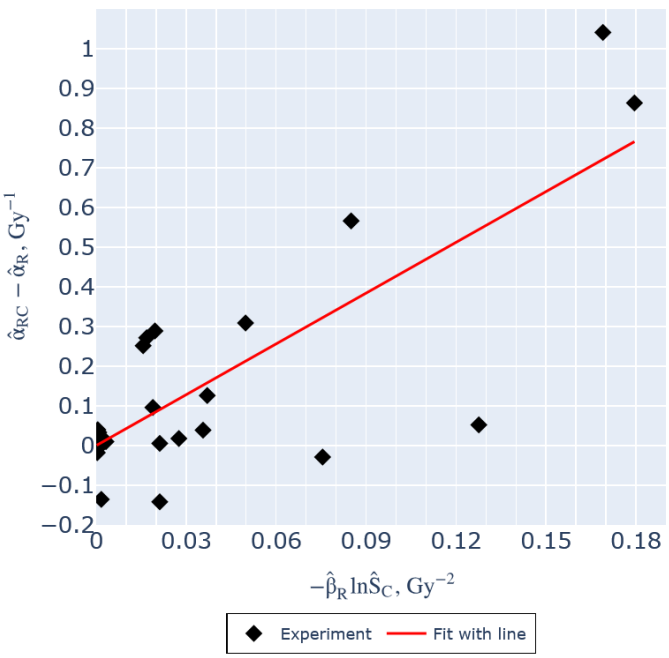

Fig. 2. Approximation of experimental values of LQ coefficient for combined exposure to radiation and cisplatin α_{RC} by linear model 8 from Table 1. R^2 = 0.703

Thus, the best model of cell survival under the combined effects of radiation and cisplatin in this work was considered to be function S_{RC} from (2) with LQ parameters corresponding to models 8 and 2 from Table 1 and Table 2, respectively:

$$\alpha_{RC} = \alpha_R + a\beta_R \ln S_C, \quad (12)$$

$$\beta_{RC} = \beta_R, \quad (13)$$

Figure 3 shows this model's description of the experimental data from Figure 1.

Figure 4 shows part of the data from Figure 3 with a constructed 95% prediction interval that predicts the outcome of individual experimental values and thus includes random error (not to be confused with a 95% confidence interval). As can be seen from Figure 4*a*, in some cases the prediction interval is too wide, and then the model's predictions may be useless for practical use. Unfortunately, for the vast majority of experimental data considered in this work, the situation in this regard is similar to Figure 4*a*.

It should be noted that in the experimental data considered there was only one case of high incubation time of cells with cisplatin — 24 hours, much longer than the others (1 hour and 2 hours). According to statistical indicators, this experiment did not stand out in any way from the general trends of the considered models.

According to model (12), α_{RC} can be considered linearly dependent on β_R and $\ln S_C$, however, this result is the average indicator for the 11 types of cells considered in the work, 5 types of photon sources, a wide range of times of incubation of cells with cisplatin and other factors. To use this model to predict the results of an individual experiment, it is necessary to take into account the random error (RSD from Table 1), as it is done in Fig. 4. Due to high RSD values, in some

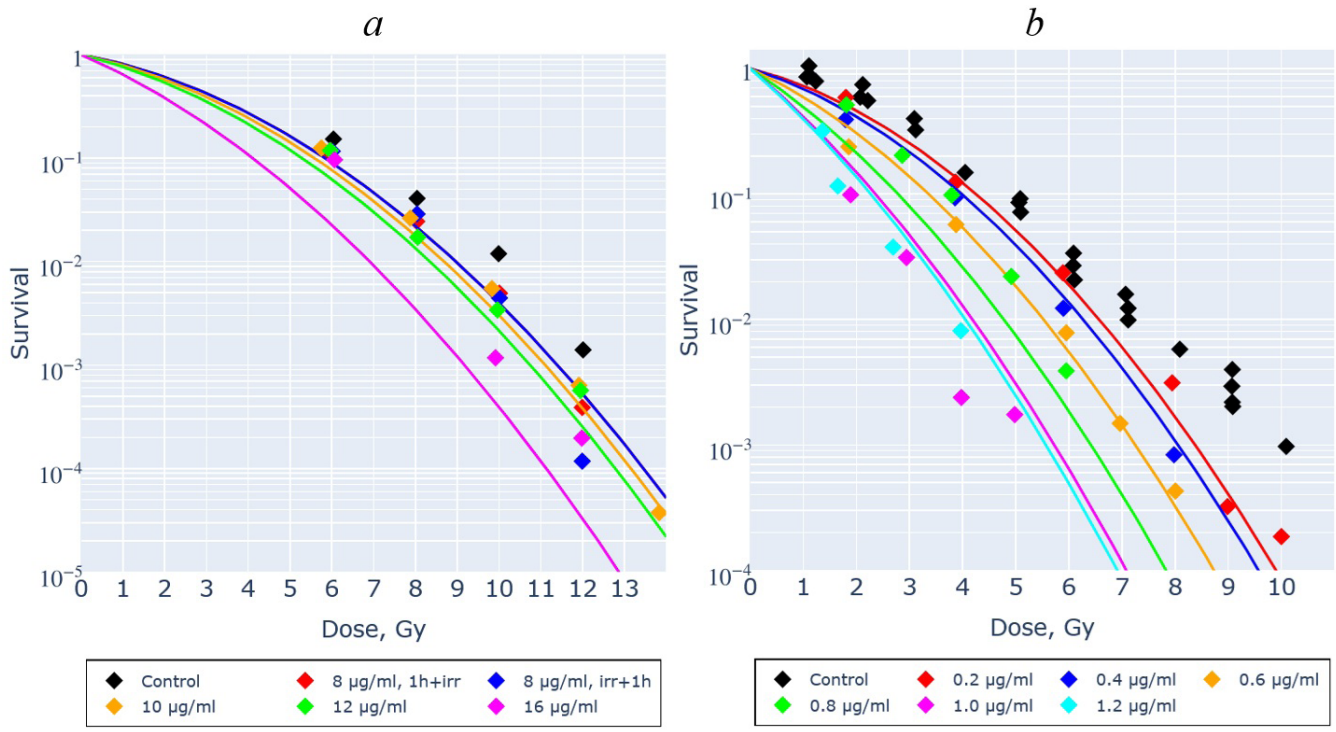

Fig. 3. Description of experimental data on cell survival under combined exposure to radiation and cisplatin from Fig. 1 by models (12) and (13): ***a*** – $\hat{\alpha}_R$ = 0.0819 Gy^{-1}, $\hat{\beta}_R$ = 0.0380 Gy^{-2}. $\hat{S}_C$ are equal to 0.573, 0.484, 0.392 and 0.137 for concentrations of 8, 10, 12 and 16 μg / ml, respectively; ***b*** – $\hat{\alpha}_R$ = 0.0923 Gy^{-1}, $\hat{\beta}_R$ = 0.0686 Gy^{-2}. $\hat{S}_C$ are equal to 0.583, 0.484, 0.290, 0.156, 0.0851 and 0.0731 for concentrations of 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 μg / ml, respectively

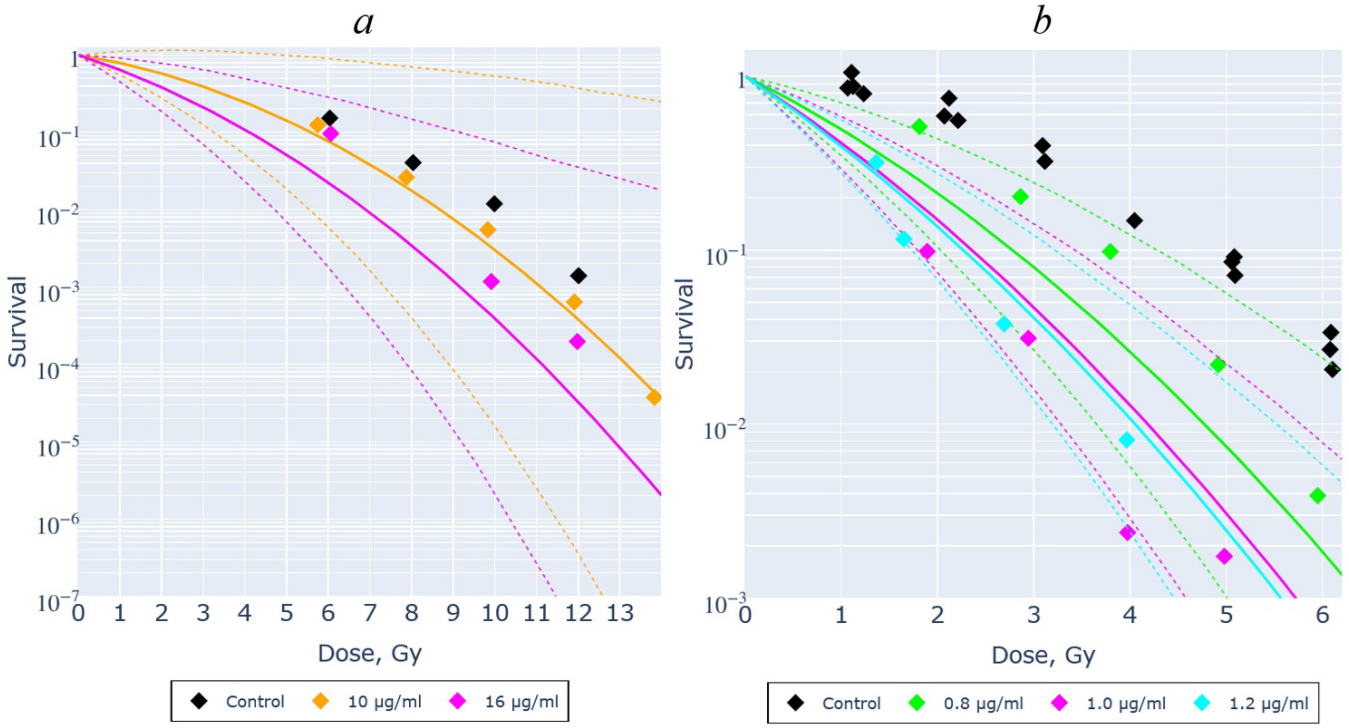

Fig. 4. Description of experimental data on cell survival under combined exposure to radiation and cisplatin from Fig. 1 by models (12) and (13), with a constructed 95% prediction interval (dashed line)

series of experiments there may not be an increase in the value of $\hat{\alpha}_{RC}$ when cisplatin is administered and even a decrease may be observed. According to model (12), one can state that $\hat{\alpha}_{RC}$ clearly increases only at sufficiently high values of $\hat{\beta}_R$ and $|\ln \hat{S}_C|$ (see Fig. 4b, in which $\hat{\beta}_R$ is equal to 0.0686, and $\hat{S}_C$ varies from 0.0731 to 0.156). Just as with the model for α_{RC}, the equality of β_{RC} and β_R (see model (13)) has a high random error, so the value of $\hat{\beta}_{RC}$ can differ significantly from $\hat{\beta}_R$ in individual experiments.

The obtained models (12) and (13) in most cases cannot provide a useful prediction of α_{RC} and β_{RC} based on the values of $\hat{\alpha}_R$, $\hat{\beta}_R$ and $\hat{S}_C$ due to the prediction intervals being too wide. To increase the accuracy of the prediction, we assumed that such a width of the intervals is due to the fact that the parameters of the models should depend on the cell type and the time of incubation of cells with cisplatin, and their obtained values are averaged over these factors. It is known that there are a number of kinetic models that claim to describe cell survival after irradiation (in the absence of drugs in the cells): MKM, LPL, RMR and others [22–24]. Such models are based on kinetic equations, the solution of which allows to express cell survival through a set of parameters that depend on the cell type and radiation. Thus, the expressions (12) and (13) should be solutions (possibly approximate ones) of such equations, generalized to the case of the presence of cisplatin in cells.

Let us create a system of kinetic equations. We will assume that damage to cells as a result of their irradiation and exposure to cisplatin can be divided into two groups: potentially lethal and lethal. By lethal we mean any events that are guaranteed to lead to the death of a cell or the loss of its reproductive functions. By potentially lethal we mean the averaged set of events that with some probability can lead to cell death or loss of reproductive functions (i.e. become lethal). Such events include various types of DNA damage, damage to cell organelles, and increase in level of oxidative stress.

Let us consider the simplest, approximate version of kinetic equations. We will assume that cisplatin was introduced into the cells before the instantaneous irradiation, and all potentially lethal events produced

by it can be considered either successfully eliminated by cellular mechanisms or became lethal at the time of irradiation. Then the system of equations can be written as follows:

$$\begin{cases} \dfrac{dU(t)}{dt} = -r_+ U(t) - r_- U(t), \quad U(0) = \kappa D \\ \dfrac{dL(t)}{dt} = r_- U(t), \quad L(0) = \eta D - \ln S_C \end{cases}, \qquad (14)$$

where $U(t)$ is the average number of potentially lethal events per cell at time t, $L(t)$ is the average number of lethal events per cell at time t, r_+ is the rate of disappearance of potentially lethal events as a result of successful cell recovery, r_- is the rate of transition of potentially lethal events to lethal ones as a result of unsuccessful recovery, κ is the average number of potentially lethal events per cell, produced by radiation per one Gy, η is the average number of lethal events per cell produced by radiation per one Gy, D is deposited dose. The term $-\ln S_C$ represents the average number of lethal events produced by cisplatin and takes into account the assumption that they are distributed over cells according to Poisson distribution. t = 0 corresponds to the time immediately after irradiation.

Let us assume that r_+ depends on the dose and the presence of cisplatin as follows:

$$r_+ = \frac{1}{A_1 + A_2\left(a_0 \ln S_C + D\right)}, \qquad (15)$$

where A_1, A_2 and a_0 are parameters that do not depend on the dose and concentration of cisplatin. Thus, we assume that the cellular recovery system from potentially lethal events is weakened by increasing radiation dose and cisplatin concentration, which is in agreement with existing data (see, e.g., [25] and [26]). Let us assume that $r_+ >> r_-$ by analogy with [22]. This approximation means that the vast majority of potentially lethal events are successfully eliminated and do not become lethal. Then the system of equations takes the form:

$$\begin{cases} \dfrac{dU(t)}{dt} = -\dfrac{U(t)}{A_1 + A_2\left(a_0 \ln S_C + D\right)}, \quad U(0) = \kappa D \\ \dfrac{dL(t)}{dt} = r_- U(t), \quad L(0) = \eta D - \ln S_C \end{cases}, \qquad (16)$$

This system has an analytical solution:

$$U(t) = \kappa D e^{-\frac{t}{A_1 + A_2\left(a_0 \ln S_C + D\right)}}, \qquad (17)$$

$$L(t) = \eta D - \ln S_C + \\ + r_- \kappa D\left(A_1 + A_2\left(a_0 \ln S_C + D\right)\right)\left(1 - e^{-\frac{t}{A_1 + A_2\left(a_0 \ln S_C + D\right)}}\right), \qquad (18)$$

For large times t, taking into account the Poisson distribution of lethal events across cells, we obtain the LQ dependence for survival:

$$S_{RC} = e^{-L(\infty)} = \\ = S_C e^{-\left(\eta D + r_- \kappa D\left(A_1 + A_2\left(a_0 \ln\left(S_C(C)\right) + D\right)\right)\right)} = S_C e^{-\left(\alpha_{RC} D + \beta_{RC} D^2\right)}, \qquad (19)$$

where

$$\alpha_{RC} = \eta + r_- \kappa\left(A_1 + A_2 a_0 \ln S_C\right), \qquad (20)$$

$$\beta_{RC} = r_- \kappa A_2, \qquad (21)$$

In the absence of cisplatin $\ln S_C = 0$, then:

$$\alpha_R = \eta + r_- \kappa A_1, \qquad (22)$$

$$\beta_R = r_- \kappa A_2 = \beta_{RC}, \qquad (23)$$

Expressing $a\kappa$ through β_R, we find:

$$\alpha_{RC} = \alpha_R + a_0 \beta_R \ln S_C, \qquad (24)$$

The obtained relations for α_{RC} and β_{RC} are fully consistent with models (12) and (13) provided that $a = a_0$.

With the approximations made, the case of irradiation of cells before the administration of cisplatin is no different from the case of irradiation after, provided

that cisplatin is administered into the cells immediately after irradiation.

Figure 5 and Figure 6 show approximations of the experimental data from Figure1 using models (23) and (24) by analogy with Figure 3 and Figure 4. When approximating, deviations of the experimental values of $\frac{\ln \hat{S}_{RC}}{D}$ from the mentioned models were considered as a Gaussian error. As can be seen from the comparison of Figures 3–6, the model predictions have improved significantly in case a) and remained approximately the same in case b). This difference in predictions is due to the large scatter of experimental data and the sharply changing "shoulder" $\hat{\beta}_{RC}$ in one direction or the other when changing the concentration of cisplatin in the latter case (see Figure 1).

Thus, in a number of cases, approximation of cell survival based on kinetic equations (14) predicts experimental data significantly better than relations (12) and (13). However, it should be noted that such an approximation requires experimental data on the survival during irradiation of a given cell type in the presence of cisplatin, while they are not needed to use relations (12) and (13). That is, it is necessary to know not only $\hat{\alpha}_R$, $\hat{\beta}_R$ and $\hat{S}_C$, but also a number of values of $\hat{S}_{RC}$, which is a serious drawback.

It should be noted that some parameters of the system (14) may be dependent on each other. At the moment, this is the subject of further research and is not addressed in this work.

As described above, system (14) is approximate, since in reality the irradiation of cells is not instantaneous, and potentially lethal events created by cisplatin exist simultaneously with those created by irradiation. However, this case is much more complex and is not considered in this paper.

Significant deviations of individual experimental values of survival from the LQ function approximating them, which in this work were interpreted as random errors, are a serious obstacle to the development of a model of cell survival, since even in cases where the model can very accurately predict the average survival value, variation in the prediction of individual survival values may be too large and have no practical

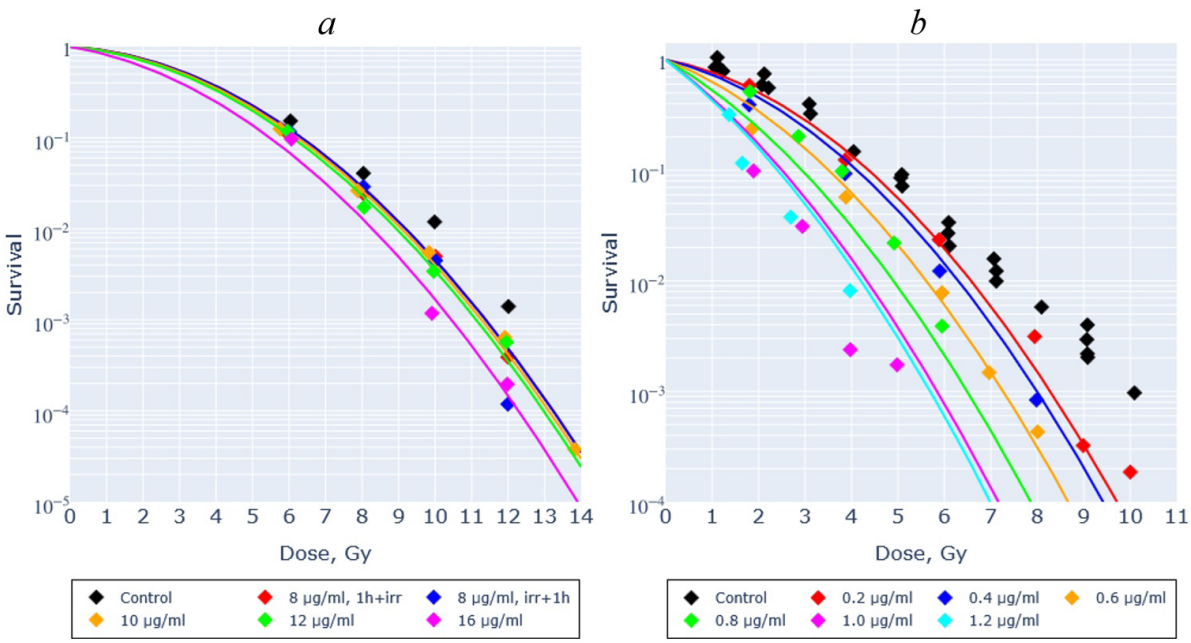

Fig. 5. Description of experimental data on cell survival under combined exposure to radiation and cisplatin from Fig. 1 by models (23) and (24): ***a*** – a_0 = −1.442 ± 0.319, α_R = 0.0175 ± 0.0327, β_R = 0.0483 ± 0.0033; ***b*** – a_0 = −3.555 ± 0.478, α_R = 0.0302 ± 0.0639, β_R = 0.0789 ± 0.0099

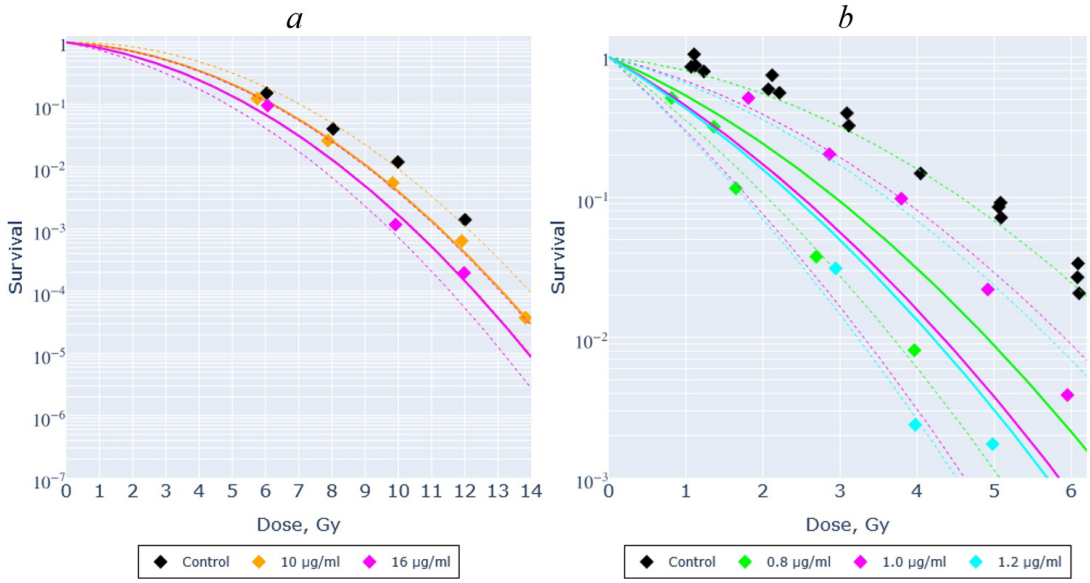

Fig. 6. Description of experimental data on cell survival under combined exposure to radiation and cisplatin from Fig. 1 by models (23) and (24), with a constructed 95% prediction interval (dashed line). In case ***a)*** one of the interval boundaries practically coincides with the solid line, which is why it is not clearly visible

application (the prediction interval constructed from the model is too wide). This makes it relevant to use a more accurate model than LQ to approximate survival data, as well as to investigate random errors in measuring cell survival, for example, whether deviations from LQ are really random errors or regular behavior and whether a significant difference in measured survival values can be avoided when the experiment is repeated (the problem of reproducibility of experimental data).

The experimental data in Fig. 1b cast doubt on the possibility of constructing a useful general cell survival model for practical application based only on the values of $\hat{S}_{RC}$ due to the sharply changing "shoulder" of $\hat{\beta}_{RC}$, first in one direction and then in the other, when the concentration of cisplatin changes. It is likely that to build such a model it is necessary to use microscopic characteristics of cells along with (or instead of) $\hat{S}_{RC}$ as input data.

Conclusion

As a result of statistical processing of experimental data, it was found that α_{RC} is statistically dependent on α_R, β_R and S_C. This dependence can be described by several models, the best of which in terms of a number of indicators is (12). It was found that β_{RC} is statistically dependent on β_R. No signs of dependence of β_{RC} on α_R and S_C were observed. The best model for β_{RC} is (13).

A new kinetic model is proposed. Its innovation is the hypothesis that the rate of recovery of cells from potentially lethal events r_+ decreases with increasing radiation dose and cisplatin concentration. This model in some cases allows to increase the accuracy of the prediction of S_{RC} in comparison with models (12) and (13), but requires the availability of a number of experimental values of $\hat{S}_{RC}$ for the same type of cells and radiation for which the prediction is made.

The results of this work will help for the future construction of more complex models of the combined effects of radiation and cisplatin, and may also have practical application for prediction of cell survival S_{RC} in the case of high toxicity of cisplatin (low values of S_C).

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Соотношения между линейно-квадратичными параметрами при облучении клеток в присутствии и отсутствии цисплатина

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Аннотация. *Актуальность.* Согласно экспериментальным данным введение препарата цисплатин в опухоль при лучевой терапии может повысить ее эффективность. На сегодняшний день не существует модели, способной предсказывать эффективность такой терапии. Разработка такой модели является важной задачей для планирования терапии. Целью настоящей работы является нахождение аналитических соотношений для выживаемости клеток, подверженных комбинированному действию излучения и цисплатина *in vitro*. *Материалы и методы.* По оцифрованным экспериментальным данным по выживаемости клеток из ряда опубликованных в открытом доступе работ найдены соответствующие коэффициенты линейно-квадратичной (LQ) аппроксимации выживаемости при облучении без препарата α_R, β_R и при

комбинированном воздействии излучения и цисплатина α_{RC}, β_{RC}. Далее произведён регрессионный анализ полученного набора коэффициентов и выживаемости клеток при воздействии одного цисплатина S_C. *Результаты и обсуждение*. Установлено, что α_{RC} статистически зависим от α_R, β_R и S_C. Данная зависимость может быть описана несколькими моделями, лучшей из которых по ряду показателей является $\alpha_{RC} = \alpha_R + a\beta_R \ln S_C$, где $a = -4,27 \pm 0,57$ — параметр, одинаковый для всех типов клеток и условий проведения эксперимента. Установлено, что β_{RC} статистически зависим от β_R. Признаков зависимости β_{RC} от α_R и S_C не обнаружено. Лучшей моделью для β_{RC} является $\beta_{RC} = \beta_R$. Указанные модели просты, но позволяют предсказать значение выживаемости клеток при комбинированном воздействии излучения и цисплатина S_{RC} по значениям α_R, β_R и S_C только приближенно. Полученным моделям сопоставлены кинетические уравнения и дана механистическая интерпретация, в основе которой лежит гипотеза об убывании скорости восстановления клеток от потенциально летальных повреждений r_+ при увеличении дозы облучения и концентрации цисплатина. *Выводы*. Установлен вид статистической зависимости LQ коэффициентов α_{RC} и β_{RC} от α_R, β_R и S_C. При высоких значениях токсичности цисплатина (низких значениях S_C) сочетание упомянутых выше моделей для α_{RC} и β_{RC} позволяет сделать полезный для практического применения прогноз выживаемости клеток S_{RC}. Результаты данной работы помогут для будущего построения более сложных моделей комбинированного действия излучения и цисплатина, а также могут иметь практическое применение в упомянутом выше случае.

Ключевые слова: цисплатин, LQ аппроксимация выживаемости клеток, фотонная лучевая терапия, регрессионный анализ, кинетические модели выживаемости клеток

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ОРГАНИЗАЦИЯ ЗДРАВООХРАНЕНИЯ И ОБЩЕСТВЕННОЕ ЗДОРОВЬЕ HEALTH POLICY AND PUBLIC HEALTH

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Сравнительная характеристика мотивации студентов, обучающихся по медицинским специальностям в медицинских вузах

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Аннотация. *Актуальность.* Дальневосточный федеральный округ является территорией опережающего развития, что требует наличие большого количества специалистов. Работа в сфере здравоохранения один из самых сложных, ответственных видов трудовой деятельности человека с высоким уровнем нагрузок психологического плана, требует внимательности, выносливости и высокой трудоспособности. Медицинское образование имеет свою специфику, даже на этапе обучения с первых курсов работает не менее 80 % студентов, которые сталкиваются с целым рядом трудностей: стрессы, лишение сна, усталость и др. которые имеют негативные последствия при обучении, поведении, общении, влияют на состояние здоровья. Построение системы мотивации один из важных шагов при обучении в медицинском вузе. Высоко мотивированный обучающийся будет вовлечен в процесс получения знаний, а следовательно, учиться по собственному желанию, активно осваивать учебную программу. Поэтому изучение мотивации студентов, обучающихся по медицинским специальностям в медицинских вузах является актуальной. *Цель исследования* — провести сравнительный анализ взаимовлияния мотивации к обучению и состояния здоровья обучающихся по медицинским специальностям в медицинских вузах Дальнего Востока. *Материалы и методы.* В рамках учебно-научно-производственного кластера «Дальневосточный» на основе договоров о сотрудничестве, в рамках социального партнерства образовательных организаций высшего образования и взаимодействия вузов Дальневосточного региона в исследовании участвовали: Дальневосточный государственный медицинский университет (ДВГМУ), Амурская государственная медицинская

академия (АГМА), Северо-Восточный федеральный университет имени М.К. Аммосова (СВФУ), Дальневосточный федеральный университет (ДВФУ), Тихоокеанский государственный медицинский университет (ТГМУ). Изучено состояние здоровья 2676 студентов 1–5 курсов в возрасте 17–24 года. В работе использованные данные групп здоровья, выставленные в результате проведения диспансеризации и профилактических осмотров, опросник «Шкалы академической мотивации — ШАМ», самооценка по разработанной индивидуальной анкете. Анкетирование обучающиеся ТГМУ, ДВФУ, ДВГМУ проходило в аудитории вуза на распечатанных бланках анкет, обучающиеся СВФУ и АГМА участвовали в анкетировании с помощью форм Google online. Для статистической обработки использовались программный пакет «Статистика 12.0» и аналитические функции программы Microsoft Office Excel. *Результаты и обсуждение.* Проведенная сравнительная характеристика мотивации к обучению обучающихся по медицинским специальностям в медицинских вузах Дальнего Востока выявила высокую от 3,4 до 4,9 внутреннюю мотивацию к обучению. Самыми высокими значениями в оценке мотивация достижения были у обучающихся СВФУ — 4,07, в ТГМУ и АГМА данный критерий составил 4,0. Выявлена взаимосвязь уровня внешней и внутренней мотивации с состоянием здоровья обучающихся. У обучающихся с 3 группой здоровья определена существенная (3Б группа $p = 0,55$) познавательная мотивация, сильная, практически приближенная к абсолютной ($p = 0,9$) — экстернальная мотивация и высокая мотивация достижения. Интроецированная мотивация была слабой (от $p = 0,2$ до $p = 0,344$) и не зависела от группы здоровья. *Выводы.* Выявлена и изучена взаимосвязь внешней и внутренней мотивации к обучению у обучающихся по медицинским специальностям в медицинских вузах с состоянием здоровья.

Ключевые слова: внешняя и внутренняя мотивация, студенты, Дальний Восток

Информация о финансировании. Авторы заявляют об отсутствии внешнего финансирования.

Вклад авторов. Крукович Е.В. — концепция и дизайн исследования, анализ полученных данных, написание текста. Кузнецов В.В. — концепция и дизайн исследования, анализ полученных данных, написание текста. Крукович А.А. — сбор и обработка материалов. Петухов Р.А. — сбор и обработка материалов. 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 декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией данной статьи.

Этическое утверждение. Все исследования проведены в соответствии с принципами биомедицинской этики, сформулированными в Хельсинкской декларации 1964 г. и ее последующих обновлениях, и одобрены Этическим комитетом ТГМУ (Владивосток, протокол № 9, от 16.05.2022 г.).

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Motivation comparative characteristics of students studying in medical specialties in medical universities

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Abstract. *Relevance.* The Far Eastern Federal District is a territory of advanced development, requiring a large number of specialists. Healthcare work is one of the most complex and demanding jobs, with high psychological stress, requiring attentiveness, endurance, and a high work ethic. Medical education has its own specifics; even in their first years, at least 80 % of students face a range of challenges: stress, sleep deprivation, fatigue, and other factors, which have negative consequences for learning, behavior, and communication, and impact their health. Building a motivational system is one of the most important steps in studying at medical universities. A highly motivated student will be engaged in the learning process, and therefore will study voluntarily and actively master the curriculum. Therefore, studying the motivation of medical students at medical schools is relevant. The aim of this study was to conduct a comparative analysis of the interaction between motivation to learn and the health status of medical students at medical universities in the Far East. *Materials and Methods.* Within the framework of the educational, scientific and industrial cluster «Far Eastern» on the basis of cooperation agreements, within the framework of social partnership of educational organizations of higher education and interaction of universities of the Far Eastern region, the following universities participated in the study: Far Eastern State Medical University (FESM), Amur State Medical Academy (ASMA), North-Eastern Federal University named after M.K. Ammosov (NEFU), Far Eastern Federal University (FEFU), Pacific State Medical University (TSMU). The health status of 2,676 first- to fifth-year students aged 17–24 was studied. The study utilized health group data obtained as a result of medical examinations and preventive checkups, the academic motivation scales (AMS) questionnaire, and self-assessment using a developed individual questionnaire. Students from Tver State Medical University, Far Eastern Federal University, and Far Eastern State Medical University completed the survey in the university classroom using printed questionnaires, while students from North-Eastern Federal University and Altai State Medical Academy participated in the survey using Google forms online. The Statistica 12.0 software package and the analytical functions of Microsoft Office Excel were used for mathematical and statistical processing. *Results and Discussion.* The conducted comparative characteristics of motivation for learning of students in medical specialties in medical universities of the Far East revealed a high intrinsic motivation for learning from 3.4 to 4.9. The highest values in assessing the motivation to achieve were among students of NEFU — 4.07, in TSMU and ASMA this criterion was 4.0. A relationship between the level of external and internal motivation with the health status of students was revealed. Students with health group 3 showed significant (group 3B $p = 0.55$) cognitive motivation, strong, almost absolute ($p = 0.9$) — external motivation and high motivation for achievement. Introjected motivation was weak (from $p = 0.2$ to $p = 0.344$) and did not depend on the health group. *Conclusion.* The relationship between extrinsic and intrinsic motivation for learning and health status among medical students at medical universities was identified and studied.

Keywords: extrinsic and intrinsic motivation, students, Russian Far East

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Author contributions. Krukovich E.V. — study concept and design, data analysis, writing. Kuznetsov V.V. — study concept and design, data analysis, writing. Krukovich A.A. — data analysis, writing. Petukhov R.A. – data analysis, writing. All authors made significant contributions to the concept development, conduct of the study, and preparation of the article; they read and approved the final version before publication.

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Ethical approval. All studies were conducted in accordance with the principles of biomedical ethics set forth in the 1964 Helsinki Declaration and its subsequent updates and were approved by the Ethics Committee of TSMU (Vladivostok, Protocol No. 9, dated May 16, 2022).

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Введение

Человеческий капитал представляет собой важным фактор развития экономики, в который значительный вклад вносят учреждения высшего образования. Дальневосточный федеральный округ обладает большими запасами природных ресурсов, многие регионы имеют морскую границу, что предопределяет развитие определенных отраслей производства и возникновение потребностей в квалифицированных кадрах узкой направленности, в том числе и медицинской. Ситуация усугубляется массовым оттоком человеческого капитала из ДВФО. В связи с этим Дальний Восток испытывает острую нехватку кадровых ресурсов для обеспечения стабильного развития региона. Несмотря на то, что с 2018 года в ДФО наблюдалась тенденция к снижению темпов оттока населения, медицинская отрасль продолжает испытывать дефицит медицинских кадров. Современные тренды в обществе на повышение качества образования, привели к изменениям образовательного процесса, интенсификации обучения, увеличению учебной нагрузки, что не может не отражаться на состоянии здоровья участников образовательного процесса, особенно обучающихся по медицинским специальностям в медицинских вузах [1, 2]. Обучение по медицинским специальностям в медицинских вузах имеет ряд особенностей. Помимо федерального (обязательного) компонента ООП, программы содержат большое количество элективных дисциплин, позволяющих формировать индивидуальную образовательную траекторию. Индивидуализация обучения тесно сопряжена с интегрированием научной составляющей в образование и выполнением научно-исследовательской работы. Дополнительные возможности индивидуализации обучения связаны с практиками симуляционного обучения. Студенты сталкиваются с большим объемом учебных материалов, практическими заданиями, экзаменами и клинической практикой, что может негативно сказываться на их физическом и эмоциональном состоянии [2, 3]. Обучающиеся 1, 2, 3 курсов различных специальностей особенно подвержены риску профессионального выгорания из-за постоянного контакта с больными, эмоциональной нагрузки и высоких требований к себе [4].

К ключевым факторам, влияющим на академическую успеваемость и успешность обучения в целом, относят состояние здоровья и мотивацию к обучению [5–9]. Построение системы мотивации является одним из важных шагов при обучении. Высоко мотивированный обучающийся будет вовлечен в процесс получения знаний, а следовательно, учиться по собственному желанию, стремиться приобрести новые знания, что поможет достичь целей обучения и выпустить грамотного специалиста.

Большинство авторов, обсуждающих проблемы мотивации, опираются на теорию мотивации Маслоу А. Теория самодетерминации Райана Р.М.

и Деси Э.Л. из University of Rochester подтверждает, что состояние здоровья, в том числе наличие заболеваний, непосредственно влияют на психологическую готовность обучающихся к эффективному восприятию образовательного процесса [3, 10, 11]. Достаточная рациональная мотивация к образовательному процессу является важным фактором его эффективности и достижения искомого результата [12–14]. Однако исследования мотивов, приводящих к формированию оптимального поведенческого рисунка, направленного на достижение конечной цели, взаимосвязь успеваемости, академической мотивации и профессионального выгорания с состоянием здоровья обучающихся по медицинским специальностям в медицинских вузах, а особенно на Дальнем Востоке недостаточно, что и явилось целью нашей работы.

Материалы и методы

Все респонденты были проинформированы о цели и задачах работы, получено их письменное информированное согласие.

Критерии включения в выборку: обучающихся по медицинским специальностям в медицинских вузах Дальнего Востока; возраст 17–24 года. Критерии исключения из выборки: обучающихся по другим специальностям в медицинских вузах; обучающихся из других регионов Российской Федерации; другой возраст обучающихся. В исследуемую группу включены 2676 студентов 1–5 курсов в возрасте 17–24 года (Таблица 1), по полу группы были репрезентативны.

В работе использованные данные групп здоровья, выставленных в результате проведения диспансеризации и профилактических осмотров в соответствии с приказом Министерства здравоохранения Российской Федерации от 27.04.2021 № 404н «Об утверждении порядка проведения профилактического медицинского осмотра и диспансеризации отдельных групп взрослого населения», Приказа Министерства здравоохранения РФ от 26 октября 2017 г. № 869н «Об утверждении порядка проведения диспансеризации определенных групп взрослого населения».

Для диагностики внутренней и внешней мотивации учебной деятельности студентов использовался опросник «Шкалы академической мотивации — ШАМ» (Гордеева, Сычев, Осин, 2014), разработанный на основе опросника академической мотивации

Распределение обучающихся по медицинским специальностям в медицинских вузах Дальнего Востока по полу (абс. / %)

Пол	ТГМУ	ДВФУ	АГМА	СВГУ	ДВГМУ	Всего
Девушки	302 (56,4 %)	368 (69,2 %)	325 (60,5 %)	270 (49,9 %)	391 (73,6 %)	1656 (61,9 %)
Юноши	233 (43,6 %)	164 (30,8 %)	212 (39,5 %)	271 (50,1 %)	140 (26,4 %)	1020 (38,1 %)
Всего	535 (19,9 %)	532 (19,9 %)	537 (20,1 %)	541 (20,2 %)	531 (19,8 %)	2676 (100 %)

Distribution of students in medical specialties in medical universities of the Far East by gender (abs. / %)

Gender	TSMU	FEFU	AGMA	SVSU	DVSMU	Total
Girls	302 (56,4%)	368 (69,2%)	325 (60,5%)	270 (49,9%)	391 (73,6%)	1656 (61,9%)
Boys	233 (43,6%)	164 (30,8%)	212 (39,5%)	271 (50,1%)	140 (26,4%)	1020 (38,1%)
Total	535 (19,9%)	532 (19,9%)	537 (20,1%)	541 (20,2%)	531 (19,8%)	2676 (100%)

Р. Валлеранда (AMS-C). Опросник состоит из 28 утверждений, составляющих 7 шкал (по 4 утверждения в каждой): три шкалы внутренней мотивации (познавательной, достиженческой и саморазвития), три шкалы внешней мотивации (самоуважения, интроецированной и экстернальной), а также шкала амотивации как отсутствия интереса и ощущения осмысленности текущей учебной деятельности. Обучающимся предлагается по 5-балльной шкале оценить различные варианты ответа на вопросы. Всего в 28 (7,1 %) анкетах из-за допущенных ошибок либо из-за отказа респондентов мы не получили полных ответов. Так как данная работа является большой и комплексной работой, в целях исследования валидности опросника использовались методики и анкеты, оцененные ранее. Академические достижения оценивались с помощью средних оценок, полученных в результате самооценки студентами в индивидуальной анкете. Анкетирование обучающиеся ТГМУ, ДВФУ, ДВГМУ проходило в аудитории вуза, полной тишине на распечатанных бланках анкет. Обучающиеся СВФУ и АГМА участвовали в анкетировании с помощью googl форм on lain. Полученные результаты вносились в сводную таблицу в программе Microsoft Excel для удобства расчета показателей. Рассчитаны — мода, медиана и среднее арифметическое по ответам на вопросы. Для сравнительного анализа (поиск взаимосвязей) мотивации студентов и состояния здоровья применен корреляционный анализ для непараметрических показателей с использованием коэффициента парной ранговой корреляции Спирмена, условием проведения которого является нормальное распределение данных. Оценивалось:

1) на наличие или отсутствие связей между двумя исследуемыми статистическими совокупностями x и y, по каждому показателю внешней и внутренней мотивации и группами здоровья; то есть вычисление коэффициента корреляции предполагает использование двух совокупности равной мощности (или с одинаковым числом элементов), что методологически существенно (n = x = y);

2) на направление связей — положительное или отрицательное: может быть (+1>ρ>0) или (-1<ρ< 0), но величина модуля |ρ| принципиально не может превышать значение 1;

3) на степень тесноты связи («сила связи»): отсутствие связи (ρ ≈ 0), «слабая» (ρ ≈ 0,2–0,3), «существенная» (ρ ≈ 0,5), «сильная» (ρ ≈ 0,7–0,9), «абсолютная» (ρ ≈ 1,0).

Результаты и обсуждение

В исследуемой выборке обучающихся по медицинским специальностям в медицинских вузах Дальнего Востока II группу здоровья имели 49,1 % обучающихся, 22,1 % студентов — имели I группа здоровья и 28,7 % — третью. Углубленный анализ в разрезе вузов Дальнего Востока показал, что «самыми здоровыми» были обучающиеся СВГУ, имеющие I группу здоровья в 22,1 % случаев, а наибольшее количество обучающихся с III группой здоровья было в ДВФУ — 47,6 %, что закономерно при выборе обучающимися с хроническими заболеваниями данной образовательной организации, имеющей наилучшую медицинскую базу и высококачественное медицинское обслуживание.

Анализ изучения уровня здоровья показал, что в структуре заболеваемости в исследуемой группе первое и второе ранговые места принадлежат XI классу заболеваний — болезни органов пищеварения (K00-K93), у 7,3+2,4 преобладали — болезни желчевыводящих путей неуточненные (K83.9), у 0,8+0,5 хронический холецистит (K81.1), у 6,5+1,4 хронический поверхностный гастрит (K29.3). Третье ранговое место занимали острые респираторные инфекции верхних дыхательных путей (J00-J06) (6,1+0,7). Нами не выявлено достоверных различий заболеваемости по данным углубленных медицинских осмотров в зависимости от пола, анализ заболеваемость в зависимости от возраста выявил достоверное (p<0,01) нарастание от 17 к 23 годам числа случаев заболеваний хроническим поверхностным гастритом (K29.3), болезнями желчевыводящих путей (K83.9) и дистониями (G24.9).

Нами проанализирована внутренняя учебная мотивация (основанная на интересе к самой учебной деятельности) и внешняя учебная мотивация

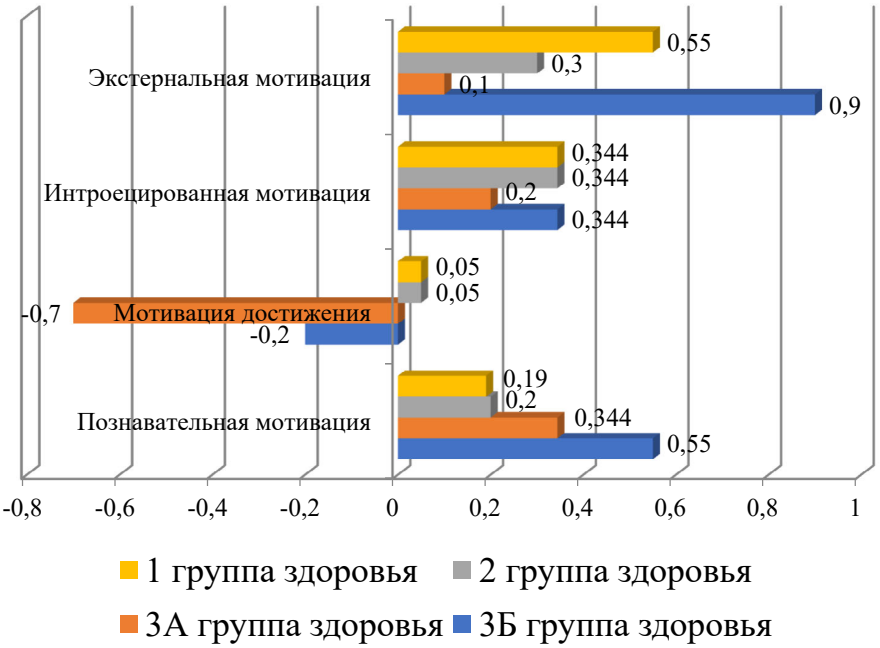
(основанная на стремлении к получению разного рода вознаграждений и поощрений или избеганию негативных последствий). Анализ внутренней мотивации позволил также проанализировать познавательную мотивацию и мотивацию достижения. Сравнительная характеристика мотивации к обучению обучающихся по медицинским специальностям в медицинских вузах Дальнего Востока выявила у обучающихся по медицинским специальностям в медицинских вузах высокую от 3,4 до 4,9 внутреннюю мотивацию. Студенты имеют более высокий внутренний стимул, были более самостоятельными, чувствовали себя инициаторами собственных действий, потребность в росте своих компетенций. Самая высокая познавательная мотивация выявлена у студентов ДВФУ – 4,44, самая низка в ТГМУ– 4,2. Наиболее высокие оценки от 4,7 до 4,9 были на вопрос «Мне просто нравится учиться и узнавать новое». Самыми высокими значениями в оценке мотивация достижения были у обучающихся СВФУ 4,07, в ТГМУ и АГМА данный критерий составил 4,0. Наиболее высоко студенты оценили вопрос «Учеба доставляет мне удовольствие, я люблю решать трудные задачи», следовательно, у обучающиеся доминирует мотив достижения, они не склонны снижать свой уровень притязаний, отказываться от возможного успеха. Анализ «внешняя мотивация» был более дифференцирован. Интроецированная мотивация достаточно высокой была у студентов ДВФУ – 4,05 и ТГМУ – 4,0, характеризуя высокое социальное сравнение и поддержание самооценки (радость и гордость за себя либо вина и стыд). У обучающиеся в АГМА при формировании ответственность за события в жизни (при обучении) не склонны приписывать причины происходящего внешним факторам — окружающей среде, судьбе или случаю, то это говорит о наличии у него внешнего (экстернального) локуса контроля и наиболее низкая экстернальная мотивация 3,71.

В результате проведенного анализа выявлена взаимосвязь уровня внутренней и внешней мотивации – к обучению и состояния здоровья у обучающихся по медицинским специальностям в медицинских вузах Дальнего Востока в общей группе обучающихся (Рисунок).

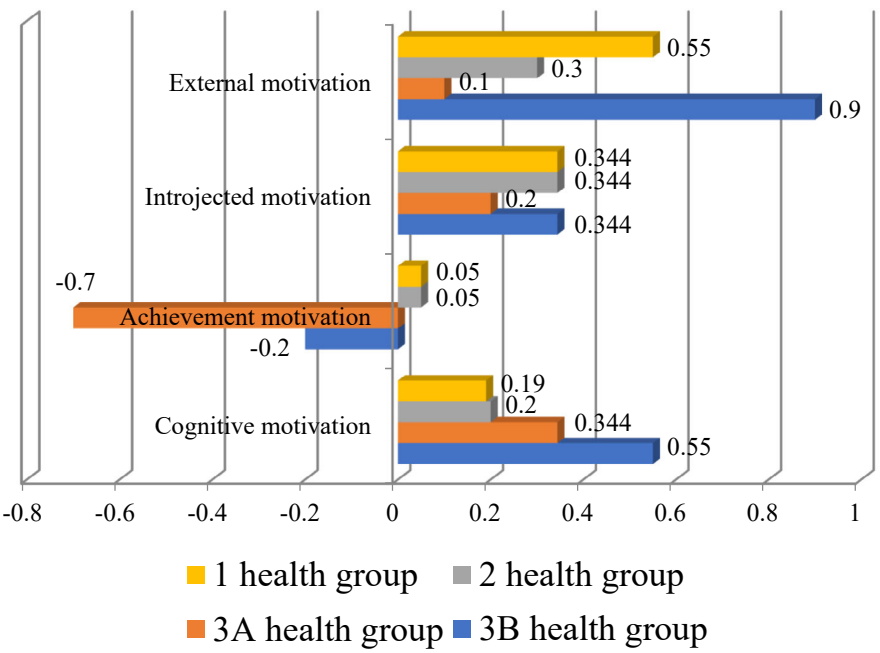
У обучающихся с 3 группой здоровья выявлена существенная (3Б группа p = 0,55) познавательная мотивация, сильная, практически приближенная к абсолютной (p = 0,9) — экстернальная мотивация и высокая мотивация достижения т.е. здоровье обучающегося влияет как на внутреннюю мотивацию, так и на внешнюю. Интроецированная мотивация, т.е. побуждение к учебе, обусловленное ощущением стыда и чувства долга перед собой и другими значимыми людьми была слабой (от p = 0,2 до p = 0,344) и не зависела от группы здоровья

Выводы

Результаты проведенного исследования выявили взаимосвязь состояния здоровья обучающихся по медицинским специальностям в медицинских вузах с уровнем внутренней и внешней мотивации. Проведенное исследование показывают, что уровень мотивации связан с состоянием здоровья и для хорошей успеваемости обучающихся высокая мотивация важна наряду с интеллектом. У обучающихся с 3 группой здоровья выявлена существенная (3Б группа p = 0,55) познавательная мотивация, сильная, практически приближенная к абсолютной (p = 0,9) — экстернальная мотивация и высокая мотивация достижения, т.е. здоровье обучающегося влияет как на внутреннюю мотивацию, так и на внешнюю. Интроецированная мотивация, т.е. побуждение к учебе, обусловленное ощущением стыда и чувства долга перед собой и другими значимыми людьми, была слабой (от p = 0,2 до p = 0,344) и не зависела от группы здоровья. Анализ состояния здоровья обучающихся по результатам профилактических осмотров и диспансеризации выявил, что в структуре заболеваемости первое и второе ранговые места занимают болезни органов пищеварения (K00-K93), у 7,3+2,4 преобладали — болезни желчевыводящих путей неуточненные (K83.9), у 0,8+0,5 хронический холецистит (K81.1), у 6,5 + 1,4 хронический поверхностный гастрит (K29.3). Третье ранговое место занимали острые респираторные инфекции



Взаимосвязь уровня внутренней и внешней мотивации к обучению и группы здоровья у обучающихся по медицинским специальностям в медицинских вузах Дальнего Востока



The relationship between the level of internal and external motivation for learning and the health group of students in medical specialties in medical universities of the Far East

верхних дыхательных путей (J00-J06) (6,1 + 0,7). Анализ заболеваемость в зависимости от возраста выявил достоверное ($p < 0,01$) нарастание от 17 к 23 годам числа случаев заболеваний хроническим поверхностным гастритом (K29.3), болезнями желчевыводящих путей (K83.9) и дистониями (G24.9). Нами не выявлено достоверных различий заболеваемости по данным углубленных медицинских осмотров в зависимости от пола. Сравнительная оценка мотивации к обучению обучающихся по медицинским специальностям в медицинских вузах Дальнего Востока выявила высокую – от 3,4 до 4,9 – внутреннюю мотивацию. Студенты имеют более высокий внутренний стимул, были более самостоятельными, чувствовали себя инициаторами собственных действий, потребность в росте своих компетенций. Самая высокая познавательная мотивация выявлена у студентов ДВФУ – 4,44, самая низкая в ТГМУ – 4,2. Анализ внешней мотивации был более дифференцирован. Интроецированная мотивация достаточно высокой была у студентов ДВФУ 4,05 и ТГМУ – 4,0, характеризуя высокое социальное сравнение и поддержание самооценки (радость и гордость за себя либо вина и стыд). У обучающиеся в АГМА при формировании ответственности за события в жизни (при обучении) не склонны приписывать причины происходящего внешним факторам — окружающей среде, судьбе или случаю, то это говорит о наличии у него внешнего (экстернального) локуса контроля и наиболее низкая экстернальная мотивация 3,71. Полученные данные позволили нам разработать рекомендации для обучающихся по медицинским специальностям в медицинских вузах, внести предложения по организации учебного процесса в медицинских вузах Дальнего Востока.

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