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ORIGINAL STUDIES

Scientific Article
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INFLUENCE OF DENTAL PROSTHESES MATERIALS ON THE CONDITION OF ORAL MUCOSA LOCAL HOMEOSTASIS

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ВЛИЯНИЕ МАТЕРИАЛОВ ОРТОПЕДИЧЕСКИХ КОНСТРУКЦИЙ НА СОСТОЯНИЕ ЛОКАЛЬНОГО ГОМЕОСТАЗА СЛИЗИСТОЙ РТА

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Objective. To study the influence of base materials used in the manufacture of removable dentures on the immune homeostasis of the oral mucosa, and, as a consequence, on the clinical condition of the oral mucosa and periodontium of supporting teeth. To create fundamental principles for the development of a pathogenetically substantiated choice of basic dental materials of various chemical natures for removable prosthetics based on the analysis of the parameters of immune homeostasis of the oral mucosa.
Materials and methods. 154 patients aged 40 to 85 using dentures based on acrylic, polyurethane plastics and thermoplastics for 6 months, participated in the study. Indicators of immune homeostasis and the identified clinical manifestations of the influence of the prosthesis material such as chronic periodontitis and gingivitis were compared using the statistical method of conjugate multifield tables.

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Results. The indicators CD4+/CD8+, CD11/CD303, CD68, CD204, CD163, Ki-67 phenotypic markers were determined in gingival biopsies of the prosthetic bed of patients using dentures based on acrylic, polyurethane and thermoplastic for 6 months. Analysis of the statistical significance of differences proved the influence of the prosthesis material on indicators of cellular immune homeostasis, with a shift of homeostasis towards the pro-inflammatory phenotype, and the suppression of the anti-inflammatory factor in circulating monocytes.
Conclusions. The study shows that, although each type of removable dentures has its own advantages and disadvantages, the response of the cellular immunity of the oral mucosa to polyurethane dentures is less than to acrylic and thermoplastic ones in relation to the control group. The use of polyurethane prostheses is reasonable as temporary ones during the healing stage of surgical interventions in the oral cavity, in particular tooth extraction and implantation. This type of prosthesis can be recommended as a permanent one for patients with a severe allergic reaction, especially to polymer compounds and dyes.
Keywords. Denture material, cellular immunity, immune homeostasis, oral mucosa, denture biopsies, phenotypic markers.

Цель. Изучить влияние различных материалов съемных протезов на состояние слизистой оболочки рта и пародонта зубов посредством исследования локального иммунного гомеостаза.
Материалы и методы. В исследовании приняли участие 154 пациента в возрасте от 40 до 85 лет, для лечения которых использовались протезы на основе акриловых, полиуретановых пластмасс и термопластов. В качестве материала исследования представлены данные иммуногистохимического анализа биоптатов десневого ложа 154 пациентов, пользовавшихся в течение 6 месяцев съемными протезами с базисами на основе акрилов, термопластов и полиуретана. С помощью статистического метода спряженных многопольных таблиц показатели локального иммунитета сопоставлены с обнаруженными клиническими проявлениями влияния материала протеза – хроническим пародонтитом и гингивитом.
Результаты. Определены показатели фенотипических маркеров CD4+/CD8+, CD11/CD303, CD68, CD204, CD163, Ki-67 в десневых биоптатах протезного ложа пациентов, использующих съемные протезы с базисами из акрила, полиуретана и термопласта через 6 месяцев с момента окончания протезирования. По результатам анализа статистической значимости различий доказано влияние материала базиса протеза на показатели клеточного локального иммунитета, которое соответствует сдвигу гомеостаза в сторону провоспалительного фенотипа, и подавление противовоспалительного фактора в циркулирующих моноцитах.
Выводы. В исследовании показано, что пользование съемными протезами ведет к изменению локального клеточного иммунитета слизистой рта: данные параметры при пользовании протезами на основе термопластов, акриловых и полиуретановых пластмасс имеют существенные различия. Изменения показателей локального гомеостаза слизистой рта напрямую коррелируют с клиническими проявлениями в области протезного ложа и тканей пародонта. Изменения морфологических и клинических параметров слизистой рта при пользовании протезами на основе полиуретана минимальны по отношению к параметрам контрольной группы.
Ключевые слова. Материал съемных протезов, клеточный иммунитет, иммунный гомеостаз, слизистая оболочка рта, биоптаты протезного ложа, фенотипические маркеры.

INTRODUCTION

Partial absence of teeth (partial secondary adentia) is one of the most common diseases: according to the results of various studies, it affects from 44 to 100 % of the population of the Russian Federation over 40 years old, depending on age and region. The absence of teeth not only affects chewing and speech functions, but also causes changes in the facial skeleton and can lead to psychological changes, disruption of social adaptation, changes in nutrition, and even contribute to the development of various diseases due to changes in the composition of oral fluid.

A population survey revealed a high level of need for dental orthopedic care – 69.9 %; already at the age of 20–29 years this figure is 55.6 %, and at the age of 60–69 years – 86.1 %, at the age of 70 years and older – 72.8 % [1].

Based on the results of the analysis of changes in the practice of dental orthopedic treatment in the regions of Russia over a 10-year period, it was revealed that the proportion of patients with partial removable dentures increased, compared to 2008, from 60 % (with clasp dentures – 67 %) to 64 % (with clasp dentures – 74 %), while the proportion of complete removable dentures decreased over this period by 6 %. Currently, with the increase in the number of elderly people, there is also an increase in patients with partial teeth loss, which increases the need for treatment.

Removable dentures, in addition to their advantages, have a number of disadvantages. More than 24 % of users of partial removable dentures complain of unsatisfactory fixation, 18 % of face aesthetic problems, more than 18 % are forced to adapt to poor-quality dentures, and 8 % face fractures of supporting teeth[1].

The impact of prosthetic materials on the immune system induces protective immune responses against pathogens and in many cases contributes to the pathogenesis and progression of diseases of the oral mucosa (OM). The resulting disruption of the homeostasis of the OM tissues causes periodontitis, one of the most common inflammatory diseases.

A large number of studies have been devoted to the study of the mechanisms of disturbance of homeostasis of monocytes and macrophages as the main cellular components of immunity in gingivitis and periodontitis [2]. Insufficient information on the impact of various base materials with different chemical natures used in dental prostheses on the local immunity of the oral mucosa in different periods after prosthetics emphasizes the importance of studying this issue and the need to develop recommendations for prosthetics with removable dentures based on the data obtained [3].

The influence of various materials used for the manufacture of removable dentures (acrylates, polyurethanes, thermoplastics) on the condition of the oral mucosa and periodontal tissue, as well as on local immune homeostasis, was studied. *The aim of the study* was to create a basis for pathogenetically substantiated selection of basic dental materials of various chemical nature in removable dentures using analysis of local immune homeostasis indicators of the oral mucosa.

MATERIAL AND METHODS

The study involved 154 people. They were divided into three experimental groups depending on the prosthesis material: acrylic, polyurethane, thermoplastic. By age, the participants were divided into groups according to G. Craig's classification of periods: middle adulthood – 40–59 years, late adulthood – 60 years. A control group was also selected, where prosthetics with a removable prosthesis was not required.

An assessment of the required sample size to confirm the statistical significance of the intergroup difference in the results of the effect of the prosthesis material on homeostasis parameters at a significance level

of $\alpha = 0.05$ and power of 0.80 for four groups showed that at least 16 people are required per group (Statistica 10.0).

The characteristics of the morphological substrate that supports cellular immunity of the oral mucosa were investigated when interacting with various materials of partial dentures, such as acrylic, polyurethane resins and thermoplastics. These materials can contribute to the occurrence of common inflammatory diseases such as chronic gingivitis and periodontitis.

Immunohistochemical analysis on paraffin sections was performed using standard methods for determining the phenotype of immunocompetent cells. Antigens on the surface of lymphocytes were identified using monoclonal antibodies that had similar binding properties and were distributed in tissues according to a certain stage of development of the cell population – the so-called clusters of differentiation (CD). CD molecules are membrane phenotypic markers of the corresponding cells.

The major immune cell populations of the oral mucosa include antigen-presenting cells such as monocytes / macrophages, dendritic cells, and epidermal Langerhans cells, as well as neutrophils and granulocytes. The presence of B cells is minimal, and the proportion of γδT cells is small – 12 %. Widespread $CD4^+$ clusters of differentiation characterize activated T helper cells – inducers of the immune response. They regulate the strength of the immune response to a foreign substance and control the stability of the internal state of the body (immune homeostasis). An increase in the number of T-helper lymphocytes indicates hyperactivity of the immune system, while a decrease indicates immunological deficiency [4].

$CD8^+$ – cytotoxic T-lymphocytes – T-killers and T-suppressors, $CD8^+$ also defines dendritic cells – leukocytes specializing in the presentation of antigens to T-lymphocytes, necessary for the activation of the T-cell response [5].

In this study, we classified different cell types, including T helper ($CD4^+$) and T suppressor ($CD8^+$) cells, which have a specific $CD4^+/CD8^+$ ratio. We also studied cell populations that express adhesion molecules such as integrins ($CD11^+/CD303^+$) on the surface of various cells including dendritic cells, monocytes, granulocytes, B and NK lymphocytes, the scavenger receptor $CD163^+$, and typed the scavenger receptor $CD204^+$, which is expressed on macrophages and some types of dendritic cells, as well as the Ki-67^+ protein in epithelial cells [6]. Comparison of three or more groups by a quantitative indicator whose distribution differed from normal was performed using the nonparametric Kruskal – Wallis test, multiple comparisons of two groups were performed using the Mann – Whitney U test with Bonferroni correction.

Statistical data processing was performed using Statistica 10.0, IBM SPSS Statistics 27.0 programs.

RESULTS AND DISCUSSION

Quantitative indices of macrophage CD markers were assessed for compliance with normal distribution using the Shapiro-Wilk test. It was shown that most of the data (about 70 %) had a non-normal

distribution, the probability of error was $p < 0.05$ (the achieved significance level was $p = 0.001$). Data with non-normal distribution are described using the median (*Me*) and the lower and upper quartiles (Q1–Q3); for normally distributed data, the mean value and 95 % confidence interval (CI) are indicated. The relationships between the prosthesis material and the patient's age group after 6 months of prostheses use are presented in Table 1.

The influence of the removable denture material factor on the absolute values of the phenotypic markers $CD68^+$, $CD4^+/CD8^+$, $CD11^+/CD303^+$, $CD204^+$, $CD163^+$, $Ki67^+$ (Kruskal – Wallis test, $p = 0.0001$) was proven; the data statistically significantly differ from the indicators of the control group (Mann – Whitney test, $p < 0.008$, Bonferroni correction) with the exception of the difference in the level of CD163, $CD11^+/303^+$, $Ki\text{-}67^+$ in the "60+" age group: *p polyurethane – control* = 0.169, which confirms an insignificant deviation from the norm when using polyurethane dentures.

Multiple pairwise comparisons in the age group 40–59 years confirm the statistical significance of differences in the levels of CD markers of immunocytes for different materials of removable dentures. In this case, in the group using orthopedic structures made of thermoplastic, the highest levels of all differentiation clusters $CD204^+$ are observed, lower in the groups with acrylic dentures and even lower in the group using polyurethane dentures (Mann – Whitney test, $p < 0.008$).

Table 1

Phenotypic markers indicators

Material	Age, years	Parameter		
		$CD68^+$	$CD4^+/CD8^+$	$CD11^+/CD303^+$
		Average (95 % CI)	*Me* ($Q_1 - Q_3$)	*Me* ($Q_1 - Q_3$)
Acryl	40–59	3.95 (3.77–4.13)	2.81 (2.60–3.04)	1.34 (1.20–1.41)
	60+	2.52 (2.41–2.63)	1.72 (1.43–1.92)	1.02 (0.98–1.18)
Thermoplast	40–59	6.52 (6.34–6.70)	3.21 (3.00–3.45)	1.62 (1.72–2.08)
	60+	3.46 (3.31–3.61)	2.10 (1.86–2.39)	1.17 (1.23–1.64)
Polyeurethane	40–59	3.19 (3.09–3.29)	2.26 (1.93–2.43)	1.25 (1.05–1.43)
	60+	1.69 (1.58–1.80)	1.63 (1.47–1.88)	0.99 (0.87–1.12)
Control	40–59	1.53 (1.35–1.71)	1.33 (1.17–1.89)	1.22 (1.01–1.41)
	60+	1.04 (0.88–1.20)	1.02 (0.81–1.14)	0.93 (0.79–1.05)
Material	Age, years	CD204+	CD163+	Ki67+
		Me ($Q_1 - Q_3$)	*Me* ($Q_1 - Q_3$)	*Me* ($Q_1 - Q_3$)
Acryl	40–59	3.04 (3.39–2.79)	2.95 (2.55–3.01)	8.67 (8.17–8.79)
	60+	2.23 (2.40–1.83)	2.23 (2.03–2.32)	7.24 (6.81–7.59)
Thermoplast	40–59	3.38 (3.57–3.15)	3.49 (3.26–3.76)	9.58 (9.36–9.93)
	60+	2.63 (2.44–2.89)	3.04 (2.86–3.67)	7.82 (7.45–8.13)
Polyeurethane	40–59	2.72 (2.58–2.98)	2.15 (1.93–2.60)	7.63 (7.44–7.74)
	60+	2.09 (1.88–2.44)	1.78 (1.53–2.43)	6.82 (6.49–7.12)
Control	40–59	1.69 (1.49–1.89)	1.86 (1.67–1.96)	6.75 (6.27–7.06)
	60+	1.40 (1.26–1.48)	1.64 (1.31–1.83)	6.37 (5.87–6.59)

In the age group "60+", the differences in the values of phenotypic markers for the materials "acrylic – polyurethane" are less pronounced, and the statistical significance of the differences was not confirmed: $CD11^+/CD303^+$ ($p_{acrylic - polyurethane} = 0.319$), which corresponds to the same level of reaction of dendritic cells, macrophages and Langerhans cells to these materials.

The distribution of $CD68^+$ in the groups 40–59 years and "60+" corresponds to the normal distribution (Shapiro-Wilk test, $p > 0.008$), the homogeneity of variances was confirmed (Levene's test, $p > 0.85$), the ANOVA analysis of variance showed the influence of the "prosthesis material" factor on the $CD68^+$ values, the Tukey post-hoc test proved the presence of statistically significant differences between all groups ($p < 0.0002$), with the exception of "acrylic – polyurethane" in both age groups (40–59: pacrylic – polyurethane = 0.219; "60+": pacrylic – polyurethane = 0.020).

The influence of the removable denture material on the level of phenotypic markers $CD68^+$, $CD4^+/CD8^+$, $CD11^+/CD303^+$, $CD204^+$, $CD163^+$, $Ki67^+$ was confirmed. The results are statistically significantly different from the control group data, with the exception of some markers in the 60+ age group. In particular, the levels of CD163, $CD11^+/CD303^+$ and $Ki\text{-}67^+$ when using polyurethane prostheses do not differ significantly from the norm. A high degree of imbalance and activation of the inflammatory immune response six months after implantation also leads to a significant increase in $CD4^+/CD8^+$: the ratio between helper and suppressor T-lymphocytes increased by 2.4 times for thermoplastics, 2 times for acrylic and 70 % for polyurethane. This indicates an imbalance between the mechanisms of inflammation and reparation, which corresponds to the transition to a chronic form of inflammation, the level of which is highest for thermoplastics, lower for acrylic and polyurethane.

The established statistically significant ratio of CD marker levels in biopsies of the mucous membrane of the prosthetic bed after 6 months of using prostheses made of different materials and the values of the control group are presented in Table 2.

Table 2

Ratio of CD marker levels to control levels

Material	Age, years	$CD4/CD8^+$	$CD163^+$	$CD68^+$	$CD11^+/303^+$	$CD204^+$	$Ki\text{-}67^+$
Acryl	40–59	2.11	1.40	2.58	1.10*	1.79	1.28
Thermoplast		2.41	1.92	4.34	1.32	2.00	1.42
Polyeurethane		1.69	1.15	2.08	1.02*	1.60	1.13
Acryl	60 and older	1.69	1.36	2.42	1.09	1.59	1.13
Thermoplast		2.06	1.85	3.32	1.25	1.87	1.23
Polyeurethane		1.53	1.09*	1.62	1.06*	1.49	1.08*

Note: * – differences with the data of the control group are not statistically significant.

Comparison of immune cell populations in the control group and patients using dentures based on different materials for 6 months shows a significant increase in inflammatory cells in biopsies, which corresponds to an active proinflammatory cellular response of gingival immunocytes to the effects of denture materials [7]. The prosthesis material has a significant effect on the level of $CD68^+$ protein, which is a marker for monocytes / macrophages. This protein is expressed on various cells, such as myeloid and dendritic cells, fibroblasts, neutrophils, osteoclasts and Langerhans cells. When using thermoplastics as a prosthesis material, the level of $CD68^+$ protein increases by 4.3 times, compared to other materials, such as acrylic and polyurethane. To determine the quantitative content of activated monocytes in biopsies of the prosthetic bed, the researchers use the scavenger receptor CD163. The expression level of this receptor also increases by more than 90 % when using thermoplastics, compared with the use of acrylic and polyurethane. The $CD163^+$ receptor triggers intracellular signals, including the secretion of interleukin-6 (IL-6), which acts as a proinflammatory cytokine during traumatic tissue injury and other damage leading to inflammation [8].

Analysis of absolute values and ratios of phenotypic markers shows that the number of proinflammatory macrophages, neutrophils, dendritic cells and Langerhans cells in biopsies of the prosthetic bed in patients using thermoplastics increases almost 6 times, compared with the data of the control group. In patients who use polyurethane and acrylic-based prostheses, this increase is 3–3.5 times.

The prosthesis material has a significant impact on the level of $CD68^+$ protein, which is a marker for monocytes / macrophages. This protein is expressed on various cells, such as myeloid and dendritic cells, fibroblasts, neutrophils, osteoclasts and Langerhans cells.

The high level of homeostasis disturbance and activation of the proinflammatory immune response 6 months after prosthetics also determines a significant increase in the $CD4^+/CD8^+$ level, corresponding to the ratio of T-lymphocytes helpers and suppressors, which increased by 2.4 times for thermoplastics, 2 times for acrylics and by 70 % for polyurethane. This indicates an imbalance between the mechanisms of inflammation and reparation and corresponds to the transition to a chronic form of inflammation, the level of which is maximum for thermoplastics, weaker for acrylic and polyurethane.

Changes in the heterogeneous population of $CD11^+/CD303^+$ markers are an indicator of the reaction of the cellular immunity of the oral mucosa to various prosthesis materials. Myeloid dendritic cells expressing the CD11c receptor specialize in the presentation of antigens to T lymphocytes. These cells demonstrate an increased ability to engulf necrotic cells, recognize viral antigens, and cross-present antigen with $CD8^+$ T cells. These cells exhibit an enhanced capacity to engulf necrotic cells, recognize viral antigens, and cross-present antigen with $CD8^+$ T cells. After cleavage from the membrane, the free (soluble) form can play

an anti-inflammatory role and serve as a diagnostic parameter for macrophage activation in inflammatory diseases. Plasmacytoid dendritic cells express exclusively the surface marker $CD303^+$ [9]. Analysis of the data in Table 2 shows an increase in the $CD11^+/CD303^+$ population by more than 30 % for thermoplastics, while for materials such as acrylic and polyurethane, the parameters do not differ significantly from the control group level.

Changes in the parameters of cellular immunity were accompanied by an increase in the Ki-67 protein of the epithelial cells of the gingival mucosa by 42 % for the group where the dentures were made of thermoplastics, 28 and 13 % for the group using acrylic and polyurethane dentures. Thus, polyurethane dentures are characterized by a long-term inflammatory process, manifested by a high level of proliferative activity of cells in the biopsy samples of the gingival bed. For patients aged 60 years and older, after 6 months, inflammation is active under the polyurethane prosthesis, the deviation of the cell proliferation level from the norm is 23 %.

In the group of patients aged 60 years and older, an increase in all parameters of cellular immunity was also noted: the highest for the thermoplastic group, average for acrylics and lower for polyurethanes. The data are also an indicator of the activation of the immune system, given that with increasing age, deviations from the norm decrease and this is associated with a decrease in the body's reactivity.

A significant difference in the obtained indicators of phenotypic markers from the norm is a sign of activation of the T-system of the oral mucosa immunity; the objective of the study is to compare the changes identified in the oral mucosa immune system with the clinical manifestations of the influence of the material – chronic periodontitis, gingivitis.

These indicators of cellular immunity correlate with clinical manifestations in the oral cavity, in particular such as hyperemia, swelling and exacerbation of inflammatory phenomena. All patients underwent the Schiller-Pisarev test to determine the fact of the inflammatory process.

Six months after prosthetics, a high level of imbalance in the body and activation of the immune system, which promotes inflammation, was recorded. The $CD4^+/CD8^+$ level (the ratio of T-lymphocytes helpers and suppressors) increased significantly for all three types of prosthesis materials, but the greatest increase was in thermoplastic prostheses (2.4 times), then in acrylic (2 times) and by 70 % in polyurethane. This indicates an imbalance between the mechanisms of inflammation and reparation, which can lead to a chronic form of inflammation. The level of inflammation was highest for thermoplastic prostheses, less pronounced for materials such as acrylic and polyurethane.

Multifield contingency tables (IBM SPSS Statistics 27.0) were used to assess the strength of the relationship between nominal variables. The material of the removable denture in the table is considered as a risk factor for the development of prosthetic complications in the form of chronic gingivitis, mild, moderate and severe periodontitis. Data on the diagnosis of oral mucosal tissue diseases were analyzed in the SPSS

Statistics system in order to identify a statistical relationship between the material of the removable denture and the severity, prevalence in the group, and stage of the disease. Table 3 presents data on the total number of patients (n = 154), in groups and by severity of the recorded disease (mild periodontitis, moderate periodontitis, severe periodontitis).

The analysis of contingency tables showed a high degree of relationship between the factor of influence of the material and the signs of chronic gingivitis, periodontitis of mild, moderate and severe severity: Pearson criterion – 56.7 ($p < 0.01$), Cramer's V criterion for multi-field tables – 0.458, contingency coefficient – 0.622 ($p < 0.001$) – corresponds to a strong relationship (Figure).

Table 3

Contingency table "Prosthesis material – diagnosis"

Material		No	Gingivitis	Mild periodontitis	Moderate periodontitis	Severe periodontitis	Total
Control	Quantity	31	5	0	0	0	36
	% in orthopedic structure	86.1	13.9	0.0	0.0	0.0	100
Polyeurethane	Quantity	6	21	9	2	0	38
	% in orthopedic structure	15.8	55.3	23.7	5.3	0.0	100
Acryl	Quantity	4	21	13	3	0	41
	% in orthopedic structure	9.8	51.2	31.7	7.3	0.0	100
Thermoplast	Quantity	2	12	15	9	1	39
	% in orthopedic structure	5.1	30.8	38.5	23.1	2.6	100
Total	Quantity	43	59	37	14	1	154
	% in orthopedic structure	27.9	38.3	24.0	9.1	0.6	100

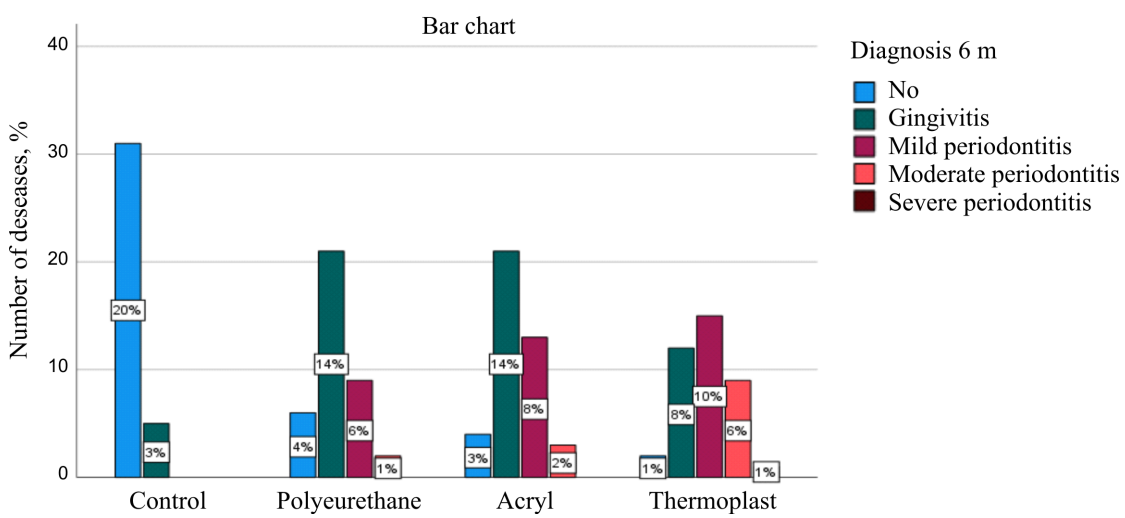

Fig. Distribution of patients with recorded diagnoses after 6 months in groups using different removable denture materials

The distribution of the severity of complications among patients using removable dentures depends significantly on the material of the orthopedic structure: in the control group, after 6 months, the occurrence of gingivitis is recorded in 13.9 %, in the group using polyurethane plastics – 84.2 %, of which 23.7 % were mild periodontitis and 5.3 % were moderate periodontitis, in the group using acrylic plastics – 90.2 %, of which 31.7 % were mild periodontitis and 7.3 % were moderate periodontitis, the largest number of patients with a diagnosis of periodontitis – 64.2 %, of which 23.1 % were moderate periodontitis and 2.6 % were severe periodontitis in the group using thermoplastic dentures. Data on the prevalence of complications in the form of gingivitis and periodontitis in groups with different materials for the bases of removable dentures correlate well with the results of the Schiller – Pisarev test, Spearman correlation coefficient $\rho = 0.84$.

Let us determine the quantitative values of phenotypic CD markers corresponding to clinical manifestations in the form of gingivitis and periodontitis. Patients in each age group were divided into three groups: without complications, complications in the form of gingivitis. Patients with complications of prosthetics in the form of periodontitis of mild, moderate and severe severity were combined into the third group to determine the average parameters of local cellular immunity.

The data presented in Table 4 show that in periodontitis, the median values of differentiation clusters are significantly higher: thus, the values for the $CD68^+$ marker in periodontitis are 2 times higher than in gingivitis, and exceed the norm by almost 4.3 times.

The severity and prevalence of gingivitis and periodontitis in abutment teeth due to the influence of the prosthesis material depend on the interaction between the microbial triggers and the host immune system, a process in which monocytes and macrophages play an important role. Macrophages can be phenotypically classified into the M1 phenotype, which promotes the proinflammatory phase of the immune response, while M2 macrophages promote the healing and resolution phase [10].

Analysis of the $CD4^+/CD8^+$ ratio, which characterizes the ratio of T-helpers and T-suppressors, on average for the age group of 40–59 years, revealed that the state of the immune system for the norm is normoergic, for the diagnosis of gingivitis – 2.6 on the

Table 4

Quantitative values of CD markers of immunocytes in gingiva of prosthetic bed of patients with clinical manifestations

Parameter	Age, years	$CD163^+$	$CD204^+$	$CD4^+/CD8^+$	$CD11^+/CD303^+$	$CD68^+$	Ki67
Norm	40–59	1.82	1.70	1.36	1.38	1.52	6.45
	60+	1.60	1.52	1.10	1.27	1.03	6.14
Gingivitis	40–59	2.19	2.67	1.78	2.29	3.22	7.53
	60+	1.78	2.27	1.59	1.90	1.71	6.98
Periodontitis	40–59	3.10	3.56	2.36	3.32	6.54	9.62
	60+	2.97	2.92	1.83	3.20	3.57	7.87

border of normoergic and hyperactive, which corresponds to an adequate reaction of the oral mucosa, while for the diagnosis of periodontitis with complications – 3.5, which corresponds to a hyperactive reaction.

The dependence of CD marker levels (in patients diagnosed with moderate and severe periodontitis) on the material of the removable denture was studied. The data of median values of the indices of differentiation clusters of immunocytes of the gingival prosthetic bed of patients for both age groups with a diagnosis of chronic periodontitis, using removable dentures made of different materials for 6 months, are presented in Table 5, the statistical significance of the differences was tested by a nonparametric median test ($p < 0.05$).

Table 5 shows the change in immune cell populations in groups of patients using removable dentures based on different materials and diagnosed with chronic periodontitis after 6 months.

In periodontitis, $CD11^+$ receptors and dendritic cells are of great importance [11]. In Table 5, the $CD11^+$ values for acrylic coincide with the control ones, for polyurethane they are slightly lower than the control values, for thermoplastics they are 29 % higher in the 40–59-year old group, and 33 % higher in the 60 year and older group, which explains the largest number of patients diagnosed with periodontitis in these groups.

The $CD4^+/CD8^+$ ratio analysis in the 40–59 age group allows us to assess the state of the immune system. Normally, this ratio is normoergic. For the diagnosis of gingivitis, the value is 2.6, which is on the border between the normoergic and hyperactive state and indicates an adequate response of the body's system to inflammation. However, for the diagnosis of periodontitis with complications, the value is 3.5, which corresponds to a hyperactive response of the immune system.

The data in Table 5 show that the $CD4^+/CD8^+$ ratio is 16 % higher when using thermoplastics as the base material compared to when using acrylates, suggesting that this is due to a reduction in the number of $CD8^+$ T cells. This corresponds to an increase in the content of M1 macrophages and a decrease in the content of M2 macrophages in the gingival tissues affected by periodontitis and may reflect a change in cellular immunity towards a pro-inflammatory phenotype – an increase in the level of pro-inflammatory factors and

Table 5

CD marker values in patients diagnosed with periodontitis

Parameter	Age, years	$CD163^+$	$CD204^+$	$CD4^+/CD8^+$	$CD11^+/CD303^+$	$CD68^+$	Ki67
Acryl	40–59	2.98	2.87	2.88	1.38	4.06	8.75
	60+	2.27	2.43	1.84	1.06	2.55	7.35
Thermoplast	40–59	3.51	3.47	3.34	1.78	6.65	9.64
	60+	3.21	2.79	2.25	1.41	3.56	7.92
Polyeurethane	40–59	2.59	2.78	2.38	1.27	3.24	7.68
	60+	2.02	2.17	1.70	1.02	1.79	7.03
Control	40–59	1.62	1.70	1.36	1.38	1.24	6.80
	60+	1.30	1.42	1.10	1.07	2.91	6.44

suppression of the anti-inflammatory factor in circulating monocytes. The obtained data are consistent with the results of a study indicating that the M1/M2 macrophage ratio is significantly higher in affected periodontium, indicating an imbalance between inflammation and reparation mechanisms [12].

For patients using thermoplastic-based prostheses, elevated levels of the $CD4^+/CD8^+$ glycoprotein ratio, which are localized on the surface of T-lymphocytes, are observed. The ratio between T-helpers and T-suppressors is more than 3, which exceeds the hyperactivity threshold – 2.4 times, compared with the normal (control) value; when using acrylate materials as the base material, this excess is 2.2 times, and for polyurethane – 1.9 times. The level of $CD4^+$ T cells, which react to pathogens and trigger an immune response, is higher than the control sample; $CD8^+$ T cells react and neutralize the infection; T suppressor cells "switch off" CD4 activity when the immune response is sufficient. An increase in the Ki67 antigen level indicates activation of proliferation processes and promotes cell regeneration and the formation of connective tissue in the inflammation site [13].

Moreover, the change in the population of the main immune cells in patients with moderate and severe periodontitis using acrylic dentures, compared to the norm, is more than 10, which indicates the activation of immunocytes associated with the base material of the removable denture.

The $CD68^+$ antigen is active on various cells, such as blood monocytes, tissue macrophages, lymphocytes, fibroblasts and endothelial cells. When using thermoplastics, its level increases by 68 % compared to acrylics and exceeds the norm by more than 5 times, and when using polyurethane, its level exceeds the norm by 2.5 times.

The most significant deviation of the parameters of local immune homeostasis of the oral mucosa from the parameters of the control group was observed when using thermoplastic materials, while less significant changes in the parameters of local cellular immunity of the oral mucosa were noted when using acrylic base materials.

The control group included patients without periodontal tissue pathologies; in the experimental groups, the condition of the soft tissues in the area of the prosthetic bed and contact with the teeth was assessed before and after prosthetics after 6 months. Based on statistical analysis of the obtained data, a strong relationship was found between the material of the removable denture and changes in the parameters of cellular immunity, signs and severity of inflammation. In particular, when examining patients, the majority of them had hyperemic and edematous mucous membranes of the lips and cheeks after prosthetics. In the group where thermoplastic prosthetics were performed, a positive Schiller-Pisarev test was detected in 90.43 % of cases in the 40–59-year-old group and in 98.57 % in the 60-year-old and older group, and correlated with the proliferative activity index values. The lowest number of patients with a positive test was detected in the group where polyurethane-based prostheses were used, which correlates with the lowest proliferation index values in the experimental groups.

The severity of periodontal diseases also correlated with the increase in the indices of

local cellular immunity of the oral mucosa. It can be noted that in percentage terms within the studied groups, the highest prevalence of gingivitis and periodontitis was also in the groups where prosthetics were performed with thermoplastic prostheses, and the lowest – in the groups where polyurethane base materials were used. These data correlate with the increase in local cellular immunity indices, which were also maximum in the group with thermoplastics and minimum in the group with polyurethane prostheses. Thus, it can be concluded that changes in the parameters of local cellular immunity directly affect the condition of the mucous membrane of the prosthetic bed, as well as the clinical manifestations of inflammation and the degree of damage to periodontal tissues, causing the presence of inflammatory symptoms and signs detected by the main and additional examination methods.

Conclusions

1. Immune homeostasis was studied in patients with partial and complete secondary adentia before the start of prosthetics. The data obtained from the study indicate that significant changes in the parameters of the immune balance of the oral mucosa occur at the age of patients from 40 to 59 years due to increased activity of the body.

2. The use of removable dentures leads to a change in the local homeostasis of the oral mucosa. Changes in the parameters of local immune homeostasis of the oral mucosa when using dentures based on thermoplastics, acrylic and polyurethane plastics have significant differences.

3. Changes in the indicators of local homeostasis of the oral mucosa directly correlate with clinical manifestations in the area of the prosthetic bed and periodontal tissues, which is characterized by the appearance of inflammatory changes in the mucous membrane, such as hyperemia and edema, a positive Schiller-Pisarev test, as well as the severity of the disease of the periodontal tissues.

4. Changes in the morphological and clinical parameters of the oral mucosa when using polyurethane-based prostheses are minimal in relation to the parameters of the control group, which allows us to recommend the use of polyurethane prostheses as immediate prostheses at the healing stage during surgical interventions in the oral cavity, in particular tooth extraction and implantation, as well as permanent ones – for patients with allergic intolerance to dental materials, especially with allergic reactions to polymer compounds and dyes.

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COMPARATIVE ASSESSMENT OF THE QUALITY OF LIFE IN PATIENTS WITH BRONCHIAL ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE BEFORE AND AFTER COVID-19

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СРАВНИТЕЛЬНАЯ ОЦЕНКА КАЧЕСТВА ЖИЗНИ У БОЛЬНЫХ БРОНХИАЛЬНОЙ АСТМОЙ И ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ В ПЕРИОД ДО И ПОСЛЕ ПЕРЕНЕСЕННОЙ ИНФЕКЦИИ COVID-19

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Objective. To compare the quality of life of patients with bronchial asthma and chronic obstructive pulmonary disease (COPD) before and after COVID-19.

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Materials and methods. 73 patients diagnosed with bronchial asthma and 78 patients with COPD who were treated at Sechenov University Clinical Hospital №4, participated in the retrospective dynamic comparative study based on the principle «from cause to effect». Assessment of the quality of the patients` life was carried out before and after COVID-19 using a visual analogue scale from 0 to 100 points and the universal EuroQol-5D questionnaire. Mobility, self-care abilities, habitual activity, severity of pain/discomfort, the presence of anxiety/depression in the post-COVID period were assessed.
Results. In patients with COPD before COVID-19, the average total score on the visual–analogue scale was 89,5 [83,8; 95], and after COVID-19 it was 70 [64,5; 80] points. In the post-covid period, 91 % of people with COPD noted some mobility limitations, 33.3 % experienced difficulties with self-care, 65.4 % of patients could not engage in habitual activities, 60.3 % suffered pronounced pain or discomfort, and 29.5 % of patients had severe anxiety or depression. In patients with asthma before COVID-19, the average total score was 90 [88,4; 91] points, and after COVID-19 it was 75 [70,2; 80,2]. In the post-ovarian period, mobility limitations were noted by 71.2 % of patients, and 64.4 % had difficulties with taking care of themselves, 54.8 % could not engage in habitual activities. At the same time, 78.1 % of patients experienced pain or discomfort, and 58.9 % had moderate anxiety or depression.
Conclusions. COVID-19 has led to a significant decrease in the quality of life in patients with asthma and COPD. This may be associated with a worsening of the course of the disease and increase in the number of exacerbations of these pulmonary pathologies, resulting in significant limitation of mobility, growing pain or discomfort, as well as the occurrence of severe anxiety or depression.
Keywords. Quality of life, bronchopulmonary pathologies, bronchial asthma, COPD, COVID-19.

Цель. Провести сравнительную оценку качества жизни пациентов с бронхиальной астмой и хронической обструктивной болезнью легких (ХОБЛ) в период до и после перенесенной инфекции COVID-19.
Материалы и методы. В ретроспективном динамическом сравнительном исследовании по принципу «от причины к следствию» проведен анализ данных 73 пациентов с установленным диагнозом бронхиальной астмы (БА) и 78 пациентов с диагнозом ХОБЛ, находившихся на лечении в Университетской клинической больнице № 4. У пациентов проводилась оценка качества жизни в период до и после перенесенной инфекции COVID-19 с помощью визуально-аналоговой шкалы от 0 до 100 баллов и с помощью универсального опросника EuroQol-5D оценивалась подвижность, способность к уходу за собой, привычная деятельность, выраженность боли/дискомфорта, наличие тревоги/депрессии в постковидном периоде.
Результаты. У пациентов с ХОБЛ до перенесенного COVID-19 среднее значение общего балла по визуально-аналоговой шкале составило 89,5 [83,8; 95], а после COVID-19 – 70 [64,5; 80]. Установлено, что в постковидном периоде 91 % лиц с ХОБЛ отмечали ограничения подвижности, 33,3 % – испытывали затруднения при уходе за собой, 65,4 % пациентов не могли заниматься привычной деятельностью, 60,3 % ощущали выраженную боль или дискомфорт, а у 29,5 % пациентов наблюдалась сильно выраженная тревога или депрессия. У пациентов с астмой до перенесенного COVID-19 среднее значение балла составило 90 [88,4; 91], а после – 75 [70,2; 80,2]. В постковидном периоде 71,2 % пациентов отмечали затруднения в передвижении, а 64,4 % – при уходе за собой, 54,8 % не могли заниматься привычной деятельностью. При этом 78,1 % пациентов испытывали боль или дискомфорт, а у 58,9 % установлена умеренная тревога или депрессия.
Выводы. Перенесенная инфекция COVID-19 привела к достоверному снижению качества жизни у пациентов с бронхиальной астмой и ХОБЛ, что может быть связано с утяжелением течения и увеличением числа обострений данных бронхолегочных заболеваний, приводящих к значительному ограничению подвижности, нарастанию боли или дискомфорта, а также возникновению выраженной тревоги или депрессии.
Ключевые слова. Качество жизни, бронхолегочные патологии, бронхиальная астма, ХОБЛ, COVID-19.

INTRODUCTION

Bronchial asthma and chronic obstructive pulmonary disease (COPD) are among the most common chronic diseases of the respiratory system, which, if severe, can lead to persistent loss of ability to work and disability of patients. During the COVID-19

pandemic, this group of patients was of particular concern due to the high risk of severe infectious pathology caused by the SARS-CoV-2 virus, which has a special tropism for the receptors of the cells of the respiratory tract mucosa, as well as due to the possible delayed consequences of the infection in this group of people.

According to the results of multicenter studies, patients with COPD were more likely to have a severe course of COVID-19 with possible adverse outcomes, including death [1–3]. However, the potential impact of COVID-19 on the course of COPD in the post-COVID period was of particular interest. According to the latest published studies, patients with COPD who have had COVID-19 experience an increased frequency and longer periods of exacerbations of this pathology in the late period against the background of the development of viral and bacterial complications, which leads to disease progression, as well as to a worsening of the general condition of this group of patients, and can significantly affect their quality of life [4; 5].

During the COVID-19 pandemic, bronchial asthma (BA) has shown itself to a lesser extent as a potential factor aggravating the course of coronavirus infection and increasing the risk of adverse outcomes [6; 7]. However, some patients also had cases of severe infection caused by the SARS-CoV-2 virus. In people with mild BA, this infection was most often asymptomatic or mild, but in patients with severe or uncontrolled BA, the risk of an unfavorable course of COVID-19 was significantly higher and in some cases was accompanied by a fatal outcome. According to recent studies, in the post-COVID period, the course of asthma in some patients becomes more severe and uncontrollable, symptoms of shortness of breath increase, there is a need to increase the stage of therapy, which can also negatively affect the quality of life in this group of patients [8; 9].

The aim of the study is to conduct a comparative assessment of the quality of life of patients with bronchial asthma and chronic obstructive pulmonary disease in the period before and after COVID-19 infection.

MATERIALS AND METHODS

A retrospective dynamic comparative study based on the "from cause to effect" principle involved 151 patients hospitalized at the University Medical Center No. 4 of Sechenov University in Moscow. A total of 73 patients with an established diagnosis of bronchial asthma who had previously had COVID-19, as well as 78 patients diagnosed with COPD and a history of COVID-19, were included in the study. The table presents a comparative characteristic of the patient groups by the main clinical parameters.

The selection of patients for participation in the study was carried out according to the following inclusion criteria: the patient's age was over 18 years, the presence of a made diagnosis of bronchial asthma or COPD, and a history of bronchial asthma or COPD, had a history of

Clinical characteristics of patients included in study

Patients' Group	Patients with COPD who have previously had COVID-19	Patients with bronchial asthma who have previously had COVID-19
Number of participants, abs.	78	73
Mean age (range, median age)	65.4 years old (40–88 years old, median – 65.5)	58 years (21–84 years old, median – 62)
Distribution by gender, abs.	Men – 53, Women – 25	Men – 27, Women – 46
Number of people in the acute stage, %	93.6	95

laboratory-confirmed coronavirus infection within a year prior to inclusion in the study, and consent to participate in the study.

Exclusion criteria: patient age under 18 years, presence of concurrent pulmonary disease, acute phase of viral or infectious disease, presence of oncological diseases, hypertension in the stage of decompensation, diabetes mellitus, chronic liver and kidney diseases, disability, pregnancy, refusal to participate in the study. Written informed consent was obtained from all patients who participated in the study. This study was approved by the local ethics committee of the FSAEI HE Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University) (protocol No. 01–22 dated 20.01.2022). The study was carried out in accordance with the code of ethics (Declaration of Helsinki).

Information was collected through oral questioning of patients using a universal validated questionnaire for a comprehensive assessment of quality of life EuroQol – 5D, supplemented by a visual analogue scale (VAS) from 0 to 100 points [10; 11]. This questionnaire allows to assess the health profile of patients according to five different parameters: mobility, self-care, usual daily activities, presence of pain or discomfort, feelings of anxiety or depression [12]. Each question has three levels of answers. An important feature of this questionnaire is the speed of its completion (from 2 to 5 minutes), an improved system for assessing psychometric characteristics, as well as the possibility of use in people with a wide range of diseases, including chronic pulmonary pathologies [13].

For statistical processing of the obtained survey results, IBM SPSS Statistics Version 20.0 software was used. The distribution was tested for normality using the Kolmogorov-Smirnov criterion.

Considering that most pairs were not normally distributed, medians and interquartile ranges (Me [Q_{25} – Q_{75}]) were calculated for quantitative variables, and categorical variables were presented as absolute values and percentages (%).

To determine statistically significant differences, nonparametric tests for paired comparisons (sign test and Wilcoxon test) were used. Results were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

In patients with bronchial asthma, the average VAS Scale score was 90 [88.4; 91] before COVID-19 infection. In the post-COVID period, most patients in this group experienced a significant deterioration in well-being, which led to a decrease in the average score to 75 [70.2; 80.2] (Fig. 1). The difference in VAS scores before and after COVID-19 in patients with BA was significant. Using nonparametric sign tests and the Wilcoxon test, statistically significant differences were established between the VAS scores in patients from this group in the period before and after COVID-19 infection ($p < 0.05$).

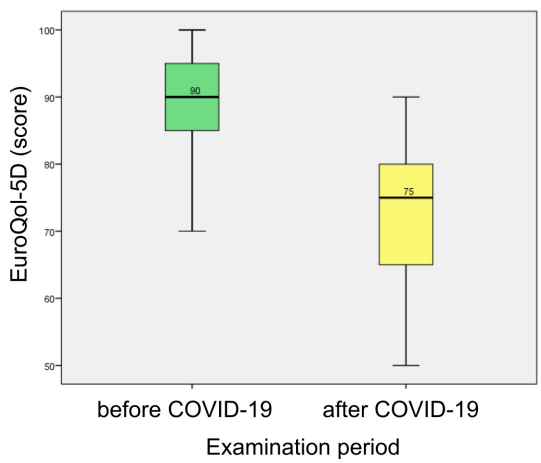

Fig. 1. Results of assessing the quality of life in patients with BA in the period before and after COVID-19 using a visual analogue Scale (VAS)

When assessing individual parameters of the health profile using the EuroQol-5D questionnaire in patients with BA after COVID-19, it was found that 71.2 % noted some difficulties in independent movement, and 11 % could not move independently. Most patients with BA (64.4 %) can fully care for themselves, a third (32.9 %) have certain difficulties associated with care. Half of the patients in the study group (54.8 %) had certain limitations associated with the need to participate in their usual activities, and 34.2 % of patients with asthma cannot perform their usual physical activities due to the severity of this pulmonary disease. When assessing the severity of pain or discomfort mediated by asthma symptoms, it was found that 78.1 % of patients experienced moderate pain or discomfort, and 15.1 % of patients in this group had severe complaints. More than half of the patients (58.9 %) had moderate anxiety or depression, 8.2 % had severe symptoms, and 32.9 % of patients did not report anxiety or depression.

Among patients with COPD before COVID-19 infection, the average value of the total score on the visual analogue Scale (VAS) was 89.5 [83.8; 95]. In the post-COVID period, the average score on the Scale decreased significantly and was already 70 [64.5; 80] (Fig. 2).

It was found that the difference between the number of points in the period before and after COVID-19 in the group of patients suffering from COPD is statistically significant ($p < 0.05$).

According to the data obtained from the five-domain health profile assessment, it was found that 91 % of patients in the COPD group reported some difficulty in moving, and 9 % could not move independently without assistance. 57.7 % of patients with COPD had no difficulty in

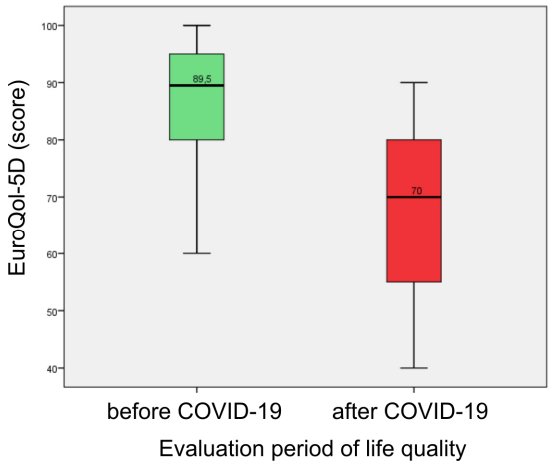

Fig. 2. Results of assessing the quality of life in a group of patients with COPD in the period before and after COVID-19 infection using a visual analogue Scale (VAS)

caring for themselves, 33.3 % reported some difficulty, and 9 % required assistance in caring for themselves. During the survey it was found that the majority of patients (65.4 %) could not perform their usual activities due to the severity of COPD symptoms, and 29.5 % experienced certain difficulties in performing daily activities, and only 5.1 % did not report such difficulties. In 60.3 % of patients from the COPD group, the presence of severe pain or discomfort associated with the severity of the disease was noted, in 38.5 %, pain or discomfort was moderate, and only 1.3 % of patients had no symptoms. Also, about a third of patients with COPD (29.5 %) noted severe anxiety or depression against the background of pulmonary disease, in the majority (62.8 %) these symptoms were moderately expressed, and were absent in 1.3 % of patients.

At present, there is an extremely limited number of publications in the literature devoted to the quality of life issue in patients with chronic pulmonary pathologies in the post-COVID period, which is associated with the novelty and poor study of the delayed consequences of COVID-19 in comorbid patients. Previously published works described the relationship between the degree of asthma control, as well as the number of COPD exacerbations and the level of quality of life of these patients [13; 14].

Thus, longer-term observation is needed in groups of patients with lung troubles who have had COVID-19, with repeated assessment of life quality in the delayed post-COVID period. In the future, additional studies will be required to identify a clear relationship between the severity of COVID-19, the worsening of BA and COPD symptoms in the post-COVID period and their impact on each individual parameter of life quality in these patients. The results obtained in the future will be able to provide additional information for improving methods for preventing delayed consequences of COVID-19 infection in individuals with chronic lung diseases.

Conclusions

After suffering from COVID-19, a reliable decrease in the indicator reflecting the quality of life was established in patients with bronchial asthma by 15 points and in patients with COPD by 19.5 points – as a result of the severe course and an increase in the number of exacerbations of these pulmonary pathologies in the post-COVID

period. Worsening of the course of asthma and an increase in its symptoms and COPD, in turn, lead to a significant limitation of mobility, increased pain or discomfort, as well as the emergence of symptoms of anxiety or depression.

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PERFORATED GASTRODUODENAL ULCERS: PERIOPERATIVE PROGNOSIS AND PREVENTION OF COMPLICATIONS

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ПЕРФОРАТИВНЫЕ ГАСТРОДУОДЕНАЛЬНЫЕ ЯЗВЫ: ПЕРИОПЕРАЦИОННОЕ ПРОГНОЗИРОВАНИЕ И ПРОФИЛАКТИКА ОСЛОЖНЕНИЙ

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Objective. To improve the effectiveness of treatment for patients with perforated gastroduodenal ulcers (PGDU) by developing criteria for predicting postoperative complications and mortality.
Materials and methods. The treatment outcomes of 127 patients with PGDU were analyzed. Prognostic scales ASA, SOFA, Peptic Ulcer Perforation Score (PULP), and the Mannheim Peritonitis Index (MPI) were used for the assessment in all the patients. Specialized classifications (DEP and ulcer defect classes) developed at Sklifosovsky Research Institute For Emergency Medicine were employed to determine the surgical approach and the extent of surgical intervention.
Results. Duodenal ulcers were observed in 97(76.4 %) patients, gastric ulcers in 28(22.0 %), and combined ulcers in 2(1.6 %). According to the clinical form, chronic ulcers were identified in 81 (63.8 %) patients, while acute ones were detected in 46(36.2 %) patients. *Helicobacter pylori* infection was revealed in all patients with chronic ulcers. The majority of patients sought medical care within the first 6 hours after perforation (53 patients, 41.7 %); from

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6 to 12 hours – 24 patients (18.9 %), 12–24 hours – 17 patients (13.4 %), and in more than 24 hours – 33 patients (26.0 %). Fatal outcome occurred in 45 (35.4 %) patients, while 82 (64.4 %) patients were discharged after the recovery had been observed. The mortality rate was significantly higher in patients with MPI grades 2 and 3, in those with an initially high risk according to the PULP scale, and those who were hospitalized more than 24 hours after perforation. Indications for laparoscopic ulcer suturing were proposed based on the scales used.

Conclusions. The risk factors for adverse outcomes in PGDU include the following criteria: surgery performed more than 24 hours after perforation, MPI 2-3 grades, and a PULP scale score more than 8. In patients with PGDU who are at high surgical-anesthetic risk and have a complicated comorbid background, the risk of sepsis development is more than 30 %. Laparoscopic techniques for suturing PGDU are preferable when performed within 6 hours of perforation, with a PULP score not more than 7, MPI grade 1, and DEP classification scores less than 9, specifically in IIC, IIIC, IVA, IVB, and IVC ulcer defect classes.

Keywords. Perforated gastroduodenal ulcers, peritonitis, prediction of postoperative complications, mortality, prognostic scales.

Цель. Повышение эффективности лечения пациентов с перфоративными гастродуоденальными язвами (ПГДЯ) за счет прогнозирования послеоперационных осложнений и летальности.

Материалы и методы. Проанализированы результаты лечения 127 пациентов с ПГДЯ. В лечении всех пациентов применялись прогностические шкалы: ASA, SOFA, Peptic Ulcer Perforation Score (PULP), Мангеймский индекс перитонита (МИП). При выборе оперативного доступа и объема оперативного лечения использовались специализированные классификации (DEP и классы язвенных дефектов), разработанные в НИИ скорой помощи им. Н.В. Склифосовского.

Результаты. Язвы двенадцатиперстной кишки встретились у 97 (76,4 %) пациентов, язвы желудка – у 28 (22,0 %), сочетанные язвы – у 2 (1,6 %). По клинической форме хронический характер язвы отмечен у 81 (63,8 %) пациента, острые язвы – у 46 (36,2 %). У всех лиц с хроническими язвами выявлена инфекция *Helicobacter pylori.* Наиболее часто пациенты обращались за медицинской помощью в первые 6 ч с момента перфорации – 53 (41,7 %) случая; от 6 до 12 ч – 24 (18,9 %), 12–24 ч – 17 (13,4 %), более 24 ч – 33 (26,0 %). Летальный исход отмечен у 45 (35,5 %) пациентов, 82 (64,5 %) человека выписаны с выздоровлением. Частота летальности была достоверно выше у пациентов со 2-й и 3-й степенями по МИП, исходно высоким риском по шкале PULP, а также госпитализацией свыше 24 ч после перфорации. На основании используемых шкал предложены показания для лапароскопического ушивания язвы.

Выводы. Факторами риска неблагоприятного исхода при ПГДЯ являются следующие критерии: операция через 24 ч после перфорации, 2–3-й степени по МИП, а также больше 8 баллов по прогностической шкале PULP. У пациентов с ПГДЯ из группы высокого операционного-анестезиологического риска с отягощенным коморбидным фоном риск развития сепсиса составляет более 30 %. Лапароскопические технологии ушивания ПГДЯ предпочтительней использовать в сроки до 6 ч от момента перфорации у имеющих не более 7 баллов по PULP, 1-й степени – по МИП, менее 9 баллов – по классификации DEP и IIC, IIIC, IVA, IVB, IVC классах язвенного дефекта.

Ключевые слова. Перфоративные гастродуоденальные язвы, перитонит, прогнозирование послеоперационных осложнений, летальность, прогностические шкалы.

INTRODUCTION

The incidence of perforated gastroduodenal ulcers (PGDU) currently remains at a fairly high level worldwide and reaches 25 cases per hundred thousand population [1]. In Russia, this figure is comparable: according to data for 2022, about 16 thousand surgical interventions were performed for PGDU, and in more than 5 thousand patients, operations were performed more than 24 hours after the perforation. Mortality in PGDU currently ranges from 6.5 to 12.5 % of cases [2–4]. Unfavorable factors

influencing the outcome include: late seeking of medical care (more than 24 hours after perforation), as well as the development of sepsis and septic shock [3]. In the Perm Krai, in 2022, medical care was provided to 358 patients with PGDU, of which 61 (17.0 %) were provided within 24 hours from the moment of perforation. Surgical interventions were performed in 354 (98.9 %) patients (of which 59 (17.7 %) – after 24 hours from the moment of perforation), of which open operations were performed in 336 (94.9 %) people, laparoscopic – in 18 (5.1 %) patients. Mortality was 16.2 %, and after 24 hours from perforation – 44.26 % [5].

The most significant risk factors for the development of PGDU are: carriage of *Helicobacter pylori (H. pylori)* infection, as well as long-term use of non-steroidal anti-inflammatory drugs. *H. pylori* infection is of predominant importance, its average prevalence in patients with PGDU is 58 % [1; 6].

Surgical methods for patients with PGDU are constantly being improved. Classical approaches include ulcer suturing or distal gastrectomy [7–8]. However, recent advances in surgery have led to the widespread introduction of minimally invasive techniques, such as laparoscopic ulcer suturing, endoscopic clipping, and stenting [9–10]. According to data from various domestic and foreign authors, laparoscopic suturing of PGDU leads to a significant reduction in the incidence of complications and mortality, compared with operations performed through a laparotomy approach [9; 11–13]. However, despite the successes achieved, the incidence of complications and mortality remains quite high, especially among older patients with concomitant diseases and a severe comorbid background.

The aim of the study is to improve the effectiveness of treatment of patients with PGDU by predicting postoperative complications and mortality.

MATERIALS AND METHODS

A retrospective study of patients with PGDU was conducted. Inclusion criteria: age over 18 years, acute and chronic gastric and duodenal ulcers (DU) complicated by perforation, previous surgery. As a result, 127 people were included in the study.

Upon admission to the emergency department, patients underwent the full range of diagnostic tests approved by national clinical guidelines. Multispiral computed tomography (MSCT) and esophagogastroduodenoscopy (EGDS) were performed in 28 (22.0 %) patients with unclear clinical symptoms. In patients with a confirmed diagnosis of PGDU, the following prognostic scales were used to determine the risk of complications and mortality: the American Society of Anesthesiologists (ASA) and the Peptic Ulcer Perforation Score (PULP) [14]. The PULP scale includes the following criteria: age over 65 years – 3 points, presence of concomitant oncological diseases or acquired immunodeficiency syndrome – 1 point, presence of cirrhosis in the patient – 2 points, previous or constant intake of glucocorticosteroids – 1 point, shock of various etiologies – 1 point, time after perfora-

tion more than 24 hours – 1 point, serum creatinine 130 mmol/l – 2 points, comorbid status according to the ASA scale 2 points – 1 point, ASA-3 – 3 points, ASA-4 – 5 points, ASA-5 – 7 points. The results of the calculation were interpreted as follows: less than 7 points – mortality risk less than 25 %, 8–18 points – more than 25 %. The Mannheim Index was used to objectify the severity and predict mortality in patients with peritonitis. When sepsis or septic shock was diagnosed in a patient, the SOFA Scale was used.

During the operation, classifications developed at the N.V. Sklifosovsky Research Institute of Emergency Care were used to objectively select the method of surgical intervention and the method of suturing the ulcer defect: DEP and classes of ulcer defects. The DEP classification includes three parameters: D (prevalence): 1 point – lesion of one area of the abdominal cavity; E (nature of exudate): serous exudate, injection of peritoneal vessels, absence or easy removal of fibrin – 1 point, purulent exudate, shiny peritoneum, absence of fibrin – 2 points, purulent exudate, dull peritoneum, removal of dense fibrinous films – 3 points, ichorous exudate, massive non-removable fibrinous deposits – 4 points; parameter P (paresis): diameter of intestinal loops 1.5–2 cm, active peristalsis – 1 point; diameter of loops 2.0–3.0 cm, weakened peristalsis with active areas – 2 points; diameter 3.0–4.0 cm, absence of peristalsis or its presence in certain areas – 3 points; diameter over 4 cm, absence of peristalsis – 4 points. The classification of ulcerative defects is based on the size of the defect and the surrounding inflammatory infiltrate. Thus, the ulcer size of 1 mm or less corresponds to class I, 2–5 mm – class II, 6–10 mm – class III, 11 mm or more – class IV. The size of the inflammatory infiltrate corresponds to an additional letter index: less than 6 mm – A, 6–10 mm – B, 11 mm or more – C. Based on the presented scales, indications for laparoscopic suturing of PGDU were set. The indications were: 9 points or more according to the DEP peritonitis classification, as well as IIC, IIIC, IVA, IVB, IVC classes according to the ulcer defect scale [15]. In the postoperative period, all patients were treated in the intensive care unit, and after stabilization, in the surgical department. For optimal recovery after surgery, all patients were treated with the Enhanced Recovery After Surgery program.

The R programming language was used for statistical processing of the obtained results and working with graphics. Quantitative data are presented as median (Me), as well as first and third quartiles. The Chi-square criterion was used to compare general dispersions of two or three independent samples.

RESULTS AND DISCUSSION

The median age of patients was 56.0 (39.0–70.0) years. There were 75 (59.1 %) male and 52 (40.9 %) female patients. All patients were distributed by time from the moment of perforation. Most often, patients sought medical help in the first 6 hours from the moment of perforation – 53 (41.7 %) people. In the period from 6 to 12 hours from the moment of perforation, 24 (18.9 %) patients sought help, 12–24 hours –

17 (13.4 %), more than 24 hours – 33 (26.0 %). According to the localization of the ulcer defect, patients with duodenal ulcers prevailed in the study – 97 (76.4 %). Among them, duodenal bulb ulcers were found in 96 (75.6 %) patients, postbulbar duodenal ulcers – in one (0.8 %). Gastric ulcers were found in 28 (22.0 %) patients, including antral ulcers – in 10 (7.9 %), pyloric ulcers – in 10 (7.9 %), body of the stomach – in 6 (4.7 %), cardiac ulcers – in 2 (2.4 %). Combined (stomach and duodenum) ulcers were observed in 2 (1.6 %) patients. Most patients had single ulcers (122 (96.1 %)), multiple ulcers were found in 5 (3.9 %) patients. According to the nature of the course, the ulcer was chronic in 81 (63.8 %) patients, acute – in 46 (36.2 %).

All patients were stratified by the number of PULP scores: in 104 (81.9 %) people the score did not exceed 7 (the risk of mortality does not exceed 25 %), in 23 (18.1 %) the score ranged from 8 to 18 (the risk of mortality exceeds 25 %). Generalized peritonitis was noted in 94 (74.0 %) patients, local unconfined peritonitis – in 19 (15.0) people, local confined – in 14 (11.0) patients. By the nature of the exudate in the abdominal cavity: serous peritonitis was noted in 5 (3.9 %) patients, serous-fibrinous – in 61 (48.0 %), fibrinous-purulent – in 61 (48.0 %). All patients with peritonitis underwent bacteriological examination of the abdominal exudate. It was noted that only 47.24 % of the cultures were positive. The spectrum of identified microorganisms was very poor, the most frequently identified etiopathogen was *E. coli* – in 23.33 % of cases. In 9 patients with abdominal sepsis and a negative bacteriological test result, the microbial composition of the exudate was additionally assessed using gas chromatography / mass spectrometry. All these patients had a polymicrobial composition of the studied samples. It should be noted that *H. pylori* was predominant in the microbial composition of all studied exudates in patients with chronic ulcers. In the work of V.A. Samartsev et al. (2021), it was shown that this microorganism is significantly more common in the exudate of the abdominal cavity in patients whose source of peritonitis is localized in the stomach and duodenum compared to exudates obtained from patients with peritonitis localized in the small or large intestine [16]. The Mannheim Index was used to objectify the severity and predict mortality in peritonitis. As a result, the 1st degree of severity (up to 21 points) was noted in 81 (63.8 %) patients, the 2nd degree (21–29 points) – in 39 (30.7 %), the 3rd degree (more than 29 points) – in 7 (5.5 %). In 37 (29.1 %) patients with ASA-IIIE and ASA-IVE, as well as 24-hour peritonitis, according to the SOFA Scale, sepsis was diagnosed.

In 103 (81.1 %) patients, suturing of the ulcer defect was performed as a method of surgical treatment, of which laparoscopic technologies were used in 9 (8.7 %) cases. The following criteria were considered indications for laparoscopic suturing of the ulcer defect: time frame up to 6 hours from the moment of perforation, a result of no more than 7 points on the PULP Scale, 1st degree of peritonitis

based on the IIP, as well as ulcer defects of IIC, IIIC, IVA, IVB, IVC classes on the scale of the N.V. Sklifosovsky Research Institute of Emergency Care [15]. In other cases, a midline laparotomy was performed. Distal gastrectomy with a Bilroth-II anastomosis was performed in 24 (18.9 %) patients. In all patients operated on using an open approach, the aponeurosis of the rectus abdominis muscles was sutured using an original technique developed by us, which consists of suturing the aponeurosis with two loop threads with an antibacterial coating (patent No. RU 2803132 C2 dated 15.02.2022). The first loop thread was used to apply a continuous suture from the lower corner to the middle of the laparotomy wound using the Small Bytes technology, capturing the peritoneum and muscular-aponeurotic layer. The aponeurosis was sutured in a similar manner with the second loop thread from the upper edge of the laparotomy wound, continuing below the knot on the first thread by 3–4 cm. Then, the first thread continued to suture upwards from the laparotomy wound. When applying the suture, the first puncture was made lateral to the border of the white line and the sheath of the rectus abdominis muscle. The puncture was made at a distance of 1.5 cm from the puncture parallel to the white line of the abdomen. After the stitch was applied, the loop was cut at the needle, the thread with the needle was stitched to the opposite side of the wound, and the threads were tied. A similar stitch was applied with the second thread from the center to the lower corner of the wound.

All patients were treated in the intensive care unit after surgery. Relaparotomy for postoperative peritonitis was required in 7 (5.9 %) cases. Complete eventration was observed in 2 (1.7 %) patients after median laparotomy. It was eliminated during repeated surgery. The low percentage of relaparotomy confirms the effectiveness of the original technique of suturing the aponeurosis after laparotomy.

After the treatment, 82 (64.5 %) patients were discharged with recovery. The duration of postoperative hospitalization in patients after laparoscopic ulcer suturing was 6.0 (5.0–6.0) days, after open ulcer suturing – 7.0 (3.5–9.0), after distal gastrectomy with Bilroth-II anastomosis – 6.5 (1.0–15) people. The duration of hospitalization did not differ statistically significantly. Diagnosis and treatment of patients with sepsis was carried out according to the Sepsis-3 criteria.

Fatal outcome against the background of development of multi-organ failure syndrome in the general cohort of patients was observed in 45 (35.5 %) people. When stratifying patients by degree according to the Mannheim Index, the mortality rate was significantly higher in patients with 2nd and 3rd degrees ($p < 0.01$) and was: 13.6 % in patients with 1st degree, 71.8 % in patients with 2nd degree, and 85.7 % in patients with 3rd degree. The high mortality rate is probably associated with the large percentage of patients in the study with late presentation (more than 24 hours – 33 (26.0 %) patients), as well as widespread peritonitis and sepsis (37 (29.1 %) patients). A signifi-

cant association was noted between the increase in mortality rate and surgical intervention performed 24 hours after perforation ($p < 0.01$). Mortality was also significantly higher in patients with an initially high risk according to the PULP Scale ($p < 0.01$). The data obtained correlate with the mortality rate in the Perm Krai in particular and in the Russian Federation as a whole [5]. It is important to note that there were no fatal outcomes in patients operated using laparoscopic technologies.

Conclusions

Risk factors for an unfavorable outcome in PGDU are the following criteria: surgery 24 hours after perforation, 2–3 degrees according to the Mannheim Index, and more than 8 points according to the PULP prognostic Scale. In patients with PGDU from the group of high surgical-anesthesiological risk with an aggravated comorbid background, the risk of developing sepsis is more than 30 %. Laparoscopic technologies for suturing PGDU are preferable to use within 6 hours from the moment of perforation, while there should be no more than 7 points according to PULP, 1st degree according to the Mannheim Index, less than 9 points according to the DEP classification and IIC, IIIC, IVA, IVB, IVC classes of ulcer defect.

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INFLUENCE OF INTESTINAL PERMEABILITY AND ENDOTOXINEMIA ON THE COURSE OF ASTHMA IN OBESE PATIENTS

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ВЛИЯНИЕ КИШЕЧНОЙ ПРОНИЦАЕМОСТИ И ЭНДОТОКСИНЕМИИ НА ТЕЧЕНИЕ БРОНХИАЛЬНОЙ АСТМЫ У ПАЦИЕНТОВ С ОЖИРЕНИЕМ

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Objective. To study the characteristics of asthma with a severe course in obese patients and to evaluate the relationship of the level of intestinal endotoxin (ET) and fecal zonulin with clinical, laboratory and instrumental indicators in such patients.
Materials and methods. The study included 98 patients with asthma combined with obesity (group 1 – mild asthma ($n = 47$), group 2 – severe asthma ($n = 51$)) and 45 obese patients without asthma composed the comparison group. A complete standard examination and tests were conducted in all the patients. Intestinal ET, fecal zonulin, TNF-α, IFN-γ, IL-4, 6, 10, 17, total IgE levels were assessed as well. The IBM SPSS Statistics 26.0 applica-

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tion software package was used for statistical calculations. The results were considered as statistically significant at the level of p <0,05.

Results. In patients of both groups, the average age of onset was 43 years. The median duration of BA characteristics was higher in patients of group 2: 14 [10; 19] years (p = 0.013). In all groups, CRPhs values increased significantly and the highest ones were in patients with severe asthma (p < 0.001). Significantly lower levels of FVC, FEV1, FEV1/FVC, IL-10 (p<0.001) with uncontrolled course of asthma (p = 0.008) and rare control (p = 0.009) occurred in patients of group 2. Higher levels of TNF-α, IFN-γ, IL-6,17, intestinal ET, fecal zonulin were revealed in patients of group 2 (p≤0.001). The level of fecal zonulin positively correlated with the level of intestinal ET in patients of group 2 (p<0.001, rs=0.813). In patients of group 2 direct correlations of the fecal zonulin and intestinal ET with BMI, WC, HC, WC/HC, lack of BA control, CRPhs, TNF-α, IL-6,17, IFN-γ, LDL were established and inverse correlations were with IL-10, HDL, FEV1, AST; a negative correlation of fecal zonulin levels with FVC was also revealed.

Conclusions. The obtained results allow us to speak about the existence of a clinical complex "severe asthma – obesity – intestinal endotoxemia and increased intestinal permeability" which is characterized by the predominance of pro-inflammatory markers, increased levels of intestinal ET and fecal zonulin, reduced function of external breathing.

Keywords. Severe bronchial asthma, obesity, intestinal endotoxin, zonulin.

Цель. Изучить особенности течения тяжелой бронхиальной астмы (БА) в сочетании с ожирением, а также оценить взаимосвязь уровня кишечного эндотоксина (ЭТ) и фекального зонулина с клинико-лабораторными и инструментальными показателями у данной когорты пациентов.

Материалы и методы. В исследование было включено 98 пациентов с БА в сочетании с ожирением (1-я группа – легкая БА (n = 47), 2-я группа – тяжелая БА (n = 51)) и 45 человек с ожирением без БА (группа сравнения). Всем пациентам выполнено комплексное стандартное обследование, а также определение уровня кишечного ЭТ, фекального зонулина, TNF-α, IFN-γ, IL-4, IL-6, IL-10, IL-17, IgE общего, аллергопробы по показаниям. Для статистической обработки данных использовался пакет программы IBM SPSS Statistics 26.0. Результаты оценивались как статистически значимые при уровне p < 0,05.

Результаты. У пациентов 1-й и 2-й групп медиана возраста дебюта составила 43 года. Медиана продолжительности БА статистически значимо была выше у пациентов 2-й группы и составила 14 [10; 19] лет (p = 0,013). В трех группах значения СРБhs существенно возрастали и были максимальными у пациентов с тяжелой БА (p < 0,001). Значимо более низкие показатели ФЖЕЛ, $ОФВ_1$, $ОФВ_1$/ФЖЕЛ, IL-10 (p < 0,001) с более частым неконтролируемым течением БА (p = 0,008) и редким контролем (p = 0,009) встречались у пациентов 2-й группы. Статистически значимо более высокие показатели TNF-α, IFN-γ, IL-6, IL-17, кишечного ЭТ, фекального зонулина были выявлены у пациентов 2-й группы (p ≤ 0,001). Уровень фекального зонулина положительно коррелировал с уровнем кишечного ЭТ у пациентов 2-й группы (p < 0,001; rs = 0,813). Были установлены статистически значимые прямые корреляционные связи показателя фекального зонулина и кишечного ЭТ у пациентов 2-й группы с ИМТ, ОТ, ОБ, ОТ/ОБ, отсутствием контроля БА, СРБhs, TNF-α, IL-6, IL-17, IFN-γ, ЛПНП и обратные корреляционные связи с IL-10, ЛПВП, $ОФВ_1$, АСТ-тестом; также выявлена отрицательная корреляция уровня фекального зонулина с ФЖЕЛ.

Выводы. Полученные результаты позволяют говорить о существовании клинического комплекса «тяжелая БА – ожирение – кишечная эндотоксемия и повышенная проницаемость кишечника», который характеризуется преобладанием провоспалительных маркеров, повышением кишечного ЭТ и фекального зонулина, сниженной функцией внешнего дыхания.

Ключевые слова. Тяжелая бронхиальная астма, ожирение, кишечный эндотоксин, зонулин.

INTRODUCTION

Bronchial asthma (BA) and obesity are widespread diseases, and in recent years there has been a significant increase in the syntropy of these two conditions. The identification of a separate phenotype of asthma with obesity indicates a significant contribu-

tion of obesity in the course of asthma1. According to research data, the "obese asthma" phenotype is characterized by a more severe course, low level of disease control, resistance to basic therapy, and frequent hospitalizations during exacerbations [1].

Severe asthma in combination with obesity is characterized by specific pathophysiological features of the inflammatory response, where the role of intestinal endotoxin, along with increased intestinal permeability, is insufficiently studied. Intestinal endotoxin is known to be associated with both neutrophilic and eosinophilic airway inflammation, airway hyperreactivity, and glucocorticosteroid resistance in asthma [2]. One of the modern directions considers the role of the intestinal microbiome and endotoxinemia in the formation of a more severe course of bronchial asthma in this group of patients. Zonulin is a protein that controls the permeability of the intestinal epithelial barrier [3]. Activation of the zonulin pathway provokes the development of leaky gut syndrome [4], and in combination with endotoxinemia, through the intestine-lung axis [5], it aggravates the course of bronchial asthma in obese patients.

The clinical complex "severe bronchial asthma – obesity – intestinal endotoxemia and increased intestinal permeability (increased zonulin levels)" is currently an object of active study in terms of revealing its pathogenetic comorbidity, prognostic risks of the course of diseases and determining patient management tactics.

MATERIALS AND METHODS

A study was conducted at the State Budgetary Healthcare Institution of the Tyumen Region "OKB No. 1" and the Federal State Budgetary Educational Institution of Higher Education "Tyumen State Medical University" of the Ministry of Health of the Russian Federation involving 143 people (98 patients were diagnosed with bronchial asthma combined with obesity, 42 patients in the comparison group were diagnosed with obesity without bronchial asthma). Inclusion criteria for the study: age 18 years and older; duration of asthma for at least one year prior to inclusion in the study; verified diagnosis of mild and severe asthma; obesity of grades I and II (BMI from 30 to 39.9 kg/m^2); signed voluntary informed consents. Exclusion criteria for the study: bronchial asthma complicated by severe somatic diseases in the decompensation stage; BMI less than 30 kg / m^2 and more than 40 kg / m^2; other respiratory diseases; pregnancy and / or lactation; use of genetically engineered biological drugs; smoking of the patient at the time of inclusion in the study. According to the developed criteria, two main study groups were formed: Group 1 – mild asthma with obesity (n = 47), Group 2 – severe asthma with obesity (n = 51). The diagnosis, severity and level of asthma control were established in accordance with GINA 2023 and Russian clinical guidelines "Bronchial Asthma" (2021). The ACT (Asthma Control Test) questionnaire was used to assess the level of asthma control. The comparison group consisted of 45 patients with obesity of grades I and II (BMI from 30 to 39.9 kg / m^2) without bronchial asthma. The clinical and instrumental examination included: anthropometric examination, spirography with a bronchodilator (Spirolan device, Laname-

dica LLC, Russia); general clinical laboratory examinations, lipid spectrum (total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL), high-density lipoproteins (HDL)), and C-reactive protein (high-sensitivity method – hs) in blood serum were performed using a Beckman Coulter reagent kit (USA). The level of total IgE in blood plasma was measured using a set of test systems from the company NPO Diagnostic Systems (Russia). The study of TNF-α, IFN-α, IL-4, 6, 10 was carried out using a set of reagents from JSC Vector-Best JSC (Russia), the determination of the cytokine IL-17 was carried out using reagents from eBioscience (USA). The level of intestinal endotoxin in the systemic circulation was studied using the micro-LAL test (Hycult Biotech, Netherlands), the concentration of zonulin in feces was determined using the Immundiagnostik AG reagent kit (Germany). Skin allergy tests were performed using the scarification method (allergen extracts from NPO Mikrogen JSC, Russia). This study was conducted in accordance with the protocol approved by the local ethics committee at the Federal State Budgetary Educational Institution of Higher Education "Tyumen State Medical University" of the Ministry of Health of the Russian Federation on 09.09.2022. The IBM SPSS Statistics 26.0 software package was used for data processing. For descriptive statistics, the median (Me) and interquartile range [Q1; Q3] were used, where Q1 is the lower quartile (25 %) and Q3 is the upper quartile (75 %). When comparing quantitative indicators in the three study groups, the Kruskal-Wallis test with Bonferroni correction for multiple comparisons was used; in two groups, the Mann – Whitney U test was used. Categorical indicators in groups were compared using the χ^2 Pearson criterion and Fisher's exact criterion. Analysis of correlation relationships was performed with the determination of the Spearman rank correlation coefficient (rs). The strength of correlations was assessed using the Chaddock scale. Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The study groups were comparable in terms of gender ($p = 0.628$), age ($p = 0.337$), anthropometric parameters (height ($p = 0.854$), weight ($p = 0.952$), BMI ($p = 0.727$), waist volume (WC) ($p = 0.275$), hip volume (HV) ($p = 0.367$), WC / HV index ($p = 0.171$)). The patients were predominantly female (more than 90 %). The median age of patients in the first group was 55 [50.5; 57.5] years, in the second – 63 [54; 67] years, in the comparison group – 61 [48; 66] years. When distributing patients by the degree of obesity and the type of fat deposition, patients with grade I obesity (51 % and more) and with the android type (WC / OB more than 0.85) of fat deposition (88 % of cases and more) predominated. In patients of groups 1 and 2, the median age of asthma onset was 43 years, which indicates a late onset of the underlying disease in combination with obesity and is consistent with data from other studies [6]. The median duration of asthma was statistically significantly ($p = 0.013$) higher in patients with severe asthma in combination with obesity and was 14 [10; 19] years, while in patients of group 1 it was 10 [7; 16] years,

which may indicate the effect of the duration of asthma on the severity of the disease [7].

An analysis of the incidence of concomitant diseases in three groups was conducted (Fig. 1). No statistically significant differences were found in the spectrum of concomitant pathology in patients in all three groups ($p > 0.05$). The most common concomitant pathology in patients with severe bronchial asthma combined with obesity was cardiovascular pathology (56.86 %), arterial hypertension (89.66 %); ENT diseases were less common – 41.18 % (AR – 80.96 %, CPRS The most common concomitant pathology in patients with severe bronchial asthma combined with obesity was cardiovascular pathology (56.86 %), arterial hypertension (89.66 %); ENT diseases were less common – 41.18 % (nasal allergy – 80.96 %, deep-rooted rhinosinusitis polyposa – 9.52 %, combination of nasal allergy and deep-rooted rhinosinusitis polyposa; pathology of endocrine system (25.49 %), of which the most common was diabetes mellitus types 1 and 2 (76.92 %) took third place (see Fig. 1).

The median level of peripheral blood eosinophils in patients in the first group was 280 [190; 358] cells per μl, in the second – 250 [135; 380], in the comparison group – 140 [95; 140]. The median level of peripheral blood neutrophils in patients in the first group was 5.6 [3.98; 6.475] (109/l), in the second – 4.8 [4.1; 5.65] (109/l), in the comparison group – 3.1 [2.5; 3.56] (109/l). Statistically significantly higher levels of peripheral blood eosinophils and neutrophils were found in patients with asthma combined with obesity compared to obese patients without asthma ($p < 0.001$). The statistically significant differences identified highlight the contribution of these cells to inflammatory processes in BA.

The median CRP hs level in the first group was 4.23 [4.04; 4.63] mg/l, in the second – 5.4 [4.9; 6.1], in the comparison group – 3.4 [3.1; 3.67]. In three groups, the values of CRP hs increased significantly and were maximum in patients with severe bronchial asthma ($p < 0.001$). The level of other laboratory parameters among the subjects was comparable ($p > 0.05$).

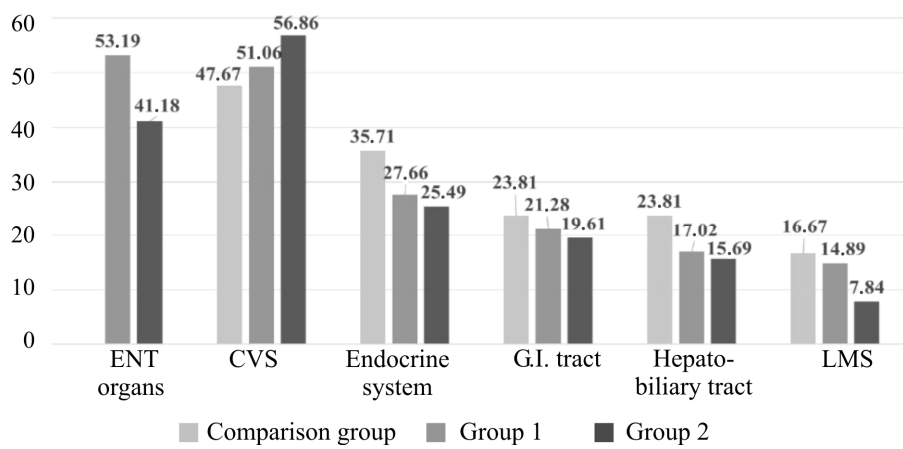

Fig. 1. Spectrum of concomitant pathology in the study groups

The median level of total IgE for patients in group 1 was 140.1 [107.65; 242.25] IU/ml, in group 2 – 135.2 [112.75; 310.45], and for the comparison group – 18.25 [10.1; 32.1]. There were no statistically significant differences in total IgE levels between patients with asthma and obesity ($p = 1.0$). There were no statistically significant differences in the presence and spectrum of sensitization between patients in groups 1 and 2 ($p > 0.05$).

In patients of the 1st group and the comparison group, the results of spirometry did not reveal any disturbances in the mechanical properties of the external respiratory apparatus. Spirometry values for all subjects are shown before the bronchodilator test (Fig. 2). In subjects with severe asthma combined with obesity, the FVC index was within the normal range, while the FEV1 and FEV1/FVC levels were below normal values, indicating more pronounced obstruction in patients with severe asthma combined with obesity. Analysis of the parameters of external respiration function in all study groups showed significant differences in such parameters as FVC ($p < 0.001$), FEV1 ($p < 0.001$) and FEV1 / FVC ($p < 0.001$), with lower values of these indicators in patients with severe asthma combined with obesity.

The analysis of the level of asthma control in the groups was based on the AST test results. The median AST test result in patients of the 1st group was 21 [19; 24] points and was significantly higher ($p < 0.001$) than the median AST test in patients of the 2nd group – 16 [10.5; 21] points.

In severe cases of asthma combined with obesity, patients were more likely to have uncontrolled disease – 58.8 %, while in mild cases of asthma combined with obesity, patients had partial control – 46.8 %. In patients with TBA combined with obesity, an uncontrolled course of the disease was more common ($p = 0.008$) and less common in control ($p = 0.009$), compared with subjects with a mild course of BA combined

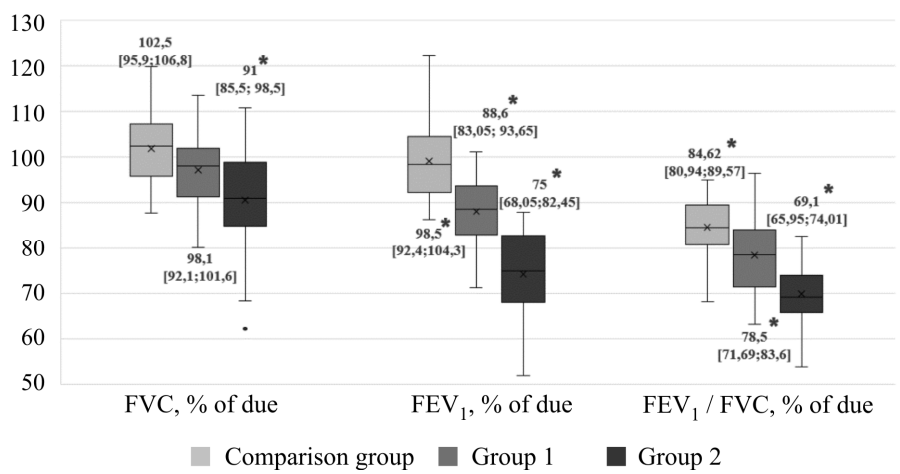

Fig. 2. Main indicators of spirometry in patients of all study groups.
*Note: * – significance of differences when comparing groups pairwise using the Kruskal – Wallis test with Bonferroni correction for multiple comparisons*

with obesity. A moderate-strength relationship was observed between the compared features (V = 0.326).

The study analyzed the spectrum of cytokines in patients of all groups (Fig. 3). The association of asthma with obesity, regardless of severity, was characterized by an increase in plasma levels of TNF-α, IFN-γ, IL-6, IL-17, IL-4 ($p < 0.05$). Statistically significantly higher levels of cytokines TNF-α, IFN-γ, IL-6, IL-17 and the lowest level of IL-10 were found in patients with severe asthma combined with obesity, compared to subjects with mild asthma combined with obesity ($p < 0.001$) and only obesity without asthma ($p \leq 0.001$). This may indicate an additional contribution of adipose tissue to "low-intensity inflammation" and the severity of asthma in this category of patients.

All patients underwent analysis of serum intestinal endotoxin and fecal zonulin levels. Statistically significantly higher values of the median level of intestinal intestinal endotoxin in blood serum – 2.1 [1.85; 2.23] EU/ml and fecal zonulin – 93 [83.45; 96] ng/ml were obtained in patients with severe bronchial asthma combined with obesity ($p < 0.001$). Kim and Baioumy also observed increased zonulin levels in patients with severe asthma in their studies [8; 9].

In a number of studies, the same trend was observed with endotoxemia, which increased with the severity of the course of bronchial asthma [10; 11]. Higher concentrations of ET in patients with severe bronchial asthma may be associated with increased shunt circulation due to frequent use of SABA against the background of uncontrolled bronchial asthma [12].

In patients of the 2nd group, a correlation analysis was performed of the level of fecal zonulin and intestinal ET with the main clinical, laboratory and instrumental indicators, markers of systemic inflammation. The level of fecal zonulin was positively correlated with the level of intestinal ET in patients with severe BA combined with obesity ($p < 0.001$; $rs = 0.813$).

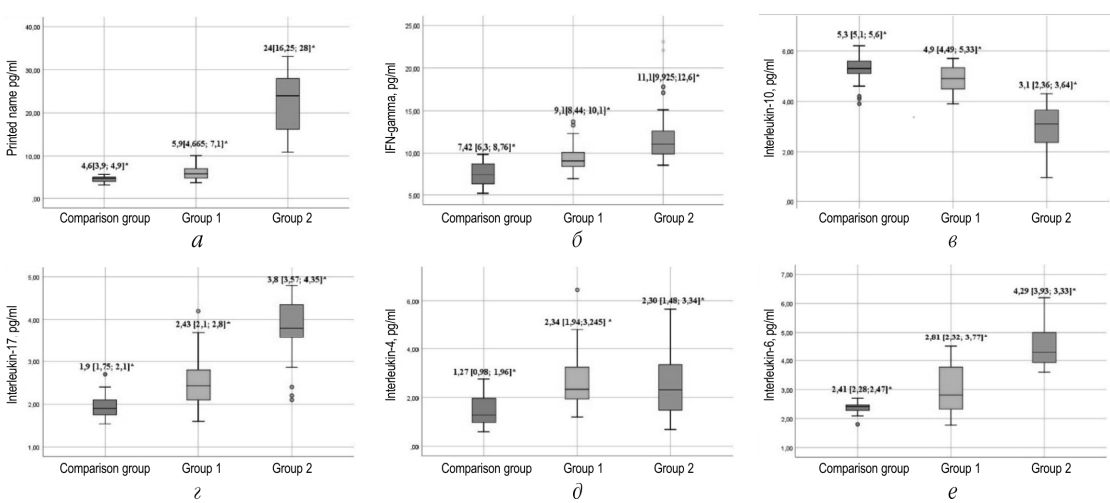

Fig. 3. The level of cytokines in peripheral blood in patients of all study groups (a–e).
Note: p – significance of differences when comparing groups pairwise using the Kruskal-Wallis test with Bonferroni correction for multiple comparisons*

The identified correlation had a high strength of connection according to the Chaddock scale. It is known that in patients with obesity, the intestinal microbial composition changes with a shift towards gram-negative bacteria, which can lead to an increase in the level of intestinal ET [13], an increase in proinflammatory cytokines and ultimately contribute to increased intestinal permeability with an increase in the level of fecal zonulin [14]. When assessing the correlation relationships between fecal zonulin and intestinal ET with anthropometric parameters in patients of group 2, statistically significant direct correlations were established with BMI (zonulin – $p < 0.001$, $rs = 0.820$; ET – $p < 0.001$, $rs = 0.888$), WC (zonulin – $p < 0.001$, $rs = 0.508$; ET – $p < 0.001$, $rs = 0.615$), HC (zonulin – $p = 0.001$, $rs = 0.446$; ET – $p < 0.001$, $rs = 0.498$), WC/HC ratio (zonulin – $p = 0.046$, $rs = 0.281$; ET – $p = 0.005$, $rs = 0.385$). In studies by Moreno-Navarrete [15] and Mörkl [16], positive correlations of zonulin levels with anthropometric parameters in obese patients were also observed. Negative statistically significant associations were found between the levels of fecal zonulin and intestinal endotoxin with FEV1 (zonulin – $p < 0.001$, $rs = -0.576$; ET – $p = 0.002$, $rs = -0.418$), AST test results (zonulin – $p < 0.001$, $rs = -0.704$; ET – $p < 0.001$, $rs = -0.551$) and a positive correlation with the lack of disease control (zonulin – $p < 0.001$, $rs = 0.550$; ET – $p < 0.001$, $rs = 0.302$), a negative correlation was also found between the level of zonulin and FVC ($p = 0.017$; $rs = -0.334$) in patients with severe asthma combined with obesity. In patients of the 2nd group with an increase in the level of fecal zonulin and intestinal ET, an increase in the level of hs-CRP (zonulin – $p < 0.001$, $rs = 0.628$; ET – $p < 0.001$, $rs = 0.533$), TNF-α (zonulin – $p < 0.001$, $rs = 0.594$; ET – $p = 0.002$, $rs = 0.433$), IL-6 (zonulin – $p < 0.001$, $rs = 0.645$; ET – $p < 0.001$, $rs = 0.841$), IL-17 (zonulin – $p < 0.001$, $rs = 0.532$; ET – $p = 0.009$, $rs = 0.363$), IFN-γ (zonulin – $p < 0.001$, $rs = 0.516$; intestinal ET – $p = 0.037$, $rs = 0.292$) and a decrease in the level of IL-10 (zonulin – $p < 0.001$, $rs = -0.556$; ET – $p = 0.001$, $rs = -0.439$). The correlations found ranged from weak to strong according to the Chaddock scale. Other studies have also found positive correlations of zonulin levels with IL-6 [15; 16], CRP [16], TNF-α [17]. The release of proinflammatory cytokines by adipose tissue may begin in response to an increase in circulating ET levels [18]. Выявленные корреляции имели от слабой до высокой тесноту связи по шкале Чеддока. В других исследованиях также были выявлены положительные корреляции уровня зонулина с IL-6 [15; 16], СРБ [16], TNF-α [17]. According to previous studies, the level of zonulin [15] and intestinal ET [19] positively correlated with LDL (zonulin – $p < 0.001$, $rs = 0.674$; ET – $p < 0.001$, $rs = 0.734$) and negatively with HDL (zonulin – $p < 0.001$, $rs = -0.537$; ET – $p < 0.001$, $rs = -0.591$), which was also revealed in our study. When the level of ET increases, it is likely that it is deposited in the "HDL+ET" complex (LDL is represented in the blood circulation) [12]. A study by Zhang et al. suggested that zonulin increases adipose tissue via the endocannabinoid pathway by increasing intestinal wall permeability and subsequently developing dyslipidemia [20].

Conclusions

Severe bronchial asthma (BA) in combination with obesity is characterized by certain features – later onset, lack of BA control in most patients, significantly lower FVC, FEV1, FEV1 / FVC, standard sensitization profile, higher levels of proinflammatory cytokines (TNF-α, IL-6, IFN-γ, IL-17), CRP, fecal zonulin, intestinal ET, low IL-10 levels. The most common concomitant disease in this group of patients was arterial hypertension. In patients with severe asthma combined with obesity, positive correlations were obtained between the levels of fecal zonulin and intestinal ET, indicating a relationship between these two indicators.

When conducting a correlation analysis in this group of patients with an increase in the level of fecal zonulin and intestinal ET, an increase in the level of CRPhs, TNF-α, IL-6, IFN-γ, IL-17, BMI, WC, HC, WC/HC, LDL, an increase in the frequency of uncontrolled asthma and a decrease in the level of IL-10, FEV1, AST test, HDL were observed. The obtained results allow us to speak about the existence of a clinical complex "severe bronchial asthma – obesity – intestinal endotoxemia and increased intestinal permeability", which is formed through the "intestine – lung" axis and is characterized by the predominance of proinflammatory markers, increased intestinal ET and fecal zonulin levels, and reduced external respiratory function.

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LITERATURE REVIEW

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MEDITERRANEAN DIET AS AN ELEMENT OF TREATMENT AND PREVENTION OF CARDIOVASCULAR DISEASES

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СРЕДИЗЕМНОМОРСКАЯ ДИЕТА КАК ЭЛЕМЕНТ ЛЕЧЕНИЯ И ПРОФИЛАКТИКИ КАРДИОВАСКУЛЯРНЫХ ЗАБОЛЕВАНИЙ

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Currently, the issues of treatment and prevention of cardiovascular diseases are still relevant, as cardiovascular pathology remains one of the leading causes of disability and mortality in all developed countries of the world. In the Russian Federation there is a high incidence of the diseases of the circulatory system, so they have the top priority among health problems, despite a slight decrease in morbidity in recent years. The main purpose of this review is to study the experience of applying the Mediterranean diet and its components in therapy and prevention of cardiovascular pathology. Research method: we searched electronic databases PubMed, Scopus, Web of Science, MedLine, Science Direct and eLIBRARY.RU using the following terms: "Mediterranean diet", "cardiovascular diseases", "prevention of cardiovascular diseases", "diet therapy of cardiovascular diseases". On the basis of numerous world clinical studies analysis, it can be assumed that the Mediterranean diet is one of the most reliable and well-studied in terms of prevention of cardiovascular pathology. The aim of this review is to draw the attention of the medical community to such a long-known, extensively studied, scientifically confirmed, accessible and simple way of rationalizing daily nutrition as the consumption of elements of the Mediterranean diet in the daily one. Further wide informing of patients about this way of nutrition from different specialists (general practitioners, cardiologists, nutritionists, gerontologists and others) is required.
Keywords. Mediterranean diet; cardiovascular diseases; treatment of cardiovascular diseases; diet Therapy of arterial hypertension; prevention of cardiovascular pathologies.

В настоящее время вопросы лечения и профилактики сердечно-сосудистых заболеваний не потеряли своей актуальности, так как кардиоваскулярная патология занимает лидирующие позиции среди причин утраты трудоспособности и смертности населения во всех развитых странах мира. В Российской Федерации болезни системы кровообращения, несмотря на некоторое снижение заболеваемости в последние годы, также имеют высокую распространенность, поэтому являются приоритетными проблемами здравоохранения. Основной целью данного обзора является изучение опыта применения средиземноморской диеты и ее компонентов в терапии и профилактике кардиоваскулярной патологии. Был выполнен поиск в электронных базах данных PubMed, Scopus, Web of Science, MedLine, Science Direct и eLIBRARY.RU на основе следующих терминов: «средиземноморская диета», «кардиоваскулярные заболевания», «профилактика сердечно-сосудистых заболеваний», «диетотерапия сердечно-сосудистых заболеваний». Анализ множества мировых клинических исследований дает возможность предположить, что средиземноморская диета является одной из наиболее достоверных и изученных в плане предотвращения сердечно-сосудистой патологии. Обзор служит целью привлечения внимания медицинского сообщества к такому давно известному, многосторонне изученному, научно подтвержденному, доступному и простому способу рационализации повседневного питания, как включение элементов средиземноморской диеты в рацион. Необходимо дальнейшее широкое информирование пациентов об этом способе питания со стороны врачей разного профиля (терапевтов, кардиологов, врачей общей практики, диетологов, нутрициологов, геронтологов и других).
Ключевые слова. Средиземноморская диета, кардиоваскулярные заболевания, лечение кардиоваскулярных заболеваний, диетотерапия сердечно-сосудистых заболеваний, профилактика кардиоваскулярных патологий.

INTRODUCTION

Prevention and comprehensive treatment of cardiovascular pathology, in addition to drug therapy, should include mandatory modification of lifestyle and nutrition. According to the National Health and Nutrition Examination Surveys, disturbances in habitual eating patterns have been associated with the development of metabolic and cardiac pathologies. Among them, the most significant were: excessive sodium consumption, a reduction in the amount of nuts and foods rich in omega-3 fatty acids in the daily diet, frequent consumption of processed meat, a small amount of vegetables and fruit in the diet, and regular consumption of artificially sweetened beverages. It has been proven that refined carbohydrates can "displace" more nutritious and healthy foods from the diet [1]. Due to the high role of alimentary factors as triggers of the development of cardiovascular pathology, in different years, Russian and foreign authors have proposed many different options for corrective nutrition [2]. They share many common principles, the main ones are reducing excess consumption of processed foods, using fresh whole ingredients, limiting consumption of foods with high amounts of sugar, and eliminating fast food from the diet [3].

The Mediterranean diet is one of the most studied and proven types of modern therapeutic nutrition in terms of cardioprotection [4]. It was formulated in the 1950s in the Seven Countries study, which for the first time identified the paradoxical fact that among the poor population of Mediterranean countries, which consumes a fairly large amount of fat in their daily diet, there was a low mortality rate from cardiovascular diseases, which served as an impetus for studying their diet and the possibility of using its components in the treatment (and prevention among risk groups) of cardiac pathology [5]. This type of diet is not based on calorie restriction, but rather on the consumption of a certain list of recommended foods, mainly of plant origin, rich in polyunsaturated fatty acids and fiber, olive oil, milk, cheese and eggs, weekly inclusion of seafood and lean meat in the diet and moderate consumption of wine, as well as limiting the amount of red meat, saturated fats and flour products in the diet [6; 7].

The main objective of this review is to study the experience of using the Mediterranean diet and its components in the treatment and prevention of cardiovascular pathology.

REVIEW OF MAIN COMPONENTS OF MEDITERRANEAN DIET AND THEIR ROLE IN PREVENTION OF CARDIOVASCULAR DISEASES

If we analyze the role of individual components of the Mediterranean diet, we should note the special importance of eating olive oil and nuts, which in a number of studies have shown a reliable effect in reducing the risk of cardiovascular events [8]. Olive oil is the main source of fat in the Mediterranean diet. The broad spectrum of

antiatherogenic effects associated with olive oil consumption may help explain the low cardiovascular mortality rate in patients with this diet. The benefits of olive oil consumption are not limited to just lowering LDL cholesterol. Olive oil has been shown to have positive effects on inflammation, oxidative damage, endothelial dysfunction, blood pressure, thrombosis, and carbohydrate metabolism [8].

Eating nuts also has a beneficial effect on the functioning of many systems and organs, including the cardiovascular system. Due to the unique profile of fatty acids contained in nuts and their derivatives (peanut butter, etc.), the level of total cholesterol and low-density lipoprotein cholesterol was significantly reduced, and the ratio of low- and high-density lipoproteins was improved. In this regard, the likelihood of developing atherosclerosis of blood vessels, including coronary ones, is significantly reduced, which, in turn, prevents the occurrence of cardiovascular events [9].

Dairy products are also important components of the Mediterranean diet. Their role continues to be debated, and the effect of fresh milk on the human body, which changes with age, is not fully understood. However, based on the results of recent large randomized controlled trials, it can be said that the positive effects outweigh the negative ones [9]. There is evidence that cheese consumption is associated with a reduced risk of cardiovascular disease. This may be related to the latter's ability to reduce LDL levels [10]. However, the data presented in the described studies is currently quite scarce, and the question of the influence of dairy products on the cardiovascular system remains open and requires new scientific research.

Products based on grain crops have been one of the main components of the human diet since ancient times. Dietary guidelines strongly recommend the inclusion of whole grains in the diet of patients of all ages, as evidence has grown in recent years that whole grains and whole grain-based products have the ability to improve many parameters of human health beyond simply providing energy and nutrients [11]. One study also found that high whole grain consumption reduced the risk of cardiovascular disease compared to those who consumed grains in insufficient quantities. At the same time, it was identified that people who consumed refined grain products did not have a change in the risk of developing cardiovascular pathology [12].

It is important to note the beneficial properties of fruits and vegetables as the main elements of the Mediterranean diet. Numerous studies have accumulated to show their effectiveness in reducing cardiovascular risk [13; 14]. The advantage of these products also lies in the fact that they are quite accessible to the population of most countries, including residents of the Russian Federation. The following vegetables and fruits have shown and proven the greatest effectiveness: apple, avocado, pomegranate, grapes. The proposed mechanism for risk reduction is through

protection of the vascular endothelium, modulation of blood pressure, reduction of oxidative stress and reduction of chronic inflammation [15].

Another component of the Mediterranean diet that has a cardioprotective effect is table red wine, taken in moderation, no more than two glasses a day. The term "French paradox" was coined in 1992 to describe the relatively low incidence of cardiovascular disease in French people despite their relatively high dietary intake of saturated fat. This paradox could be explained by the moderate consumption of natural red grape wine, which was popular among the French. Later, through several clinical studies, it was established that wine has multiple effects on all phases of the atherosclerotic process – from atherogenesis to plaque rupture and vascular occlusion [16–18].

Having considered all the main components of the Mediterranean diet, it is important to note that, despite the proven role of each product and the substances it contains in preventing the development of cardiac pathology, the greatest preventive effect of the diet is achieved precisely due to their complex action and long-term adherence to them in the diet, especially in combination with a healthy lifestyle [19–21].

The role of the Mediterranean diet in the treatment and prevention of circulatory diseases is reflected in a number of large studies [22–26]. One of the most well-known studies on the Mediterranean diet is the PREDIMED project. A 2003 study included 7,447 participants aged 55 to 80 years, 43 % men and 57 % women, who had risk factors for cardiovascular disease, namely dyslipidemia, obesity, type 2 diabetes, and a family history of cardiovascular disease. According to the results of the work, with adherence to the Mediterranean type of diet, the risk of development, progression and mortality from cardiovascular pathology is significantly reduced, the effect of the diet was comparable to the therapy of arterial hypertension with ACE inhibitors and beta-blockers.

The SUN (Seguimiento Universidad de Navarra (University of Navarra)) project presented a prospective cohort study conducted in Spain among university graduates [27]. The study followed 13,609 participants (60 % women, mean age 38 years) without cardiovascular disease (CVD) for 4.9 years. Respondents were given a 136-item questionnaire on the frequency of consumption of various foods, assessed on a 9-point scale. During the observation period, 100 cases of cardiovascular diseases were registered. In multivariate analyses, participants with the highest adherence to the Mediterranean diet (score > 6) demonstrated lower cardiovascular risk (odds ratio = 0.41, 95 % confidence interval [CI]: 0.18–0.95) compared with those with the lowest score (< 3). For each 2-point increase, the adjusted hazard ratios were 0.80 (95 % CI: 0.62–1.02) for total CVD and 0.74 (CI: 0.55–0.99) for coronary heart disease. This study demonstrated how adherence to Mediterranean diet foods reduces the risk of cardiovascular disease.

The EPIC Norfolk (European Prospective Investigation of Cancer) study, con-

ducted in the UK on 23,902 participants over 12.2 years, also proved the role of the Mediterranean diet in preventing mortality from cardiovascular disease [28]. Based on the obtained results, it was suggested that overall cardiovascular morbidity and mortality may be reduced by increasing adherence to the Mediterranean diet.

Data from several studies have convincingly proven [29–32] that rational nutrition is a key factor in promoting a healthy lifestyle and preventing many chronic diseases. In particular, a large number of studies have established the protective effect of the Mediterranean diet against a number of chronic diseases, including diabetes, cardiovascular disease, cancer, aging disorders, as well as against overall mortality.

Currently, the role of nutritionology as a system of knowledge about proper nutrition for a patient who does not have a clinically developed picture of the disease, but has risk factors, including cardiovascular pathology, is increasing [33]. Modern clinical studies confirm that elements of the Mediterranean diet have a cardioprotective effect and are capable of exerting a positive therapeutic and preventive effect on cardiovascular pathology [34]. The Mediterranean diet is recommended and included in the list of mandatory non-drug recommendations in Russia and other countries [35; 36]. However, there remains insufficient awareness among both the population and doctors about the benefits of this type of diet for reducing the risk of developing and progressing cardiovascular diseases [37; 38].

Conclusions

Based on numerous global clinical studies, it can be assumed that the Mediterranean diet is one of the most reliable and studied in terms of preventing cardiovascular pathology. Many authors have confirmed (in the PubMed database for the period from 2020 to May 2024 alone, there are 5649 publications for the query mediterranean diet, 672 for the query mediterranean diet and hypertension, and 836 for the query mediterranean diet and cardiovascular prevention) that the Mediterranean diet reduces the risks of developing coronary heart disease and heart failure, along with a reduction in overall mortality from cardiovascular disease, which once again emphasizes the relevance of this literature review.

The use of elements of the Mediterranean diet in the general scheme of measures for the prevention and treatment of cardiovascular pathology shows a positive effect. Recognition of the health benefits of the Mediterranean diet has made its widespread adoption an urgent priority. Despite the difficulties associated with adherence to this diet, such as the financial capabilities of the population, the eating habits and preferences of certain peoples and social groups, the unavailability of some products on a permanent basis, the Mediterranean diet can be called one of the most convenient of the therapeutic diets with a certain plasticity, where it is not necessary to completely change your diet, but only to follow the principles of choosing products.

This review serves the purpose of drawing the attention of the medical community to such a long-known, comprehensively studied, scientifically proven, accessible and simple way of rationalizing everyday nutrition as the inclusion of elements of the Mediterranean diet in the diet. Further widespread information of patients about this way of nutrition is necessary from doctors of various profiles (therapists, cardiologists, general practitioners, dietitians, nutritionists, gerontologists and others).

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INFLUENCE OF INTESTINAL MICROBIOTA ON THE METABOLISM OF MAIN CARDIOTROPIC DRUGS

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ВЛИЯНИЕ МИКРОБИОТЫ КИШЕЧНИКА НА МЕТАБОЛИЗМ ОСНОВНЫХ КАРДИОТРОПНЫХ ПРЕПАРАТОВ

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The intestinal microbiota is one of the most important pathogenetic links in the development of cardiovascular diseases. Every year the world scientific community finds new interactions at the level of signaling molecules, metabolites and microorganisms, identifying more and more patterns and cause-and-effect relationships which indicate the commonality of the intestinal microbiota (GM) and cardiovascular diseases. The state of the host's intestinal community, its qualitative and quantitative composition, directly and indirectly affects the fundamental pathogenetic mechanisms of the development of cardiovascular diseases.

Despite the fact that there are scientifically based methods of treatment, cardiovascular diseases remain the leading cause of death in the world. This phenomenon is partly due to wide variations in individual response to cardiovascular drugs. The pharmacological effects of cardiotropic drugs are quite different even within groups of patients comparable in age and gender. Every year intestinal microbiota is more and more evident to be responsible for this intraspecific variability.

Gut microbes influence drug metabolism in several pharmacokinetic ways, and conversely, drugs can have significant effects on the microbiome and therefore pharmacodynamic processes. Drugs can alter the gut microenvironment and microbial metabolism, influence bacterial growth, thereby changing the composition and functions of the microbial community.

One of the most important functions of GM, related to “intestinal-cardiovascular system”, is participation in the metabolism of major cardiotropic medications, such as digoxin, statins, ezetimibe, antithrombotic drugs, calcium channel blockers (CCBs), beta blockers (BB), gliflozins and inhibitors of the renin-angiotensin-aldosterone system (RAAS).

Keywords. Gut microbiota, alpha diversity, beta diversity, short-chain fatty acids, statins, ezetimibe, gliflozins, *Bacteroides*, *Firmicutes*.

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Микробиота кишечника является одним из важнейших патогенетических звеньев в развитии сердечно-сосудистых заболеваний. С каждым годом научное мировое сообщество находит новые взаимодействия на уровне сигнальных молекул, метаболитов и микроорганизмов, выявляя все больше закономерностей и причинно-следственных связей, указывающих на общность микробиоты кишечника и сердечно-сосудистых заболеваний. Состояние кишечного сообщества хозяина, его качественный и количественный состав напрямую и опосредованно влияет на фундаментальные патогенетические механизмы развития кардиоваскулярных заболеваний.

Несмотря на существование научно обоснованных методов лечения, сердечно-сосудистые заболевания остаются ведущей причиной смерти во всем мире. Частично этот феномен обусловлен широкими индивидуальными различиями в реакции на сердечно-сосудистые препараты. Фармакологические эффекты кардиотропных препаратов проявляются по-разному у людей, страдающих от сердечно-сосудистых заболеваний, даже внутри сопоставимых по возрасту и полу групп. С каждым годом появляется все больше данных о том, что за эту внутривидовую изменчивость ответственна микробиота кишечника.

Кишечные микробы влияют на метаболизм лекарств посредством нескольких фармакокинетических путей, и наоборот – лекарства могут оказывать значимое влияние на микробиом и, следовательно, на фармакодинамические процессы. Лекарственные препараты могут изменять микроокружение кишечника, микробный метаболизм и влиять на рост бактерий, тем самым изменяя состав и функции микробного сообщества.

Одной из важнейших функций микробиоты кишечника, представляющей интерес в плоскости «кишечник – сердечно-сосудистая система», является участие в метаболизме основных кардиотропных препаратов, таких как дигоксин, статины, эзетемиб, антитромботические препараты, блокаторы кальциевых каналов (БКК), бета-блокаторы (ББ), глифлозины и ингибиторы ренин-ангиотензин-альдостероновой системы (РААС).

Ключевые слова. Микробиота кишечника, альфа-разнообразие, бета-разнообразие, короткоцепочечные жирные кислоты, статины, эзетимиб, глифлозины, *Bacteroides*, *Firmicutes*.

INTRODUCTION

Despite the existence of evidence-based treatments, cardiovascular disease remains the leading cause of death worldwide. This phenomenon is due in part to wide individual differences in response to cardiovascular drugs. For example, genetic variations in metabolic enzymes such as cytochrome P-450 have been shown to alter the metabolism, transport, and even the site of drug application and can be used to predict individual responses, personalizing drug therapy [1; 2].

The pharmacological effects of cardiotropic drugs manifest themselves differently in people suffering from cardiovascular diseases, even within age- and gender-matched groups. Every year, more and more data are emerging that the intestinal microbiota (IM) is responsible for this intraspecific variability.

Gut microbes influence drug metabolism through several well-known pharmacokinetic pathways, including the production of microbial enzymes that transform drug molecules, the production of microbial metabolites that interfere with drug metabolism, the alteration of inflammatory pathways that alter host gene expression, and the modification of host genes or enzymes that metabolize drugs [3]. Conversely, drugs can have significant effects on the microbiome and, consequently, on pharmacodynamic processes. Drugs can alter the gut microenvironment, alter microbial metabolism, and influence bacterial growth, thereby altering the composition and function of the microbial community.

One of the most important functions of MC, which is of interest in the "gut – cardiovascular system" plane, is participation in the metabolism of the main cardiotropic drugs, such as digoxin, statins, ezetimibe, antiplatelet agents, anticoagulants, calcium channel blockers (CCB), beta-blockers (BB), gliflozins and renin-angiotensin-aldosterone system (RAAS) inhibitors [4–6].

ACETYLSALICYLIC ACID

A large number of studies have found that antibiotic use can alter the pharmacological effects of aspirin. These changes are due to the ability of the gut microbiota to metabolize acetylsalicylic acid, converting it into an intermediate substance, salicylic acid. The first studies [7] showed a connection between the increase in the antithrombotic activity of aspirin in rats and the intake of ampicillin. Limiting the intestinal microbial landscape changed the pharmacokinetics of acetylsalicylic acid. Antibacterial therapy significantly reduced the activity of intestinal microbial metabolism and thereby prolonged the bleeding time in rats receiving aspirin. These data suggest that concomitant use of antibiotics and antiplatelet agents may mutually modulate metabolism and pharmacokinetics by suppressing the metabolic activity of intestinal microbiota, which may enhance therapeutic efficacy. Another study found that rats given aspirin and amoxicillin had reduced counts *of Helicobacter pylori* and *Prevotella copri*. These parameters affected metabolic activity by reducing the rate and amount of aspirin converted to the metabolite salicylic acid [8], which in turn led to increased plasma aspirin concentrations. In 2020, Zhao et al. found that *Lysinibacillus sphaericus* affected the bioavailability of aspirin by destroying it [9]. Germ-free mice fed *L. spaericus* had lower plasma aspirin levels than controls. The study [10] found that the type of medication taken has a much greater impact on the gut microbiome than the amount of medication taken. NSAIDs, particularly aspirin, were particularly associated with distinct microbial populations. Four operational taxonomic units (OTUs) (*Prevotella, Bacteroides, Ruminococcaceae, Barnesiella*) distinguished aspirin users from nonusers.

CLOPIDOGREL

Clopidogrel was nominally associated with multiple gut microbiota profiles in the United Kingdom Twins cohort, suggesting potential interactions between clopidogrel and the gut microbiome [11]. In another large population metagenomic analysis, clopidogrel was classified as a class of platelet inhibitors that was associated with increased microbial diversity. Finally, metabolomic analysis of plasma metabotypes (groups of metabolically similar metabolites) revealed a potential role of dysbiotic MC in inducing adverse drug events causing high platelet reactivity, which hinders the achievement of therapeutic outcome. Plasma metabotypes contained metabolites associated with dysbiotic MC, such as choline, trimethylamine, and L-phenylalanine. Although high platelet reactivity during treatment is multifactorial, it is associated with gut microbiome dysbiosis [12].

STATINS

The efficacy of statins has been demonstrated in numerous randomized trials, but there is evidence that their use increases the risk of developing type 2 diabetes [13]. Type

2 diabetes is a multifactorial disease, and recent studies have highlighted the importance of the gut microbiome in its development [14]. A study investigating statin treatment in a mouse model revealed profound changes in the gut microbial composition. The composition of the microbial landscape of the microbiota was altered, increasing the proportion of *Bacteroides* and decreasing the presence of the gram-positive phylum *Firmicutes*. This shifts the microbiota toward a higher energy production capacity (from butyrate to acetate, lactate, and succinate), similar to what is observed in MC associated with diet-induced obesity [15]. Statin therapy, in addition to its primary effect of inhibiting HMG-CoA reductase, is supported by a number of pleiotropic properties. On the one hand, there is a growing literature demonstrating a reduced risk of bacterial infection in patients taking statins. Retrospective studies have shown that statins can reduce mortality in patients with pneumonia and sepsis, and reduce the risk of postoperative infections [16]. One study in hospitalized patients found a reduced risk of developing Clostridial C. *difficile* (a member of the *Firmicutes* phylum) infection in those taking statins [17]. Atorvastatin increased bacterial diversity in rats fed a high-fat diet compared with levels observed in controls fed a normal diet [18]. Conversely, MC has been shown to influence the cholesterol-lowering effect of atorvastatin. In antibiotic-induced microbiome-depleted mice, the lipid-lowering effect of atorvastatin was reduced and the expression of genes regulating cholesterol levels in the liver and intestine (*Ldlr, Srebp2, and Npc111*) was altered [19]. In addition to the effects on cholesterol levels, mouse models show changes in intestinal bile acid levels that the authors suggest are related to MC. Bacteria are required to enzymatically catalyze bile acid deconjugation so that bile can be passively absorbed from the intestine into the systemic circulation [20]. In hypercholesterolemic humans treated with atorvastatin, the drug helped restore the relative abundance of several dominant and important taxa, such as *Faecalibacterium prausnitzi* and *Akkermansia muciniphila*, which were significantly reduced at baseline in hypercholesterolemic individuals [21]. Incubation of lovastatin with human and rat fecalase preparations revealed four metabolites: the demethylbutyryl metabolite, the hydroxylated metabolite, the active metabolite of the hydroxy acid M8, and the hydroxylated M8 [22]. In rats concomitantly treated with antibiotics, the systemic concentration of the active metabolite M8 was lower. These results suggest that gut microbes may be involved in the metabolism of lovastatin, and antibiotic treatment may reduce the biotransformation of orally administered lovastatin by gut bacteria. In a mouse study, rosuvastatin treatment significantly affected bile acid metabolism [23]. In rats, dysbiosis was associated with decreased efficacy of rosuvastatin, as reflected by a smaller reduction in blood LDL levels [24]. These studies showed that rosuvastatin affects the microbial composition of the gut, prompting further studies in humans. The first study found that the efficacy of rosuvastatin was associated with microbial variations in the community composition. Sixty-four patients with hyperlipidemia were treated with rosuvastatin (10 mg / day) and divided into rosuvastatin responders and non-respon-

ders based on blood lipid levels above or below normal. The gut microbiome from collected feces differed significantly, with rosuvastatin responders having higher abundance of *Firmicutes*, butyrate-producing bacteria such as *Ruminococcaceae, Lachnospiraceae, Clostridiaceae*, and lower abundance of *Bacteroidetes* [25]. The second study presents conflicting data, as faecal samples from a randomized control trial of 66 participants receiving rosuvastatin (20 mg / day) or placebo did not reveal any significant changes in microbial composition. However, changes in the expression of microbial genes encoding proteins associated with the choline / betaine – TMA pathway were detected, suggesting that rosuvastatin affects gut microbial metabolism [26]. In a systematic evaluation of small molecules, Kaddurah-Daouk et al. examined the correlation between baseline metabolite levels and therapeutic efficacy of simvastatin in 100 subjects to predict response to statin treatment [27]. The results indicate that microbial-derived secondary bile acids, including taurocholic and glycocholic acids, as well as coprostanol, can predict the LDL-lowering effect of simvastatin, indicating a microbial effect on the gut. Coprostanol, used as a biomarker for the presence of human feces, is produced by intestinal bacteria by hydroxylation of cholesterol [28]. Results suggest that patients with higher levels of coprostanol-producing bacteria before treatment will respond better to statins. In addition, simvastatin appears to have antibacterial activity against many Gram-positive bacteria such as staphylococcus and streptococcus, making the drug a good candidate for future studies as an antimicrobial resistance breaker [29].

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Comparative use of captopril and lisinopril in an experiment on mice allowed us to establish that animals that received captopril for a week had a significant decrease in body weight. Weight loss is associated with changes in their intestinal microbiome with a predominance of the anaerobic metabolic pathway. In the work [30], captopril therapy decreased vascular wall permeability, reduced fibrosis, caused reverse remodeling of the muscle layer, and even partially restored the length of intestinal epithelial villi in rats with spontaneous and angiotensin-II-induced arterial hypertension. In animal experiments, benazepril increases the species diversity of microflora, bringing its composition closer to the normoflora, in contrast to the flora characteristic of "hypertensive" rats. However, enalapril therapy in the experiment did not reveal reliable differences in the intestinal microbiome of rats, but at the same time, a decrease in the concentration of the toxic metabolite TMAO, which is associated with an increase in cardiovascular risk, was recorded in blood samples. Captopril was shown to modulate the intestinal microbiota in rats. Another study in rats revealed an increase in the number of bacteria during captopril treatment even after its discontinuation [31]. The authors suggest that these results demonstrate that long-term exposure to captopril is associated with changes in MC. In addition to the long-term effect of captopril, another study in rats shows that maternal treatment with this drug reduces hypertension in male offspring by altering microflora, particularly the orders *Clostridiales* and *Erysipelotrichales* [32]. Thus, captopril has been shown to affect MC with

long-lasting and potentially transgenerational effects. Similar changes in MC were observed in a rat study with benazepril, where the authors noted changes in the ratio of *Firmicutes* to *Bacteroidetes*, as well as *Coccus* to *Bacillus* [33].

ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin receptor blockers as a class have evidence of effects on MC. Telmisartan reduced colonic inflammation in rats with colitis [34]. The finding that telmisartan reduced colonic inflammation led to investigation of the drug's effects on atherosclerosis [35]. In mice, a high-fat diet was associated with lower colonic microbial diversity. However, telmisartan treatment restored the induced dysbiotic *Firmicutes* / *Bacteroidetes* ratio, leading to subsequent beneficial effects. In fact, telmisartan was more effective than the probiotic *Lactobacillus rhamnosus* in altering MC. Candesartan and losartan treatment in hypertensive mice similarly restored the altered *Firmicutes* / *Bacteroidetes* ratio and protected against hypertension-induced intestinal pathophysiological changes [36]. Irbesartan improves stress-induced microbiota changes. Stress markedly reduces the percentage of faecal taxa, whereas irbesartan treatment corrects these changes in community structure [37]. In contrast, olmesartan has a unique side effect called sprue-like enteropathy, which is characterized by chronic diarrhea, weight loss, and biopsy revealing villous atrophy and mucosal inflammation. In patients followed at the Mayo Clinic, discontinuation of olmesartan improved symptoms and resulted in histologic recovery [38]. It is unclear why the gastrointestinal effects of olmesartan differ from those of other ARBs such as telmisartan, candesartan, losartan, and irbesartan, which have beneficial effects on MC.

CALCIUM CHANNEL BLOCKERS

Amlodipine is a dihydropyridine calcium channel blocker that is commonly prescribed for the treatment of hypertension and coronary heart disease. A study by Yoo et al. reported the metabolism of amlodipine upon incubation with human fecalase, indicating the involvement of gut microbiota in amlodipine metabolism [39]. Unchanged amlodipine was reduced by 9 % upon 24-hour incubation with human fecalase. In addition, it was found that antibiotic administration can increase the bioavailability of amlodipine in rats. At ampicillin doses of 10 and 20 mg/kg, the concentration of amlodipine in plasma increased by 42 and 133 %, compared with the corresponding data of the control group. Amlodipine itself also has bactericidal properties. Of the 504 bacterial strains tested, amlodipine had varying degrees of antimicrobial activity, most notably against *Staphylococcus aureus, Vibrio cholerae, Vibrio parahemolyticus*, *Shigella* species, *Salmonella* species, and *Bacillus* species [40]. Song et al reported a reduction in gastrointestinal side effects with amlodipine plus probiotics. Amlodipine, like bacterial dysbiosis, is associated with diarrhea. The known side effect and the association between dysbiosis and diarrhea prompted the authors to investigate amlodipine and probiotics in a rat model. The probiotic mixture alleviated intestinal complications and induced changes in MC composition in rats. An et al. investigated what metabolite changes occurred due to induced changes in microbiota composition in mice treated with amlodipine compared

to amlodipine and probiotics [41]. The lipid metabolic profile was altered in mice treated with amlodipine, with cholesterol, phosphatidylcholines, and triglycerides with a high number of double bonds increased in total. The amlodipine group also showed a reduction in triglycerides with few double bonds. The authors believed that amlodipine alters the composition and balance of metabolites produced by bacteria that ultimately contribute to gastrointestinal side effects. Similarly, nifedipine and nimodipine, the calcium channel blockers, have been investigated for antimicrobial properties. Due to the high permeability of nimodipine through the gastrointestinal tract, the study examined its bacterial degradation in dilutions with human feces. Using colonic bacteria as a model, Vertzoni et al. observed rapid degradation of nimodipine in feces [42]. More recently, Zhang et al. demonstrated that gut microbes are involved in the metabolism of nifedipine *in vitro.* After 24-hour incubation in rat fecal suspensions, nifedipine concentrations decreased by more than 50 %, indicating that gut microbes are involved in the metabolism and biotransformation of nifedipine and nimodipine.

AMIODARONE

Organ toxicity, induced by amiodarone, is potentially serious due to the long half-life of the drug, so its bioavailability is of particular importance. Amiodarone has been shown to affect typical strains of intestinal bacteria. Co-administration of the probiotic *Escherichia coli* Nissle 1917 demonstrated an increase in the bioavailability of amiodarone (43 %) and its metabolite N-desethylamiodarone in rats [43]. The authors suggest that the modulation of amiodarone metabolism is associated with the administration of *E. coli* Nissle 1917, resulting in better absorption of the drug in the gastrointestinal tract. Another study showed that amiodarone has bactericidal activity *in vitro* against pathogenic human strains such as *S. epidermidis*, *E. coli*, and *Klebsiella* [44]. Both studies reflect that amiodarone therapy has a microbiome component, albeit through different mechanisms.

BETABLOCKERS

Metoprolol is the most commonly prescribed beta-adrenergic blocker used to treat cardiovascular diseases including coronary artery disease, hypertension and heart failure. Metoprolol is metabolized via a saturable pathway, namely hepatic cytochrome 2D6 (CYP2D6). This drug is primarily metabolized to O-desmethylmetoprolol and α-hydroxymetoprolol. Approximately 85 % of metoprolol and related metabolites are excreted in the urine, making it an ideal target for monitoring. Brocker et al. analyzed the urine of patients taking metoprolol using metabolomics data. They found increased levels of methyluric acid, hydroxyhippuric acid, and hippuric acid in the urine of hypertensive patients after oral metoprolol administration. These three compounds are considered to be gut microbiome metabolites [45]. Hippuric acid is formed by the conjugation of glycine and benzoic acid by gut microbial metabolism, and hydroxyhippuric acid is a microbial end product, both of which arise from the metabolism of polyphenols in the gut microbiota. These compounds reflect the composition of the gut microbiota [46]. This indicates that long-term metoprolol treatment may affect the microbial composition and diversity of the gastrointestinal tract.

Moreover, metagenomic analysis of feces samples from patients with atherosclerotic cardiovascular disease showed that metoprolol treatment was positively correlated with changes in the metagenomic linkage group (MLG) [47]. Therefore, the drug may affect the microbiome by affecting gene expression in the gut microbiome. As mentioned above, metoprolol therapy appears to alter the gut microbiome, indicating that metoprolol may directly or indirectly influence the composition of the gut microbiota.

EZETEMIBE

Ezetimibe is a selective inhibitor of intestinal cholesterol absorption that acts on the brush border of the small intestinal mucosa, specifically binds to the C1-like Niemann-Pick transporter 1 on the intestinal mucosa and selectively inhibits the absorption of exogenous cholesterol. This drug is currently the second line in the treatment of dyslipidemias accompanied by elevated LDL levels [48]. In a study by Jin Jin et al., a group of mice were exposed to a high-fat diet for 20 weeks with and without ezetimibe. Ezetimibe intervention significantly reduced serum TC and HDL-cholesterol levels. In addition, after long-term treatment with the cholesterol absorption inhibitor, the alpha diversity of the gut microbiota was significantly reduced. Ezetimibe caused changes only in some low-abundance bacteria, which was expressed as a decrease in Proteobacteria and *Desulfovibrio* and an increase in *Bacteroides* [49].

GLIFLOZINS

The SGLT-2 class inhibits glucose reabsorption in the proximal convoluted tubule of the nephron, resulting in glucosuria and concomitant natriuresis. In addition to its well-known effects on glucose control in patients with type 2 diabetes, it has been shown to improve many conditions such as NAFLD, CHF independent of EF, and chronic kidney disease. In mouse studies, dapagliflozin, empagliflozin, and canagliflozin have shown beneficial effects on the microbiota, regardless of the underlying disease that is the primary indication for the drug [50–53]. The researchers used different categories of rats, ranging from mice fed a high-carbohydrate diet to animals with nephropathy, and this heterogeneity made it difficult to analyze the effects of SGLT-2 on the microbiota. In other animal studies, dapagliflozin treatment altered the microbial diversity in type 2 diabetic mice, particularly *Bacteroidetes* and *Proteobacteria*. Moreover, the *Firmicutes* to *Bacteroidetes* ratio was significantly lower ($p < 0.05$) in diabetic mice than in controls [54].

In a study [55], empagliflozin significantly altered the structure and composition of gut microbiota in patients with type 2 diabetes and cardiovascular risk factors after three months of treatment: empagliflozin was found to increase levels of short-chain fatty acid-producing bacteria such as *Roseburia, Eubacterium*, and *Faecalibacterium* species and to decrease levels of some harmful bacteria including *Escherichia-Shigella, Bilophila*, and *Hungatella*.

CONCLUSIONS

Knowledge gained from the synthesis of clinical studies demonstrates that the influence of the gut microbiota and its metabolites on the major classes of cardiotrophic drugs continues to be studied in depth. The characteristics of the individ-

ual's gut microbiota can be used as a factor to personalize therapy, directly influencing the choice of dose, a specific drug within a class, or even the class of drugs themselves.

Further studies of specific mechanisms that determine changes in intestinal diversity and biochemical iterations within the "intestinal" pharmacokinetics of the drug are needed. Managing the quantitative and qualitative composition of the intestinal microbiota and its metabolites may become a new therapeutic target and will allow direct and indirect influence on the prognosis of patients with cardiovascular diseases.

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MODERN METHODS OF TREATMENT OF COMPLICATED FORMS OF PILONIDAL CYST

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СОВРЕМЕННЫЕ ПРИНЦИПЫ ЛЕЧЕНИЯ СЛОЖНЫХ ФОРМ ЭПИТЕЛИАЛЬНОГО КОПЧИКОВОГО ХОДА

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There are several theories of the origin of diseases of the epithelial coccygeal tract: empirical, neurogenic, ectodermal and acquired. Most Russian scientists consider this pathology to be congenital, while foreign colleagues believe that it is a consequence of sacrococcygeal area injuries. This pathology is quite common, affecting more than 5 % of the adult population, it also occurs in children and adolescents. This disease decreases the quality of patients` life significantly, affecting all aspects of their life.

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Conservative methods of treatment do not provide a complete cure, since they do not eliminate the causes of the disease. These include sclerotherapy and obliteration of the cavity with silver nitrate or hydrochloric acid. These methods are not used nowadays.
Surgical treatment is the most effective one for this pathology. Surgical intervention, despite its apparent simplicity, turns out to be quite complex, which makes it inaccessible to any general surgeon. Treatment results are often disappointing due to the high incidence of complications after surgery, as well as the long period of activity limitation. Therefore, the resulting rough scar is a cosmetic defect, and the risk of recurrence remains quite high. Studying the literature data, one can see that the authors` opinions concerning surgical tactics for this disease differ. At the moment, there is no single approach and surgical tactic for the treatment of epithelial pilonidal cyst. The problem of creating and introducing new methods of treatment of pilonidal disease remains relevant nowadays.
Keywords. Epithelial coccygeal tract, pilonidal cyst, methods of surgical treatment.

Теорий происхождения заболеваний эпителиального копчикового хода выделяют несколько: эмпирическая, нейрогенная, эктодермальная и приобретенная. Большинство российских ученых считают эту патологию врожденной, в то время как зарубежные коллеги склоняются к мнению, что она является последствием травм крестцово-копчиковой зоны. Данная патология встречается довольно часто, затрагивая более 5 % взрослого населения, в том числе детей и подростков. Данное заболевание существенно ухудшает качество жизни больных, вызывая снижение качества жизни, отражаясь на всех аспектах их жизнедеятельности.
Консервативными методами не достигается положительный результат лечения эпителиального кончикового хода, потому что не устраняется причина заболевания. К консервативным методам относятся склеротерапия и облитерация полости азотнокислым серебром или соляной кислотой, что на сегодняшний день не применяется.
Оперативное лечение является наиболее эффективным методом лечения эпителиального копчикового хода. Хирургическое лечение, невзирая на простоту выполнения, является достаточно скрупулёзным. Высокая частота осложнений после операций и длительный срок нетрудоспособности зачастую разочаровывают хирургов. Поэтому образующийся грубый рубец имеет нежелательный косметический эффект, а вероятность рецидивов остается достаточно высокой. Оценивая литературные данные, можно увидеть, что мнения авторов относительно хирургической тактики при этом заболевании различаются. На данный момент не существует единого подхода к хирургической тактике лечения эпителиального копчикового хода. Проблема создания и внедрения новых методов лечения пилонидальной болезни остается актуальной и в наше время.
Ключевые слова. Эпителиального копчиковый ход, пилонидальная киста, способы оперативного лечения.

INTRODUCTION

Epithelial coccygeal tract (ECT), epithelial coccygeal cyst (ECC) are located in the subcutaneous fat tissue in the intergluteal space. The ECC cavity communicates with the environment through fistula tracts, primary and secondary [1; 2]. Infection in the primary fistula tracts causes inflammation of the ECT and abscess formation [3; 4]. This disease most often develops in young, able-bodied males, whose ages range from 16 to 45 years. The ratio between men and women is 4:1 [2; 4]. According to statistics, the incidence of pilonidal cyst reaches 2 % of all surgical pathology [5]. At the same time, inflammation of the artificial circulation reaches 15 % of the total number of surgical purulent-septic diseases [2; 4; 6]. The most effective method of treating this pathology is surgical removal.

In the mid-19th century, A. Anderson first described the technique of radical excision of artificial circulation within healthy tissues in a letter to the Boston Medical Journal [7]. However, when excising a cyst or pilonidal cyst, a rough and deep postoperative wound is formed, which is why surgeons continue to debate about wound closure. In turn, this leads to the search for various methods of surgical treatment of pilonidal cyst [8]. The incidence of true relapses after radical excision of the pilonidal cyst, according to A.V. Kibalchich, is quite rare (up to 6 %) [9], and 94 % are false relapses caused by infectious complications – hair getting into the wound cavity, the healing of which is complicated by the development of a purulent process. Pilonidal cyst mainly recurs in the area of the intergluteal fold along the midline. The cause of relapses, according to many authors, is the high position of the buttocks, deep intergluteal fold, obesity, and thick hair in this area. Due to the extensive and deep postoperative wound and uneven healing, cavities are formed that contribute to the development of infection and relapse.

All surgical interventions in the treatment of artificial circulation are divided into three main groups: the first group is open: with the help of various dressings and vacuum therapy, the postoperative wound regenerates by secondary tension. The second group is closed: the postoperative wound is sutured tightly (using interrupted sutures or Donati sutures). The third group is semi-open: a drainage tube is installed in the cavity of the postoperative wound or a drainage channel is formed, after which the postoperative wound is sutured (excision of the epithelial-coccygeal passage with Moshkovich sutures) [7].

One of the methods of treating the epithelial-coccygeal tract using vacuum therapy is described by F.P. Benderwald [17]. After excision of the fistula tract, a removable drainage dressing is applied and round-the-clock vacuum therapy is performed with a negative pressure of 125 mm Hg in a constant mode. The dressing is changed every two days. The course of vacuum therapy lasts from 4 to 9 weeks. Vacuum therapy is stopped after complete granulation of the wound, and complete healing of the wound occurs within 9–22 weeks.

The healing of an infected postoperative wound takes quite a long time, and, as a result, after healing, a rough postoperative scar is formed. As a result, most surgeons use a two-stage surgical treatment method for inflammation of the ECT in the acute phase. At the first stage, the abscess is opened, then the abscess cavity is sanitized (which consists of daily rinsing, and water-soluble ointments are introduced into the abscess cavity). After these manipulations, the inflammatory process is stopped, and the patient undergoes radical surgical treatment [19; 20]. Delayed surgical treatment is carried out after five days from the moment of the first stage, and during this period the patient continues to be treated in hospital. The second stage of surgical treatment is performed three months after

the first stage, on a planned basis. Delayed surgical treatment has a number of advantages: first of all, when excising the intergluteal fold, more skin tissue is preserved, and the sutures are applied in such a way as to achieve maximum alignment of the edges of the postoperative wound. Based on data from other researchers [22; 23], the number of relapses caused by suppuration reaches 20 %, which explains the ineffectiveness of this surgical treatment method for suppurating ECC [24].

In the post-Soviet space, a method of surgical treatment is used in which the edges of the postoperative wound are sutured to the bottom. This surgical treatment method involves excision of the ECT and adjacent tissues in a single block. After which the skin edges of the postoperative wound are sutured with interrupted sutures to the sacrococcygeal fascia in such a way that a narrow wound surface remains between the edges of the postoperative wound. There are several methods for performing this operation. The difference between the methods lies in the different ways of suturing the edges of the postoperative wound to the bottom. For example, there is a method where the edges of the postoperative wound are sutured only on both sides [19]. There is also a technique where the postoperative wound is sutured on all sides [26].

Most surgeons are inclined to believe that the postoperative wound should be sutured tightly, using both O-shaped and U-shaped sutures. However, the resulting extensive wound is technically difficult to suture, and even after suturing such a wound, a cavity is formed, which leads to contamination of the wound, which entails a relapse.

The literature also describes methods in which secondary sutures are applied to a granulating postoperative wound. V.Kh. Kosumyan used the Subbotin-Redon wound drainage method, which consists of active aspiration of the exudate accumulating in the wound cavity, and tight suturing of the wound according to Donati. In patients with tension of the wound edges, relaxing skin incisions were made. This method has proven itself to be good, showing high healing results. P. Alberti emphasizes the advantages of using a closed method of surgical treatment using certain improved methods. S.C. Nahas describes the results of treatment of 154 patients, 83 % of whom were aged 11 to 30 years. In 74.7 % of patients, the method of opening and drainage of the epithelial-coccygeal tract was used. The method of excision of the epithelial-coccygeal tract was performed in 25.3 % of cases. In patients who underwent excision of the epithelial-coccygeal tract, a relapse was noted in two cases (5.1 %). When opening and draining the abscess, a relapse was observed in one patient (0.9 %).

In the classification of chronic fistulous forms of ECT, V.I. Pomazkin describes both the anatomical features of the sacrococcygeal region and the gradation by the degree of spread of the inflammatory process to adjacent tissues. He developed a classifica-

tion of chronic fistulous forms of the epithelial coccygeal tract with gradation by three levels of complexity:

I – a single fistula tract with minimal inflammatory infiltrate or its absence with external fistula openings located in the projection of the middle of the intergluteal fold or no more than 3 cm from it with unfavorable anatomical features of the sacrococcygeal region;

IIA – fistula tracts with secondary external fistula openings located at a distance of more than 3 cm from the middle of the intergluteal fold, but not extending beyond the inner slope of the buttocks;

IIB – fistula tracts with secondary external fistula openings located at a distance of more than 3 cm from the middle of the intergluteal fold, but not extending beyond the inner slope of the buttocks in the presence of unfavorable anatomical features;

III – multiple fistula tracts with external openings extending beyond the inner surface of the buttocks, in the presence of pronounced scars and infiltrates around the fistulas [20].

When choosing a method of surgical treatment of complex forms of ECT, preference should be given to those methods in which granulation of the postoperative wound proceeds most favorably, which, in turn, reduces the risk of relapse. It is necessary to perform reconstruction of the anatomy of the sacrococcygeal region: plastic surgery is performed, in which the postoperative wound is sutured [20]. When the inflammatory process is limited or this pathology occurs together with other proctological diseases, it is necessary to perform one-stage or two-stage operations during the period of stagnation of the inflammatory process.

When treating ECC, to reduce the risk of relapse during the preoperative preparation period, it is necessary to take a bacteriological culture from the fistula tract. Subsequently, the microflora is determined, which allows choosing adequate antibiotic therapy with high sensitivity to this microflora. When draining abscesses, it is necessary to wash the fistula tracts and wound cavity daily using bactericidal agent. These manipulations are performed until the inflammatory process is completely relieved, which, in turn, makes it possible to prepare the skin well, which can then be used during the operation for plastic surgery of the extensive wound defect formed after excision of the ECT [23].

The literature describes techniques that involve excision of affected tissues using an elliptical incision. This technique is easy to perform, but has its drawbacks. The main drawback of this technique is the excision of more healthy tissue than necessary with a very large axis of the elliptical incision. Such patients usually develop a rough and long postoperative scar, which makes it impossible to match the edges of the wound and apply sutures.

In 2001, A. Vorobey used the technique of diamond-shaped excision for plastic closure of a defect forming in the sacrococcygeal region, in which the defects that arise as a result of tissue excision are closed with a

skin flap taken from adjacent tissues. The use of this technique has shown positive results. Based on the principles of local plastic surgery, when performing diamond-shaped excisions of inflamed tissue areas, additional incisions are made, thanks to which it is possible to perform plastic closure of the wound defect. For the successful application of this technique, there are certain conditions that must be met: first of all, the rhombus must be symmetrical, that is, it must consist of two isosceles triangles. It is necessary to achieve stable hemostasis using electrocoagulation, after which rhomboid plastic surgery is performed: first of all, it is necessary to match the edges of the postoperative wound and suture it, then plastic surgery is performed with the movement of two opposing triangular flaps. The postoperative wound is treated with double-row U-shaped sutures using catgut suture material: the first suture is placed closer to the bottom of the wound, and the second suture is placed subdermally. Drainage of the wound cavity is not performed during such operations [10].

In Russia, the method of marsupialization and wound defect plastic surgery using skin flap transplantation is widely used [10]. The marsupialization method was first proposed by L. Buie in 1937, and this method was subsequently modified several times [11]. One of the frequently used marsupialization methods is excision of the ECC and subsequent suturing of the postoperative wound with Moshkovich sutures [7]. When analyzing all of the above methods of surgical treatment of ECC, a number of disadvantages were identified, such as long healing times for the postoperative wound and, as a consequence, long-term inpatient treatment. Relapses after surgical treatment are not excluded – according to statistics, from 5 to 50 % [10; 12; 14].

Complications in the postoperative period are not uncommon, such as necrosis of the skin edges of the postoperative wound, which subsequently leads to cutting through and failure of the sutures on the skin, bleeding due to unstable hemostasis, secondary infection of the postoperative wound and the development of a purulent process. This increases the duration of inpatient treatment for patients and, accordingly, their period of incapacity for work [10; 12; 14]. Such patients, as a rule, after discharge from the hospital, undergo outpatient treatment for a long time and cannot lead a full social life [10; 13–15]. All of the above complications are assessed by most surgeons as a natural course of the postoperative period.

The introduction of modern high-energy lasers into medical practice, which deliver radiation directly to the pathological focus via flexible light guides, has made it possible to actively use them for intratissue and intracavitary therapeutic manipulations, and the use of modern ultrasound equipment has made it possible to visualize and monitor the treatment process of many cystic formations: hygromas, bursitis, cysts of various localizations [18].

Muhammad A. Albahadili (2016) used laser coagulation with a diode laser with a

wavelength of 980 μm for the treatment of ECC. In the preoperative period, the patient underwent ultrasound examination of the coccygeal area to determine the diameter of the coccygeal passage, as well as to identify the presence of additional passages. On average, the length of the passage is about 5 cm. Only one patient had a relapse after the surgery. The duration of the surgery according to this method is 10 min (range 6–15 min). Patients are examined on the second day after the surgery, and subsequent examinations are carried out once a week [18].

Based on all of the above, certain aspects are formed, the presence of which will lead to the determination of the most effective method of surgical treatment of ECT. One of these aspects is knowledge of the anatomy of the fistula tract, its relation to the skin, the presence of additional fistula tracts and purulent cavities. It is also necessary to know at what distance the external channel of the fistula tract is located in relation to the primary source of infection. All these nuances must be diagnosed in the preoperative period to determine the most rational and effective method of surgical treatment, which will avoid complications and relapses in the postoperative period.

Conclusions

An analysis of the literature showed that surgeons currently use various surgical techniques for complex forms of ECT. Despite the variety of methods, there is no single tactic for surgical treatment of complex forms of ECT, there is no method of treatment that guarantees patients the absence of relapses. All known methods of treating ECC condemn patients to long rehabilitation periods in the postoperative period and the formation of coarse postoperative scars. In this regard, the search for new methods of surgical treatment of ECC remains relevant.

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THE INFLUENCE OF ADHESIVE CREAMS ON THE PERIOD OF ADAPTATION TO REMOVABLE DENTURES

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ВЛИЯНИЕ АДГЕЗИВНЫХ КРЕМОВ НА ПЕРИОД АДАПТАЦИИ К СЪЕМНЫМ ЗУБНЫМ ПРОТЕЗАМ

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Adentia, whether partial or complete, is a common condition in the population, especially among older individuals. Although removable orthodontic devices are an effective solution for adentia, dentures can cause irritation in the oral cavity. The nature and duration of symptoms experienced by patients using dentures for the first time depend on various factors, such as the condition of their teeth and gums, jaw bone density, prosthesis design, psychological factors, and previous dental work. Studies have shown that special adhesive agents can improve the fit of removable dentures, leading to faster adaptation and better stability, even in challenging oral conditions. Using adhesives not only helps with new prostheses but also enhances comfort with existing ones, reduces movement while eating, and prevents food from getting trapped under the denture. This ultimately improves the patient's psychological well-being, reduces the foreign body sensation, and enhances quality of life. Proper maintenance and use of removable dentures can prevent jaw bone atrophy and degenerative changes in the oral tissues.

Literature review revealed the numerous variables that impact the successful treatment of total or partial tooth loss in patients. The incorporation of bonding agents unquestionably enhances the adjustment process to removable orthodontic devices by enhancing stability, a critical factor in the early stages of prosthesis use. However, it is essential to consider other various factors that influence the complexity and duration of adaptation, such as the characteristics of the dental structure, oral mucosa condition, jaw bone atrophy level, prosthesis selection and design, patient's psychological state, presence of macroglossia, previous prosthetic work, or its absence.

Keywords. Adentia, removable dentures, adjustment, bonding agents.

Задача обзора литературы заключается в оценке ключевых факторов, влияющих на эффективность адгезии съемных протезов, определении роли современных адгезивных средств в процессе адаптации пациентов к съемным ортопедическим конструкциям.

Частичное или полное отсутствие зубов относится к распространённым заболеваниям, особенно часто диагностируремым у пациентов старших возрастных групп. Использование съемных ортопедических конструкций является оптимальным решением проблемы адентии, однако протезы являются комбинированными раздражителями зубочелюстной системы. Характер и длительность жалоб пациентов, начинающих использовать съемные протезы, зависят от многих факторов. Исследователи рекомендуют практикующим врачам учитывать тип окклюзии, особенности костной структуры челюсти, слизистой оболочки рта, размеры языка пациента, проведение иммедиат-протезирования после удаления зубов и другие аспекты. Авторы приведенных в обзоре исследований изучали влияние клеевых композиций на надежность фиксации и уровень комфорта пациента при использовании протеза. Адгезивные средства в виде крема или порошка помогают надежно зафиксировать протез в полости рта даже при наличии «сложной» анатомии протезного ложа. Доказано, что пациенты, использующие данные средства, быстрее привыкают к наличию инородного тела в полости рта и имеют меньший уровень тревожности. Обследованные, уже использующие съемные протезы в течение длительного времени и привыкшие к ним, также сообщают о положительном влиянии адгезивных композиций: снижается балансирование конструкции при жевательной нагрузке, при более плотном прилегании протеза пища перестает травмировать слизистую оболочку полости рта. Таким образом, улучшается психологическое состояние пациента, протез все меньше воспринимается как инородное тело, повышается качество жизни протезируемого. При правильном использовании и тщательном уходе за съемными зубными протезами приостанавливается атрофия костной ткани челюсти и предотвращаются дистрофические изменения подлежащих тканей.

Анализ литературы позволил выявить, что эффективность лечения пациентов с частичным или полным отсутствием зубов зависит от множества различных факторов. Использование адгезивных средств значительно улучшает процесс адаптации к съемным ортопедическим конструкциям за счет повышения уровня фиксации, особенно на начальном этапе использования протезов. Однако необходимо учитывать и другие аспекты, влияющие на сложность и продолжительность адаптации: структуру зубочелюстного аппарата, состояние слизистой оболочки полости рта, уровень атрофии

челюстной кости, выбор и характеристики протеза, психологическое состояние пациента, наличие макроглоссии, а также проведенное предварительное протезирование или его отсутствие.
Ключевые слова. Адентия, съемные протезы, процесс адаптации, адгезивные средства.

INTRODUCTION

Despite significant advances in dentistry and a fairly high level of prevention of dental diseases, the prevalence of complete and partial absence of teeth is slightly decreasing and in different regions of the world is diagnosed in more than 25 % of those examined among elderly and senile patients. One of the obstacles to the use of removable dentures is the possible traumatic impact, therefore, today an important task of orthopedic dentistry is their adaptation.

USE OF DENTAL PROSTHETICS AND STUDY OF PROBLEMS RELATED TO PERIOD OF PATIENTS' ADAPTATION TO PROSTHESES

Tooth extraction can lead to problems with chewing, speech, the appearance of teeth and face, and contribute to the development of various pathologies, such as jaw deformations and abrasion of hard dental tissues. The main goal of dental prosthetics is to restore the function of the dentoalveolar system. Elderly patients prefer removable prostheses, often refusing prosthetics on implants due to their high cost [1].

It is important to understand that the process of adaptation to removable orthopedic structures is quite long and, according to V.Yu. Kurlyandsky, is from 10 to 33 days and depends on various factors. He identified several phases of adaptation to the denture, starting from irritation and ending with complete adaptation of the nervous system.

Such a factor as macroglossia has a negative impact on the process of adaptation to removable prostheses. It was found that according to Kennedy's classification, there is a certain connection between the development of macroglossia and the class of adentia. The study showed that macroglossia most often occurred in patients with bilateral terminal defects of the dental arch, which corresponds to class 1, while it was least often observed with included defects in the anterior part of the dental arch, which corresponds to class 4 [3].

Researchers have found that partial absence of teeth is the most common, followed by complete absence and much less common is congenital adentia. Research by P.J. Dhanrajani (2003) showed that primary adentia is observed in 5.5–6.5 % of the population, while the absence of six or more teeth is detected in 0.3 % of the population. Other scientists note that congenital adentia occurs in approximately 2 % of cases. Although this pathology is rare, patients from this group also require prosthetics [4].

The study by A.N. Ramakrishnan, O. Röhrle and C. Ludtka analyzed age groups of patients with missing teeth. The first group included 66 patients aged 60 years and older, the second group included 68 patients aged 40 to 60 years, and the third group included 36 patients aged 25 to 40 years. Each group contained an equal num-

ber of men and women. According to the initial analysis, 38.5 % of patients had already undergone prosthetics. Most of them were aged 60 years and older. In a subsequent analysis, it was found that 66 % of patients used removable partial dentures, predominantly in the 40–60 age group. Fewer patients (9.1 %) in the 25–40 age group used removable prostheses. The highest number of installed removable partial dentures were in patients with secondary edentulous class 1 (48.8 %) and 2 (34.8 %) according to Kennedy, while the lowest number (2.3 %) was in patients with edentulous class 4. It was also found that the adaptation period to removable prostheses was the longest – up to 30–33 days in patients with partial absence of teeth of class 1 (absence of chewing units on both sides of the dental arch) and class 2 (unilateral terminal defect of the dental arch) aged 60 years and older. Most patients who underwent the examination complained of discomfort caused by the direct impact of the orthopedic structure on the tissues of the prosthetic bed. They noted rubbing, pressure on certain areas of the oral mucosa, pain in the masticatory muscles. These complaints indicated the need for adjustments to the denture. Some patients made other complaints. The application of the prosthesis in the oral cavity provoked gagging in 11.2 % of patients, 5.8 % experienced hypersalivation, 10.7 % had a foreign taste in the mouth, 25.8 % had pronunciation problems, and 49.9 % experienced psychological discomfort from wearing the dentures. It is noteworthy that patients aged 25 to 40 years adapted to removable structures more easily compared to the older contingent. At the same time, patients of this age group, despite recommendations, did not remove the prostheses from the mouth at night (62.5 ± 11.6 %) [5].

One of the main complaints revealed during the patient survey is the pronunciation disorder. This problem seriously affects the quality of life and causes psychological discomfort, especially in people whose professional duties include communication. It was found that this complaint persists the longest – up to one month – in respondents over 60 years old. At the same time, in patients aged 25 to 40, the speech defect disappears in 7–10 days. Observations show that the vast majority of respondents with complete loss of teeth get used to removable structures much longer than patients with partial loss of teeth. This is due to the fact that patients with partial adentia redistribute the chewing load on their own teeth, which leads to uneven pressure on the prosthetic bed [6].

The research data obtained by S.Ye. Zholudev showed that after the installation of the denture in the oral cavity, the nature and intensity of complaints in patients changes over time. On the first day of using the prosthesis, 96 % of patients complained of a feeling of inadequacy of the denture size and discomfort, but after a day this complaint decreased to 52 %, and by the fifth day the number of complainants decreased to 32 %. After a month of using the prostheses, only 8 % of patients continued to have complaints. This is a completely natural process, when after installing the denture, the patient feels it as a foreign body in the mouth, but then begins to adapt

to it, and the complaints practically disappear. On the day of installing the dentures, 37 % of patients complained about the violation of fixation and mobility of the denture on the upper jaw, and 62 % – on the lower jaw. After 24 hours, unsatisfactory fixation on the upper jaw was noted by 18 % of patients and by 36 % on the lower jaw. Five days after the prosthesis was installed, problems with fixation were noted by 8 % of patients on the upper jaw and 21 % on the lower jaw. After 5–30 days, only 2 % of patients complained of poor fixation of the denture on the upper jaw and 11 % on the lower jaw [7].

The works of V.N. Trezub, A.S. Shcherbak, L.M. Mishnev and other researchers revealed a relationship between the time elapsed since the installation of the denture and patients' complaints about problems with pronunciation. 58 % of patients experienced a deterioration in pronunciation on the first day after the installation of complete removable prostheses, but after 24 hours this figure dropped to 48 %. After 1–5 days, only 38 % of patients complained of pronunciation problems, and after 5–30 days, only 12 %. It was also found that 88 % of patients had difficulty chewing food on the first day after the installation of dentures, but after 24 hours this figure dropped to 78 %. These data highlight the importance of patient comfort when using dentures and the individual nature of the process of getting used to them [8; 9].

V.A. Klemin, B.S. Kozlov and V.E. Zhdanov worked with two categories of patients: in the first category, patients immediately after tooth extraction received dentures, in the second category, patients did not undergo immediate prosthetics. Analysis of the comparative correlation in the first category of patients who received immediate prosthetics and the second category of patients who did not undergo this procedure revealed a very strong positive relationship. Evidence has been obtained that immediate prostheses prevent jaw bone tissue atrophy and promote the formation of normal bone structure. Immediate prosthetics is an indispensable stage before permanent prosthetics [10].

Researchers S.Ye. Barinov, E.Kh. Romodanovsky and others studied in detail the clinical symptoms and pathological changes in tissues in denture stomatitis in patients using removable dentures. According to their research, one of the main signs of denture stomatitis is the appearance of spots of various shapes and sizes. There is a variety in their location, size and shape. Scientists have identified the main factors leading to pathomorphological changes in the denture bed: improper fit of prostheses, uneven distribution of chewing load, presence of pores and irregularities on the surface of dentures, as well as poor care of them. The study also showed that with denture stomatitis, pathological changes affect all structures of the denture bed – from the epithelium to the bone [11].

Research by A.V. Sevbitov, N.Ye. Mitin and A.S. Brago indicate that pathological processes occur in the epithelium of the prosthetic bed in cases where patients do not seek retrofitting a removable prosthesis after manufacture or use "old" dentures without relining for more than 2–3 years. The data obtained confirm that the entire epithelial layer of the prosthetic bed is consistently in-

volved in the inflammatory process. The outcome of this pathological process is atrophy and thinning of the stratum corneum of the epithelium, a decrease in the regenerative capacity of tissues. In parallel with infiltration, degenerative changes are detected in the vessels of the tissues of the prosthetic bed in the form of their thickening and sclerosis [12].

The researchers conducted a deep analysis of pathomorphological processes in all tissues of the prosthetic bed. They found that the pathological process affects nerve fibers, leading to their destruction under the influence of compression. At the initial stages of inflammation of the periosteum of the prosthetic bed, an increase in the number of osteoblasts is observed, then the periosteum degrades, being replaced by fibrous tissue. With a long course of the pathological process, pinpoint and diffuse hemorrhages appear in the periosteum. It is noted that the main cause of pathomorphological disorders in the tissues of the prosthetic bed is circulatory disorders due to compression. The authors emphasize the fact that patients adapt to the prosthesis, but any removable structure is subject to mandatory replacement after 2–3 years of use [13; 14].

In the studies of V.I. Kulazhenko it was noted that the lack of vertical compliance of the mucous membrane of the denture is the result of excessive and prolonged compression, which is observed with prolonged use of prostheses. M.I. Sadykov joins the opinion of other researchers regarding the need for immediate prosthetics and notes the absolute importance of the correct placement and grinding of artificial teeth to ensure successful adaptation to orthopedic structures [15].

Correction of prosthesis after the initial application in the oral cavity is a necessary stage. The patient is explained that discomfort during the first period of wearing the denture is normal, but it is necessary to perform mandatory relining of the base within 1–3 days. Monitoring of adaptation to the denture continues on average for 30–33 days, which corresponds to the onset of the inhibition stage in the cerebral cortex.

To determine the effectiveness of the orthopedic treatment, the following indicators can be identified: the patient's self-assessment of the function of the prosthesis and the stability of the dentures, their compliance with aesthetic standards, clarity of pronunciation of sounds and the ability to comfortably consume a variety of food [16].

ANALYSIS OF THE RELIABILITY OF FIXATION OF DENTAL PROSTHESIS USING VARIOUS MATERIALS

The importance of reliable fixation of the prosthesis to prevent injury to the tissues of the oral cavity is emphasized by researchers M.I. Sadykov, A.M. Nesterov, S.V. Vinnik, A.R. Ertesyan and others. They note that existing methods for improving the fixation of removable dentures are constantly being improved using various techniques for obtaining impressions, volumetric modeling, elastic materials, surgical preparation and implants. These methods facilitate more effective adaptation to removable dentures. Together with the main adaptation methods, adhesive preparations can provide psychological comfort for pa-

tients. Adhesive agents have been used for a long time, including tragacanth powder to accelerate adaptation to complete removable dentures during initial use. The first means for fixing dentures were plant extracts such as Gum karaya resin and Astragalus Verus extract. Adhesive compositions are not a new phenomenon in dentistry and have been invented in the union of the chemical industry and practical medicine since 1913. Currently, the dental materials market offers adhesive compositions in the form of fixing pads, powders and gels [17].

T. Kurogi, H. Murata and E. Yamaguchi found that the use of cream denture adhesives significantly increased their retention ($p < 0.01$) and occlusal strength ($p < 0.05$). However, no significant differences were found between the initial strength and the post-intervention strength in the groups using powder denture adhesive and the control group. However, no significant differences were found between the baseline and post-intervention strengths between the denture powder adhesive and control groups. Within-group comparisons showed that cream denture adhesives improved both the retentive and occlusal strengths. Statistically significant results ($p < 0.05$) showed that the use of powder denture adhesives resulted in improved occlusal strength ($p < 0.01$) [18].

According to the data obtained during the study by A. Slaugter and R.V. Katz, the use of adhesives for prosthesis can significantly improve the level of comfort and quality of life in people using complete dentures [19].

The use of adhesive compositions in patients with xerostomia is quite effective; in particular, it has been determined that when using some types of adhesives for fixation, the holding force of prosthesis increases over time, reaching a maximum 10 minutes after application, but they are easily washed off, while other types of compositions show high holding force and good durability immediately after application [20].

Based on the research conducted by Ye.A. Buyanov, V.I. Shemonaev, O.G. Strusovskaya, R.I. Zodorov and A.N. Parkhomenko, it was revealed that some of the most popular fixing creams in Russia are Corega, Lacalut, President, Protefix. The study included patients aged 38 to 91 years. The questionnaire assessed such parameters as the degree of atrophy of the alveolar processes of edentulous jaws in accordance with the classification of I.M. Oksman (1978), the type of dentures used (partial or complete), the duration of use of the structures, as well as the reliability of their fixation, the presence of pain when applying the prosthesis and during chewing, the state of oral hygiene before and after using the adhesive, and adaptation periods. After application of Corega cream, corresponding assessments were made. According to patients' feedback, fixation of the prosthesis improved by 19 ± 2.4 %, becoming good by 47 ± 1.0 % and excellent by 34 ± 2.6 %. Patients who had their dentures repeated or relined noticed faster and easier adaptation to the structures in 1–3 days, while patients who had their prostheses made for the first time needed 4–8 days. 96 ± 0.7 % of patients did not experience pain after application of the cream, and in 4 ± 0.7 % it was significantly reduced. 27 ± ± 3.1 % said that it became easier for them to

clean the denture from food residues. Patients assessed the moisture content of the oral mucosa as satisfactory, and the perception of food taste did not change. The authors emphasize the importance of including the formation of a positive communicative position in rehabilitation programs for the elderly [21].

J. Mendes, J.M. Mendes, P. Barreiros, C. Aroso and A.S. Silva noted the important influence of adhesive compositions, which contribute to strengthening of adhesion. The use of adhesives provides significant advantages: when eating, the prosthesis is maximally stable in the oral cavity, chewing pressure when eating is distributed more evenly, food particles do not get under the denture and do not irritate the mucous membrane, and the bone structure of the jaw is also indirectly preserved. Studies have also shown that the pressure on the oral mucosa using denture adhesive decreased to 0.15 MPa, while for the model without adhesive it was 0.25 MPa. Thus, it can be concluded that the use of adhesives helps relieve the soft tissues of the denture bed and ensures its decompression [22; 23]. In addition, various adhesives have been developed that contain antifungal and antibacterial components, which significantly expands the range of their application [24].

When analyzing modern adhesives for removable dentures, a detailed comparison of several known drugs reveals significant differences in their chemical composition, adhesive properties and clinical effectiveness. These differences emphasize the need for careful selection of the preparation taking into account the individual needs of the patient.

For example, Corega Ultra Cream, which uses a zinc-free formula containing polyvinyl acetate and polyvinyl alcohol, demonstrates high retention properties, especially in conditions characterized by high salivary flow. This formulation not only improves mucosal adhesion, but also reduces the potential toxicity of zinc that was associated with previous generations of zinc-containing adhesives. Clinical trials have shown that Corega Ultra provides a 12-hour bonding, outperforming formulations such as Fixodent Original, which remain effective for approximately 8–10 hours.

In contrast, Poligrip Super Denture Adhesive, which is also zinc-free, uses a combination of carboxymethylcellulose and sodium alginate. These biopolymers offer a distinct advantage to patients with xerostomia, where moisture retention and mucosal adhesion are compromised. Poligrip Super, although providing a slightly shorter moisture retention time than Corega Ultra (10–12 h), offers increased comfort due to its softer gel-like consistency, which reduces mucosal irritation [25].

Secure Denture Adhesive is another product that contains aluminum / magnesium silicates in a hydrophobic base. The use of this composition provides long-term adhesion even in low humidity conditions, which makes it especially effective for patients with extensive alveolar ridge resorption. Secure Denture Adhesive maintains its retention properties for more than 12 hours, which significantly reduces the need for reapplication, which is a common requirement for other adhesives such as Ef-

fergrip, which maintains adhesion for only 6–8 hours in similar conditions.

A more recent innovation in denture adhesives is Super Poligrip Extra Care, a formulation that incorporates multifunctional acrylate copolymers and silicone-based compounds. This adhesive has improved viscoelastic properties, providing excellent distribution of occlusal forces and reducing the risk of denture-induced ulcers. Comparative studies have shown that Super Poligrip Extra Care is superior to traditional adhesives such as Orafix Denture Adhesive Cream, especially in patients with fragile mucosa or thin gums [26; 27].

Fixodent Plus Scope incorporates flavor additives along with adhesive properties using a unique blend of cellulose gum and polymer resins. Although the primary function of Fixodent Plus Scope is to stabilize the denture, the inclusion of flavors such as thymol and eucalyptol significantly improves patient compliance, especially in cases, where prolonged denture wear results in halitosis. Despite its advantages, Fixodent Plus Scope has a slightly shorter fixation time (8–10 h) compared to other formulations [28].

OlivaFix Gold is a premium adhesive that is distinguished by the fact that it contains extra virgin olive oil and silicone-based polymers. This formula is indicated for use in patients with sensitive oral mucosa or allergies to synthetic compounds. The oil base of OlivaFix Gold improves fixation and patient comfort, providing adhesion for up to 12 hours, comparable to Corega Ultra, but with the additional benefit of reducing irritation of the mucous membrane [29; 30].

Finally, Protefix Active Denture Adhesive, containing sodium carboxymethylcellulose and tragacanth gum, combines sufficient adhesion with comfort in relation to the mucous membrane. Protefix Active is especially effective for patients with deep palatal vaults or complex alveolar ridges, where traditional adhesives cannot provide uniform coverage and retention. This adhesive maintains its effectiveness for 10–12 hours, slightly exceeds Fixodent Original, but is inferior to the Secure Denture Adhesive composition [31; 32].

The variety of adhesive formulations highlights the importance of selecting an adhesive based on a comprehensive assessment of patient-specific factors, including oral anatomy, salivary composition, and mucosal health. Continuous advances in adhesive technologies, characterized by the integration of new polymers and bioactive compounds, promise further advances in denture stabilization and patient comfort [33; 34].

Another example of a modern adhesive is the Pectafix gel, produced by Vladmiva JSC. This product is affordable to most buyers. A study conducted by Zh.B. Zhilbakieva revealed the main characteristics of this product. The polysaccharide pectin is a natural component obtained from apples or citrus fruits. In addition to moderate adhesive properties, pectin is able to absorb toxic substances. The disadvantages of this adhesive include a short fixation time and the absence of bactericidal properties [35; 36].

Also, researchers [37; 38] analyzed and described the features of another well-known glue in Russia – a gel called “Denta-

fix", modified by adding components that enhance its fixation ability and protection against bacteria. This helps improve the fixation of removable dentures and speed up the process of patient adaptation to them.

The Dentafix gel contains such components as apple pectin, polyvinylpyrrolidone, sodium benzoate, food colorings and water with silver ions – all these components are present in silver-containing preparations, which are of great value for medical use. The unique properties of silver are due to its ions, which are capable of preventing the development of diseases caused by fungal, bacterial or viral infections. In addition, silver ions promote tissue healing under excessive functional load.

The researchers obtained the following significant conclusions: differences in the adhesive properties of two means for fixing removable dentures were studied. The first group, including 20 patients, applied the Pectafix gel, and the second group, consisting of 22 people, used the Dentafix adhesive agent. The clinical trial lasted for five days, after which a survey and examination were conducted. It turned out that the time of reliable fixation of the denture: for the Pectafix gel was 3–5 hours, and for the Dentafix gel – 6–7 hours. The use of the Dentafix gel revealed several advantageous factors: the structure was more firmly held on the prosthetic bed, pain during eating was minimized, food particles got between the prosthesis and the mucous membrane much less often, the adaptation period was reduced from 2–3 weeks to 10–12 days. The adhesive composition of the Dentafix gel showed excellent results and can be a good auxiliary means for fixing prostheses. When choosing adhesives, it is important to take into account the individual characteristics of patients [39; 40].

Conclusions

From the literature review it becomes obvious that adaptation to removable prostheses depends on many factors. The use of adhesives can significantly improve the process of adaptation to removable orthopedic structures, especially in the initial period of using dentures. However, it is worth remembering that adhesives are auxiliary means. It is necessary to take into account many factors that affect the process of getting used to orthopedic structures, in particular – the class of adentia, the age of patients, the type of occlusion, the degree of bone loss, the material from which the denture is made, the patient's readiness to overcome difficulties during adaptation, the presence / absence of macroglossia, the presence of a stage of preliminary or immediate prosthetics and others. The use of adhesives should not be prescribed instead of correction or re-manufacturing of the denture.

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A.V. Sevbitov – development of the concept and design of the study.

A.Ye. Dorofeev – development of the concept and design of the study.

A.S. Utyuzh – collection of the material and the analysis of the obtained data.

V.V. Kireev – development of the concept and design of the study.

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POSSIBILITY OF ENTERAL TUBE FEEDING IN SEVERE SURGICAL PATHOLOGY

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ВОЗМОЖНОСТЬ ПРИМЕНЕНИЯ ЭНТЕРАЛЬНОГО ЗОНДОВОГО ПИТАНИЯ ПРИ ТЯЖЕЛОЙ ХИРУРГИЧЕСКОЙ ПАТОЛОГИИ

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Objective. To study the possibility of using new GASTROAXILIUM mixtures in complex therapy of patients with severe surgical abdominal pathology.
Materials and methods. The study of characteristics of the developed mixtures was carried out by standard and non-standard methods in an accredited laboratory. Clinical studies were conducted in accordance with the Procedure for conducting studies of the effectiveness of specialized dietary therapeutic and dietary preventive food products. Statistical processing was carried out using analysis of variance.
Results. GASTROAXILIUM, specialized food product for tube feeding developed by the specialists of the Research and Production Center for Healthy Nutrition Technologies of Saratov State Medical University named after V.I. Razumovsky, differs from foreign ones in its technological solutions. In the main group a statistically significant reduction in the duration of postoperative intestinal paresis was noted, both in planned and emergency surgeries**,** in contrast to the comparison group.
Conclusions. We consider that the results of the use of daily nutritional complex of oligomeric dry mixtures for enteral nutrition GASTROAXILIUM are in agreement with the literature data, they will successfully complement the scientific data on the necessity for nutritional support and will play an important role in improving the quality of treatment of patients with severe postoperative abdominal pathologies.
Keywords. Possibilities of enteral tube feeding, enteral nutrition mixtures, effectiveness of nutritional support, surgical patient, severe surgical pathology.

Цель. Исследование возможности применения новых смесей GASTROAXILIUM в комплексной терапии пациентов с абдоминальной патологией.
Материал и методы. Исследование характеристик разработанных смесей проводили стандартными и нестандартными методами в аккредитованной лаборатории, клинические исследования – в соответствии с «Порядком проведения исследований эффективности специализированной диетической лечебной и диетической профилактической пищевой продукции». Статистическая обработка проводилась с применением дисперсионного анализа.
Результаты. Разработанный специалистами Научно-производственного центра технологий здорового питания Саратовского ГМУ им. В.И. Разумовского специализированный пищевой продукт для зондового питания GASTROAXILIUM имеет отличные от зарубежных технологические решения. В основной группе, в отличие от группы сравнения, отмечено статистически значимое сокращение срока послеоперационного пареза кишечника как при плановых, так и при экстренных операциях.
Выводы. Считаем, что результаты применения суточного нутрицинного комплекса олигомерных сухих смесей энтерального питания GASTROAXILIUM у пациентов с хирургическими патологиями находятся в согласии с литературными данными, успешно дополняют научные данные о необходимости нутрицинной поддержки и будут играть важную роль в повышении качества лечения тяжелой абдоминальной патологии.
Ключевые слова. Энтеральное зондовое питание, смеси для энтерального питания, эффективность нутрицинной поддержки, хирургический пациент, тяжелая хирургическая патология.

INTRODUCTION

In modern conditions of development of surgery, anesthesiology and resuscitation, the question of choosing a method for correcting metabolic disorders in surgery remains open. Initial nutritional disorders in patients who have undergone traumatic surgical interventions inevitably lead to significant metabolic and functional changes already in the perioperative period with the formation of hypermetabolism-hypercatabolism syndrome, characterized by changes in the energy consumption system, protein breakdown, activation of lipid peroxidation, excessive accumulation of free fatty acids, and decreased glucose tolerance. An important role in solving this issue is given to perioperative nutritional support [1–3].

During both major traumatic and minimally invasive surgeries, patients are exposed to surgical stress [4]. Surgical stress is the main cause of perioperative dysfunction of various organs and systems. Surgical stress is a major cause of perioperative dysfunction of various organs and systems.

A number of publications indicate that, depending on the type of pathology, protein-energy deficiency develops in 20–50 % of surgical patients directly in the hospital in the early postoperative period [5]. A relationship has been reliably established between the severity of protein-energy malnutrition and the frequency of adverse outcomes in critically ill patients undergoing surgery [6].

One of the main criteria of the modern concept of the "Enhanced Recovery After Surgery" (ERAS) is the assessment of the patient's nutritional status and the provision of nutritional support throughout the entire perioperative period. The ESPEN Nutritional Risk Scale (NRS) is used as a screening tool for malnutrition [7]. Complex and traumatic operations place special demands on perioperative patient care. The outcomes of highly traumatic surgeries depend on many factors, which are reflected in the concept of early recovery after surgery (ERAS) (Enhanced Recovery After Surgery) [8] and include a number of factors, including: preoperative preparation of the patient, anesthesia, pre- and postoperative nutritional support [9]. The outcomes of highly traumatic surgeries depend on many factors, which are reflected in the concept of early recovery after surgery (ERAS) (Enhanced Recovery After Surgery) [8] and include a number of factors, including: preoperative preparation of the patient, anesthesia, pre- and postoperative nutritional support [9].

In order for the time required to restore the body's homeostasis after surgical injury and for wound healing to be optimal, the body must receive a sufficient amount of energy and nutrients [10]. However, the body's own energy and plastic resources may be insufficient due to the traumatic nature of the surgical intervention or a pre-existing protein-energy deficiency.

Saratov State Medical University named after V.I. Razumovsky has its own developments of enteral mixtures based on domestic raw materials, unique in technology, different from Western production, without the use of separate (isolated) components, more physiological and economically feasible. Technologies of oligomeric enteral mixtures

for nutritional support of patients with abdominal pathology have been developed.

In connection with the above, the aim of the study is to analyze the possibility of using new GASTROAXILIUM mixtures in the complex therapy of patients hospitalized with abdominal pathology who are on tube feeding.

MATERIALS AND METHODS

During the conduct of this study, interstructural interaction was carried out within the Federal State Budgetary Educational Institution of Higher Education Saratov State Medical University named after V.I. Razumovsky of the Ministry of Health of the Russian Federation between the Department of Faculty Surgery and Oncology, which conducted clinical studies, and the Scientific and Production Center for Healthy Nutrition Technologies (SPC HNT) – the developer and manufacturer of GASTROAXILIUM mixtures in accordance with the unique technology.

The study of the characteristics (content of proteins, fats, carbohydrates) of the daily nutritional complex of oligomeric dry enteral nutrition mixtures GASTROAXILIUM was carried out by generally accepted methods in the accredited Testing Laboratory of Food Products and Food Raw Materials of the ETI (branch) of the Saratov State Technical University named after Yu.A. Gagarin. Osmolality was determined on a cryoscopic osmometer model 3250, Osmol (made in the USA), acidity – on a portable pH meter (made in China) based on the laboratories of the Saratov State Medical University named after V.I. Razumovsky.

Clinical studies of the effectiveness of enteral nutrition GASTROAUXILIUM were conducted in accordance with the "Procedure for conducting studies of the effectiveness of specialized dietary therapeutic and dietary preventive food products" developed by the Federal Research Center for Nutrition, Biotechnology and Food Safety (methodological guidelines, Ministry of Health, Moscow, 2016).

The study was approved by the decision of the local ethics committee of the Federal State Budgetary Educational Institution of Higher Education Saratov State Medical University named after V.I. Razumovsky (recommendations of the ethics committee of the Federal State Budgetary Educational Institution of Higher Education Saratov State Medical University named after V.I. Razumovsky of the Ministry of Health of the Russian Federation dated 06.07.2023 (protocol version 1.0) with an amendment to the new name of enteral nutrition mixtures GASTROAXILIUM dated 28.06.2024 (protocol version 2.0)).

The study included 80 patients hospitalized with severe surgical or oncological pathology who were on tube feeding. The patients were randomly divided into two groups: the main group of 46 people (matched by age and gender, receiving a specialized product for tube feeding GASTROAXILIUM, developed by the Scientific and Practical Center of TZP) and a comparison group of 34 people (matched by age and gender and receiving a standard (available at the clinic) product for tube feeding (similar to the product in group 1) with a standard con-

tent of essential substances based on the total daily intake of 30–35 kcal / kg / day and 1.2–1.5 g of protein / kg of body weight / day according to recommendations for nutritional support of patients).

For inclusion in the study, patients were selected according to the inclusion criteria, with their consent to participate with a signed "Informed voluntary consent to participate in a clinical study", who were indicated for surgical treatment for the main disease. It should also be noted that patients without concomitant diseases were selected. The identification number was assigned according to the patient's medical history number (Tables 1 and 2).

Table 1

Underlying disease and degree of nutritional status impairment (main group)

ID	Prior Disease	General Health Status	Violation of Nutritional Status
3467	Gastric cancer	Moderate	Moderate
3643	Gastric cancer	Moderate	Moderate
3801	Gastric cancer	Moderate	Moderate
3759	Acute adhesive intestinal obstruction	Moderate	Mild
3965	Acute adhesive intestinal obstruction	Moderate	Moderate
4029	Strangulated inguinal hernia	Moderate	Moderate
4206	Acute cholecystitis, peritonitis	Bad	Moderate
4369	Incarcerated femoral hernia	Moderate	Mild
4257	Gastric cancer	Moderate	Moderate
4318	Gastric cancer	Moderate	Moderate
4522	Acute adhesive intestinal obstruction	Moderate	Mild
4375	Duodenal ulcer complicated by bleeding	Moderate	Mild
4535	Perforated duodenal ulcer	Moderate	Mild
4629	Duodenal ulcer complicated by bleeding	Moderate	Mild
4775	Acute adhesive intestinal obstruction	Moderate	Moderate
4688	Biliary fistula	Moderate	Mild
4450	Gastric cancer	Moderate	Mild
4397	UC, intestinal bleeding	Moderate	Mild
4912	Penetrating stab wound to the abdomen	Moderate	Negative
4879	Acute adhesive intestinal obstruction	Moderate	Mild
4885	Dumping syndrome, anastomosis	Relatively satisfactory	Mild
4919	Acute appendicitis. Peritonitis	Moderate	Moderate
5136	Duodenal ulcer complicated by bleeding	Moderate	Moderate
5148	Chest and abdominal wounds. Bowel injury. Peritonitis	Moderate	Mild
4785	Acute pancreatitis. Pancreatic necrosis	Moderate	Moderate
4955	Chronic pancreatitis. Pancreatic cyst.	Moderate	Mild
5347	Pancreatic cancer. Jaundice	Moderate	Moderate
5268	Metastasis of ovarian cancer to the small intestine. Acute intestinal obstruction	Moderate	Severe

End of Table 1

ID	Prior Disease	General Condition Status	Violation of Nutritional Status
5592	Duodenal ulcer complicated by bleeding	Moderate	Moderate
5501	Duodenal ulcer complicated by bleeding	Moderate	Mild
5847	Pancreatic cancer. Jaundice	Moderate	Moderate
5833	Duodenal ulcer. Gastric stenosis. Adhesions	Moderate	Mild
5839	Duodenal ulcer complicated by bleeding	Moderate	Moderate
6126	Cancer of the cecum. Carcinomatosis	Moderate	Severe
5724	Stomach ulcer	Moderate	Moderate
5616	Duodenal ulcer complicated by bleeding	Moderate	Severe
5947	Perforation of the sigmoid with a fishbone	Moderate	Mild
6228	Sigmoid cancer. Acute intestinal obstruction.	Moderate	Moderate
6235	Pancreatic cancer. Jaundice	Moderate	Moderate
6574	Gastric ulcer complicated by bleeding	Moderate	Moderate
5042	Ischemic heart disease. Acute cerebrovascular accident. Gastric ulcer. Gastrointestinal tract disease.	Тяжелое	Moderate
6348	Acute adhesive intestinal obstruction	Moderate	Moderate
6489	Gallstone disease. Pancreatic cyst. Jaundice.	Moderate	Moderate
6387	Gastric cancer T2N0M0	Moderate	Moderate
6413	Gastric cancer T2N0M0	Moderate	Moderate
6745	Gastric cancer T4N3M1, stenosis.	Severe	Severe

Table 2

Primary disease and degree of nutritional status impairment (comparison groups)

ID	Prior Disease	General Condition Status	Violation of Nutritional Status
3472	Acute pancreatitis. Peritonitis.	Severe	Severe
3711	Gallstone disease. Acute pancreatitis. Peritonitis.	Moderate	Mild
4033	Appendicular abscess. Peritonitis.	Moderate	Moderate
4042	Diverticulitis of the sigmoid colon. Peritonitis.	Moderate	Moderate
4375	Acute pancreatitis. Peritonitis. Abdominal phlegmon.	Severe	Moderate
4412	Acute appendicitis. Peritonitis	Moderate	Mild
4189	Thrombosis of mesenteric vessels.	Severe	Moderate
4203	Acute adhesive intestinal obstruction	Moderate	Moderate
4817	Acute intestinal obstruction.	Moderate	Mild
4214	Stomach cancer	Moderate	Moderate
4826	Liver cirrhosis. AO. Primary peritonitis.	Moderate	Moderate
4925	Gallstone disease. Acute cholecystitis.	Moderate	Mild
4822	Cancer of the cecum T3N0M0. Peritonitis.	Moderate	Moderate

End of Table 2

ID	Prior Disease	General Condition Status	Violation of Nutritional Status
5167	Gastric ulcer. Completed gastrointestinal tract infection. Phytobezoar.	Moderate	Moderate
5394	Rectal cancer T4NxM1 mts in liver. Acute intestinal obstruction.	Severe	Severe
5430	Gastric cancer T4N3M1, carcinomatosis. Acute intestinal obstruction.	Severe	Moderate
5412	Adhesive intestinal obstruction	Moderate	Moderate
5436	Transverse colon cancer T3N0M0. Acute intestinal obstruction.	Moderate	Mild
5414	Gastric ulcer complicated by bleeding.	Moderate	Moderate
5516	Perforated duodenal ulcer. Peritonitis.	Moderate	Moderate
5732	Sigmoid cancer T3N0M0. Peritonitis.	Moderate	Moderate
5625	Pancreatic cancer T3N0M0. Jaundice. Diabetes mellitus.	Severe	Mild
5862	Sigmoid colon cancer. Acute intestinal obstruction.	Moderate	Moderate
5798	Pancreatic cancer T4N2M0. Jaundice.	Moderate	Mild
6134	Sigmoid cancer T3N0M0. Acute intestinal obstruction.	Moderate	Moderate
5842	Acute adhesive intestinal obstruction	Moderate	Moderate
6315	Perforated duodenal ulcer. Peritonitis.	Moderate	Moderate
6324	Cancer of the sigmoid colon. T3N0M0. Acute intestinal obstruction.	Moderate	Moderate
6350	Small bowel lymphoma	Moderate	Mild
6361	Gastric ulcer. Stenosis.	Moderate	Moderate
6392	Perforated ulcer of the duodenum. Peritonitis. AO.	Moderate	Mild
6404	Retroperitoneal sarcoma.	Moderate	Moderate
6618	Pancreatic tumor. Jaundice	Moderate	Mild
6623	Retroperitoneal sarcoma.	Moderate	Mild

The daily nutritional complex of oligomeric dry enteral nutrition mixtures GASTROAUXILIUM was introduced into the duodenum or the initial sections of the small intestine using a nasogastrointestinal tube installed intraoperatively. For the main group of patients, a manual method of active portioned (bolus) administration of the nutritional mixture was used. It is administered in portions using a Janet syringe. In this case, a single volume for the stomach and small intestine should not exceed 200 ml after 3–4 hours, administered slowly over 5–10 minutes. The nutritional mixture "Fresubin" (FresiniusKabi) was administered using a dropper at a rate of 5–10 ml/min through the perfusion channel of the probe.

The daily nutritional complex of oligomeric dry enteral nutrition mixtures

GASTROAXILIUM has been developed based on the principle of physiological perception of nutrition by the human body with adequate distribution of the caloric content of the daily diet by feeding, which allows for labile control of metabolic stress.

The technology of the nutritional complex of oligomeric dry enteral nutrition mixtures GASTROAXILIUM is based on the use of natural dietary hypoallergenic domestic raw materials, combined in accordance with the rules of food combinatorics and technology of preparing dishes for dietary therapeutic nutrition, converted into a semi-elemental state using enzyme technologies with subsequent dehydration. The characteristics of the daily nutritional complex of oligomeric dry enteral nutrition mixtures GASTROAXILIUM, developed by the Scientific and Production Center of TZP, are presented in Table 3.

Comparative characteristics of the daily nutritional complex of oligomeric dry enteral nutrition mixtures GASTROAXILIUM, developed by the Scientific and Production Center of TZP, and the mixture "Fresubin" are presented in Table 4.

Table 3

Characteristics of daily nutritional complex of oligomeric dry enteral nutrition mixtures GASTROAXILIUM

Daily Nutritional Complex of Oligomeric Dry Enteral Nutrition Mixtures GASTROAXILIUM					Osmolality, mOsm/kg H2O	pH
Nutrition Frequency	Nutritional and Energy Value GASTROAXILIUM					
	Proteins, g	Fats, g	Hydrocarbons, r	Energie, kcal		
Morning feeding (breakfast)	7.3	3.7	25.8	165.5	494	4
Lunch feeding (dinner)	23.7	2.9	10.3	161.5	438	4
Afternoon feeding (afternoon snack)	7.1	7.5	26.2	164.9	362	3.8
Evening feeding (dinner)	19.8	2.64	14.3	160.3	432	4
Total	57.9	16.7	76.6	652.2	Average 431.5	4

Note: each portion of the feeding mixture is diluted with 150 ml of water at 40–42 °C, 4-time feeding provides 1 ml/1.1 kcal (9.7 g protein/ 108.7 kcal / 100 ml). Depending on the patient's condition, weight and if 4-time use of the PI is insufficient to replenish the nutritional needs, the patient will receive an additional feeding.

Table 4

Comparative characteristics of daily nutritional complex of oligomeric dry enteral nutrition mixtures GASTROAXILIUM, developed by scientific and production center of tzp, and mixture “Fresubin” (FresiniusKabi)

Mixture Name	Nutritional and Energy Value				Osmolality, mOsm/kg H2O	pH
	Proteins, g	Fats, g	Hydrocarbons, r	Energie, kcal		
GASTROAXILIUM	57.9	16.7	76.6	652.2	431.5	4
“Fresubin”	50	16	64.5	610	740	6.7

The nutritional complex of oligomeric dry enteral nutrition mixtures GASTRO-AXILIUM has a microbiome-forming effect due to its high antioxidant activity, anti-inflammatory and anti-cancer effects due to the presence of natural polyphenols, anthocyanins, ascorbic acid, and vitamins of group P. The food raw materials used in the production of enteral nutrition are hypoallergenic, dietary, have a low glycemic index, and are gluten-free. To collect data and implement communications during the study, a patient observation scheme was used, including: screening conducted on the day of the patient's hospitalization, namely: identification of the degree of malnutrition Nutritional Risk Screening 2002 (NRS 2002) [9], assessment of the general condition of the patient, laboratory monitoring (complete blood count, BH blood test), collection of complaints and anamnesis, and objective examination.

All actions with the research base were recorded on paper and electronic media. Primary and secondary analysis are presented by descriptive statistics. All continuous variables were summarized using the following parameters: *n* (sample range of available patients), mean, standard deviation, median, 25th and 75th percentiles, or maximum and minimum. Critical *p*-values and confidence intervals were calculated as two-sided. The study adopted a statistical significance level of 0.05. Continuous variables were described using mean, standard deviation, 95 % confidence intervals, median, upper and lower quartiles. Primary and secondary endpoint analyses were performed on the full data set.

RESULTS AND THEIR INTERPRETATION

All patients had nutritional status disorders to varying degrees (Table 5).

Table 5

Degree of nutritional status impairment in groups in comparison

Degree of Nutritional Status Impairment	Group	
	Basic	Comparison
Negative	1	–
Mild	16	10
Middle	25	22
Severe	4	2

The data in Table 5 show that the degree of nutritional status impairment in patients in all groups is identical. In the main group, there are more patients with mild and severe nutritional status impairment, in contrast to the comparison group, where there are more patients with moderate impairment. Nevertheless, the highest percentage of patients is with moderate impairment of nutritional status.

From the data in Table 6 it is evident that in 46 patients receiving the GASTROAUXILIUM complex of oligomeric dry enteral nutrition mixtures as nutritional support. The average duration of paresis was 3.4 days, while in 34 patients receiving Fresubin as nutritional support, the average duration of paresis was 4.5 days. At the end of the observations, a comparison was made of the mean values (median and quartiles) of the duration of intestinal paresis resolution by the number of days in the main group and in the comparison group (Table 7): in the comparison group, the duration of paresis

Table 6

Summary data on effectiveness of paresis resolution in groups

Pathology	PI Support		Support with Fresubin Drug	
	Number of Observations, abs.	Paresis Resolution Period, Days.	Number of Observations, abs.	Paresis Resolution Period, Days.
Diseases of Stomach (Tumor, Perforation-damage to the Wall)				
Gastrectomy	4	3.2	1	4
Gastric Resection	14	3.2	3	4
Gastroenteroanastomosis	1	3		
Suturing of the stomach wall and duodenum	3	3	3	4
Acute Surgical Pathology				
Peritonitis	7	3.5	9	6.1
Acute intestinal obstruction	9	3.8	10	4.7
Pancreatic tumor	3	3.6	3	4.3
Strangulated hernia	2	3		
Other diseases of the gastrointestinal tract	3	4.3	5	4.5
TOTAL	46	3.4	34	4.5

Table 7

Duration of intestinal paresis resolution in groups

Group	Number of Patients	Duration of Intestinal Paresis
Basic	46	3 [3; 4]*
Comparison	34	5 [4; 5]

Note: * – differences with the comparison group are significant at $p < 0.05$.

resolution was, on average, 2 days longer than in the study group.

The significance of differences between groups in the duration of paresis resolution was confirmed using the nonparametric Kolmogorov – Smirnov test ($Z = 2.21$; $p < 0.001$). Moreover, regardless of the type of disease, the duration of paresis resolution (Figure) was shorter in the main group. In patients with peritonitis, duodenal ulcer and gastric cancer, resolution of paresis occurred on the 3rd day, only in patients with acute intestinal obstruction the duration of resolution of paresis in the study group was one day longer.

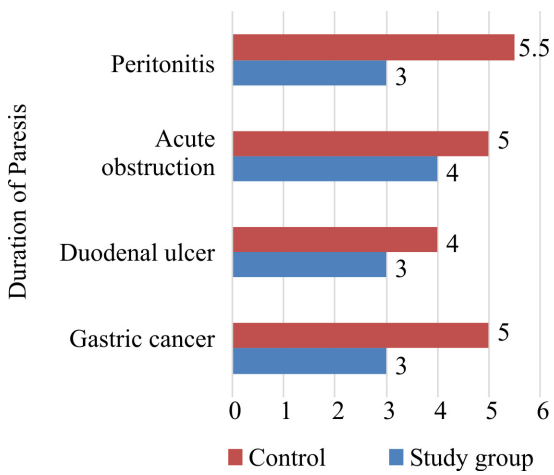

Fig. Duration of paresis resolution depending on disease

Table 8

Results of study of local complications

Group	Number of Patients	Feces Features	
		Soft decorated	Liquid
Basic	46	43	3
Comparison	34	6	28

Table 9

Results of study of common complications

Group	Number of Patients	General Complication	
		Diarrhea	Pain in Stomach
Basic	46	–	6
Group	34	18	7

The duration of paresis resolution in the comparison group was longer in all cases, and the longest in patients with peritonitis.

It should be noted that peritonitis developed as a postoperative complication in the main group in 3 cases out of 46 (6.5 %), and in the comparison group – in 7 cases out of 34 (20.6 %). Thus, the proportion of postoperative complications in the comparison group was 14.1 % higher than in the main group. When comparing the two groups by the peritonitis criterion using the chi-square test, there were no significant differences between the groups at $p < 0.05$ (the χ^2 value = 3.537).

As a local complication (Table 8), liquid stool was observed in 3 out of 46 patients (6.5 %) in the study group and in 28 out of 34 patients in the comparison group (82.4 %).

Comparison of two groups according to the "stool type" criterion using the chi-square test allowed us to identify reliable differences between the groups at $p < 0.001$ (χ^2 value = 47.366).

As a general complication (Table 9), diarrhea was not observed in patients of the main group, but in patients of the comparison group, diarrhea was a frequent occurrence – in 18 cases out of 34 (52.9 %). Abdominal pain was present in some cases both in the main (13 %) and in the comparison group (20.5 %).

Comparison of two groups on the criterion of diarrhea using the chi-square test allowed us to identify reliable differences between the groups at $p < 0.001$ (χ^2value = = 31.423).

The presence of diarrhea indicates poor absorption of nutrients in enteral nutrition. In the main group, diarrhea was not observed, which is a sign of good absorption of the mixture in the intestinal lumen. Diarrhea was noted in more than half of the cases in the comparison group. Diarrhea develops when unabsorbed water-soluble substances accumulate in the intestine, which attract water along the osmotic gradient. Osmotic diarrhea occurs when certain substances that cannot be absorbed through the wall of the colon remain in the intestine. These substances lead to the fact that an excess amount of water remains in the feces, causing diarrhea.

Abdominal pain was more common in the comparison group than in the main group. When comparing the groups by the criterion of "abdominal pain" using the chi-square test, there were no significant differences at $p < 0.05$ (the value of $\chi^2 = 0.277$).

Table 10

Results of study on probe removal in groups

Group	Number of Patients	Probe Removal, days
Basic	45	4 [3; 4]
Comparison	32	5 [4; 6]

When comparing the mean values (median and quartiles) of the time of tube removal (Table 10) in both groups, it was noted that the tube was removed in the main group on average one day earlier than in the comparison group.

The significance of differences between groups in probe removal time was confirmed using nonparametric Kolmogorov – Smirnov criterion ($Z = 2.204293659$; $p < 0.001$).

Further in Table 11 the indicators of general and biochemical blood analysis in patients of two groups before and after surgical treatment are presented.

In the comparison group, after surgery, there was a significant decrease in the number of leukocytes ($p < 0.05$), an increase in the level of total protein and albumin ($p1 < 0.05$ and $p2 < 0.001$, respectively), and a decrease in the level of ALT and AST ($p1 < 0.001$ and $p2 < 0.05$, respectively).

In the main group after the operation, there was a significant increase in hemoglobin ($p < 0.01$), a decrease in the number of leukocytes ($p < 0.01$), a decrease in the level of urea and creatinine ($p < 0.01$), an increase in the level of total protein and albumin ($p < 0.01$), a decrease in the level

Table 11

Results of general and biochemical blood tests in patients of main group and comparison group

Value	Comparison Group		Study Group	
	Preoperatively: *Me* [25 %; 75 %]	Postoperatively: *Me* [25 %; 75 %]	Preoperatively: *Me* [25 %; 75 %]	Postoperatively: *Me* [25 %; 75 %]
Hemoglobin	133[127.75; 137.25]	130[124.75; 135.25]	125 [104.25; 135]	131[129; 135.25]**
Erythrocyte	3.85[3.6; 4.2]	3.75[3.5; 4.2]	3.8[3.45; 4.23]	3.8[3.7; 4.2]
Leukocytes	11.4[9.98; 13.13]	7.25[6.6; 8.35]*	12.45[11; 14.6]	7.3[6.75; 7.8]**
Thrombocytes	229.5[194.5; 267.8]	202.5[196.2; 251.3]	232[199; 304.8]	227[210; 250.3]
Urea	7.15[6.38; 7.55]	7.8[6.85; 8.65]	9.45[9; 11.3]	7.1[6.38; 8]
Creatinine	107[89.75; 121.25]	99.5[88.75; 114]	126[120; 138.5]	99[87; 105]
Total protein	58[55.75; 61]	64[62; 65.25]*	54[49.75; 57]	75[69.75; 78]
Albumin	29[28; 31]	35[34; 37]*	29[26; 32]	48.5[46; 50]
ALT	50[43; 62]	43[34.75; 45]*	58.5[49; 89]	42.5[39; 44]
AST	49[42.5; 61.25]	44.5[41.25; 49]*	62 [53; 87.75]	46.5[44; 48.25]
Bilirubin	15.6[13.78; 17.83]	15.5[14.75; 16.55]	18.3[15.8; 20.28]	14.9[14.3; 15.73]
Glucose	5[4.5; 5.73]	5.1[4.6; 5.5]	5.3[4.8; 5.6]	4.9[4.4; 5.23]

Note: * – differences with the comparison group before surgery are significant at $p < 0.05$.

of ALT and AST 9 ($p < 0.01$), a decrease in the level of bilirubin and glucose ($p < 0.01$).

When comparing the biochemical blood test parameters after surgery, the main group showed a lower urea level ($p < 0.05$), a more pronounced increase in the level of total protein and albumin after the therapy ($p < 0.01$), compared with the corresponding data of the comparison group. No reliable differences were found between the patient groups for other parameters of the general and biochemical blood test after surgery.

The decrease in the urea level in the main group indicates favorable processes of deamination reactions of amino acids supplied with the patient's diet, in contrast to the comparison group, where the urea level does not decrease, but, on the contrary, increases slightly.

The increase in the amount of protein and albumin in the blood of patients in the main group indicates a significantly more successful elimination of protein-energy deficiency than in the comparison group, where an insignificant increase was statistically confirmed.

In our study, virtually all patients had some degree of nutritional status impairment. Only one patient out of 80 had no nutritional status impairment.

Early initiation of enteral nutrition is recommended [13]. The standard polysubstrate isocaloric enteral diet is the basis for initiating enteral nutrition.

Over the last three decades, our country has widely used foreign-made enteral formulas, the nutrient composition of which is known and is used depending on the state of the body. There are 17 global companies producing enteral nutrition, and it is known that modern enteral formulas are produced by mixing individual nutrients obtained on high-tech equipment, assembling, like a food designer, according to a given nutritional value. However, the raw material base and technologies used by foreign manufacturers in the manufacture of such formulas are in top-secret mode. In the conditions of uncertainty, sanctions and the current geopolitical crisis, our country is in dire need of its own enteral nutrition technologies.

The specialized food product for tube feeding GASTROAUXILIUM, developed by specialists of the Scientific and Production Center for Healthy Nutrition Technologies of the Saratov State Medical University named after V.I. Razumovsky, has technological solutions that are different from foreign ones, based not on the principles of high-tech production and the isolation of individual nutrients from the food raw material base, but on the principles of food combinatorics of natural domestic food products, enzyme technologies and IR dehydration processes. Such technological solutions are import-independent, economically feasible and physiologically justified.

Enteral food product for tube feeding GASTROAUXILIUM, intended for severe postoperative patients with abdominal pathologies, is a complete means of enteral nutrition with an innovative technological component, possessing a native microbiome-forming nutrient composition, a complete isocaloric formula. It differs from well-known enteral mixtures – food constructors of isolated nutrients – by its completely natural composition of food raw

materials with a preserved bioactive profile, combined according to the rules of dietary nutrition with minimal technological impact on the product (without ultra-processing), without the addition of food additives: stabilizers, preservatives.

The present study of the effectiveness of enteral mixtures for tube feeding GASTROAUXILIUM in comparison with the standard Fresubin was conducted during a 28-week randomized controlled trial. During the study of enteral mixtures for tube feeding GASTROAUXILIUM, we obtained convincing data on the effectiveness and safety of the studied product.

In our opinion, the most important endpoints are the following: in the main group, compared with the comparison group, the duration of paresis resolution was, on average, statistically significantly 2 days shorter.

As a local complication, diarrhea was observed in 3 patients out of 46 (6.5 %) in the main group, in 28 patients out of 34 (82.4 %) in the comparison group. As a general complication, diarrhea was not observed in patients in the main group, in patients in the comparison group, diarrhea was a frequent occurrence and was observed in 18 cases out of 34 (52.9 %).

When comparing the mean values (median and quartiles) of the time of probe removal in both groups, it was noted that the probe was removed in the main group on average one day earlier than in the comparison group. These data obtained a statistically significant result.

Changes in blood parameters (urea, total protein, albumin) were statistically significant, which proves the successful elimination of protein-energy deficiency in patients of the main group, in contrast to the comparison group.

Conclusions

We believe that the results of the study of the daily nutritional complex of oligomeric dry enteral nutrition mixtures GASTROAXILIUM are in agreement with the literature data, successfully complement the scientific data on the need for nutritional support and will play an important role in improving the quality of treatment of severe postoperative patients with abdominal pathologies.

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NAVIGATION LITERACY OF PRIMARY HEALTH CARE PERSONNEL (USING THE EXAMPLE OF THE HEADS OF MEDICAL AND OBSTETRIC CENTERS IN ORENBURG REGION)

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НАВИГАЦИОННАЯ ГРАМОТНОСТЬ МЕДИЦИНСКИХ РАБОТНИКОВ ПЕРВИЧНОГО ЗВЕНА ЗДРАВООХРАНЕНИЯ (НА ПРИМЕРЕ ЗАВЕДУЮЩИХ ФЕЛЬДШЕРСКО-АКУШЕРСКИМИ ПУНКТАМИ ОРЕНБУРГСКОЙ ОБЛАСТИ)

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Objective. To assess navigation literacy of primary health care personnel (using the example of the heads of medical and obstetric centers in Orenburg region).
Materials and methods. Navigation literacy of primary health care personnel was assessed among all heads of medical and obstetric centers in Orenburg region ($n = 58$). For this purpose, a single-stage continuous online survey was conducted using a combined questionnaire developed by the Central Research Institute for Healthcare Organization and Informatization of the Ministry of Heath of the Russian Federation.
Results. The level of navigation literacy among the heads of the medical and obstetric centers of Orenburg region in 65.7 % of cases was excellent and sufficient. In the list of navigation skills, the heads of the medical and obstetric centers noted difficulties in the implementation of: issues of medical insurance (48.3 %), legal aspects of medical care and protection of patients' rights (27.5-48.3 %), healthcare reform (36.2 %). It was found out that from 63.7 % to 91.4 % of the heads of the medical and obstetric centers are aware of the ongoing state measures in the field of public health. The majority of the respondents (60.0 %) noted that they search for necessary information for professional purposes using digital tools. However, every third respondent (32.7 %) mentioned the difficulties in finding it on legislative issues, interpreting the quality and safety of food products according to their product labeling (27.6 %), solving problems related to mental health and well-being (18.9 %). These data demonstrate the need to improve navigation literacy of medical and obstetric centers managers in the digital environment.
Conclusions. The modern multilevel and multicomponent healthcare system is associated with the need to improve the navigation literacy of medical personnel. The data obtained determined the main directions for improving navigation literacy of the heads of medical and obstetric centers.
Keywords. Navigation literacy, primary healthcare, heads of the medical and obstetric centers.

Цель. Оценить навигационную грамотность медицинских работников первичного звена здравоохранения (на примере заведующих фельдшерско-акушерскими пунктами Оренбургской области)
Материалы и методы. Навигационная грамотность медицинских работников первичного звена здравоохранения оценена среди всех заведующих фельдшерско-акушерскими пунктами Оренбургской области ($n = 58$). Для этого был проведен одномоментный сплошной онлайн-опрос по комбинированному опроснику, разработанному Центральным научно-исследовательским институтом организации и информатизации здравоохранения Министерства здравоохранения Российской Федерации.
Результаты. Уровень навигационной грамотности у заведующих фельдшерско-акушерскими пунктами Оренбургской области в 65,7 % случаях был отличным и достаточным. Трудности в реализации навигационных навыков заведующие фельдшерско-акушерскими пунктами испытывали в сфере медицинского страхования (48,3 %), правовых аспектов оказания медицинской помощи, защиты прав пациентов (27,5–48,3 %), реформирования здравоохранения (36,2 %). Установлено, что от 63,7 до 91,4 % заведующих фельдшерско-акушерскими пунктами осведомлены о проводимых государственных мерах в сфере общественного здоровья. Большинство заведующих фельдшерско-акушерскими пунктами – это 60,0 % респондентов – отметили, что поиск необходимой информации в профессиональных целях осуществляют с помощью цифровых инструментов. Однако каждый третий (32,7 %) респондент отметил трудности её поиска по вопросам законодательства, интерпретации качества и безопасности продуктов питания согласно их товарной маркировке (27,6 %), решения проблем, связанных с психическим здоровьем и благополучием (18,9 %), что диктует необходимость совершенствования навигационной грамотности заведующих фельдшерско-акушерскими пунктами в цифровой среде.
Выводы. Современная многоуровневая и многокомпонентная система здравоохранения сопряжена с необходимостью повышения навигационной грамотности медицинских работников. Полученные данные определили основные направления совершенствования навигационной грамотности заведующих фельдшерско-акушерскими пунктами.
Ключевые слова. Навигационная грамотность, первичное звено здравоохранения, заведующий фельдшерско-акушерским пунктом.

INTRODUCTION

In the last decade, there has been an active transformation of the healthcare system [1–5], which is currently characterized by a multi-component and multi-level architecture[1] [6]. Particular attention is paid to improving and increasing the quality and accessibility of primary health care (PHC) [7; 8]. In this regard, for regions with a high proportion of rural population, for example in the Orenburg region, it is especially important to provide high-quality primary medical and health care at feldsher-obstetric stations (FOS) [9]. This is due to the fact that the organization of the work of the FAS and the level of work descriptors of paramedics largely determine the quality of primary health care in rural areas [10; 11]. At the same time, taking into account the arsenal of all regulated tasks of the FAS[2], the presence in the recommended staff of the FAS from among medical workers with secondary medical education of only the head of the FAS, the work function of the head of the FAS is not limited only to the management of a structural unit in organizations providing primary pre-medical medical care to the population[3], but also expands to the direct implementation of all areas of providing primary health care to the rural population. As a result, it is important for the head of the FAS not only to be able to directly provide primary health care at the request of the population, but also to be able to organize it. In order to make adequate decisions regarding the entry point into the patient's healthcare system, taking into account the required type and form of medical care [12; 13], the head of the FAS must have a sufficient level of navigational literacy in healthcare and be familiar with the current measures of state policy in the field of public health. As is known, the navigational literacy of the population itself is in most cases low [14]. As noted by L. Giese et al. [15], effective use of the healthcare system and navigation within it requires a special form of comprehensive health literacy – navigational literacy, that is, the ability to process information to successfully navigate the healthcare system and find the right help at the right time [16; 17]. In this regard, it is currently becoming relevant to study the navigation literacy of not only the population itself, but also health workers providing primary medical and social care in regions with a high proportion of rural population, in order to improve the efficiency of the health care system.

MATERIALS AND METHODS

An assessment of the navigation literacy of primary health care workers and the level of awareness of the already implemented measures of state policy in the field of public health was conducted among all heads of feldsher-obstetric stations in the Orenburg region ($n = 58$). For this purpose, a one-time continuous online survey was

[1] Schaeffer D., Hurrelmann K., Bauer U., Kolpatzik K., Altiner A., Dierks M., Ewers M., Horn A., Jordan S., Kickbusch I., Klapper B., Pelikan J.M., Rosenbrock R., Schmidt-Kaehler S., Weishaar H., Woopen C. National Action Plan Health Literacy. Promoting health literacy in Germany. 2018, available at: https://api.semanticscholar.org/CorpusID: 191667984.

carried out using a combined questionnaire developed by the Central Research Institute of Occupational Health and Social Development [18].

The navigational literacy in health issues (NL) of the heads of FAS was assessed by calculating the navigational literacy index, the formation of which is based on the results of the answers to a separate block of questions [19] according to the formula:

$$I_{ngs} = \frac{\text{Number of answers “simple”/ “very simple” of the question pool}}{\text{Number of reliable responses}}.$$

The final result of the navigation literacy index ranged from 0 (low level) to 100 points (high level). According to the European methodology for grading the obtained index results [20], each navigation literacy index was interpreted depending on the range of values it fell within. The problematic level of the oil-and-gas pool index was established in the case of its values from 50.0 to 66.6 points. If the oil-and-gas pool index values were less than 50 points, the level was considered insufficient. The obtained results of the navigation literacy indices were compared with the all-Russian data obtained during a survey among 2627 respondents over 18 years old, whose average age was 42 years [18]. The level of statistical significance of differences between the compared groups was determined using the χ^2 Pearson criterion. Differences were considered statistically significant at $p \leq 0.05$. All calculations of statistical indicators were performed in the Statistica 10.0 program.

In this study, 58 Heads of FAS of the Orenburg region over 18 years of age took part in the survey; the average age of respondents was 49.6 ± 1.37 years. Most of the surveyed Heads of FAS (75.9 %) lived with their official spouse in a marriage and had children over 15 years of age (63.9 %) (Table 1). The majority of respondents belonged to the social group passive (50.0 %), were social-safe (84.5 %), had high social integration (53.4 %), and also not in a difficult financial situation (65.5 %) (Table 2).

At the next stage, in order to detail the leading factors in the formation of the navigation literacy index, an assessment was made of the respondents’ answers to each question in the block. Data for each question and the answers chosen by the majority of respondents were presented in the form of Me [Q25; Q75]. For this purpose, the respondents' answers to each question were interpreted into a point score (Table 3). In addition, for each question, the proportion of respondents from all those who indicated the answer "Difficult" and / or "Very difficult" was calculated. To do this, the respondents’ answers to each question were interpreted into a point score (Table 3). In addition, for each question, the proportion of respondents from all those who indicated the answer “Difficult” and / or “Very difficult” was calculated.

RESULTS AND DISCUSSION

It was found that the average navigation literacy of FAS Heads corresponded to a sufficient level (75.8 points), which is 1.6 times

Table 1

Socio-demographic characteristics of respondents

Parameter	*n*	%
Gender:		
female	58	100.0
male	0	0.0
Marital status:		
I live with my official spouse in the same household	44	75.9
single / I live alone	4	17.2
single not married / I live in a civil marriage in one household	10	6.9
In an official / in a civil marriage, but live separately	0	0.0
Having children:		
No children	2	3.4
Less than 15 years	13	22.4
Less than 15 and more than 15 years	6	10.3
More than 15 years	37	63.9
Level of education:		
Secondary special	58	100.0

Table 2

Social activity of respondents

Question	Social Parameter	*n*	%
Social activity			
How many close people do you have that you can count on if you have serious personal problems?	Social passive	29	50.0
	Medium active	11	18.9
	Social active	18	31.1
Social safety			
How easy is it for you to get help from your neighbours if you need it?	Socially safe	49	84.5
	Socially unsafe	9	15.5
Social integrity			
How much attention / interest do people show in what you do (e.g. work / hobbies)	Much enough	31	53.4
	Average	13	22.4
	Little	14	24.2
Financial position			
How easy or difficult is it for you to pay your bills at the end of the month?	Not heavy	38	65.5
	Heavy	20	34.5

Table 3

Interpretation of scores of the level of proficiency of fas heads in navigation literacy in the field of healthcare

Parameter	Number of Scores			
	1	2	3	4
Interpretation (level of proficiency)	Very difficult	Difficult	Light	Very light

Таблица 4

Proportion of respondents with different levels of navigation literacy in health issues, %

Level Ings	Observation Group	
	FAS Heads	All-Russian Population Survey Data
Excellent	55.2	26.8
Sufficient	15.5	10.8
Problematic	8.7	12.6
Insufficient	20.6	49.6

higher compared to the all-Russian data (48.8 points). At the same time, the majority of respondents had an excellent and sufficient level of Ings (70.7 %). Nevertheless, 20.6 % of respondents had an insufficient level of Ings (Table 4).

Taking into account the age of the respondents, it was found that the lowest Ings was among people aged 55–64 years (71.5 points), and the highest was among people aged 25–34 years (90.2 points). Moreover, in all age categories Ings Head of paramedics was 1.5–1.7 times higher compared to all-Russian data and 1.4–1.8 times higher compared to the data of the Volga Federal District population survey (Fig. 1).

According to the data presented in Fig. 2, it is evident that the majority of FAS Heads chose the answer "Easy" for 9 questions out of 12, as evidenced by the calculated median, Q25 and Q75, the value of which was "3". However, when calculating the proportion of respondents who answered the questions with the answers "Difficult" and / or "Very difficult", it is noteworthy that up to 48.3 % of respondents experienced difficulties associated with forecasting the costs of medical services in relation to their compensation under the compulsory medical insurance policy. Every third Head of FAS had difficulties interpreting changes in the provision of medical care associated with changes in the legal regulation of the healthcare sector. 27.5 % of respondents had difficulty finding information on legal issues regulating relationships between patients and healthcare providers. For every fifth head of FAS, it is difficult to conduct a preliminary assessment of the predicted satisfaction of patients with the planned medical service. Up to 22.4 % of respondents experienced difficulties in comprehensively understanding the functioning of the healthcare system. Every fifth head of FAS also indicated difficulties in finding funds and officials in the healthcare system who would allow them to clarify issues regarding the details of providing medical care (18.9 and 17.2 %).

Most Heads of FAS are aware of the actively implemented state policy in the area of prevention of chronic non-communicable diseases and risk factors for their development and progression (Fig. 3).

Probably, the measures implemented within the framework of the federal project to combat diabetes, aimed at training medical personnel from 2023, determined the

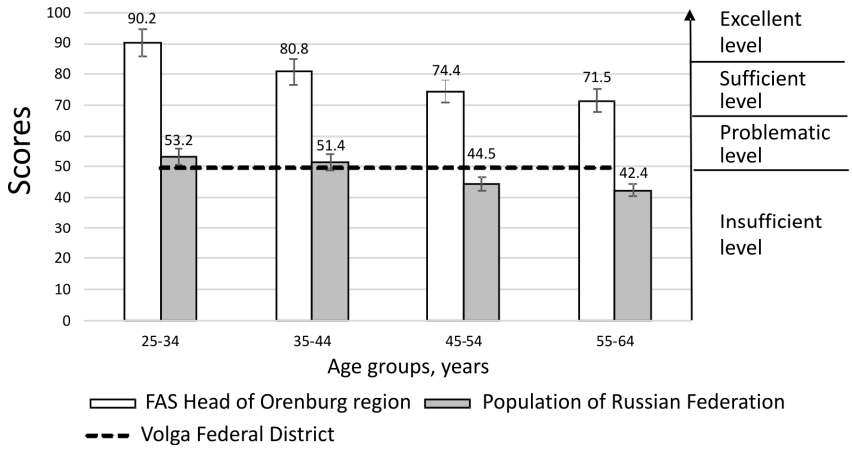

Fig. 1. Literacy index of health navigation taking into account age and territory of survey respondents

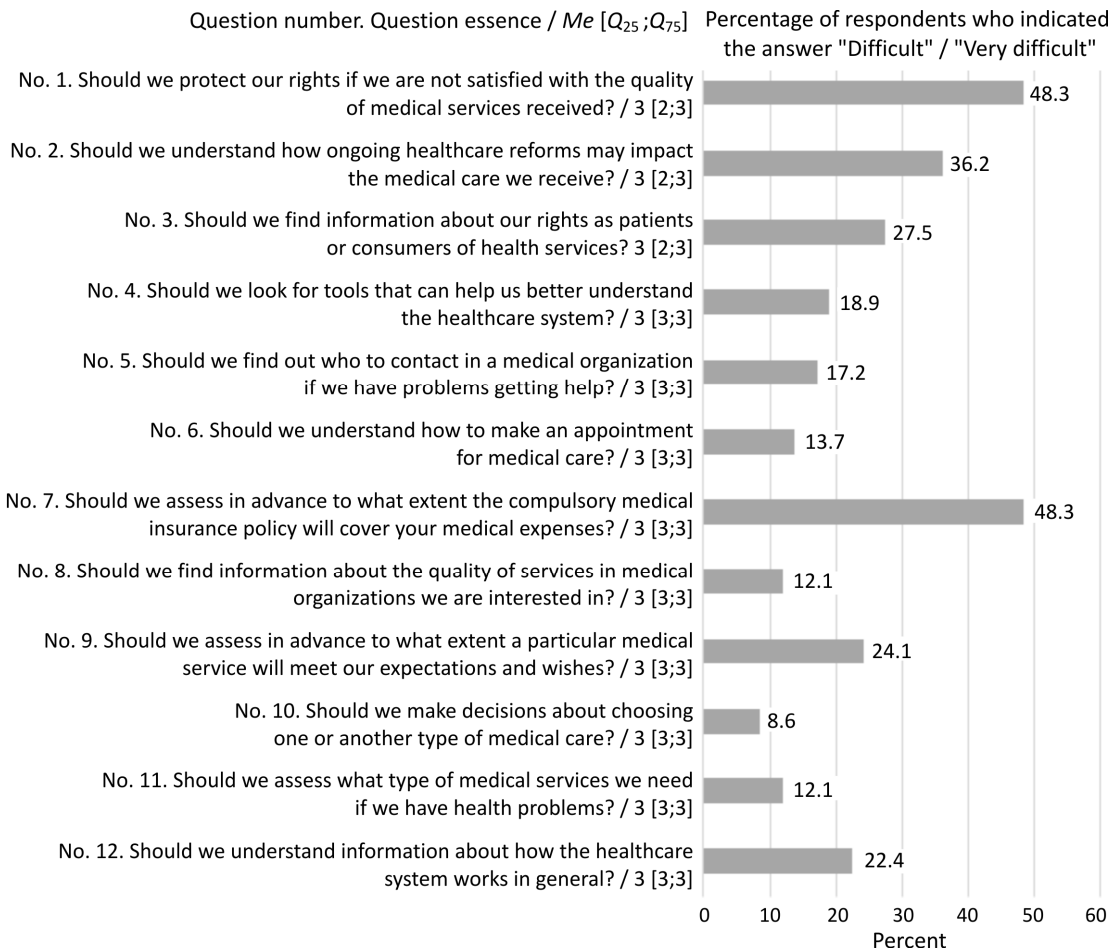

Fig. 2. Indicators of level of navigation skills in healthcare system of heads of FAS

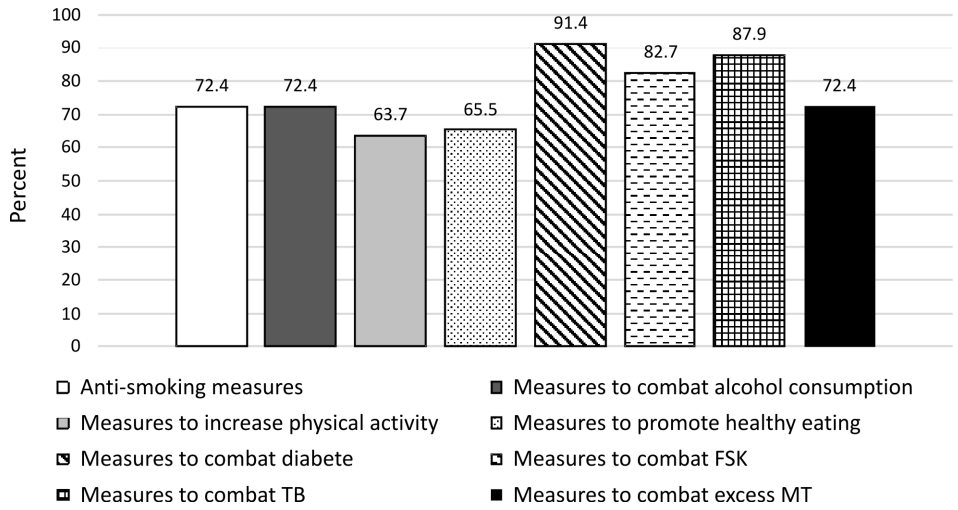

Fig. 3. Awareness of respondents about measures of state policy implemented in field of public health

highest proportion of Heads of FAS aware of measures to combat diabetes (91.4 %), compared with other measures of state policy. It is noteworthy that the minimum number of respondents aware of the implemented state policy measures was identified in the area of increasing physical activity (63.7 %), while it is known that this factor plays a leading role in preventing the development of chronic non-communicable diseases, and also significantly determines the patient's well-being and the course of an existing disease. Despite the fact that the majority of Heads of FAS are aware of the state policy measures in various areas, the fact that from 27.6 to 36.3 % of respondents had an insufficient level of awareness of the measures being implemented in the territory of the Russian Federation in the area of combating bad habits, physical inactivity, excess body weight, as well as in the area of popularizing healthy eating remains alarming.

It is known that most of the information about the implemented state policy measures, as well as data on the implemented federal projects, are presented in sufficient detail on the official websites of the Ministry of Health, as well as on specialized portals. In the digital environment, information is systematically updated by developers of projects and reforms. In this regard, it is important that healthcare workers are aware of them. Along with official sources, there are many platforms in the digital environment that broadcast information that does not reflect modern scientific achievements, as well as government policy in the field of healthcare. It is also becoming relevant for health workers to be critical in assessing the information analyzed in the digital environment. It has been shown that up to 96.6 % of FAS Heads searched for information on medical topics and health. Moreover, when it was necessary to search for information on health issues, 60.1 % of FAS Heads used digital resources: the Internet, social networks, and every third (33.4 %) consulted with colleagues (Fig. 4).

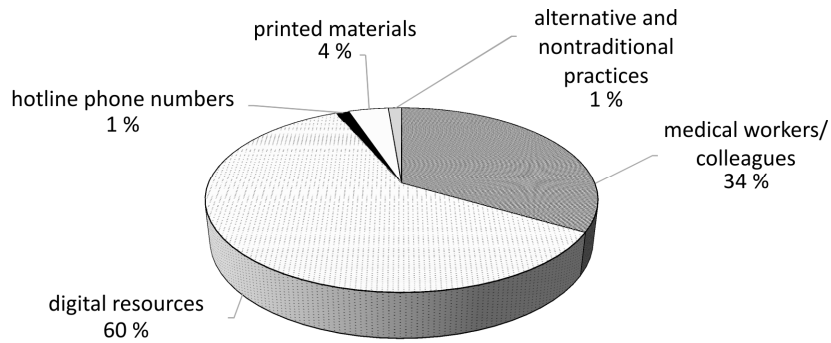

Fig. 4. Structure of respondents' answers about sources used to search for information on medical topics and health issues

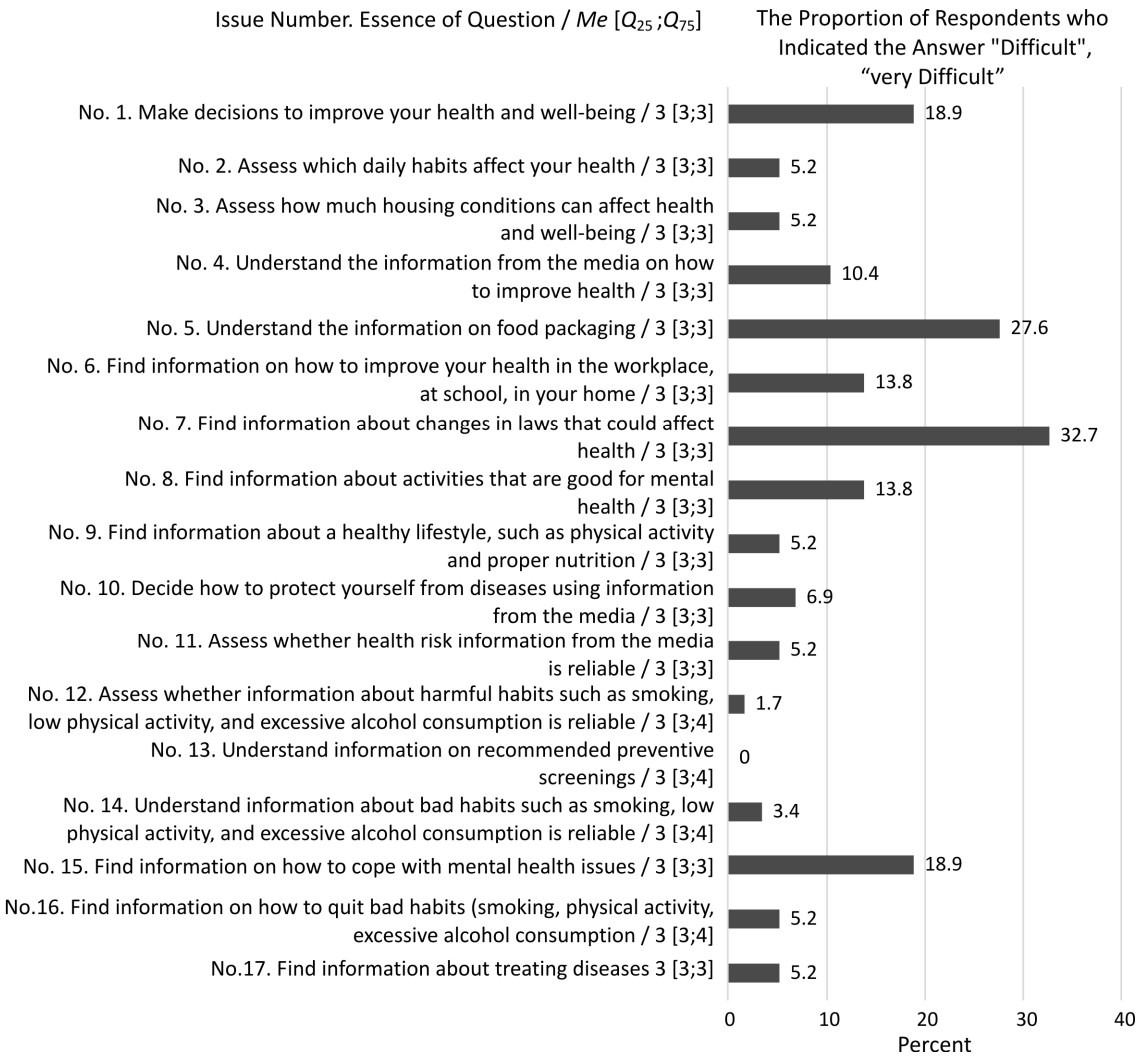

Fig. 5. Indicators of level of navigation skills in health care system of heads of FAS

It is shown that for the Heads of FAS it is easy and very easy to find, understand, evaluate and apply information on medical issues in the field of health, as evidenced by the data obtained from the respondents' answers (Fig. 5). At the same time, attention is drawn to the proportion of FAS Heads who noted difficulties in finding, understanding, evaluating and applying information on some medical issues in the field of health. Thus, every third respondent experienced difficulties in finding information about changes in the area of legislation regulating healthcare issues (32.7 %).

Between 13.8 and 18.9 % of respondents experienced difficulties in finding information on issues of regulating mental well-being and promoting health at their place of professional activity or study, respectively. For every third head of FAS, it was difficult or very difficult to understand the information placed on the packaging of food products (27.6 %), which requires the inclusion of hygiene topics on assessing the quality and safety of food products in advanced training programs. It is also necessary to pay attention to the fact that every fifth respondent finds it difficult and / or very difficult to make a decision on the implementation of measures aimed at health and well-being, which indicates an insufficient level of development of professional skills in this area.

CONCLUSIONS

1. The modern multi-level and multi-component health care system is associated with the need to improve the navigation literacy of health workers. Improving the organization and provision of primary health care to the rural population is possible by increasing the level of navigation literacy of health workers of FAS as one of the supporting structures for the provision of primary health care to the population living in rural areas.

2. The level of navigation literacy among the Heads of FAS of the Orenburg region was excellent and sufficient in 65.7 % of cases, which is 1.8 times higher than the all-Russian data. The level of navigation literacy was maximum among FAS Heads aged 25–34 years (90.2 %) and minimum – among those aged 55–64 years (71.5 %).

3. Heads of FAS have been found to have difficulties in implementing navigation skills in the field of health insurance (48.3 %), legal aspects of providing medical care, protecting patients' rights (27.5–48.3 %), and healthcare reform (36.2 %).

4. Most Heads of FAS are aware of the state measures in the sphere of public health (63.7–91.4 %). At the same time, every third has an insufficient level of awareness regarding the implementation of state measures to combat bad habits, physical inactivity, excess body weight, and unhealthy diet, against the background of a high level of awareness regarding the fight against diabetes, tuberculosis, and diseases of the circulatory system.

5. The established fact of commitment to searching for information using digital resources (60.0 %) and the difficulty of searching using this method for information on a number of preventive issues, such as: changes in legislation regulating the work of the healthcare system (32.7 %), interpreta-

tion of the quality and safety of food products according to their product labeling (27.6 %), solving problems related to mental health and well-being (18.9 %), dictates the need to improve the navigation literacy of FAS Heads in the digital environment.

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Authors Contribution.

D.N. Begun, V.V. Bulychev, Ye.V. Bulycheva – concept and study design.

Ye.V. Bulycheva – data collection.

V.V. Bulychev – analysis and results interpretation.

Ye.L. Borschuk – literature review.

Ye.V. Bulycheva, D.N. Begun – manuscript preparation.

Ye.L. Borschuk – editing the manuscript.

All authors reviewed the results of the work and approved the final version of the manuscript.

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CLINICAL CASE

Scientific Article
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A CLINICAL CASE OF TREATMENT OF TEMPOROMANDIBULAR JOINTS DISEASE CAUSED BY OCCLUSIVE DISORDERS

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КЛИНИЧЕСКИЙ СЛУЧАЙ ЛЕЧЕНИЯ ДИСФУНКЦИОНАЛЬНОГО СОСТОЯНИЯ ВИСОЧНО-НИЖНЕЧЕЛЮСТНЫХ СУСТАВОВ, ОБУСЛОВЛЕННОГО ПАТОЛОГИЧЕСКОЙ ОККЛЮЗИЕЙ

А.М. Шаров*, О.В. Орешака, А.В. Ганисик, Е.А. Дементьева
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A method of treatment, described in this clinical case, is aimed at eliminating disorders of occlusal relationships of the dentition, (Patent No. 2797641 dated 06/07/2023) contributing to the normalization of TMJ functioning. At the first stage of treatment, a repositioning occlusal splint was used, applied to all teeth of the lower jaw, which was being corrected for six months. This stage was considered completed on the basis of the following criteria: absence of the patient`s complaints and smooth movements of the mandible without deviations and clicks on objective examination, as well as formation of symmetrical graphs of the TMJ condyles movement on axiographic ex-

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amination, an optimal location of the TMJ condyles on sagittal projections of MSCT and positive changes in the bioelectric activity of the masticatory muscles, towards higher and more symmetrical values on both sides.
Further treatment was carried out by an orthodontist with a non-removable technique, using a brace system. Wearing of the occlusal splint continued until the braces system was put on the teeth of the lower jaw. It was then replaced by composite linings in the projection of the first molars of the upper jaw.
Dynamic monitoring of the patient for half a year after the end of the treatment indicated remission of TMJ disease.
Normalization of occlusal relationships of dentitions in intact dentitions and small defects through splint therapy followed by the use of a brace system is a minimally invasive and effective method of treatment TMJ diseases.
Keywords. Axiography, electroneuromyography, brace system, temporomandibular joint.

Существует проблема повышения эффективности функциональной реабилитации пациентов с заболеваниями височно-нижнечелюстного сустава путём применения комплексного подхода к коррекции окклюзии.
В представленном клиническом случае описан способ лечения, направленный на устранение нарушений окклюзионных взаимоотношений зубных рядов (патент № 2797641 от 07.06.2023), способствующий нормализации функционирования височно-нижнечелюстного сустава (ВНЧС). На первом этапе лечения использовали репозиционную окклюзионную шину, наложенную на все зубы нижней челюсти, коррекцию которой проводили на протяжении шести месяцев. Критериями для окончания данного этапа служило отсутствие жалоб пациента, а при объективном обследовании – плавные движения нижней челюсти без девиаций и щелчков, а также формирование симметричных графиков движения мыщелков ВНЧС при аксиографическом исследовании, наличие оптимального расположения мыщелков ВНЧС на сагиттальных проекциях МСКТ и положительных изменений показателей биоэлектрической активности жевательных мышц в сторону более высоких и симметричных значений с обеих сторон.
Последующее лечение проводилось врачом-ортодонтом несъёмной техникой посредством брекет-системы. Ношение окклюзионной шины продолжалось до этапа расположения брекет-системы на зубах нижней челюсти, в этот период она была замещена композитными накладками в проекции первых моляров верхней челюсти. Динамическое наблюдение за пациентом в течение полугода после окончания лечения свидетельствовало о ремиссии заболевания ВНЧС.
Таким образом, нормализация окклюзионных взаимоотношений зубных рядов посредством сплинттерапии с последующим применением брекет-системы при интактных зубных рядах и малых их дефектах является малоинвазивным и эффективным способом лечения заболеваний ВНЧС.
Ключевые слова. Аксиография, электронейромиография, брекет-система, височно-нижнечелюстной сустав.

INTRODUCTION

According to domestic and foreign studies, temporomandibular joint (TMJ) diseases are a fairly common pathological condition in patients [1–3]. In turn, the World Health Organization notes that dysfunctional TMJ conditions are included in the triad of the most frequently occurring diseases in dental patients [4–6].

Violation of somatic homeostasis, neuromuscular dysfunctions, occlusal disorders are directly related to the state of the TMJ [7–9]. Modern diagnostic methods allow us to determine both the structural component of the disorder and the functional one; however, having a polyetiological nature, TMJ diseases often require an interdisciplinary approach to treatment [10–13].

According to modern data from domestic and foreign authors, there is a tendency towards an increase in the number of young people with TMJ pathology, including those with intact dental arches [14–16]. As a rule,

this is due to the presence of orthodontic pathology or previously conducted irrational orthodontic treatment [17; 18].

The problem of treating patients with TMJ pathology with intact dental arches and minor defects requires a more detailed study and the introduction of new approaches to the rehabilitation of this category of patients.

Clinical Case

Patient M., 26 years old, came in April 2021 with the following complaints: constant painless clicking in the parotid-chewing area on the right when opening the mouth.

The patient's medical history is not complicated. He denies the presence of other somatic diseases.

Progression of the present disease: In February 2021, severe clicking in the right TMJ, which limited opening of the mouth, accompanied by pain, first appeared. After seven days of taking NSAIDs, the pain gradually subsided.

Palpation of the TMJ and masticatory muscles is painless. When opening the mouth, a deviation of the lower jaw is determined with a click at the beginning of opening the mouth in the area of the right and left TMJ, asynchronous movement of the condyles. The midline is shifted to the right by 5 mm.

In the oral cavity: the mucosa is without visible pathological changes, the anterior teeth of the upper jaw overlap the same teeth of the lower jaw by 1/2 of their height, vestibular displacement 1.3, 2.2, crowded arrangement of the anterior teeth of both jaws.

The closure of the dental arches in the position of central occlusion is sharply hampered with a distal and rightward shift at the end of mouth closure.

The absence of 4.6, the presence of recurrent caries 2.6; artificial metal-ceramic crowns of satisfactory quality 1.5, 2.7 are determined (Fig. 1).

According to the electroneuromyography data, significant differences in the biopotentials of the masticatory muscles were found in the patient's initial state, due to the predominance of muscle contraction on the left (Table 1).

The results of the axiography performed at the diagnostic stage indicated a dysfunctional state of the TMJ, which was characterized by the intersection of tracks during vertical movements of the lower jaw (Fig. 2).

Based on the results of the main and additional research methods, the following diagnosis was established: K07.61 – "clicking jaw" syndrome, forced distal-lateral

	П	П	К	П									П/С	К	
8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
	П	О												П	

Fig. 1. Dental formula according to Viola of Patient M.

Table 1

Results of electroneuromyography of masticatory muscles before treatment

Muscle localization	Average amplitude, μV	
	Right (dex)	Left (sin)
Central occlusion position		
Masticatory	485	750
Temporal	358	690
Muscles of the floor of the mouth	135	288

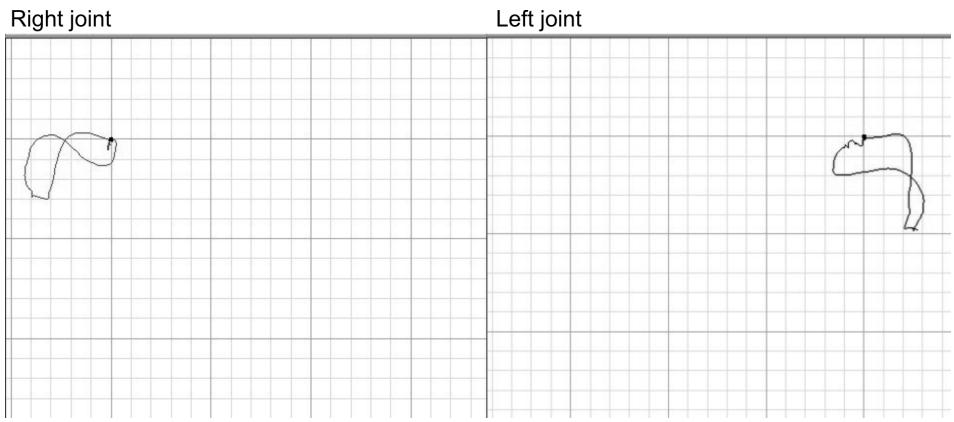

Fig. 2. Axiography of movements of TMJ condyles during vertical movements of the lower jaw before treatment

Fig. 3. The repositioning occlusal splint is located on the teeth of the lower jaw

occlusion, myodysfunctional syndrome, K07.31 – displacement of 1.3, 2.2, K07.30 – crowding of the anterior teeth, K08.1 – partial absence of teeth on the lower jaw, class III according to Kennedy, K02.1–2.6 recurrent dentin caries, class I according to Black.

Treatment: the initial stage was the sanitation of the oral cavity, according to the dental formula, then the production of an occlusal repositioning splint was performed (Fig. 3), for this purpose an analog impression was obtained from the lower jaw, according to which a plaster model was made, necessary for the stage of determining the most optimal position of the lower jaw in relation to the upper one using a wax template, according to which an occlusal splint was made from colorless plastic using hot polymerization (Belacril-E GO, Vladmiva, Russia) (see Fig. 3).

Subsequently, periodic reline of the splint occlusal surface was performed for six months. To confirm the effectiveness of the occlusal reline stage, diagnostic measures were repeated, which were characterized by the absence of patient complaints, and during an objective examination, smooth movement of the lower jaw without deviations and clicks.

The graphic representation of the movements of the lower jaw, recorded using axiography, indicated a positive change in the trajectories of the movement of the condyles of the TMJ, which were characterized as symmetrical, harmoniously concave tracks (Fig. 4).

The MSCT visualized the optimal and symmetrical position of the condyles in both TMJs (Fig. 5).

The values of the biopotentials of the masticatory muscles by the end of splint therapy according to electroneuromyography data had minimal differences, which indicated their almost symmetrical contraction on the left and right halves of the face (Table 2).

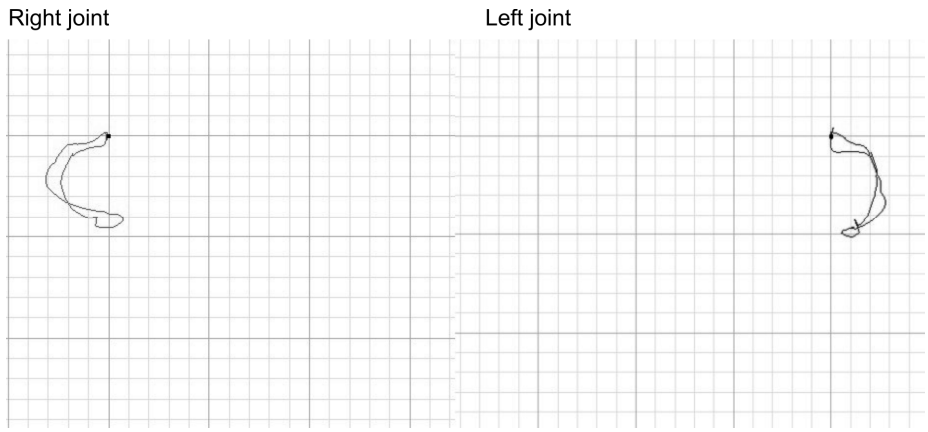

Fig. 4. Axiography of the TMJ during vertical movements of the lower jaw with an occlusal splint

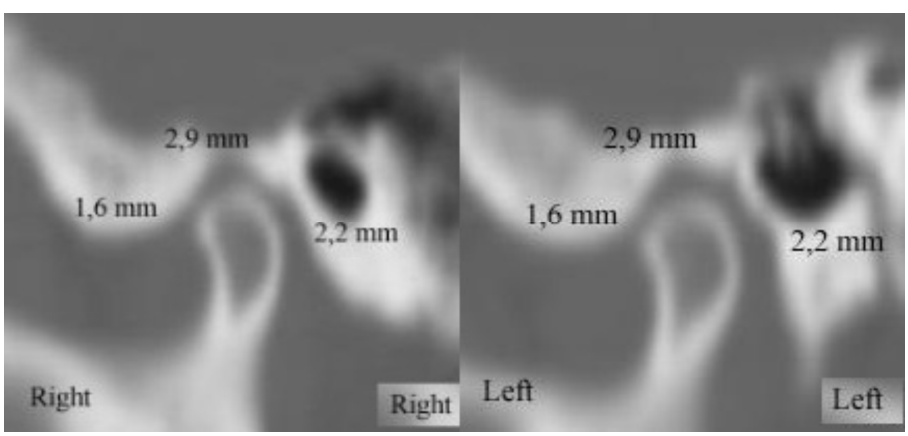

Fig. 5. MSCT of the TMJ (in the position: closed mouth) in the sagittal projection with an occlusal splint

Table 2

Results of electroneuromyography of masticatory muscles with occlusal splint

Muscle localization	Average amplitude, μV	
	Right (dex)	Left (sin)
Central occlusion position		
Masticatory	785	780
Temporal	688	695
Muscles of the floor of the mouth	300	305

The results of the conducted studies allowed us to move on to orthodontic treatment, which consisted of the sequential application of the bracket system first to the teeth of the upper jaw; wearing of the occlusal splint continued at this stage (Fig. 6).

Fig. 6. Braces on the teeth of the upper jaw

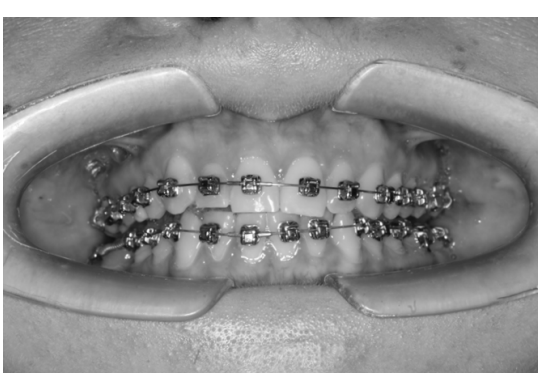

Fig. 7. The stage of applying the brace system to the teeth of the lower jaw

After three months, the bracket system was fixed to the lower row of teeth (Fig. 7) and fixation of photocomposite overlays, which in this clinical case were located in the area of teeth 1.6, 2.6, wearing of the splint was completed at this stage (Fig. 8).

Completion of orthodontic treatment was accompanied by the removal of the bracket system with the installation of retainers on the oral surface of the anterior teeth of the upper and lower jaws, as well as prosthetics with an artificial crown on an implant in the area of the missing 4.6 (Fig. 9).

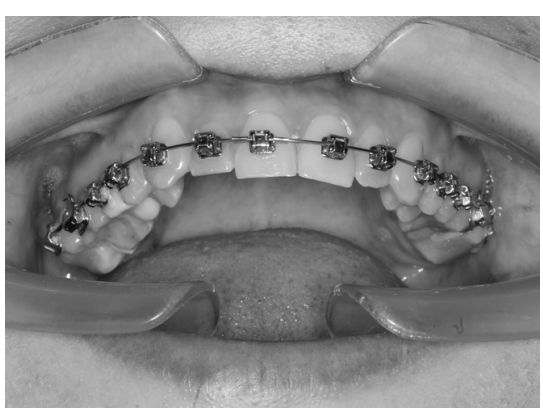

Fig. 8. Photocomposite onlays on the occlusal surfaces of the first molars of the upper jaw

Fig. 9. Closing of the dental arches after completion of treatment

Results and discussion

The presented clinical case describes a method for correcting disorders of the occlusal relationships of the dental arches and, as a consequence, normalizing the functioning of the TMJ.

At the stage of clinical examination, asynchronous movement of the TMJ condyles, clicks, deviation of the lower jaw during opening and closing of the mouth, and the presence of orthodontic pathology of individual groups of teeth were determined.

The graphs obtained during axiography were characterized by the formation of asymmetrical tracks, and the results of measuring the biopotentials of the masticatory muscles during an electroneuromyographic study indicated an asymmetry in the tension of the masticatory muscles of the left and right halves of the face.

At the diagnostic and treatment stage, a repositioning occlusal splint was used on the lower row of teeth. During periodic examinations over a period of six months, the occlusal splint was adjusted until the therapeutic position of the lower jaw was achieved. The criteria for the effectiveness of this stage were the absence of complaints, symptoms in the TMJ area and masticatory muscles during palpation, as well as data from additional diagnostic methods – the formation of symmetrical graphs of the movement of the TMJ condyles during an axiographic study, the presence of an optimal location of the TMJ condyles on the sagittal projections of MSCT and changes in the bioelectrical activity of the masticatory muscles towards higher and symmetrical values on both sides.

Subsequent treatment was performed by an orthodontist using fixed equipment using a bracket system. Wearing an occlusion splint continued until the bracket system was placed on the teeth of the lower jaw, at which time it was replaced by composite overlays in the projection of the first molars of the upper jaw.

Conclusions

Normalization of occlusal relationships of dental arches by means of splint therapy followed by the use of a bracket system for intact dental arches and minor defects is a minimally invasive and effective method of treating TMJ diseases.

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A CLINICAL CASE OF SKIN LYMPHOCYTOMA IN A YOUNG WOMAN

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КЛИНИЧЕСКИЙ СЛУЧАЙ ЛИМФОЦИТОМЫ КОЖИ У МОЛОДОЙ ЖЕНЩИНЫ

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A 25-year-old woman came to consult a dermatovenerologist. The woman complained of a rapidly progressing painless lump on the right wing of her nose which developed after photo-rejuvenation treatment and the development of herpetic infection.in the place of a previous lipoma removed by radio wave surgery. The clinical picture was characterized by a solitary disc-shaped plaque, 2 cm in size, bluish-reddish-brownish in color, of a doughy consistency, significantly protruding above the skin surface, with clear borders and a smooth, shiny surface. There was a complex differential diagnostics, the final diagnosis was confirmed by the results of a histological examination, which revealed changes characteristic of lymphocytoma. The patient was treated with aminoquinoline preparations and topical glucocorticosteroids and rapid positive dynamics with complete regression of the skin pathological process was observed.

A clinical case of skin lymphocytoma that occurred after several successive trigger factors such as lipoma formation and removal, photo rejuvenation procedures, and herpes infection is presented in the article. This is a fairly rare disease that does not have a pathognomonic clinical picture, so it is difficult to differentiate and diagnose it. The results of a pathomorphological examination are essential for the diagnosis. A positive effect with a complete regression of skin changes can quickly occur if treated correctly.

Keywords. Skin lymphocytoma, trigger effect, solitary plaque, pathomorphological examination.

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Представлен клинический случай лимфоцитомы кожи. К дерматовенерологу обратилась женщина, 25 лет, у которой на правом крыле носа, на месте предшествующей липомы, удаленной методом радиоволновой хирургии, после серии процедур фотоомоложения и развития герпетической инфекции возникло быстро прогрессирующее безболезненное образование. Клиническая картина характеризовалась солитарной бляшкой дискообразной формы размером 2 см, синюшно-красно-буроватого цвета, тестоватой консистенции, значительно выступающей над поверхностью кожи, с четкими границами и гладкой, блестящей поверхностью. Проведена сложная дифференциальная диагностика, окончательный диагноз подтвердили результатами гистологического исследования, при котором выявили характерные для лимфоцитомы изменения. В лечении применялись аминохинолиновые препараты и топические глюкокортикостероиды, которые привели к быстрой положительной динамике с полным регрессом кожного патологического процесса.

Таким образом, в данном случае определена лимфоцитома кожи, возникшая после нескольких последовательных триггерных факторов: образования липомы и ее удаления, процедур фотоомоложения, герпетической инфекции. Это достаточно редкое заболевание, не имеющее патогномоничной клинической картины, поэтому его сложно дифференцировать и диагностировать. Решающее значение для диагностики имеют результаты патоморфологического исследования. При корректных лечебных мероприятиях может быстро наступить положительный эффект с полным регрессом кожных изменений.

Ключевые слова. Лимфоцитома кожи, триггерное воздействие, солитарная бляшка, патоморфологическое исследование.

INTRODUCTION

Lymphocytoma (benign lymphoplasia of the skin, benign lymphadenosis of Befferstedt, sarcoidosis of Spiegler-Fendt, lymphoid hyperplasia of the skin) is a rare dermatosis caused by benign reactive hyperplasia of the lymphoid tissue of the skin [1]. The disease was first described by E. Spiegler in 1894 and H. Fendt in 1900, but the term "lymphocytoma" was only proposed in 1921 by Kaufmann – Wolf [2]. It is observed mainly in young women. The etiology is not fully understood. Provoking factors include trauma, insect bites, infectious skin diseases, ultraviolet radiation, and external irritating drugs [3].

There are several clinical forms of the disease. The localized form is characterized by the development of a solitary plaque or node of a hemispherical shape, 2 cm in size, sharply protruding above the skin level, of a doughy or dense elastic consistency, pink-bluish-brownish in color, with a smooth shiny surface, without subjective sensations. Diascopy reveals a yellowish color [4]. In the superficial infiltrative form, slightly raised above the skin disc-shaped infiltrates of a pinkish-bluish color are determined [5]. The disseminated form is characterized by the appearance of multiple asymmetrically located brownish-brown nodules the size of a pea. A combination of several clinical forms may be observed [6].

The pathological process affects the skin of the face, ears, neck, genitals, inguinal and axillary areas. The general condition does not suffer. Blood tests show lymphocytosis. The disease has a chronic relapsing wave-like course lasting up to three years, sometimes with spontaneous regression [7].

Lymphocytoma is quite difficult to diagnose, since it has clinical similarities with

a number of dermatoses: cutaneous B-cell lymphoma, lymphosarcoma, lymphangioma, leukemides, hypereosinophilic syndrome, sarcoidosis, discoid lupus erythematosus, eosinophilic granuloma of the face, Kimura disease, keratoacanthoma, basal cell skin cancer, tuberculous lupus [8].

Of decisive importance in diagnosis is the pathomorphological examination, which reveals an intradermal lymphocytic infiltrate with an admixture of other immunocompetent cells, separated from the unchanged epidermis by a strip of collagen. Sometimes follicle-like structures with germinal centers and macrophage reaction are observed [9]. Phagocytized material – "polychromatic bodies" – is found in the cytoplasm of macrophages. An increase in the number of vessels with hyperplastic endothelium and proliferation of stromal elements with the development of fibrosis are noted.

Nonsteroidal anti-inflammatory drugs, aminoquinoline drugs, intralesional administration and external use of glucocorticosteroids are used in treatment. In case of infectious predictors of the disease, antibacterial or antiviral drugs are added to the therapy [10].

We present a description of a clinical case of cutaneous lymphocytoma. Patient S., born in 1998, complained of a formation on the right wing of the nose, not accompanied by subjective sensations or changes in the general condition.

Anamnesis morbi: in 2020, a lipoma was observed at the same place, which was removed by radio wave surgery with the formation of a normotrophic scar. From October 2023 to January 2024, a series of facial photo rejuvenation procedures were performed. In February 2024, a herpes simplex appeared in the area of the scar, after which the right wing of the nose turned red and began to change shape. The pathological process progressed rapidly. She repeatedly consulted dermatovenerologists, but no diagnosis was made, an assumption was made about the malignant nature of this disease and it was recommended to completely remove the skin changes with their subsequent histological examination.

Anamnesis vitae and objective condition are unremarkable. General blood analysis shows minor lymphocytosis (lymphocytes – 4.22 x 109/l; in the leukocyte formula they make up 56 %). The immunogram also shows lymphocytosis – 4.26 x 109/l, with an increase in the level of B-lymphocytes – 0.98 x 109/l; 24 %.

Status localis: the skin pathological process is limited, localized on the right wing of the nose, represented by a solitary plaque of a disc-shaped form, 2 cm in size, significantly protruding above the surface of the skin, with clear boundaries, bluish-red-brownish in color, doughy consistency, with a smooth, shiny surface (Fig. 1). Diascopy reveals a yellowish color of the element.

Pathomorphological examination of skin biopsy: the epidermis is unchanged. In the dermis around the skin appendages and vessels, a lymphocytic infiltrate with inclusions of eosinophils, plasma cells, histiocytes is determined, separated from the epidermis by a narrow strip of collagen.

Fig. 1. Clinical presentation of cutaneous lymphocytoma in a 25-year-old woman

Fig. 2. Regression of the pathological process after the therapy

Based on the presented data, a diagnosis was made: cutaneous lymphocytoma, treatment was carried out: hydroxychloroquine 200 mg 2 times a day for two weeks and externally clobetasol cream 0.05 % once a day for a month, after which a complete regression of the skin pathological process was noted (Fig. 2).

The present disease developed in a young woman aged 25 after a series of local effects on the skin: the formation of a lipoma and its removal, photo rejuvenation procedures, herpes infection. The dermatosis was characterized by a rapidly progressing course and was characterized by the presence of a solitary disc-shaped plaque on the right wing of the nose, 2 cm in size, bluish-red-brownish in color, sharply protruding above the surface of the unchanged skin. Complex differential diagnostics were carried out. The final diagnosis was established based on the results of pathomorphological examination, which revealed changes characteristic of lymphocytoma. The treatment led to rapid and complete regression of skin changes.

Conclusions

1. Surgical and cosmetic procedures can be triggers in the development of cutaneous lymphocytoma.

2. It is difficult to clinically differentiate cutaneous lymphocytoma from a number of other dermatoses, therefore the diagnosis is established based on the results of a pathomorphological study.

3. This determines the correct choice of treatment measures on which the patient's health depends.

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V.D. Elkin – edited and finally approved the manuscript sent to the editors.

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RETRO AND PROSPECTIVE ANALYSIS OF COMPLEX TREATMENT OF A PATIENT WITH A POLYOSTOTIC FORM OF OSTEOCLASTOMA OF THE MAXILLOFACIAL REGION: CLINICAL OBSERVATION

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РЕТРО- И ПРОСПЕКТИВНЫЙ АНАЛИЗ КОМПЛЕКСНОГО ЛЕЧЕНИЯ ПАЦИЕНТА С ПОЛИОССАЛЬНОЙ ФОРМОЙ ОСТЕОКЛАСТОМЫ ЧЕЛЮСТНО-ЛИЦЕВОЙ ОБЛАСТИ: КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

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In global literature there is not sufficient information on the course of the polyostotic form of osteoclastoma and methods of its treatment. For this reason, the analysis of this clinical case may be interesting for oncologists, maxillofacial surgeons and dentists of various specialties, who can reveal both the onset and recurrence of the disease. A characteristic feature of the course of this disease is the relapse of neoplasms with localization of foci in various parts of the upper and lower jaw.

A clinical case of polyostotic form of jaw osteoclastoma and patient`s management tactics from 2006 to 2024 are described in the article. The disease was first diagnosed in 2006, when a neoplasm was revealed in the

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right part of the lower jaw. The neoplasm was removed by resection and mandibular defect was replaced by a carbon implant with further prosthesis.
In 2011 a new neoplasm was detected on the left side in the frontal part of the upper jaw. At the same time a relapse of the disease was diagnosed with a new tumor focus in the lower jaw on the right. Surgical treatment was performed. Firstly, the neoplasm in the frontal area of the upper jaw was removed with replacement of the defect with a resection prosthesis. And secondly, a removal of the tumor on the lower jaw with resection of the chin within healthy tissues and replacement of the defect with an implant made of carbon-carbon material "Uglecon M" were performed.
In 2023 the patient was invited to the dental hospital of the Clinical Multidisciplinary Medical Center of E.A. Vagner Perm State Medical University for dispensary observation and evaluation of the results of the treatment.
The obtained results indicate the need for medical follow-up of patients after surgery for osteoblastoclastoma. The effectiveness of jaw implants made of carbon-carbon composite material " Uglecon M" was proved as well.
Keywords. Polyostotic form of osteoblastoclastoma, osteoblastoclastoma of the jaw bones, relapse, carbon implant, complex treatment.

В отечественной и зарубежной литературе недостаточно сведений о течении полиоссальной формы остеокластомы и методах лечения пациентов при ее выявлении. В связи с этим разбор данного клинического случая может представлять интерес для челюстно-лицевых хирургов, онкологов и для стоматологов разного профиля, которые могут выявить как дебют, так и рецидив заболевания. Особенностью течения полиоссальной формы остеокластомы является повторное появление новообразования после удаления с локализацией очагов в различных участках верхней и нижней челюсти.
Представлено описание клинического случая и тактика ведения пациентки с полиоссальной формой остеокластомы челюстей в период с 2006 по 2024 г. Заболевание у пациентки впервые диагностировано в 2006 г., когда было выявлено новообразование в области нижней челюсти справа. Лечение заключалось в удалении опухоли путем резекции нижней челюсти, замещении дефекта челюстным имплантатом из углерод-углеродного материала «Углекон-М» и последующего протезирования. В 2011 г. было обнаружено новообразование во фронтальном отделе верхней челюсти слева и диагностирован рецидив заболевания в виде нового очага опухоли в области подбородочного отдела нижней челюсти справа. Проведено оперативное лечение – удаление новообразования в области фронтального отдела верхней челюсти слева с замещением дефекта резекционным протезом и на нижней челюсти – удаление опухоли с резекцией подбородочного отдела в пределах здоровых тканей и замещением дефекта имплантатом из углерод-углеродного материала «Углекон-М».
В 2023 г. пациентка была вызвана в стоматологическую больницу Клинического многопрофильного медицинского центра Пермского государственного медицинского университета имени академика Е.А. Вагнера Минздрава России (далее – КСБ ПГМУ) для проведения диспансерного наблюдения и оценки результатов проведенного лечения.
Полученные результаты свидетельствуют о необходимости диспансерного наблюдения пациентов после оперативного вмешательства по поводу остеобластокластомы, а также об эффективности использования челюстных имплантатов из углерод-углеродного композиционного материала «Углекон-М».
Ключевые слова. Полиоссальная форма остеобластокластомы, остеобластокластома челюстных костей, рецидив, углеродный имплантат, комплексное лечение.

INTRODUCTION

Currently, benign tumors and tumor-like bone lesions account for 40–50 % of all cases of bone neoplasia. However, these figures may be reduced due to the difficulties of differential diagnosis and the possible long-term asymptomatic course of the disease [1–7]. One example of such tumors is osteoblastoclastoma (osteoclastoma), localized in various parts of the skeleton, often in the jaw bones, especially in the

body of the lower jaw. The prevalence of this disease in women of reproductive age (18 to 35 years) is twice as high as in men.

There are cellular, cystic and lytic forms of osteoblastoclastoma, which differ in growth rates and the nature of bone tissue lysis. Resection of the affected bone areas with simultaneous reconstructive restoration of the integrity of the jaw is the optimal and most rational surgical method for treating this pathology1 [1; 2]. Malignant variants of osteoblastoclastoma are less common and are classified by origin and degree of lytic destructive activity [8–10].

The literature, both domestic and foreign, covers in detail aspects of surgical technique and tactics of managing patients with osteoblastoclastoma of the jaw bones [3]. However, there is very little information on the treatment of the polyostotic form of the disease. In this regard, the analysis of the presented clinical case is relevant.

The aim of the study is to analyze a clinical case of complex treatment of a patient with a polyostotic form of osteoclastoma of the jaw bones.

Clinical Case

Patient M., 19 years old, came to the clinical dental hospital of Perm State Medical University in 2006 with complaints about the presence of a neoplasm in the area of the lower jaw on the right (Fig. 1, *a, b*), mobility of the lower teeth and paresthesia in the area of the lower lip on the right.

The diagnosis of osteoclastoma of the lower jaw on the right (ICD code – D 16.5) was verified by performing an incisional biopsy followed by pathohistological examination.

An individual comprehensive treatment plan was developed by an interdisciplinary team consisting of a maxillofacial surgeon, an orthopedic dentist and an anesthesiologist, and consisted of the following stages: planning the resection zone; conducting an anthropometric study to select an implant; preliminary orthopedic preparation for surgery; planning anesthesia; surgical treatment; delayed prosthetics; rehabilitation.

At the stage of choosing surgical treatment options, autoplasty, replacement of the postoperative defect with a reconstructive plate or an orthotopic implant made of carbon-carbon material "Uglekon-M" were considered. Taking into account the properties of implant systems made from the “Uglekon-M" material, in particular high biological inertness, dimensional stability over time, compliance of the structure and physical and mechanical characteristics with the native bone indicators, the possibility of restoring the shape of the face, and the absence of the need for additional surgical interventions, the choice was made in favor of this implant material.

At the first stage, preliminary orthopedic preparation was carried out, which consisted of the manufacture and fixation of a non-removable orthopedic structure to hold the fragments of the lower jaw. Then we proceeded to the next stage – the surgical treatment itself. Under endotracheal anesthesia, the tumor was removed with partial resection of the lower jaw and simultaneous replacement of the postoperative defect with an orthotopic carbon implant “Uglekon-M” (Fig. 2), wound suturing and drainage installation. Since the implant was individually

a *b*

Fig. 1. The patient's appearance before complex treatment: a – full face, b – profile (2006)

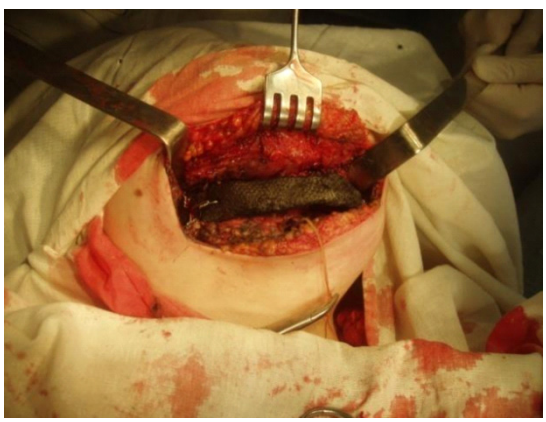

Fig. 2. Installation of an orthotopic implant made of Uglekon-M material

modeled according to the shape and dimensions of the suspected defect, a good aesthetic and functional result was ensured.

Based on the results of the pathohistological examination, the diagnosis was confirmed: osteoblastoclastoma of the lower jaw.

On the control orthopantomogram, an implant is fixed in the area of the defect of the lower jaw on the right, the fixation is satisfactory. The shadows of metal-density ligature sutures are visible in the area of the right lower jaw branch and the chin section of the lower jaw (Fig. 3).

The patient was discharged in satisfactory condition on the 10th day after the operation.

Six months after the surgery, a removable dental prosthesis with a metal base and clasp fixation was made and fixed to the patient's lower jaw. The patient had no complaints and did not attend examinations as part of the dispensary observation due to her residence in a remote area of the Perm Territory.

In 2011, during pregnancy, the patient noticed the appearance of a neoplasm and its growth in the frontal region of the upper jaw on the left. In the postpartum period he contacted the Clinical Hospital of Perm State Medical University.

A CT scan of the upper jaw was performed. In the area of the frontal part of the upper jaw on the left, a neoplasm of a non-uniform structure, cellular in shape in the projection of teeth 1.3–1.1, with a cuff-shaped thickening of the alveolar part was found (Fig. 4).

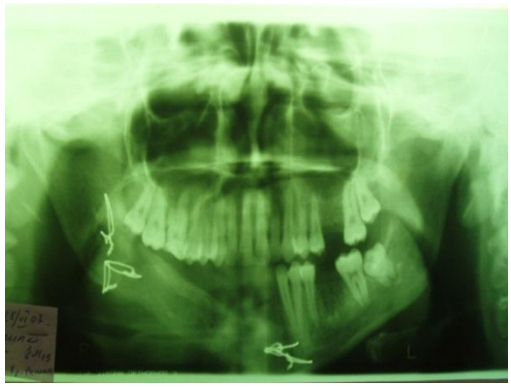

Fig. 3. Orthopantomogram, condition six months after surgery (removal of osteoclastoma of the lower jaw in the body area on the right with simultaneous replacement of the defect with an orthotopic carbon implant "Uglekon-M")

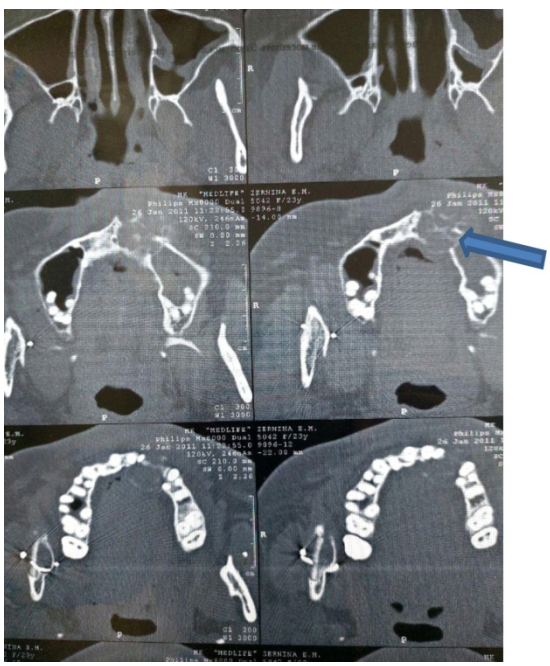

Fig. 4. CBCT: tumor in the upper jaw area, 2011

After receiving the results of an incisional biopsy, a diagnosis of osteoclastoma of the frontal maxilla was established (ICD 10 code – D16.4). A resection dentofacial prosthesis for the upper jaw was made according to the defined boundaries of the partial resection of the upper jaw. Surgical treatment was performed – removal of a neoplasm in the area of the frontal part of the upper jaw on the left with partial resection of the upper jaw, with closure of the surgical wound with a flap from the mucous membrane of the cheek and one-stage replacement of the defect with a resection prosthesis. In the postoperative period, a course of anti-inflammatory therapy was administered. As a result of additional examination, a control CBCT scan revealed a neoplasm in the frontal part of the lower jaw on the right side from the lingual side. An incisional biopsy was performed. The diagnosis was established: D16.5 – osteoclastoma of the lower jaw on the right, relapse (Fig. 5), confirmed by the results of pathohistological examination.

Patient M. was re-hospitalized for planned surgical treatment.

Due to the presence of a polyostotic form of osteoclastoma of the jaw bones in the patient, autotransplantation was contraindicated. After conducting an anthropometric study and selecting an orthotopic carbon implant, the neoplasm was removed with partial resection of the chin section of the lower jaw and replacement of the carbon orthotopic implant of the lower jaw "Uglekon-M" with a new one.

During the surgical intervention, complete osseointegration was revealed and formation of a bone-implant unit with the ingrowth of bone tissue into the structures of the implant made of carbon-carbon composite material (Fig. 6).

Fig. 5. CBCT: osteoclastoma of the lower jaw on the right, relapse, 2011

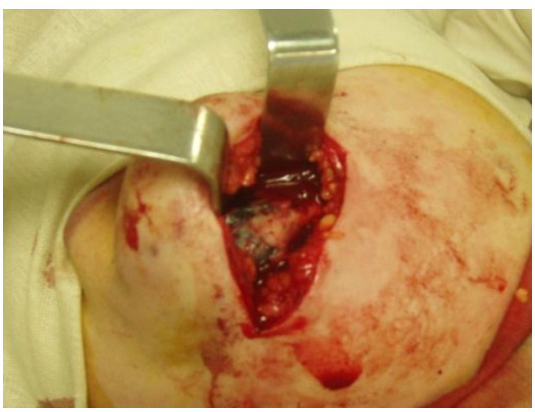

Fig. 6. Osteoclastoma of the lower jaw on the right, relapse (intraoperative), 2011

RESULTS AND DISCUSSION

In December 2023, the patient was called to the Clinical Hospital of Perm State Medical University for a follow-up examination. Upon examination, the facial configuration and shape of the lower jaw were satisfactory, the scar in the submandibular region was pink, smooth, and even. The movements of the temporomandibular joints are synchronous, smooth, and painless. The mouth opens freely, up to 4.0 cm. In the oral cavity: the crown of tooth 3.7 is completely destroyed, its roots are pigmented. On the lingual side in the projection of tooth 3.7, a bulge of the outer cortical plate of a round shape with a diameter of up to 1.5 cm was found, painless upon palpation. Percussion of tooth 3.7 is moderately painful. The mucous membrane above the neoplasm is not changed in color, there is a pale pink scar in the area of the implant. The midline is located centrally, the defects of the dental arches are replaced by removable dentures for the upper and lower jaw. When palpating the lower jaw, no mobility is determined in the area of the bone-implant junction. The patient is satisfied with the achieved treatment result (Fig. 7).

When collecting the patient's life history, it was found that in 2016 there was a second pregnancy, which ended in childbirth. In the summer of 2023, the patient noticed a change in the shape of the alveolar part in the area of tooth 3.7, but did not seek medical help. CBCT was performed – a focus of bone rarefaction was found,

Fig. 7. Condition when viewed (side view, bottom view, straight), 2023

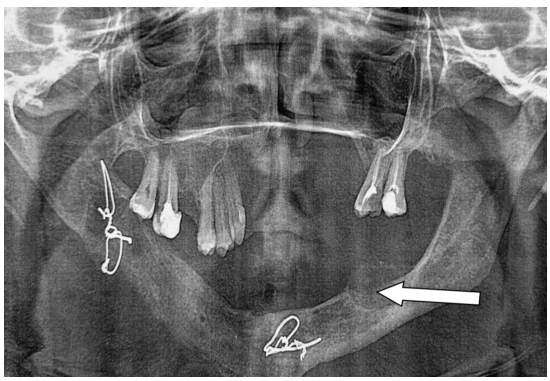

Fig. 8. OPTG: neoplasm in the lower jaw area on the left, 2023

heterogeneous in density in the projection of tooth 3.7, up to 1.5 cm (Fig. 8). Bulging of the cortical plate on the lingual side. here are no signs of relapse of the neoplasm in the upper jaw and in the area of implant fixation on the lower jaw. Osteointegration is observed at the border of the bone-implant unit. A preliminary diagnosis is chronic periodontitis of tooth 3.7, neoplasm in the area of the alveolar process of the lower jaw on the left.

Patient M. underwent extraction of tooth 3.7, scraping of the neoplasm was performed, the material was sent for cytological examination. Given the clinical picture of the polyostotic form of osteoclastoma, in terms of differential diagnostics, it was recommended to conduct an X-ray examination of all bone structures in order to exclude myeloma disease. After receiving the research results, myeloma disease was not confirmed.

As a result of X-ray, cytological examination and subsequent pathohistological examination, the diagnosis was established: fibroma of the lower jaw on the left, the presence of relapse of osteoblastoclastoma was not confirmed. In April 2024, the fibroma of the lower jaw on the left was removed at the Clinical Hospital of Perm State Medical University using intraoral access. At the time of discharge, the patient's condition was satisfactory, orthopedic treatment and further dispensary observation were recommended for the patient.

Conclusions

A rare clinical case of treatment of a patient with localization of osteoclastoma in the lower jaw on the right, in the frontal part of the upper jaw on the left, with re-

currence of the formation in the lower jaw on the right in the late stages after treatment is presented, which indicates the presence of a polyostotic form of osteoclastoma of the jaw bones in the patient.

The emergence of a new focus and relapse of the neoplasm occurred after a previous pregnancy, therefore, a connection between this pathology and changes in hormonal levels occurring during pregnancy cannot be ruled out, however, this factor has not been confirmed and requires study.

The analysis of the described clinical situation allowed us to prove that timely surgical treatment and verification of the diagnosis provide a good result, while regular dispensary observation in the form of examination at least once a year for patients who underwent surgery to remove osteoclastoma is strictly mandatory. Particular attention in this aspect should be paid to women of reproductive age.

The use of implants made of carbon-carbon composite material "Uglekon-M" in the polyostotic form of osteoclastoma is the method of choice, which has proven its effectiveness in replacing post-resection defects of the lower jaw.

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STUDY OF ANTI-INFLAMMATORY ACTIVITY AND ACUTE TOXICITY INDICATORS OF NEW SILVER SALT OF PYRAZOLE-3-CARBOXAMIDE

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ИЗУЧЕНИЕ ПРОТИВОВОСПАЛИТЕЛЬНОЙ АКТИВНОСТИ И ПОКАЗАТЕЛЕЙ ОСТРОЙ ТОКСИЧНОСТИ НОВОЙ СЕРЕБРЯНОЙ СОЛИ ПИРАЗОЛ-3-КАРБОКСАМИДА

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Objective. To study the anti-inflammatory activity and some toxicological indicators of the new derivative of pyrazole-3-carboxamide SSP.
Materials and methods. To assess the biological activity of the compound, its anti-inflammatory effect was studied in the model of acute inflammatory edema caused by sub-plantar injection of carrageenan solution into a rat`s hind leg. The duration effect was assessed by the intensity of suppression of the inflammatory re-

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sponse in relation to the control level. In order to study the safety of the substance, the local irritant effect was determined when applied cutaneously in the experiments on rats. The severity of the irritant effect was assessed by the erythema degree, the amount of edema and the increase in local skin temperature. In addition, acute toxicity of the substance under study was determined. The test compound and reference drugs were applied to the skin.

Results. The study of acute toxicity of the compound SSP and the reference drug nystatin when applied cutaneously to rats showed that LD_{50} of both substances was more than 2500,0 mg/kg. Indicators of the degree of local irritating effect of the drugs demonstrate its absence. At the same time, the studied SSP compound has no anti-inflammatory effect administered either orally or cutaneously.

Conclusions. The data obtained allow us to classify the new silver salt of pyrazol-3-carboxamide SSP as a class 5 non-toxic substance. The studied SSP compound has no local irritant effect and does not demonstrate anti-inflammatory activity in the carrageenan inflammation model.

Keywords. Silver salt of pyrazol-3-carboxamide, acute toxicity, carrageenan inflammation model, local irritant effect, nystatin, nimesulide.

Цель. Изучить противовоспалительную активность и некоторые токсикологические показатели нового производного пиразол-3-карбоксамидов SSP.

Материалы и методы. Для оценки биологической активности соединения исследовали его противовоспалительное действие на модели острого воспалительного отека, вызванного субплантарным введением в заднюю лапу крысы раствора каррагенина. Эффект длительности оценивали по выраженности торможения воспалительной реакции по отношению к контрольному уровню. С целью изучения безопасности вещества определяли местно-раздражающее действие в экспериментах на крысах при накожном нанесении. Выраженность раздражающего действия оценивали по степени эритемы, величине отека и увеличению местной температуры кожи. Кроме того, определялась острая токсичность изучаемого вещества. Исследуемое соединение и препараты сравнения наносились на кожу.

Результаты. Исследование острой токсичности соединения SSP и препарата сравнения нистатина при накожном нанесении крысам показало, что $ЛД_{50}$ обоих веществ составила более 2500,0 мг/кг. Показатели, позволяющие оценить степень местно-раздражающего действия препаратов, свидетельствуют о его отсутствии. При этом исследуемое соединение SSP не проявляет противовоспалительной активности ни при пероральном, ни при накожном применении.

Выводы. Полученные данные позволяют отнести новую серебряную соль пиразол-3-карбоксамида SSP к 5-му классу практически нетоксичных веществ. Соединение SSP не проявляет местно-раздражающего действия и не обладает противовоспалительной активностью на модели каррагенинового воспаления.

Ключевые слова. Серебряная соль пиразол-3-карбоксамида, острая токсичность, каррагениновая модель воспаления, местно-раздражающее действие, нистатин, нимесулид.

INTRODUCTION

Superficial mycoses that are caused by dermatophytes and also yeast fungi are an important public health problem affecting different age groups of the population [1–4]. Topical agents are more often used for the treatment of this pathology. They are the most popular on the pharmaceutical market and account for more than 90 % of sales of all antimycotics [5].

In this regard, the search for new compounds with antifungal activity, which can potentially be used for topical therapy of mycoses, is an actual direction of pharmacy. The fact that the substance has additional pharmacological effects, such as anti-inflammatory activity, may contribute to the

acceleration of the recovery process during this pathology.

The most important characteristic of the supposed pharmaceutical substance is the absence of negative effects on the human body, which is reflected by such indicators as acute toxicity, irritant effect.

The aim of the study is to investigate the anti-inflammatory activity and some toxicological indicators of a new pyrazole-3-carboxamide derivative SSP.

MATERIALS AND METHODS

The biological activity of a new silver salt of pyrazole-3-carboxamide, SSP was evaluated. It showed high antifungal activity in planktonic culture (pMIC501.0 mg/L, pMIC90 15.6 mg/L) and biofilm (sMIC50 11.8 mg/L) [6]. The studies were conducted in experiments on animals obtained from the nursery "Andreevka", Moscow region. The animals were kept in compliance with the rules of laboratory practice (GLP) and the Order of the Ministry of Health of the Russian Federation No. 199n dated 01.04.2016 "Rules of Good Laboratory Practice", as well as the terms of the guidelines for conducting preclinical studies of pharmaceuticals [7]. The conducted studies were approved by the Bioethics Commission of the Federal State Budgetary Educational Institution of Higher Professional Education PGFA of the Ministry of Health of the Russian Federation (protocol No. 7 of 20.01.2023).

Indomethacin ointment for external use produced by BIOSINTEZ PJSC (Russia), nimesulide produced by Ozon LLC (Russia) and nystatin produced by BIOSINTEZ PJSC (Russia) were used as reference pharmaceuticals.

Determination of acute toxicity of the compound at the dermal application was realized according to the guideline P 1.2.3156-13 "Assessment of toxicity and danger of chemical substances and their mixtures for human health ". The study included experiments on rodents (rats). Animals were randomly divided into groups by randomization. The absence of external signs of disease and homogeneity of groups by body weight (± 10 %) were considered as criteria for acceptable randomization.

The experimental medication in the suspension form in dimethyl sulfoxide and the comparison medication were applied on the skin in the back area using a dispenser in increasing doses according to Litchfield-Wilcoxon method. The fur of the animals was removed at the site of application 24 h before the beginning of the experiment. Control animals were dosed with diluent, which was dimethyl sulfoxide. Dosing was carried out according to the total mass of the sample. Groups of five animals of the same sex were used for the study of each medication dose. Besides, there were similarly sized groups of control animals, which were applied to comparison medications in the same way in an amount equivalent to the maximum tested dose of the medication.

The animals were observed for 14 days from the beginning of the experiment. Mor-

tality, time of animal death, symptoms of poisoning, daily observation of general condition and behavior, weighing, evaluation of feed and water consumption were recorded. The dead animals were autopsied and macroscopically examined. All intoxicated animals were euthanized in a CO_2 chamber and autopsied after 14 days. Macroscopic description and determination of mass ratios of internal organs and histologic studies were conducted.

Anti-inflammatory activity was determined on non-linear white rats weighing 180–250 g, both sexes, sexually mature – on the model of acute inflammatory edema caused by subplantar injection of 0.1 ml of 1 % aqueous solution of carragenin into the back paw of the rat at different routes of injection into the body [7]. The studied compound in the form of a suspension in dimethyl sulfoxide in the amount of 0.5 ml was applied on the skin of the foot of rats of the first group 1 h before injection of the phlogogenic agent. The second group of animals was injected orally at a dose of 50 mg/kg 1 h before carrageenan injection.

Animals that did not receive the medication served as a control. The increase in foot volume, indicating the development of edema, was evaluated oncometrically after 3 h after injection of the phlogogenic agent, which means at the peak of edema formation. The anti-inflammatory effect was evaluated by the expression of inhibition of the inflammatory reaction in relation to the control level. If this indicator was more than 30 %, the result was considered as positive.

The local irritant effect of the medication was studied in experiments on nonlinear white rats weighing 180–210 g, of both sexes, sexually mature – by dermal application. The studied substance was placed in an amount of 0.5 g in the form of a paste on a previously depilated skin area of about 6 cm2. These skin areas were covered with gauze attached with a plaster. The exposure period lasted 4 h, after which the substance was removed. The evaluation of the irritant effect was conducted for 14 days. The expression of irritant effect was evaluated by the degree of erythema, the amount of edema (thickness of the skin fold at the application site) and the increase of local skin temperature. The degree of erythema was evaluated using colorimetric rulers of S.V. Suvorov in points. Skin fold thickness was measured using a thickness gauge TR-1–10 in millimeters. Skin temperature was measured using an electrothermometer. Animals, to which the comparison medication was applied in the same way, were used as control.

Statistical analysis of the results was conducted using the following program package Statistica 8.0. The results were analyzed by variation statistics using the Fisher-Student method [8].

RESULTS AND DISCUSSION

Evaluation of the acute toxicity of the compound SSP and the comparison medication nystatin by dermal application on rats showed that the LD50 of both sub-

stances was more than 2500.0 mg/kg. The obtained data indicate that sex differences in the acute toxicity indices of the two substances do not appear. There were no lethal effects when applied it on the skin. The use of the compared compounds in doses higher than 2500.0 mg/kg was practically impossible.

Thus, the compound SSP and the comparison medication nystatin are practically equivalent (equitoxic) in terms of acute toxicity. The clinical picture of intoxication at their single use in maximum possible amounts is characterized by the absence of signs of toxic effect, changes in the general condition and behavior of animals. Species and sex differences were not observed in the course of intoxication. The clinical picture of intoxication, caused by both compared medications, is the same.

The results of body weight measurements of the animals that experienced intoxication when the medications were applied topically at maximum doses are presented in Table 1.

Dynamics of body weight of experimental animals in all groups does not significantly differ from control data. There are no statistically significant deviations in body weight of animals in the groups receiving the compared medications.

All animals that survived intoxication, as well as animals of the control group, were euthanized in a CO2 chamber at the end of the study. External examination of rats that were killed after 14 days from the beginning of the experiment, did not reveal any significant differences between the experimental animals and the control animals. All rats are of standard proportions, with average weight. Fur is shiny, clean looking, there are no bald areas. There is no discharge from natural orifices. Visible mucous membranes are pale, shiny, smooth. According to the data of autopsy and macroscopic examination dermal application of the

Table 1

Effect of the compared medications on body weight (g) of rats after a single dermal application, $M \pm m$

Observation time	Experimental group and sex					
	"Control"		"SSP"		"Nystatin"	
	male	female	male	female	male	female
Background	176.9 ± 4.0	175.8 ± 1.9	171.6 ± 3.6	177.0 ± 2.7	173.9 ± 3.4	179.2 ± 3.4
2nd day	179.9 ± 3.3	179.4 ± 3.0	173.3 ± 3.2	172.9 ± 3.1	168.6 ± 3.7	176.1 ± 3.5
7th day	187.1 ± 4.2	188.2 ± 3.2	189.3 ± 5.4	186.6 ± 3.3	183.6 ± 4.7	187.4 ± 2.8
14th day	193.9 ± 4.4	199.6 ± 3.6	193.4 ± 5.2	195.5 ± 2.8	191.7 ± 3.4	196.5 ± 2.7

compared preparations in the studied doses to rats of both sexes does not cause visible changes of internal organs, including endocrine glands, gastric and intestinal mucous membranes, as well as the brain.It was found in the course of histologic study that the skin and soft tissue material of laboratory animals showed focal epidermal sloughing foci with keratin, which is a result of mechanical impact in the framework of the experiment. Inflammatory cell infiltration in the underlying dermis in areas of epidermal sloughing is not detected in all examined samples. Single perivascular dermal mononuclear cells are normal unchanged elements of skin-associated lymphoid tissue (SALT-structures). Dystrophic, alterative and inflammatory changes were not revealed in the liver and kidneys of laboratory animals. Focal disorders of blood circulation in the form of full blood of capillaries of kidneys, liver are expressions of blood redistribution in the agonal period. The obtained data allow to refer to the compound SSP to the 5th class of practically non-toxic substances (GOST 32419-2022 “International Standard. Hazard classification of chemical products. General requirements").

The results of the anti-inflammatory activity of the compound are presented in Tables 2 and 3.

The injection of phlogogenic agent into animals causes a significant increase in foot volume by the third hour of observation, the increase reaches 104.8 %, this index was taken as a control value. The use of such a medication as “Indomethacin” ointment showed that the increase in carrageenan edema statistically significantly decreased, compared to control data, to 13.7 %, that is, the inhibition of the inflammatory response reaches 86.9 %. It is successfully used in practical medicine as an anti-inflammatory agent. Pre-application of the studied compound on the skin of the foot of rats causes inhibition of the inflammatory response, as compared to the

Table 2

Anti-inflammatory activity of the silver salt of pyrazole-3-carboxamide by dermal application, $M \pm m$

Compound	Volume gain of the foot after 3 h, %	Inhibition of reaction after 3 h, %
SSP suspension	94.32 ± 7.48, $p = 0.220$, $p' = 0.005$	10.0
“Indomethacin” ointment	13.7 ± 1.7, $p = 0.001$	86.9
Control group	104.8 ± 12.1	

Note: p – level of statistical significance in comparison with control data; p' – level of statistical significance in comparison with “Indomethacin” ointment.

Table 3

Anti-inflammatory activity of the silver salt of pyrazole-3-carboxamide during oral injection, $M \pm m$

Compound	Volume gain of the foot after 3 h, %	Inhibition of reaction after 3 h, %
SSP	103.1 ± 9.9, $p = 0.845$, $p' = 0.001$	1.65
Nimesulide	39.2 ± 2.9, $p = 0.001$	62.59
Control group	104.8 ± 12.1	

Note: p – level of statistical significance in comparison with control data; p' – level of statistical significance in comparison with nimesulide.

control data, only by 10 %, which is not a statistically significant result ($p > 0.05$).

It was found that under the action of the comparison compound nimesulide the growth of carrageenan edema was statistically significantly inhibited compared to the control data. The increase of the foot volume in rats is 39.2 % ($p < 0.001$), i.e. inhibition of the reaction reaches 62.59 %. At the same time the studied compound SSP does not show anti-inflammatory activity, the increase of inflammatory edema by the third hour of the experiment goes with the same intensity as in the control experiments.

In the process of studying the biological activity of SSP compound, the study of local irritant effect of the compound had a special importance. It was evaluated by the degree of erythema, the amount of edema (thickness of the skin fold at the application site) and the increase in local skin temperature. The results of the study are presented in Tables 4–6.

There is no increase in the thickness of skin folds during the dermal application of SSP and nystatin. Thus, it is established that the medications do not cause the development of edema.

Table 4

Skin fold thickness in rats after dermal application, $M \pm m$

Group	Thickness of skin fold in the area of medication injection, mm				
	Study terms, days				
	Control	1st	3rd	5th	14th
"SSP"	3.3 ± 0.2	3.4 ± 0.2	3.5 ± 0.3	3.5 ± 0.4	3.4 ± 0.2
"Nystatin"	3.4 ± 0.3	3.5 ± 0.3	3.6 ± 0.2	3.6 ± 0.3	3.4 ± 0.3

Table 5

Surface skin temperature in rats after dermal application, $M \pm m$

Group	Surface temperature *t*, °C				
	Study terms, days				
	Control	1st	3rd	5th	14th
"SSP"	37.6 ± 0.5	37.8 ± 0.5	37.7 ± 0.4	37.7 ± 0.6	37.7 ± 0.4
"Nystatin"	37.5 ± 0.3	37.5 ± 0.4	37.6 ± 0.3	37.8 ± 0.3	37.5 ± 0.3

Table 6

Severity of skin erythema in rats after dermal application

Group	Level of erythema in points				
	Study terms, days				
	Control	1st	3rd	5th	14th
"SSP"	0	1	0	0	0
"Nystatin"	0	0	0	0	0

The temperature of the skin areas at the application site did not increase when applying the SSP compound and nystatin. There were no statistically significant differences between the parameters and control data (at $p < 0.05$).

Analysis of the level of erythema showed that, in general, with both nystatin and the SSP compound, it was rated as zero, i.e., absent.

Conclusions

1. The obtained data allow to assign the new silver salt of pyrazole-3-carboxamide SSP to the 5th class of practically non-toxic compounds.

2. The compound SSP does not show local irritating effect.

3. The studied silver salt of pyrazole pyrazole-3-carboxamide does not show anti-inflammatory activity on the model of carrageenan inflammation.

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INFLUENCE OF GLYCODELIN ON THE FORMATION OF IMMUNE RESPONSE AT THE LEVEL OF T-HELPERS AND T-REGULATORY CELLS IN AN *IN VIVO* EXPERIMENT

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ВЛИЯНИЕ ГЛИКОДЕЛИНА НА ФОРМИРОВАНИЕ ИММУННОГО ОТВЕТА НА УРОВНЕ Т-ХЕЛПЕРОВ И Т-РЕГУЛЯТОРНЫХ КЛЕТОК В ЭКСПЕРИМЕНТЕ *IN VIVO*

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Objective. To study the influence of glycodelin on T-helpers and Tregs level in the process of forming an immune response to the introduction of allogeneic bone marrow (BM) cells in a dynamic experiment on Wistar rats.

Materials and methods. The original experimental model "host versus transplant reaction" on male Wistar rats without preliminary conditioning in recipients was used in the study. Animals were administered recombinant glycodelin against the background of allogeneic intraperitoneal transplantation of BM cells in a dynamic experiment. The level of peripheral T-helpers ($CD4^+$) and Tregs ($CD4^+CD25^+FOXP3^+$), and the expression of FOXP3 in the spleen and mesenteric lymph nodes were assessed. The material was collected on the 3rd and 21st days of the experiment.

Results. Glycodelin was shown to reduce the absolute number of T-helpers in the peripheral blood (on the 3rd and 21st days) and to increase the proportion of Tregs on the 21st day of the experiment against the background of the introduction of allogeneic BM cells. It was found out, that glycodelin reduced the level of Tregs in the white pulp of the spleen on the 3rd day of the experiment, while the number of these cells on the 21st day increased, reducing the number of T-helpers at the same time. At the level of the mesenteric lymph nodes, glycodelin reduced the level of T-helpers on the 21st day of the experiment, simultaneously increasing the number of Tregs. In general, a unidirectional and distributed effect of glycodelin on the immune response at the level of T-helpers was observed, that was a decrease of T-helpers, but an increase of Tregs on the 21st day of the experiment.

Conclusion. Thus, glycodelin had an immunomodulatory effect on T-helpers and Tregs formation. The vector of the obtained effects was immunosuppressive in nature and contributed to the suppression of the immune response to allogeneic cells.

Keywords. Glycodelin, allogeneic transplant, immune response, T-helpers, T-regulatory lymphocytes, FOXP3, Wistar rats.

Цель. Исследование эффектов гликоделина на количество Т-хелперов и Treg в ходе развития иммунного ответа на введение аллогенных клеток крысам Wistar в динамике.

Материалы и методы. Учитывая тот факт, что гликоделин является фетоплацентарным белком с иммуносупрессорной активностью, изучали терапевтический потенциал этого белка в эксперименте *in vivo*. Работу проводили с использованием авторской экспериментальной модели реакции «хозяин против трансплантата». Реципиентами были самцы крыс Wistar, не подвергавшиеся предварительной цитостатической терапии. Животным вводили рекомбинантный гликоделин на фоне аллогенной внутрибрюшинной трансплантации клеток КМ в динамическом эксперименте, оценивая следующие параметры: уровень периферических Т-хелперов ($CD4^+$) и Treg ($CD4^+CD25^+FOXP3^+$), экспрессию CD4 и FOXP3 в селезенке и брыжеечных лимфатических узлах. Материал забирали на 3-и и 21-е сут эксперимента.

Результаты. Установлено, что в процессе развития иммунного ответа на аллоантигены гликоделин снижал абсолютное количество Т-хелперов в периферической крови крыс на 3-й и 21-й день после аллотрансплантации и увеличивал число Treg через три недели эксперимента. На 3-и сут было отмечено снижение уровня Treg в белой пульпе селезенки, в то время как на 21-е сут наблюдалось увеличе-

ние количества этих клеток при одновременном снижении Т-хелперов. В брыжеечных лимфатических узлах гликоделин также снижал уровень Т-хелперов на 21-е сут эксперимента, одновременно повышая количество Treg. В целом наблюдался однонаправленный и распределенный эффект гликоделина на формирование иммунного ответа на уровне Т-хелперов, заключающийся в снижении количества Т-хелперов, но повышении уровня Treg на 21-е сут эксперимента.

Выводы. Таким образом, гликоделин оказывал иммуномодулирующее действие на формирование Т-хелперов и Treg. Вектор полученных эффектов носил иммунодепрессивный характер и способствовал подавлению иммунного ответа на аллогенные клетки.

Ключевые слова. Гликоделин, аллогенный трансплантат, иммунный ответ, Т-хелперы, Т-регуляторные лимфоциты, FOXP3, крысы Wistar.

INTRODUCTION

Glycodelin (PP14, PAEP, alpha-2-microglobulin) is a dimeric glycoprotein with a molecular weight of 42-56 kDa, a biomarker of endometrial receptivity that predetermines successful implantation. In 2018, A. Dixit with co-author in an experiment on mice showed that processing of alloactivated mononuclear cells with glycodelin prevented graft rejection [1]. This study revealed the potential of this protein as a basis for a biopreparation that debilitates post-transplantation complications. For example, Schneider and co-author suggested the possibility of using glycodelin in lung transplantation [2]. It is obvious that glycodelin can be used as a pharmacological agent not only in transplantology, but also in immunotherapy of autoimmune diseases [3]. Despite the fact that the immunosuppressive effects of glycodelin are well known [4], its role in the regulation of the immune response at the level of T-helper (Th) and T-regulatory cells (Treg) is not studied well.

The immune response is a chain of sequential complex cooperative processes occurring in the immune system in response to an antigen. T cells, namely T-helper cells, play one of the key roles in these processes. These cells help B-cells in the production of antibodies. They stimulate macrophages to increase bactericidal activity, involve phagocytes in sites of infection and inflammation, and regulate the immune response with the help of cytokines and chemokines. T-helper cells can differentiate into different subpopulations that differ in the spectrum of the produced cytokines. Activation of these cells is accompanied with the appearance of CD25 molecule on their membrane, which is the α subunit of interleukin-2 receptor (IL-2Rα)) [5]. The activated T helper cells (CD4+CD25+ T cells) are a heterogeneous population that includes several subpopulations which differ phenotypically and functionally. These also include CD4+CD25highFOXP3+ regulatory T lymphocytes (Treg) [6]. These cells show highly suppressive functions and play an important role in many immunologic processes. Thus, they are involved in the prevention of hypersensitivity, autoimmune diseases and suppression of graft versus host reaction (GvHD), they maintain T-cell homeostasis. The regulator of Tregs differentiation and function is the FOXP3 transcription factor expressed only in this subpopulation. Therefore, the human and rodent Treg phenotype

can be defined as CD4+CD25+FOXP3+ [7]. It should be noted that these Treg function not only directly in the site of alloantigen penetration and immune organs, but also in the peripheral blood.

The spleen is the most important secondary organ of the immune system. The content of lymphocytes in the white pulp of the spleen reaches 85 % of the total number of cells, which is almost 25 % of all lymphocytes in the body [8]. Thus, the spleen with lymph nodes provides an adequate immune response, and that is the reason why we evaluated the differentiation of T-helper cells and Treg both in peripheral blood and in spleen and mesenteric lymph nodes.

The aim of the study is to analyze the effect of recombinant form of glycodelin on the number of T-helper cells and Treg in peripheral blood, spleen and mesenteric lymph nodes in the dynamics of development of immune response to allogeneic cells administration to Wistar rats.

MATERIALS AND METHODS

The experiments were conducted in the vivarium of the Perm State National Research University on 2–3-month-old male white Wistar rats with an average weight of 250 g ($n = 38$). The animals were held in conditions appropriate to the all-Union State Standart 33216-2014 ("Rules for working with laboratory rodents and rabbits"). Bioethical standards (European Convention for the Protection of Experimental Animals (86/609/EEC; 1986)) were followed in all experiments.

The study was conducted with the author's experimental model of the "host vs. graft" reaction described earlier [9].

BM cells from femoral bones were tested by cytostatic camptothecin to prevent the development of an immune response of donor cells against recipient cells ("graft versus host" reaction). The animal's mortification was conducted by decapitation in accordance with international rules of work with experimental animals at early (3 days) and late (21 days) development of immune response. At the same time, peripheral blood, spleen and mesenteric lymph nodes were sampled. A minimum of four different preparations of each organ for an individual animal was examined.

Rats were divided into three experimental groups: The first group ($n = 8$) – intact rats; the second group ($n = 12$) – glycodelin control (animals were injected with allogeneic bone marrow cells intraperitoneally); the third group ($n = 12$) – experimental animals proper (after intraperitoneal injection of allogeneic cells intramuscular injections of recombinant glycodelin (#MBS718444, "MyBioSource", Germany) on the 1st, 5th, 9th and 12th days). The calculated achievable concentration of the medicine in the blood of animals was ≈ 0.75 μg/mL.

Assessment of Th and Treg levels. The level of these cells was evaluated according to the previously described method [9]. Cytometric determination of the cells number in subpopulations was conducted by using a ready-made antibody set to rat T-cell surface molecules FlowX Rat Regulatory T Cell Kit (R&D Systems, USA), which includes anti-CD25-PE,

anti-CD4-FITC and anti-FOXP3-AlexaFluor 647 antibodies. Thawed blood samples were analyzed. They showed no signs of hemolysis and the cells remained well viable. CytoFLEX S flow cytometer (Beckman Coulter, USA) was used for this purpose. The results of cytometric analysis are presented as the percentage of cells in CD4+ (T-helper), CD4+CD25+FOXP3- (activated T-helper), and CD4+CD25+FOXP3+ (regulatory E-cells) populations.

In addition to relative counts (percentage), the data were recalculated into absolute values based on the total number of lymphocytes per ml of peripheral blood.

Immunohistochemical study was conducted by the previously described method [10]. Monoclonal antibodies (Cloude-Clon Corp, USA) to CD4 (SP35) and FOXP3 (recombinant; Tyr191-Glu412) were used to determine the qualitative composition. The positive result of immunohistochemical reaction was specific staining of cells. The results of the enumeration are presented in the form of the number of cells with positive expression of CD4 or FOXP3 in the field of view.

Statistical processing of data was performed in the GraphPad Prizm 8 program using two-factor dispersion analysis and Tukey's posterior test.

Pearson correlation coefficient between CD4/FOXP3 expression values and the number of helper and regulatory T cells was also calculated. The significance level was taken as 0.05.

RESULTS AND DISCUSSION

T-helper cells (CD4+ T cells) play a central role in immune defense. Naive CD4+ T cells after encountering an antigen can differentiate into key subpopulations of Th1, Th2, Th17 and Treg cells under the influence of a set of signals [6]. Treg have suppressive activity toward effector immune cells. Treg have suppressive activity toward effector immune cells, controlling the preservation of autotolerance, which prevents the development of inflammatory autoimmune diseases. They control the preservation of autotolerance, which prevents the development of inflammatory autoimmune diseases. Besides, Treg are important in controlling the immune response to allograft [11].

Effect of glycodelin on the level of T-helpers and Treg in the peripheral blood of experimental animals. It was found that BM injection did not affect the percentage and absolute content of T-helper cells in the peripheral blood of rats (Fig. 1). Glycodelin injection caused a decrease of the absolute number of these cells both on the 3rd and on the 21st days of the experiment. The decrease was significant both in relation to intact animals and animals that received allogeneic BM. Thus, glycodelin reduced the Th level in this experiment.

At the same time, it was found that the transplantation of BM to rats did not affect the level of activated T-helper cells (CD4+CD25+). Glycodelin injection also had no impact on the content of activated Th (see Fig. 1).

Besides, it was found that the percentage and absolute number of Treg in the total population of CD4+ T-cells significantly decreased on the third day after administration of allogeneic cells to animals in relation

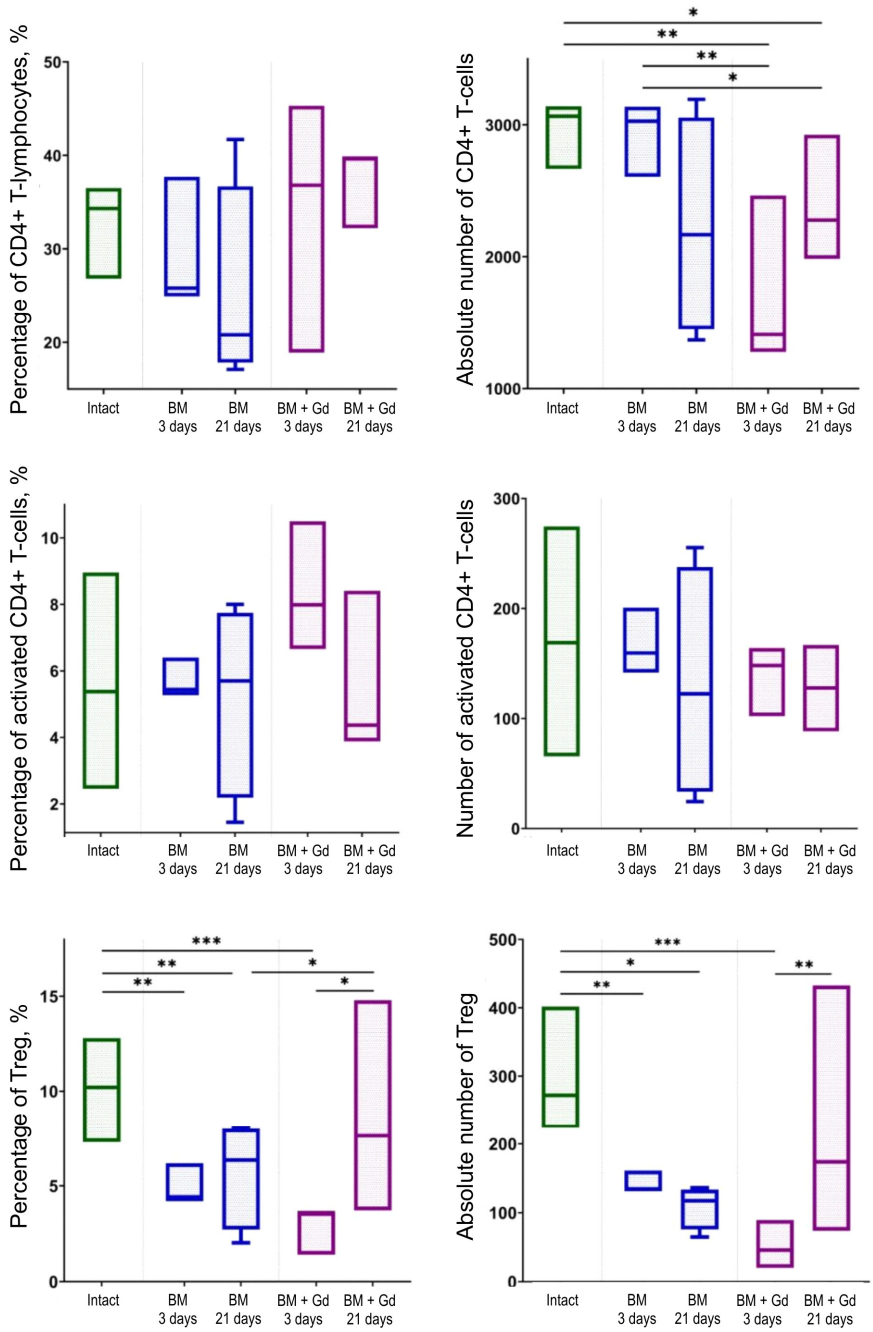

*Fig. 1. Percentage content and absolute number of T-helper (CD4+), activated T-helpers (CD4+CD25+FOXP3-) and Treg (CD4+CD25+FOXP3+) in the peripheral blood of rats during injection of allogeneic BM cells and glycodelin therapy on the background of allogeneic transplantation (n = 4, M ± m): data are presented as the average and standard error of the average; * – p < 0.05; ** – p < 0.01; *** – p < 0.001 (two-factor ANOVA, Tukey's a posteriori test for multiple comparisons)*

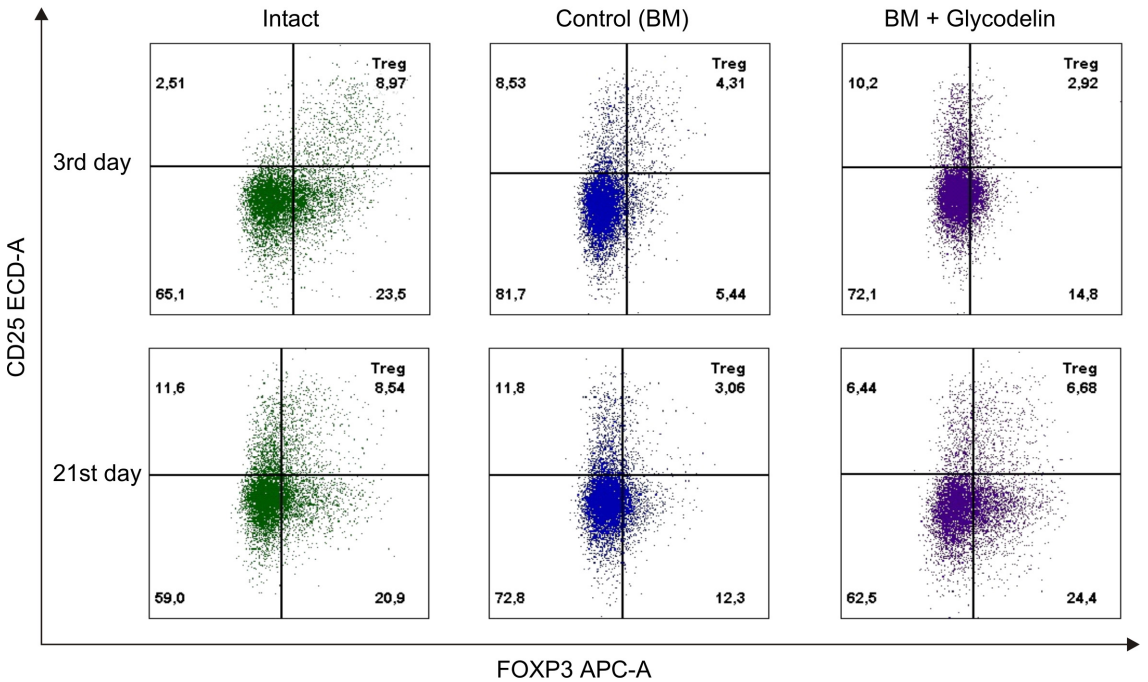

Fig. 2. The Treg level in the blood of experimental animals on the 3rd and 21st days after BM transplantation and glycodelin injection as an example of one experiment: on the abscissa axis is the fluorescence intensity of cells stained with anti-FOXP3-antibodies; on the ordinate axis is the fluorescence intensity of cells stained with anti-CD25-antibodies

to the indexes of intact rats. Glycodelin injections did not result of the changes in these indices (see Fig. 1). Apparently, the injection of allogeneic BM cells itself decreased the number of Treg, which is consistent with the data of Korsunsky and co-author [12]. On the 21st day after injection of allogeneic BM cells in the 2nd group of animals (glycodelin control), the percentage and absolute amount of Treg per ml of blood were also lower than in the group of intact animals. At the same time, glycodelin increased the percentage of Treg, bringing the level of these cells closer to that among the intact animals in the 3rd group of animals (experiment) (see Fig. 1). Apparently, on 21 days of the experiment we can talk about antigen-specific Treg. Thus, glycodelin is able to increase the level of Treg in the case of immune response.

Thus, injection of glycodelin on the background of allogeneic BM transplantation caused a decrease in the absolute number of T-helper cells. At the same time, the level of activated T-helper cells in the blood of the experimental groups of animals remained unchanged. The increase of the proportion of peripheral Treg in the final experiment was demonstrated (on the 21st day) under the influence of glycodelin in comparison with the group to which BM was injected.

Generally, the increase of Treg under the influence of glycodelin is a highly important immunomodulatory effect that re-

sults in suppression of the immune response to allogeneic cells.

The effect of glycodelin on the number of T-helper cells and Treg in the spleen of experimental animals. Well-developed functional areas were seen in the spleen of rats without any exposures (group 1). Wide cell-filled Billroth cords were clearly defined in the red pulp. A moderate accumulation of CD4+ lymphocytes (T-helper cells) was observed in them. The vessels of the red pulp were moderately dilated and filled with blood cells. Visual assessment showed that the white pulp covered about one-third of the organ area. The periarterial lymphoid muff (PALM) looked large and multicellular. Lymphocytes formed clusters with predominance of CD4+ cells along the edge of the PALM. The observed lymphoid nodules (B-area) varied in the size, most of them were active. CD4+ -lymphocyte clusters were detected in the marginal area. The volume of white pulp increased in the spleen of injected animals with only allogeneic BM (group 2) starting from the 3rd day. There was moderate, occasionally single presence of positively stained CD4+-cells in its areas.

Cells expressing CD4 molecule were detected in the marginal area. The white pulp areas looked active and large until the 21st day of the experiment. Multiple lymphocytes were seen, which formed diffuse clusters or lymphocyte sheaths around brush arterioles in the pulp. There was a high level of CD4 T-helper molecule expression mainly detected in the marginal area of the white pulp. More intense staining of CD4+ cells was found in the Billroth cords of the red pulp (Fig. 3).

Large and small vessels of the venous channel with a wide lumen and with blood cells were determined in the spleen of rats in the experimental (3rd) group (allogeneic BM + glycodelin) on the third day after allotransplantation. Large accumulations of CD4+-lymphocytes were observed in the Billroth's cords, overfilled with cells. The white pulp covered more than 40 % of the organ area. All its areas looked developed and active, B-area was represented by large lymphoid nodules with signs of proliferation, and T-areas constituted a significant part of the white pulp, forming a dense cluster around the central artery. The expressing CD4-lymphocytes were located along the edge of the PALM. Although the functional areas of the white pulp remained active until the end of the experiment, the sizes of the T- and B-areas were reduced or unchanged. Visually, the number of CD4+-cells decreased, proliferation was slightly reduced, however, there was an accumulation of T-helper cells in the Billroth cords masses, where their differentiation process is usually completed (Fig. 3).

Statistical processing of the obtained data was conducted for detailed analysis by comparing the expression of CD4 molecule and transcription factor FOXP3 in the white pulp of the spleen of different animals groups. As a result, it was found that in intact animals the number of T-helpers (CD4+) were higher than the number of T-effectors (CD8+). BM injection (2nd group) resulted in a rapid increase in the level of T-helper cells in the

white pulp of the spleen, which was observed on the 3rd and 21st days of the experiment. The use of glycodelin (3rd group) did not affect the level of T-helper cells, but on the 21st day of the experiment resulted in a decrease in the number of these cells in the white pulp of the spleen. Thus, glycodelin reduced the level of T-helper cells on the 21st day of the experiment (Table).

It was shown that BM injection did not change the level of FOXP3 expression in the white pulp of the spleen in experimental animals. The use of glycodelin on the background of BM injection led to a reliable decrease in the level of FOXP3 on the 3rd day, but on the 21st day the effect was opposite, and the differences were also reliable in relation to the group of comparison (see the table).

Thus, glycodelin has an independent increasing effect on the expression of the Treg marker FOXP3, which may lead to a localized decrease of the immune response to alloantigens. This aspect of glycodelin is the most important and interesting if we consider this protein from the approach of immunopharmacology.

Effect of glycodelin on the level of T-helper and Treg in mesenteric lymph nodes in experimental animals. It was shown by evaluating the dynamics of CD4 expression in the mesenteric lymph nodes that when allogeneic BM cells were injected into the lymph nodes from the first days of the experiment, the expression of the T-helper marker was verified in the lymph nodes in the sinuses of the cortical substance and in the form of clusters in the cortical areas. The positively stained cells were present in groups in deep layers of the cortical substance, in the inter-nodal spaces and formed large clusters in the medullary substance cords by the 21st day.

Glycodelin injection at the beginning of the experiment (3rd day) did not affect the level of T-helper cells (CD4+), but increased this index on the 21st day. Analysis of FOXP3 expression showed that BM injection did not affect the level of Treg on the 3rd and 21st days. FOXP3 expression on the 3rd day was observed in single cells located diffusely within the cortical substance of the organ, in the inter-nodal spaces and in the subcapsular sinus. FOXP3 expression was verified in diffuse single cells within the cortical substance and in the form of clusters in the subcapsular sinus of the organ by the end of observation (21st day). Glycodelin injection significantly increased the expression of Treg marker on the 21st day of the experiment.

Correlation analysis showed that there is a close direct correlation between CD4 expression parameters in the spleen and mesenteric lymph nodes under the influence of glycodelin ($r = 0.88$; $p < 0.05$), whereas there are no correlations with the level of peripheral T-helper cells. A correlation between peripheral Treg levels and FOXP3 expression in the spleen was found in regard to FOXP3 expression under glycodelin exposure ($r = 0.74$; $p < 0.05$).

Thus, glycodelin reduced the level of T-helper cells at the level of mesenteric lymph nodes on the 21st day of the experiment, at the same time increasing the number of Treg. In general, increased Treg level leads

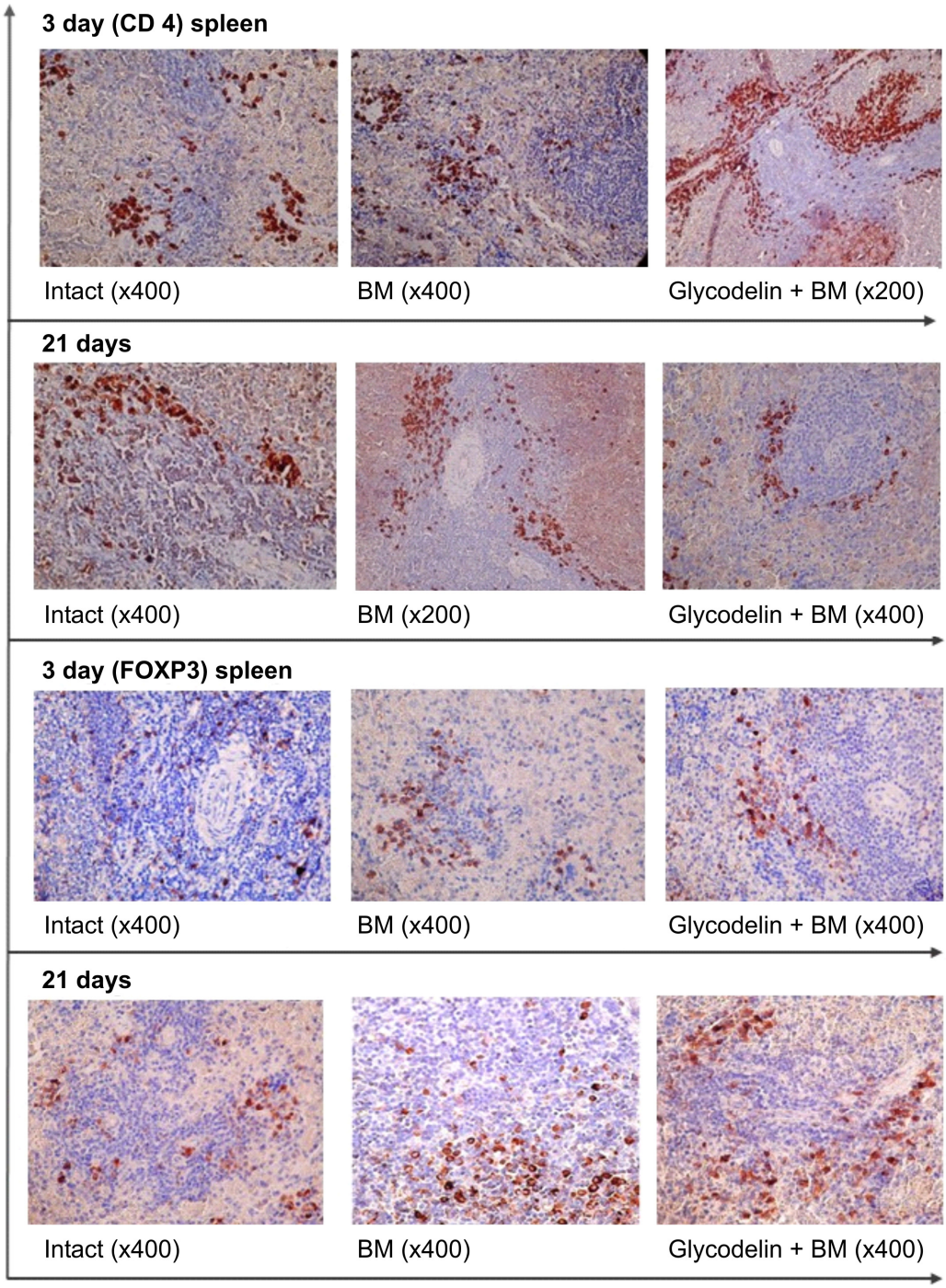

Fig. 3. CD4/FOXP3 expression in the spleen of experimental animals, immunohistochemistry, ×200, ×400, based on individual slices

Effect of glycodelin on CD4 and FOXP3 expression in the white pulp of spleen, *M ± m*

Marker expression, % of cells	Intact, *n* = 8	BM, 3rd day, *n* = 12	BM, 21st day, *n* = 12	BM+Gd, 3rd day, *n* = 12	BM+Gd, 21st day, *n* = 12
Spleen					
CD4	15.34 ± 4.56	25.83 ± 6.43*	29.11 ± 7.23*	21.74 ± 6.24*	20.57 ± 7.76*#
FOXP3	9.54 ± 3.13	9.06 ± 4.22	6.14 ± 2.43	6.33 ± 2.78#	12.11 ± 6.42*#
Mesenteric lymph nodes					
CD4	12.04 ± 4.87	14.68 ± 5.44	14.77 ± 6.14	22.43 ± 7.76*	15.02 ± 5.69#
FOXP3	9.76 ± 4.74	9.55 ± 5.12	7.63 ± 4.32	7.87 ± 5.02	12.66 ± 7.13*#

Note: # – differences between time-matched BM and BM + Gd groups, * – differences with regard to the group of intact animals, indicated only significant ($p < 0.05$) differences (two-factor ANOVA, Tukey's posterior test for multiple comparisons).

to more successful transplantation of allogeneic cells.

Conclusions

It was found that glycodelin reduced the absolute number of T-helpers in the peripheral blood of rats on the 3rd and 21st day after allotransplantation and increased the number of Treg on the 21st day of the experiment. In the white pulp of spleen glycodelin decreased the level of Treg on the 3rd day, but increased their number on the 21st day, while decreasing the number of T-helpers. At the level of mesenteric lymph nodes, glycodelin decreased the level of T-helpers on the 21st day of the experiment, while increasing the number of Treg. In general, a unidirectional and distributed effect of glycodelin on the formation of immune response at the level of T-helpers was observed, which consisted in the decrease of T-helpers but increase of Treg on the 21st day of the experiment. Obviously, we observed a more expressed effect of glycodelin on the 21st day of the experiment, when antigen-specific Treg are formed.

Generally, glycodelin decreased the number of T-helper cells both in secondary organs of the immune system and in the peripheral blood, with a correlation between the pool of CD4+ cells in the spleen and lymph nodes. Typical for this experiment is that a correlative connection between Treg in the periphery and the level of FOXP3 in the spleen also appears.

It is important to mention that previously we have shown that glycodelin in similar experiments provided normalization of the content of proteins of the acute phase of inflammation (CRP, orosomucoid and α-2M) to the level of intact animals [9], and also reduced the level of proinflammatory cytokine IL-17A [13]. Histologic study of spleen slices revealed that glycodelin activated immune system cells by stimulating their proliferation (Ki-67) and their differentiation, which was demonstrated by an

increase in the number of plasma cells. The content of macrophages (CD68+) significantly decreased by the end of the study (21st day), and eosinophilic infiltration was observed [14]. Thus, glycodelin is able to realize immunosuppressive effect in relation to allogeneic cells, which leads to more successful graft implantation.

It is known that at the level of human cells recombinant glycodelin under conditions of long-term cultivation in vitro increased the level of antigen-specific Treg and FOXP3 de novo expression with simultaneous inhibition of the functions of effector T-cells. The authors conclude that glycodelin has a potential therapeutic effect in autoimmune diseases by preventing the development of effector T-cells and inducing antigen-specific Treg [15]. Thus, our data also demonstrate an immunosuppressive effect of glycodelin, leading to suppression of the immune response to allogeneic cells.

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