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# **CONTENTS**

### MORPHOLOGY, PATHOLOGY, PHYSIOLOGY

### ULTRASONOGRAPHIC ANATOMY

### PHARMACOLOGICAL STUDIES

Elena Kovtun, Liudmila Pogrebnyak,
Eleonora Stepanova, Andrey Pogrebnyak,
Yuri Morozov, Dmitri Bokov
PREPARATION OF COMPONENTS OF ULTRASONIC EXTRACT
OF GINKGO BILOBA, PHYSICO-CHEMICAL
AND PHARMACOLOGICAL ANALYSIS
AND MOLECULAR DESIGN

#### NEONATOLOGY

Yulia Vychristuck, Svetlana Lebedeva	
CAUSES OF MORTALITY IN NEONATES	
WITH EXTREMELY LOW AND VERY	
LOW WEIGHT	29

#### NEPHROLOGY

.

Darya Savitskaya, Liubov Popova,	
Anton Popov, Olga Poselyugina	
ACUTE TUBULOINTERSTITIAL NEPHRITIS	
WITH UNDERLYING UNDIFFERENTIATED	
CONNECTIVE TISSUE DISEASE.	
A CLINICAL CASE STUDY	32

#### NEUROLOGICAL DISEASES

#### THERAPY

# **CONTENTS**

#### SURGERY

#### PEDIATRIC SURGERY

#### REHABILITATION

#### DENTISTRY

# **CONTENTS**

# EDITORIAL

# NEWEST HEALTHCARE INDUSTRY TRENDS TO COMBAT COVID-19

Dr. Georg Tyminski D Editor-in-Chief

COVID-19 has an unprecedented impact not only on all facets of our life and healthcare but it brings to life new trends in healthcare industry. The combat with the pandemic has resulted in explosive development of new technologies entitled for disinfecting, limiting transmission, detecting disease spread, treatment protocols, patient management, and vaccination.

However, the pandemic revealed numerous flaws and deficits in the functioning of the healthcare system, such as logistics, work of outpatient facilities and digitalization. This caused delays in output of statistic data from hospitals (number of available beds, number of people who were vaccinated, infected, getting sick or tested). As a consequence of making ineffective decisions including the political ones, there was a lower confidence and uncertainty in the population.

The advancements in the healthcare industry encompass e-consultations, telemedicine, real-time diagnosis allow accessing digital therapeutics provided by immersion technology tools.

Introduction of genetic analysis, clinical data storage, big data & analytics, artificial intelligence, internet of medical things enable to utilize devices of remote monitoring in the mode of real time and to broaden the use of personalized medicine, to improve the control and planning, to make the health services faster, stronger and smarter.

These solutions enhance workflows and planning of staff scheduling, provide connected infrastructure, devices and systems to render prompt and addressed clinical services.

There are a number of priority issues in healthcare industry trends (1):

# **1. ARTIFICIAL INTELLIGENCE**

replaces conventional labor-intensive and time-consuming processes in healthcare services with remotely accessible and real-time solutions for diagnosis, treatment, and disease prevention (1,2).

# 2. INTERNET OF MEDICAL THINGS (CIOMT)

Internet of Medical Things is the potential for the development of products requiring fewer personnel to provide modern healthcare services. According to Frost & Sullivan analysis, the global IoMT market was worth \$22.5 billion in 2016; it is expected to reach \$72.02 billion by 2021, at a compound annual growth rate of 26.2% (3).

Cognitive IoMT is a recent development, which integrates sensory information, automatic processing, and communication through networks for real-time diagnosis, monitoring, tracking, and disease control.

The use of such technologies provides more solutions on working with patients due to automatic disinfection, smart diagnosis, remote patient management etc employing fewer personnel (1).

### 3. TELEMEDICINE

Telemedicine reduces the load on medical facilities and without incurring any costs on the use of personal protective equipment. Telemedicine also aids to assist elderly people remotely, reduces bed space, and conserves clinical supplies. (1, 4)

# 4. BIG DATA & ANALYTICS

Big Data & Analytics provide tools and solutions for analyzing unstructured and huge volumes of medical data. This expands patient-based services and enables to detect diseases earlier better understanding disease mechanisms (5).

# 5. IMMERSIVE TECHNOLOGY

Immersive Technology can be used in different fields of medicine: and can be employed for therapy

and rehabilitation of psychiatric and physical disorders. It plays an important role in medical education. Immersive technology can be applied in invasive medicine, for example, for projection of patient information during surgical procedures and holographic images (1,6).

# 6. MOBILE HEALTH (MHEALTH)

Solutions provided by mHealth have had a decisive impact combating the spread of COVID-19 pandemic. It supported contact tracing, monitoring, quarantine control. It helped testing and distribution of relevant information (1,7).

# 7. 3D PRINTING

3D printing has becoming more common in the healthcare industry. It is widely used for printing lightweight prosthetics, bionics, and casts for fracture repair (8).

# 8. BLOCKCHAIN

Blockchain is used in many fields of healthcare services such as electronic medical records, remote patient monitoring, pharmaceutical supply chain, and health insurance claims. Blockchain is capable of tackling drug counterfeiting (9).

# 9. CLOUD COMPUTING

Cloud Computing enables doctors to have control over the treatment progress and logistics, to store and process data on medical services rendered with the use of telemedicine and remote monitoring. Cloud Computing provides streamlined data access, data backup and recovery, smart data potential, and data interoperability (10).

# **10. GENOMICS**

Recently, significantly efforts have been made in developing genomics tools for different applications. Gene therapy and gene-based therapy solutions in clinical medicine and specialized care has solved problems that seemed unsolvable before (1).

These newest healthcare trends is only a part of the rigorous research that has been carried out in recent years. Nevertheless, a major prerequisite for developing new technologies in medicine is to accelerate the digital transformation in healthcare. It is of vital importance in the fight against COVID-19.

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#### MORPHOLOGY, PATHOLOGY, PHYSIOLOGY

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# CHARACTERISTICS OF INTESTINAL MICROBIOME IN CHILDREN WITH AUTISM

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ABSTRACT — The aim of the study was to assess the prevalence of dysbiosis in children with autism spectrum disorders (ASD). The study was observational, cohort, comparative. All the patients included in it were divided into 2 groups. The first (main) group (n=46) consisted of children aged  $4.92\pm1.57$  years with an established diagnosis of ASD. The second (n=20, comparison group) included conditionally healthy children (1 and 2 health groups) aged  $5.10\pm1.16$  years, not suffering from ASD. It was stated that in children with autism a reduced content of lactobacilli (p=0.056), the practical absence of lactic acid streptococci (p=0.019), a rarer detection of individual strains of Enterobacter bacteria (Ent. cloacae; p=0.033), an increase of 2 or more times in the frequency in level of hemolytic Escherichia coli (E. coli; p=0.041), some strains of bacteria of the genus Klebsiella (Kl. Pneumoniae; p=0.080) and Citrobacter (Citr. freundii, p=0.015); Staphylococcus aureus (14% vs. 6%, p>0.050) and Candidae fungi (11% vs. 6%, p>0.050) were found more often than in healthy children. In addition, patients with autism have enough level of Bifidobacterium and Escherichia coli. The study showed the presence of shifts in the gut microbiome in children with autism spectrum disorders. At the same time, structure of microbiome differed significantly from that typical for healthy children.

**KEYWORDS** — autism, children, gut microbiota, dysbiosis.

# INTRODUCTION

According to the largest epidemiological studies in the world, there is a tendency to increase the prevalence of autism [4–6]. So, for 18 years, the prevalence rate has increased from 30.8 per 10,000 children in 2000 to 169 per 10,000 children in 2018 [3, 7]. One of the world's largest information and analytical systems Autism and Developmental Disabilities Monitoring (ADDM) of the Center for Disease Control and Prevention reports that the prevalence of autism among 8-year-olds in the United States of America in 2014 was 1.68%, which is 14% higher than in 2012 and 2010 [1, 4].

It is known that autism spectrum disorders (ASD) are characterized by a large number of comor-

bid conditions affecting various other organs and systems. At the same time, pathological conditions of the gastrointestinal tract (gastrointestinal tract) are described as the most common among concomitant diseases in patients with ASD (according to some data, almost 12% of people with ASD have concomitant gastrointestinal pathology) [1, 2, 6].

Separate studies show that the qualitative and quantitative composition of the intestinal microbiota in patients with ASD differs significantly from that typical for practically healthy people [1, 3, 5]. Thus, in patients with ASD, a smaller variety of microbial associations was noted, a decrease in the number of bacteria of the genera Prevotella, Corprococcus and Veilonellaceae, an increased ratio of Firmicutes / Bacteroidetes, high levels of Lactobacillus, Desulfovibrio, Sutterella; a high prevalence of microorganisms of the genus Clostridium among patients with ASD [1, 6]. Various types of abnormal RAS-associated intestinal metabolites have been studied. In particular, the number of reports of excessive production of short-chain fatty acids, para-cresol and ammonia has increased in recent years [3, 5, 6]. Based on this, a hypothesis has been put forward about the presence of pronounced shifts in the intestinal microbiome in ASD and the etiopathogenetic role of dysbiosis disorders in the development of the pathology under consideration [3, 5]. At the same time, there is not enough data in the literature to confirm it.

#### The aim of the study

was to assess the prevalence of dysbiosis in children with autism spectrum disorders.

#### MATERIAL AND METHODS

The study was observational, cohort, comparative. All the patients included in it were divided into 2 groups. The first (main) group (n=46) consisted of children aged 4.92 $\pm$ 1.57 years with an established diagnosis of ASD. The second (n=20, comparison group) included conditionally healthy children (1 and 2 health groups) aged 5.10 $\pm$ 1.16 years, not suffering from ASD. The diagnosis of ASD was verified according to the examination of a psychiatrist using ADOS and ADIR [1, 2, 6].

The examination of children of both groups included the collection of complaints, an objective examination by a pediatrician, a bacteriological study of the qualitative and quantitative composition of the intestinal microflora, interviewing the mother /guardian of the child using a questionnaire *Studying the medical and social causes of the formation of health abnormalities and diseases in children*, the answers to which reflected the presence/absence of the child's biomedical risk factors of the mother's pregnancy and childbirth; risk factors of early childhood and risk factors associated with the child's living conditions.

This study was initiated with the approval of the Local Ethics Committee of the Volga Research Medical University of the Ministry of Health of the Russian Federation (Protocol No. 3 of 02/21/2020).

Statistical data processing was carried out using the Statistica 6.0. for Windows application software package. Parametric and nonparametric statistics were used. The analysis of the type of distribution of the trait was carried out using the Kolmogorov Smirnov method. Descriptive statistics included median (ME) and interquartile range [Q25-Q75]. Comparison of quantitative features in groups was carried out using the Wald-Wolfowitz criterion, used to compare two independent small samples; comparative analysis of qualitative features was carried out using the Pearson criterion22; the relationships between the features were evaluated by the gamma  $(\gamma)$  correlation analysis and the method of paired and/or multiple regression; the presence of statistical significance of differences in the groups was assumed at p < 0.05.

### RESULTS

The results of the assessment of the state of intestinal microbiocenosis and the severity of its disorders are presented in Table 1. It was revealed that children with ASD were characterized by the most frequent detection of intestinal dysbiosis in general (p=0.019) and the detection of significant dysbiotic disorders in the form of intestinal dysbiosis of 3–4 degrees (p=0.049).

The qualitative and quantitative composition of the intestinal microbiota in patients with ASD differed significantly from that in children in the comparison group. Along with significant differences in the absolute content in the feces of individual representatives of the intestinal microbiota in children with ASD, there

 Table 1. Frequency of detection of intestinal dysbiosis in children with ASD (%)

	Healthy children (N=17)	Children with autism (N=37)	P-value
No dysbiosis	41	3	0,001
Dysbiosis of 1 degree	18	32	0,250
Dysbiosis of 2 degree	35	35	0,144
Dysbiosis of 3-4 degree	6	30	0,049

was a change in the frequency of their increase and/or decrease.

Thus, in children with autism a reduced content of lactobacilli (p=0.056), the practical absence of lactic acid streptococci (p=0.019), a rarer detection of individual strains of Enterobacter bacteria (Ent. cloacae; p=0.033), an increase of 2 or more times in the frequency in level of hemolytic Escherichia coli (E. coli; p=0.041), some strains of bacteria of the genus Klebsiella (Kl. Pneumoniae; p=0.080) and Citrobacter (Citr. freundii, p=0.015); Staphylococcus aureus (14% vs. 6%, p>0.050) and Candidae fungi (11% vs. 6%, p>0.050) were found more often than in healthy children. In addition, patients with autism have enough level of Bifidobacterium and Escherichia coli.

### CONCLUSION

Thus, the study showed the presence of shifts in the gut microbiome in children with autism spectrum disorders. At the same time, structure of microbiome differed significantly from that typical for healthy children.

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# THE ROLE OF CD34-POSITIVE CELLS IN THE ANGIOGENESIS OF MALIGNANT TISSUES

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ABSTRACT — Development of methods for targeted treatment aimed at inhibiting angiogenesis in malignant tissues is of great importance for modern oncology. The features of expression of CD34-positive cells at the border of the tumor and malignant tissue were studied. High expression of CD34-positive cells in small and large vessels during malignancy and is in correlation with the size of the tumor and the age of the disease. A promising target for targeted treatment is VEGF, as the main regulator of angiogenesis during tissue malignancy.

KEYWORDS — angiogenesis, CD34, Vascular endothelial growth factor (VEGF), malignancy, vessels, targeted treatment, inhibition of angiogenesis

# RELEVANCE

High mortality due to insufficient understanding of carcinogenesis in general and the role of angiogenesis mechanisms in the pathogenesis of malignant tissues in particular, indicate the undoubted relevance of studies aimed at solving these issues. Angiogenic factors that are significant in the physiological vascularization of structures also play an important role in ensuring cellular interactions during the malignancy of various tissues. [1]. The question of a targeted conservative effect on tumors with the use of angiogenesis inhibitors in the zone of malignancy remains open. As previously noted in 2012, Eleftherios P. Diamandis, Robert C. Bast, Jr. PhilGold [2], and at the present stage, despite the emergence of powerful genomic, proteomic, epigenomic, metabolomic, microarray and other technologies, the efficiency of timely diagnosis and target treatment of tumors remains  $\log[3, 4, 5]$ .

Improving targeted treatment methods aimed at key morphological substrates that support carcinogenesis is of great importance in predicting outcomes. [6, 7, 8]. The issues of pathogenetically substantiated induction and inhibition of angiogenesis in human tumor tissue and prevention of cancer cell metastasis remain poorly understood.

#### **Objective**

To study the expression of CD34-positive precursors of endothelial cells, as well as VEGF-positive, secreting endothelial vascular growth factor in the tissue at the border with the tumor and directly in the tumor.

### MATERIAL AND METHODS

The paper analyzes and discusses the results of our own studies of biopsy specimens from tumor tissues in 11 patients obtained in accordance with the order of the Ministry of Healthcare of the Russian Federation dated 04.29.94 N82 "On the procedure for conducting pathological autopsies", according to the rules of the regulating instructions on the procedure for autopsy Committee of FEFU. The control group consisted of 4 patients who died as a result of traumatic brain injuries incompatible with life, presumably without somatic pathology at the age from 24 to 56 years. Using the methods of immune histochemistry, a quantitative analysis of vascular endothelial growth factors and CD34 expression in tumor tissue and at the border of unchanged tissue with a tumor was carried out. The biopsy material was recorded according to the appropriate protocols to prepare for histological studies immediately after collection. The exclusion of possible artifacts is based on the data obtained by Yu.I. Pigolkin. (1995), indicating that when corpses are kept at a temperature of 4-7° C for 4-6 hours, no microscopically visible changes are observed in the morphology of various organ systems, except for a slight decrease in the intensity of specific reactions to enzymatic activity. We used classical histological research methods with staining with hematoxylin and eosin to obtain a general morphological picture, as well as the method of immune histochemistry to identify the expression of CD34 and VEGF. Analysis of preparations and production of illustrations were performed using an Olympus Bx52 microscope and a DP25 digital camera.

# RESEARCH RESULTS AND DISCUSSION

We found that cells expressing CD34 were identified in all normal tissues of control vascular samples by pronounced and continuous staining. At the same time, VEGF was not expressed in normal unaltered tissues of various organs. It is known that vascular endothelial growth factor (VEGF) and VEGF receptors — VEGFR1 and VEGFR2 signaling are powerful activators of angiogenesis. The percentage of VEGFRpositive tumor cells was quantified in brain tumors. The density and diameter of microvessels was also analyzed using immune histochemistry for VEGF and CD34 expression. Although it was originally thought that the expression of VEGFR1 and VEGFR2 is limited to endothelial cells, now from Clara C.A., Marie S.K., de Almeida J.R. et al. (1914) it is known that both receptors can also be expressed in tumor cells [9]. In addition, we, based on the work of Jung S., Moon K.S., Jung T.Y., et al. (2006), it was considered that expressing CD34 cells are co-expressing the receptor VEGF2 [10]. Analysis of our own data and presented in the available literature Golab-Janowska M., Paczkowska E., Machalinski B., et al. (2018) showed that VEGFR — positive brain tumor cells provide an increased regulation of VEGF signaling on VEGFR [11]. We have noted a higher content of VEGFR1 and VEGFR2 — positive tumor cells than in tissues with thermal injuries. Higher mobilization of cells expressing CD34 occurs in trauma, respectively. It was also noted that CD34 is expressed not only in small, but also in larger vessels of tumors, which is consistent with the results of the study by TamuraR., SatoM., MorimotoY., (2020) [5]. We noted that the level of VEGF expression significantly correlated with the activity and expression of CD34. The analysis showed that there are no significant statistically significant differences in the expression of VEGF and CD34 in the age aspect, which is in correlation only depending on the size of the tumor and the age of the disease. Vascular endothelial growth factor, VEGF, is considered the main regulator of angiogenesis in tissue malignancy and in various tumors [12]. Intratumoral hemorrhage, as one of the pathogenetic links in the development of complications in various tumor conditions, occurs mainly in malignant tumors. Recent studies have shown that overexpression of vascular endothelial growth factor (VEGF) may play a role in the loss of vascular integrity and subsequent bleeding [13]. In our opinion, bleeding can be associated with both imperfection of the vascular wall and the absence of pericytes in the membrane of small vessels, which play not only the role of regulators of the vascular tone of small vessels and capillaries of the microvasculature, but also inhibitors of the proliferative activity of endothelial cells. The spectrum of influence of various factors on tumor development in the nervous tissue is complemented by a role in angiogenesis, neuroinflammation and cerebral ischemia performed by matrix metalloproteinases and tissue inhibitors of metalloproteinases[14, 15]. With physiological immaturity of the endothelium, there are no transport enzymes, such as alkaline phosphatase, which corresponds to the high ability of the immature endothelium to diffuse blood from the lumen of the vessels into the surrounding tissue under conditions of malignancy. This explains the high expression of CD34-positive cells during malignancy against the background of the lack of specialization of endothelial precursor cells in the tumor tissue.

### CONCLUSION

Strategies for the normalization of vascular histophysiology, aimed at improving the trophic supply of the structures of the tissues surrounding the tumor due to the full trophic supply with a decrease in hypoxia, are treatment methods that can improve the outcome in cancer patients undergoing rehabilitation treatment after surgery by inducing an increase or inhibition of gene expression. responsible for the secretion of proteins VEGF and CD34.

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# COMPARATIVE MORPHOMETRIC ANALYSIS OF AGE-RELATED CHANGES IN THE PYRAMIDAL NEURONS OF THE HUMAN PREFRONTAL AND POSTERIOR ASSOCIATIVE CORTEX FROM BIRTH TO 7 YEARS

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ABSTRACT — AIM: This article is devoted to the study of age-related changes in the body volume of pyramidal neurons (VP) of the human prefrontal (PFC) and posterior associative cortex (PAC) in children from birth to 7 years of age.

METHODS: The material consisted of left cerebral hemispheres obtained from 60 male individuals. We studied the areas 8, 45 and 10 in the PFC and area 37 in subareas 37ac, 37a, 37d in the PAC. For morphometry of pyramidal neurons in cortical sublayer III3, we used virtual images of serial frontal paraffin sections of cortex 10 thick stained by Nissl. We determined the mean value of VP (mean VP), the standard error of the mean, and the confidence interval for each age group.

RESULTS: The most significant changes in the mean VP in all studied cortical areas occurred during the first 6 months of life. The greatest increase in the VP was detected in the PFC from 3.5 to 7 years, and in the PAC from 1.5 to 3 years of age. There are close positive correlations between agerelated changes in the size of neurons in the PFC and in the PAC.

CONCLUSION: In children, the development of pyramidal neurons of the external pyramidal plate in the PAC occurs earlier and at a more intensive pace compared to the PFC. We suggest that VP is an important quantitative indicator that allows us to assess the timing and rate of age-related structural changes in the cerebral cortex.

**KEYWORDS** — cerebral cortex in children, prefrontal cortex, posterior associative cortex, body volume of pyramidal cells, morphometry, postnatal ontogenesis.

# INTRODUCTION

The study of neuronal growth and development in the human cerebral cortex is of considerable interest [9]. However, this issue has not been sufficiently studied to determine how neuronal growth processes in different cortical areas differ from each other during the early stages of postnatal ontogenesis. Pyramidal neurons in the outer pyramidal plate of the associative cortical zones — prefrontal cortex (PFC) and posterior associative cortex (PAC) — attract special attention. They play an important role in perception, attention, speech activity, auditory-motor and visual-motor coordination, mechanisms of working and long-term memory, cognitive activity, and behavior control in general [1, 5, 11]. Recently, researchers have been paying more and more attention to the quantitative analysis of the structural organization of the human cerebral cortex and nervous system during ontogenesis [14, 18]. One of the most important indicators of microstructural transformations in the cerebral cortex is the change in body volume of pyramidal cells (VP). The increase in nerve cell body volume correlates with the growth and development of their dendritic arborizations, complication of axon branching and synaptic apparatus, which serves as a significant indicator of subtle rearrangements in the brain structure underlying the improvement of its functions with age [6, 12].

The aim of the present study was to identify the timing and quantitative characteristics of age-related changes in the pyramidal neurons of the prefrontal cortex and posterior associative cortex in children aged from birth to 7 years.

### MATERIALS AND METHODS

The material included the left cerebral hemispheres of 60 boys aged from birth to 7 years who died from injuries without brain damage. The Ethics Committee in the Institute of Developmental Physiology of the Russian Academy of Education allowed the collection of the necessary sectional material (protocol No. 3 of 23.05.1996) in forensic morgues in Moscow and the Moscow region. The histological material was divided into 5 age groups, including: newborns (n = 11), 6 months (n = 13), 12 months (n = 10), from 1.5 to 3 years (n = 10) and from 3.5 to 7 years (n = 16).

The cortical areas for the study were selected according to K. Brodmann's cytoarchitectonic map. After fixation in 10% neutral formalin, tissue fragments were excised in the anterior part of area 8 (frontal eye field, BA 8), in the speech-motor area 45 (Broca's area, BA 45), on the lateral surface of the frontal pole in area 10 (BA 10) and in area 37 (BA 37) of the PAC. In area 37, we selected subareas 37ac, 37a, and 37d for the study in accordance with the Atlas of cytoarchitectonics of the human cerebral cortex [4]. In the upper section of the 37ac subarea (SA 37ac), a fragment was isolated in the hMT/V5 multimodal region, which is involved in the processing of tactile and visual information about the direction of moving objects [17]. On the inferior medial surface of the temporal lobe, we investigated subarea 37a (SA 37a) in the fusiform face area (FFA) [8], and on the medial surface, subarea 37d (SA 37d, or V8 zone). V8 zone is included in a system of anatomically related structures that are essential for declarative memory (conscious memory for facts and events) [15].

We carried out a morphometric analysis of pyramidal neurons bodies volume (VP) in sublayer III3 of the cortex on virtual images of frontal paraffin sections 10 μm thick, stained with Nissl cresyl violet. For this purpose, we used Image Tools technology (National Institutes of Health, USA) and ImageExpert<sup>™</sup> Gauge geometric measurement software for microobjects (NEXSYS, Russia), as well as a Biolam-15 LOMO microscope with a built-in USB camera UC-MOS01300KPA (Altami, Russia). In each area in 5 age groups, we measured the height of 800-1000 pyramidal neurons and the width of the basal part of their bodies, then the volume of the cell body of each neuron was calculated using the cone volume formula. Statistical processing of the obtained data included checking the normality of the distribution of values in the compared samples, and analyzing the probability distribution of quantitative signs [10]. We calculated mean body volume of pyramidal cells (mean VP), standard error and confidence interval using SigmaPlot software package (SYSTAT Software, USA) for different age groups. Significance of differences between mean values of different age groups was determined using two-sample t-criterion at P>95% (p<0.05).

To study the relationship between age-related changes in the size of pyramidal neuron bodies in the compared cortical areas, the study material was grouped into 9 age groups: newborns, children 6 months, children 12 months, and then the age groups were followed in annual intervals from 2 to 7 years. To assess the relationship between age-related changes in mean body volumes of pyramidal neurons in different cortical areas, we calculated Spearman's rank correlation coefficient (Rs) and its statistical significance using Student's criticality table.

#### RESULTS

It was found that in newborns in the PFC the largest volume of pyramidal neurons was observed in BA 8. In this area, the sizes of pyramidal neurons were 1.2 times larger than in BA 10 and BA 45 (Table 1).

Growth rates mean VP in different areas of the PFC were different during the first months. By 6 months in BA 8 and BA 10, this indicator increased 1.5 times, and in field 45 - 2.7 times compared with newborns. As a result, in boys of 6 months, the sizes of pyramidal neurons in BA 45 were on average 1.6–1.8 times larger than in BA 8 and BA 10. In the second half of the year, mean VP in BA 8 and BA 10 continued to grow, increasing on average 1.6 times as compared with the indicators of children 6 months old. By the end of the first year of life in BA 45, the average somal volume did not change, the sizes of the pyramidal neurons of the PFC did not differ between areas. During 2 and 3 years of life, mean VP in BA 8 and BA 45 remained stable, and in BA 10 it increased 1.2 times compared with one-year-old children. In children 2–3 years old, we did not observe significant differences in mean VP between the areas of the PFC. In the group of children from 4 to 7 years old, the size of pyramidal neurons in the PFC increased in comparison with children 2–3 years old: in BA 8 – 1.8 times, in BA 10 — 1.6 times, and in BA 45 — in 1.4 times. Pyramidal neurons in BA 8, on average, had 1.3 times the volume in comparison with BA 45.

A number of obvious trends were observed in the formation of pyramidal neurons in the PFC. In functionally different areas, a significant increase in the size of pyramidal neurons occurred synchronously during the first six months of life and heterochronously in subsequent years of ascending ontogenesis: in the BA 8 (frontal eye field) — by 1 and 7 years, in BA 10 of the frontal pole — by 1, 3, and 7 years, BA 45 (speech motor area) — by the age of 7. The increase in mean VP in different areas of the PFC occurred heterodynamically, that is, at different rates and with different intensities. During the first 6 months, the sizes of pyramidal neurons increased most intensively in the BA 45, in the second half of life — in the BA 8, over 1.5-3 years — in BA 10, and within 3.5–7 years — again in BA 8. At the stage of 3.5–7 years, a significant increase in mean VP occurred in all studied areas of the PFC, which signaled

Age group	n	Area 8	Area 10	Area 45
Newborns	11	458,9±24,0	377,7±14,7	390,0±16,9
6 months	13	678,3±49,5*	581,4±46,5*	1053,7±118,9*
1 year	10	1112,4±72,2*	928,4±69,9*	983,6±81,1
1.5–3 years	10	1127,6±69,3	1071,1±55,8*	1080,5±64,1
3.5–7 years	16	2014,2±147,5*	1688,5±108,1*	1498,5±77,6*

Table 1. Age-related changes in the average body volume of pyramidal neurons in III3 sublayer of the prefrontal cortex in children (M+m) (mkm<sup>3</sup>)

Note to Tables 1 and 2: \* — the differences are significant (at p < 0.05) in comparison with the same area of the previous age group

an increase in the functional activity of distributed neural networks with its participation.

In the PAC in newborns, the highest mean VP was in SA 37d, located on the border with the limbic lobe, and the lowest in SA 37a in the FFA region. The difference in the average group indicators in these subfields was 1.2 times (Table 2).

The volume of pyramidal neurons in SA 37a was on average 1.3-fold greater than in SA 37ac. In children aged 4 to 7 years, the mean body volume of pyramidal cells in SA 37ac increased by 1.2 times in comparison with children 2–3 years old, and did not change in SA 37a and SA 37d. As a result, the differences in the sizes of pyramidal neurons between SA 37ac and SA 37a,

**Table 2.** Age-related changes in the average body volume of pyramidal neurons in III3 sublayer of the posterior associative cortex in children (M+m) (mkm<sup>3</sup>)

Age group	n	Subarea 37ac	Subarea 37a	Subarea 37d
Newborns	11	446,3±30,9	392,0±22,4	488,4±14,3
6 months	13	1202,5±86,9*	975,5±51,6*	1019,8±44,5*
1 year	10	1369,9±51,9	1462,4±93,1*	1733,4±88,1*
1.5–3 years	10	1813,2±121,7*	2372,6±133,4*	2046,3±111,7*
3.5–7 years	16	2189,3±118,8*	2402,3±134,8	2081,9±116,3

By the end of the first half of the year, mean VP increased 2.6 times in SA 37ac and SA 37a, and 2.1 times in SA 37d compared with newborns. The sizes of SA 37ac pyramidal neurons were, on average, 1.2 times larger compared to SA 37a and did not differ significantly from SA 37d. Interestingly, in this segment of postnatal ontogenesis, the growth rates mean VP in the BA 37 subfields are similar to the growth rates of pyramidal neurons in BA 45 and are significantly higher compared to BA 8 and BA 10 of the PFC. In the second half of the first year of life, the size of pyramidal neurons did not change in SA 37ac, increased 1.5-fold in SA 37a, and 1.7-fold in SA 37d compared to 6-month-old children. By the end of the first year of life, the average volume of neuronal soma in SA 37d was 1.3 times larger compared to SA 37ac.

In 2–3-year-old boys, the mean VP in the PAC increased synchronously and heterodynamically compared to those in children aged 1 year: 1.3-fold in SA 37ac, 1.6-fold in SA 37a, and 1.2-fold in SA 37d.

which we noted in children 2-3 years old, smoothed out by the age of 7 years.

In the PAC, we noted a synchronous increase in the size of pyramidal neurons in SA 37a and SA 37d during the first year of life, as well as in the age group of children 1.5–3 years old. In SA 37ac, synchronously with the rest of the fields of the PAC, the mean VP increased during the first 6 months of life and in the age group of children 2–3 years old. In the age group of children 3.5–7 years old, we noted an increase in mean VP in SA 37ac. The heterodynamic nature of the increase in the size of pyramidal neurons was illustrated by the fact that during the first 6 months the mean VP increased most intensively in SA 37ac and SA 37a, in the second half of the year — in SA 37d, over 2–3 years — in SA 37a, and during 4–7 years — in SA 37ac.

To assess the relationship between the rates of age-related changes mean VP in functionally different zones of the PFC and PAC in children, we used Spearman's rank correlation analysis. The number of rank pairs (n = 9) of the compared values corresponded to the number of age groups from birth to 7 years in annual intervals, taking into account the indicators of newborns and children at the age of 6 months. Significant correlation coefficients Rs between mean VP in BA 8, BA 10 and BA 45 and SA 37ac, SA 37a and SA 37d are presented in Table 3.

**Table 3.** Areas with significant positive correlations of age-related changes in the mean body volume of pyramidal neurons in sublayer III3 in children from birth to 7 years

n=9	Rs	t-stat
Area 8 – Area 10	0,95	0,34
Area 8 — Area 45	0,92	0,43
Area 8 – Subarea 37ac	0,75	0,71
Area 8 – Subarea 37a	0,82	0,62
Area 10 — Area 45	0,90	0,47
Area 10 — Subarea 37ac	0,90	0,47
Area 10 — Subarea 37a	0,77	0,69
Area 10 – Subarea 37d	0,83	0,59
Area 45 — Subarea 37a	0,85	0,57
Subarea 37a – Subarea 37d	0,95	0,34

**Note:** n is the number of rank pairs of compared values; Rs is the Spearman's correlation coefficient; t-stat is Student's t-test. Two-sided level of significance (p-value) < 0.05.

It follows from the table that a statistically significant strong and direct two-way relationship existed between age-related changes in the size of pyramidal neurons in all the studied areas of the PFC. In the PAC, we detected a strong and direct bilateral relationship between changes in the dimensional parameters of pyramidal neurons only in SA 37a and SA 37d, whereas SA 37ac, located on the lateral surface of the hemisphere, had no significant correlations with these subareas. We also found statistically significant strong and direct two-way correlations between changes in the mean VP in BA 10 and in all subfields of BA 37. Similar correlations existed between BA 8 and subareas 37ac and 37a, and between BA 45 and SA 37a.

# DISCUSSION

Our study, carried out on a large histological material grouped into 5 age groups from birth to 7 years, showed that the most significant changes in mean VP in the areas of the PFC and PAC of the left cerebral hemisphere occurred in children during the first 6 months of life. During postnatal development, the greatest increase in mean body volume of pyramidal cells was found in the PFC at the age interval from 3.5 to 7 years, and in the PAC — from 1 to 3 years.

It should be noted that the increase in the size of pyramidal neurons continues after 7 years [2], which can be traced by analyzing the redistribution of the relative number of neurons in the cell population in the direction from small-cell to large-cell size classes [16]. An increase in pyramidal neuron body volume is accompanied by lengthening of dendrites, complication of their terminal branching and an increase in the number of synaptic contacts, which up to a certain limit expands the receptive fields of neurons, and also affects excitability and intracellular changes associated with learning and memory [13]. As a result, competitive conditions are created for the selective activity of neurons in the system of distributed neural networks and fine tuning of the previously established intercellular interaction [7]. In our opinion, it is this natural process that underlies the transition from generalized cortical reactivity at the early stages of postnatal ontogenesis to the gradual formation of specialized and locally structured responses to modally specific stimuli in children and adolescents.

The presence of close correlations between neuronal size changes in BA 10 of the PFC and the BA 37 subareas indicates the important role of the frontal pole cortex in controlling the processes of visual perception, attention and goal-directed behavior, which are based on signals received from the inferior temporal associative cortical areas [3]. The close selective relationship between neuronal size changes in areas 45 and 37a reflects the important role of visual facial perception for the development of speech articulation. Similar connections between oculomotor area 8 and subareas 37ac and 37a serve as the basis for recognition of moving objects and spatial visual memory.

## CONCLUSIONS

Thus, we conclude that in children from birth to 7 years of age, the development of pyramidal neurons of the external pyramidal plate in the posterior associative cortex occurs earlier and at a more intensive pace compared to the PFC. We were also convinced that the pyramidal neuron body volume is one of the important indicators that allow us to evaluate not only the timing and rate of age-related structural changes in the cerebral cortex, but also to obtain informative data on the morphofunctional relationship between different cytoarchitectonic cortical areas at different stages of postnatal ontogenesis.

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# ANTHROPOMETRIC PARAMETERS AFFECTING THE LINEAR DIMENSIONS OF THE RIGHT LIVER LOBE

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**ABSTRACT** — The anthropometric parameters and linear ultrasound diameters of right liver lobe were taken from 212 adult healthy volunteers (90 men and 122 women). In men anthropometric parameters correlate with linear dimensions of the right liver lobe much more than in women. The anteroposterior diameter of the right lobe is the most anthropometrically dependent liver's dimension in both men and women, and the craniocaudal diameter of the right lobe is the least anthropometrically dependent liver's dimension. The strongest correlations were found in both men and women between the anteroposterior diameter of the right lobe and weight, chest circumference and waist circumference.

**KEYWORDS** — Anthropometric parameters, ultrasound, linear dimensions of the liver, right liver lobe, gender differences.

# INTRODUCTION

As it is known that the size of the liver can be influenced by many factors, such as weight, height, age, gender, size and shape of the body, presence of anatomical abnormalities of the liver, obesity, cirrhosis of the liver, alcohol abuse, as well as the respiratory phase during the measurement and the method of diagnostic visualization and position of patients throughout the examination [1; 2; 3; 4; 5; 6; 7; 8]. However, the influence's degree of factors on the liver's size varies according to point of view of different authors.

Some authors consider the size of the liver in men is larger than in women [3; 5; 6; 7], others that the difference has no clinical significance [2] or not at all [1].

Some authors [2; 7] consider the body mass index is determinative when measuring the oblique craniocaudal maximum diameter of right liver lobe but their parameters in relation to height and weight differ. In the previous study we have already determined the difference in linear dimensions of the right liver lobe for men and women [8].

#### The purpose of this study

was to determine the influence of anthropometric parameters on the linear dimensions of the right liver lobe in men and women.

# MATERIALS AND METHODS

We have carried out measurements of anthropometric parameters and ultrasound examination of abdominal cavity's organs with determining of linear dimensions of the right liver lobe in 212 healthy volunteers (90 men μ 122 women) aged 18 to 69 years.

Height, weight, infrasternal angle, chest circumference (CC) and waist circumference (WC) were measured. The posterior semicircle of CC matches with the line just below the inferior scapula's angle, the anterior semicircle of CC in men crosses the nipples and matches with the line just below mammary gland in women. WC was measured at the level of the navel. Thickness of subcutaneous adipose tissue of anterior abdominal wall (SAT of AAW) was measured at 3 cm to the right side from navel with ultrasound linear transducer. Body mass index (BMI) was calculated using standard formula.

Ultrasound examinations of liver were performed using following ultrasound systems: Aixplorer (Supersonic Imagine, France), SonoScapeS6 (China) and Mindray DC-8 (China) with convex transducers. All patients were investigated in the supine position with the both arms placed above the head, the stretched legs and with quiet breathing.

Right lobe was measured in the anterior axillary line with transducer orientated longitudinallythrough the VII–X intercostal spaces. We have measured oblique craniocaudal maximum diameter (OCC max, length), craniocaudal diameter (CC) and anteroposterior diameter (AP, depth) (Fig. 1).

All data were analyzed using the Statistical Package for the Social Sciences 23.0 (SPSS) software recommended for analysis of biomedical data. Correlation was assessed using Spearman's rank correlation coefficient. Chaddock`s scale was used for the assessment of correlation [9]. P-values of less than 0.05 were considered statistically significant.



**Fig. 1.** Ultrasound measurements of the right liver lobe in volunteer M., 43 years old. Transducer orientated longitudinally in the VII-X intercostal spaces in the anterior axillary line. Blue color indicates the oblique maximum craniocaudal diameter, white — the craniocaudal diameter, yellow — the anteroposterior diameter

# RESULTS

The correlation and its statistical significance between anthropometric parameters and linear dimensions of the right liver lobe in men and women are represented in the Table 1. When measuring the right liver lobe the strongest correlations were revealed for the AP diameter both in men and in women.

In men there were noticeable direct correlations between the right lobe with weight (r = 0.611), CC (r = 0.574), and WC (r = 0.562). Moderate direct correlations were found in men between the AP with height (r = 0.359), BMI (r = 0.469), infrasternal angle (r = 0.355), and thickness of SAT of AAW (r = 0.388). Moderate direct correlations in women were found between AP diameter and weight (r = 0.483), BMI (r = 0.404), infrasternal angle (r = 0.448), WC (r = 0.407), and thickness of SAT of AAW(r = 0.300).

There is the study showing that the AP diameter of the right lobe is the most correlated linear dimension with the volume of the liver [10]. Thus, it may be necessary to take this into account that AP diameter of right lobe when not only assessing linear diameters accordingly to anthropometric parameters but also for assessing the liver volume.

# CONCLUSION

Anthropometric parameters correlate differently with right liver lobe linear dimensions. In men correlations are stronger than the same in women.

Anthropo-metric parameters	OCC max		CC		AP	
	men (n=90)	women (n=122)	men (n=90)	women (n=122)	men (n=90)	women (n=122)
height	0,509	0,153	0,452	0,110	0,359	0,125
	(p <0,001)	(p=0,092)	(p<0,001)	(p=0,226)	(p=0,001)	(p=0,169)
weight	0,427	0,118	0,304	0,067	0,611	0,483
	(p< 0,001)	(p=0,197)	(p=0,004)	(p=0,462)	(p< 0,001)	(p<0,001)
BMI	0,153	0,018	0,040	-0,005	0,469	0,404
	(p=0,149)	(p=0,846)	(p=0,711)	(p=0,957)	(p<0,001)	(p<0,001)
infrasternal angle	0,188	0,121	0,089	0,113	0,355	0,448
	(p=0,076)	(p=0,183)	(p=0,404)	(p=0,217)	(p=0,001)	(p<0,001)
СС	0,223	0,081	0,112	0,031	0,574	0,456
	(p=0,035)	(p=0,374)	(p=0,293)	(p=0,732)	(p=0,000)	(p=0,000)
WC	0,286	0,041	0,100	-0,009	0,562	0,407
	(p=0,006)	(p=0,655)	(p=0,350)	(p=0,921)	(p<0,001)	(p<0,001)
thickness of SAT	0,018	-0,085	-0,136	-0,102	0,388	0,300
of AAW	(p=0,867)	(p=0,354)	(p=0,200)	(p=0,264)	(p<0,001)	(p=0,001)

Table 1. Correlation coefficients of anthropometric parameters and linear diameters of the right liver lobe in men and women

It's shown on the table that the anthropometric parameters with the diameters of the right lobe correlate more in men than those in women.

Noteworthy statistically significant relationships for OCC max and CC diameters were found only in men with such parameters as height and weight (for OCC max r = 0.509 and r = 0.427, respectively, for CC r = 0.452 and r = 0.304, respectively). Both height and weight affect on all the reviewed right liver lobe linear dimensions (oblique craniocaudal maximum diameter, craniocaudal diameter and anteroposterior diameter) in men. The craniocaudal diameter of the right lobe is the least anthropometric dependent linear dimension of the right liver lobe.

The dimension most closely correlated to anthropometric parameters (weight, BMI, infrasternal angle, chest circumference, waist circumference and thickness of subcutaneous adipose tissue of anterior abdominal wall) for both men and women is the anteroposterior diameter of the right lobe.

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# FACTORS INFLUENCING THE EFFECTIVENESS OF ANTIPLATELET THERAPY

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ABSTRACT — In recent years, significant advances in the diagnosis and treatment of cardiovascular diseases have been achieved in the healthcare of most countries. However, among the causes of mortality in patients with coronary heart disease, arterial thrombosis takes one of the leading positions. Antiplatelet drugs are prescribed to prevent thrombotic complications, which can be used as mono- or two-component therapy. In case of atherosclerosis in arteries, acetyl-salicylic acid (ASA) or clopidogrel can be used as monotherapy; treatment of acute coronary syndrome (ACS) and percutaneous coronary interventions (PCI) required using of double antiplatelet therapy (DAT), including acetylsalicylic acid drugs together with one antiplatelet agent from the group of thienopyridine derivatives — blockers of P2Y12 platelet receptors (clopidogrel, ticagrelor, prasugrel).

In patients with ACS who underwent primary PCI or thrombolysis followed by PCI, the duration of DAT is 12 months, and clopidogrel is the drug of choice [16, 30]. According to various literature sources about 20–40% of patients have low effectiveness of antiplatelet therapy, which can lead to thrombosis, stent thrombosis and thromboembolic complications. This review provides an analysis of modifiable and nonmodifiable factors contribution to the development of clinical and laboratory resistance of antiplatelet agents.

**KEYWORDS** — acute coronary syndrome, acetylsalicylic acid, clopidogrel, biotransformation genes, clinical and phenotypic features.

# INTRODUCTION

All over the world, mortality from cardiovascular diseases remains extremely high, re-gardless of recent years achievements related to the development of new methods of diagno-sis, treatment, updating of clinical recommendations and treatment protocols.

In Russia, at least 49% of all patients die due to cardiovascular diseases, among which coronary heart disease is determined as the cause of death in 28.4%, and cerebrovascular diseases (including stroke) — 14.4% [50]. More than 54 thousand people died from a heart stroke in Russia in 2019 only according to Rosstat data.

For all patients with coronary heart disease: stable angina pectoris, ACS with and without ST segment elevation, antiplatelet agents are an essential part of treatment. It should be realized that long-term administration of antiplatelet agents is always a fine balance be-tween thrombosis and bleeding. On the one hand, it can be explained by the complexity of the thrombosis chain and the complexity of acting simultaneously on all components that trigger and support the process of blood clot formation. On the other hand, a variety of scientifically and clinically proven exogenous and endogenous factors can influence the individual respon-siveness of patients to antiplatelet therapy.

In patients resistant to antiplatelet therapy, there is an increase in the frequency (2.5–3.5 times) of myocardium infarction, ischemic strokes compared to patients susceptible to it, which makes extremely relevant the problem of antiplatelet agent's resistance develop-mentstudying [13, 15, 17].

The aim

of this review was to summarize the available results of foreign and national studies devoted to the study of the antiplatelet drugs resistance development.

# MATERIALS AND METHODS

For this review we used data of scientific publications from open and accessible sources in the period 2001–2021, published in electronic databases: pharmgkb.org, PubMed, Scopus, Web of Science Core Collection, Elibrary, Google Scholar. Search queries — "anti-aggregational therapy + therapy resistance", "COX polymorphism + aspirin resistance", "GPIa gene polymorphism, P2Y1 + aspirin resistance", "CYP2C19+clopidogrel+ antiplatelet therapy efficacy"; "clopidogrel resistance + CYP2C19 polymorphism" in both Russian and English.

# **RESULTS AND DISCUSSION**

#### Antiplatelet therapy resistance

The efficacy of ASA low doses prescribing in patients with coronary heart disease has been confirmed in more than 200 studies conducted over the past 30 years [26]. The role of ASA as a secondary prevention drug has been conclusively demonstrated, which reduces the chance of serious cardiovascular events over 25%.

The mechanism of ASA antiplatelet effect is the inhibition of COX-1 formation and the of thromboxane A2 (THA2)synthesis, which leads to a decrease in the residual platelet reactivity. Optical aggregometry, also called light transmission aggregometry, is the *gold standard* in evaluating the influence of aspirin on platelet reactivity. Such methodin the presence of unquestionable advantages, has a number of disadvantages, including related to the complexity of the process. Currently, portable devices such as optical detection of platelet agglutination (VerifyNow) have been introduced into practical healthcare to evaluate platelets reactivity directly at the patient's bedside.

Overall, ASA resistance is defined as *the inability* of ASA to protect a patient from thrombotic complications; prolong bleeding time; inhibit THA2 biosynthesis; inhibit platelet function in one or more in vitro tests [38].

However, there are differences between laboratory and clinical resistance. Laboratory resistance refers to the lack of residual platelet reactivity (RPR) blocking effect.Clinical resistance suggests the development of atherothrombotic events on the background of the ASA use [20, 21, 22].

Among the causes of clinical resistance to ASA, the following are identified: defects in the effect on a specific platelet receptor, ineffective acetylation of COX-1 and lack of thromboxane A2 (TXA2)inhibition[37].

There are studies confirming the involvement of the ASA taking duration factor in the development of resistance to aspirin. Thus, according to Pulcinelli F.M. et al., in 150 patients, despite an adequate decrease in aggregation 2 months after the start of ASA treatment, a permanent decrease in sensitivity to it was observed in the longer term [40].

The classification of resistance to ASA suggested by Weber AA in 2002 also makes it possible to identify the pharmacokinetic, pharmacodynamic type and *pseudo-resistance.* 

The first type includes cases of ASA platelet aggregation activity (PA) suppressionand synthesis of TXA2 only in vitro. With the pharmacodynamic type, it is not possible to suppress PA in vitro or in vivo. All cases of "thromboxane-independent platelet aggregation" belong to the pseudo-resistance to ASC, when high residual platelet reactivity (HRPR) persists with adequate pressure of TXA2 biosynthesis [46].

It is explained by the fact that in addition to platelet activation by stimulation of thromboxane A2

receptors, there are alternative activation pathways, including stimulation of platelet membrane glycoproteins (platelet receptors) by collagen (GPIa/IIA), von Willebrand factor (GP Ib/V/IX), ADP, thrombin, epinephrine, serotonin [5, 11, 13]. Moreover, it was found that in patients in the early post-infarction period there is a possibility of platelet activation through Toll-like receptors 2/1, which is not stopped by standard antiplatelet therapy [31].

#### Clopidogrel resistance

Large placebo-controlled trials of the last 15–20 years have proven the advantage of clopidogrel as a supplement to aspirin as part of dual antiplatelet therapy (DAT) in ACS, which was confirmed by improved treatment results after PCI in both the short and long term, which marked the beginning of DAT active clinical use [28, 36, 41, 44, 48].

Today, clopidogrel is the most frequently prescribed drug in the group. Regardless to the large number of studies confirming the individual variability of the response to clopidogrel and the presence of ethnic specificity in the distribution of polymorphic alleles frequencies of enzyme gene that metabolizes it into the active form, clopidogrel does not cause such a large number of bleeding compared to its analogues. Clopidogrel is a prodrug, which requires its transformation in the liver to an active metabolite. Absorption of the drug in the intestine takes place with the involvement of P-glycoprotein, the synthesis of which is regulated by the MDR1 (ABCB1) gene. In the case of ABCB1 (CC, CT, TT) gene polymorphic alleles carrying, the activity of clopidogrel during absorption can change. Approximately 85% of the absorbed drug is inactivated by liver enzymes, while 15% with the involvement of cytochrome P450 isoenzymes CYP1A2, CYP2B6 and CYP2C19, are converted into an intermediate metabolite of 2-oxo-clopidogrel (thiolactone). Further, an active compound R130964 is formed from an intermediate inactive metabolite, mainly with the involvement of CYP2C19, which inhibits platelet aggregation by irreversible blockade of ADP P2Y12 on the platelet surface [8, 18].

Clopidogrel resistance refers to the drug's inability to block the target P2U12 receptor and effectively suppress platelet aggregation. Currently, the factors affecting the metabolic processes of clopidogrel at all its stages and the reasons that reduce its effectiveness have been established. Hereditary factors of the defect in the clopidogrel active metabolite formation, clinically significant interactions with other drugs that are inhibitors of CYP2C19, ethnicity, smoking, hyperglycemia, hypercholesterolemia, obesity, age, etc. are intensively discussed [49]. According to various meta-analyses, the average rate of clopidogrel resistance is 21% [44]. The prevalence of resistance to ASA varies quite widely between 2 and 43% [38]. Up to 6% of patients may have an insufficient response to dual antiplatelet therapy (aspirin + clopidogrel) [27].

The presence of laboratory resistance to ASA and/or clopidogrel enhances the com-parative risk of repeated cardiovascular events up to 4 times [CI 2.9; 5.6] over 18 months of follow-up, compared with a group of individuals not showing signs of resistance to antiplate-let agents [10].

Genetic, unmodified factors affecting responsiveness to antiplatelet therapy

In order to assess the contribution of hereditary factors to the formation of ASA resistance, the polymorphisms of the COX-1 genes were most fully studied: C22T, C50T/A842G, G128A, C644A, C714A, C10427A, G1446A, G765C; GPIa gene polymor-phism C807T; GPIba — C5T gene; GPIIIa — T196C GPVI — T13254C gene; P2Y1receptor gene — C893T; P2Y1 — A1622G; P2Y12 — H1/H2 [3, 4].

Thus, it was found that in the examination of two single-nucleotide polymorphisms A-842G and C50T COX-1 in heterozygotes according to the haplotype A-842G/C50T, significantly greater inhibition (p=0.01) of ASA formation of prostaglandin was observed compared with homozygotes according to the wild allele [34].

Yi.Xingyang et al. (2017) revealed that arachidonic acid and ADP induced significantly greater platelet aggregation in patients with point mutations (including rs20417, rs1371097, rs2317676) of the GPIIb/ IIIa gene than in patients without these genotypes. It was suggested by the authors that the combination of rs20417, rs1371097 and rs2317676 may potentially lead to initially high platelet aggregation among these people, thereby increasing the risk of aspirin resistance and early cardiovascular complications [47]

In a study of T. Goodman et al. (2008) a particular association was found between the carrier of the PlA1/A2polymorphic variant and resistance to aspirin in healthy people, and the effect decreased in the presence of cardiovascular diseases [33].

According to Kapustin S.I. (2017), in patients with deep vein thrombosis (DVT) and pulmonary embolism (PE), a more than 10-fold rise in the proportion of P2Y12 H2 variant homozygous carriers of the platelet receptor ADP gene was found -3.4% versus 0.3% in patients with isolated DVT, OR = 10.7, 95% CI: 1.2 - 97.0; p = 0.023) [7].

In developing personalized approaches to clopidogrel usage, a lot of attention is paid to the polymorphic carriage of the CYP2C19 gene [1, 6, 8, 18]. The results of fundamental studies devoted to the evaluation of individual responsiveness to antiplatelet agents under the guidance of Professor D.A. Sychev are widely presented in the publications [18, 19, 23].

According to the results of the multicenter GRAVITAS study (USA), which examined 1152 blood samples and 40 polymorphisms, including CYP2C19 \*2, \*3 \*4, \*5, \*6, \*7, \*8, and \*17; ABCB1 and PON1, it was found that patients with one or two polymorphic alleles of the CYP2C19 gene, at which its functional activity is lost, do not respond even to a double dose of clopidogrel. There was an 11-fold rise in the risk of a sustained increase in platelet reactivity for 30 days in patients with homozygous carriers of the CYP2C19\*2 gene, compared with patients who had a functionally active wild type gene. Heterozygotes also retained HRPR — up to 62% compared to carriers of the wild, rapid allele [39].

A genome-wide association GWAS study carried out by the International Pharmaco-genetic Consortium (ICPC) has shown that the response to clopidogrel has significant variability. In this case, according to the authors, alleles of CYP2C19 function loss make up only a certain part in the structure of the low response causes to the drug. The study involved 2750 people of Europeans whose DNA was tested. The GWAS study did not reveal any other SNP, except for CYP2C19\*2, which would have reached genome-wide relevancy [45].

An association was found between the CYP2C19 genotype and the fact of the *end-point* of cardiovascular death, non-fatal myocardial infarction in young patients who had suffered a myocardial infarction and received clopidogrel in a dose of 75 mg/day. It was found that in patients with CYP2C19\*2 genotype (28%), the risk of recurrence acute coronary event during the first year was several times higher than in patients with wild genotype. Moreover, the authors have positioned the cyp2c19 genotype polymorphism as the only sig-nificant predictor of the primary outcome in this patient population [29]

A study was conducted in Europe in patients with myocardial infarction (MI) with ST segment elevation and without ST elevation (n=2208 people) treated with clopidogrel [42]. All patients were genotyped for the following genes: CYP2C19; CYP3A5; ABCB1; P2Y12, P2RY12; ITGB3 (IIB–IIIA receptor).The frequency of CYP2C19 alleles\*2, \*3, \*4 and \*5 occurrence was studied for CYP2C19. A criterion which was used in this study is the *end point* or the primary result, which included death from any causes (strokes, myocardial infarctions, stent thrombosis, etc.) during the first year after the MI. Among patients with cardiovascular events and thrombotic complications, the frequency of single-nucleotide polymorphisms in the CYP3A5, P2RY12 and ITGB3 genes was significantly higher (in comparison with group without the *end point*). Patients with two alleles of the CYP2C19 gene were more at risk of *end point* developing than in the group of patients not carrying polymorphic alleles [42].

The influence of clinically significant alleles variants of the CES1, PON1, ABCG2, CYP4F2, CYP3A4, IGTB3, P2Y12, PEAR1, B4GALT2 genes carriage on the antiplatelet effect of clopidogrel and clinical outcomes of patients with ACS and atrial fibrillation was studied. It was found that CYP4F2 C(VAL433MET), PEAR1 rs41273215 C>T polymorphisms were statistically significantly associated with a higher frequency of significant bleeding on the background of antithrombotic therapy (p=0.008;p=0.035). The polymorphic variant CT+TT B4GALT2 rs1061781 was significantly associated with an increased frequency of strokes and TIA (p=0.041) [23]. The research for new predictors of the formation of the HRPR continues.

The modern direction of the HRPR genetic predictors research is the study of the plasma micro-RNAs expression levels. Thus, a correlation was established between the level of plasma microRNA expression and the indicators of residual platelet reactivity in patients taking P2Y12 receptor inhibitors [19].

# Modifiable factors affecting antiplatelet therapy responsiveness

Possible causes of aspirin resistance associated with insufficient compliance to therapy, low bioavailability of drugs, inadequately prescribed dose, poor intestinal absorption, clinically significant interactions with other drugs, functional immaturity of platelets, smoking, hypercholesterolemia, hyperglycemia, obesity, stress, comorbid pathology, high levels of pro-inflammatory cytokines, which are an additional source of thromboxane TXA2 and other fac-tors have been widely discussed in the publications [14, 20, 21, 22, 24, 49].

The patient's compliance to therapy is of great importance in achieving an adequate antiplatelet effect. The credibility and professionalism of the doctor largely determines how much the patient will follow all the prescribed recommendations on the dosage of the drug, the intake regimen, interaction with food etc., which finally will certainly affect the effectiveness of the prescribed drugs. Some studies have shown how the regularity of admission is influenced not only by motivational factors, but also by the packaging features that provide simplicity and convenience of admission. Thus, with the use of a calendar blister in elderly and geriatric people, the level of compliance was higher than in receiving drugs in an ordinary bottle.

Co-administration of antiplatelet agents with calcium channel blockers, beta-blockers, statins, may lead to a change in the efficacy and safety profile of antiplatelet agents, due to the effect on the functional activity of P glycoprotein, which ensures the drug absorption. In proton pump inhibitor therapy, hydrochloric acid production decreases and the pH increases above the dissociation constant of acetylsalicylic acid (3,5), which converts aspirin into an ionized state, lowering its lipophilicity and absorption.

The dose of the prescribed drug also affects the bioavailability. In 2002, a meta-analysis of the Antithrombotic Trialists Collaboration was published, summarizing the results of 287 randomized trials involving 135 thousand patients who had suffered some kind of cardiovascular event. It has been shown the use of ASA in a dose of 75–150 mg leads to a signif-icant decrease in the risk of repeated cardiovascular events in general by 25%, nonfatal myocardial infarction by 30%, nonfatal stroke — by 25%, cardiovascular mortality — by 17% [26]. There are references in the publications to the administration of higher doses of ASA, proba-bly to increase bioavailability and provide a better antiplatelet effect, but the inhibition of TXA2 is completely dose-dependent and is implemented in the range of minimum doses — 75–150 mg.

Hyperglycaemia and obesity contribute to a decrease in the platelet activation endothe-lial inhibitors levels and, as a result, increase the risk of thrombosis. Elevated levels of glucose and hyperinsulinemia in platelets lead to activation of protein kinase C, a decrease in NO synthesis and an increase in oxygen synthesis 2. Platelet membrane contains glycoproteins (GP) — receptors of adhesive proteins. In patients with metabolic syndrome (MS), there is an increased expression of glycoprotein Ib (GPIb) on the platelet surface, which determines platelet binding to the Willebrand factor. The interaction of GPIb and Willebrand factor induces an intracellular signal that leads to the activation of the GP IIb/IIIa complex, which allows the binding of plasma fibrinogen and Willebrand factor. At the same time, there can be a decrease in endothelial antiplateletfactors — nitrogen oxide and prostacyclin, and an increase in the formation of platelet activators [2, 11, 13, 25.]

The results of clopidogrel's antiplatelet effect studied in patients with obesity are presented. It appeared that the frequency of clopidogrel resistance in patients with obesity was significantly higher (60.8%) than in non-obese patients (35%; p=0.014). Resistance to clopidogrel in patients with diabetes mellitus was also significantly more frequently recorded: in 18 (66.7%) people compared to 29 (39.7%; p=0.017) [14, 15].

A rise in the level of inflammatory markers, which include C-reactive protein (CRP), interleukin 6 (IL-6), IL-10, CD40, tumor necrosis factor (TNF), fibrinogen, can also lead to HRPR. This is explained by the fact that inflammatory mediators are alternative non-platelet sources of TXA2 [14, 15].

Smoking is another factor affecting the effectiveness of antiplatelet therapy. The effect of nicotine increases cholesterol levels, promotes atherosclerosis, is a risk factor for the development of cardiovascular diseases and sudden cardiovascular events. In recent years, so-called *smoker's paradox* has been discussed in the publications [9]. A number of studies, including a meta-analysis carried out by J. J. Gagne et al., showed how the use of clopidogrel was associated with a decrease in the frequency of the combined endpoint, including death from cardiovascular causes, myocardial infarction and stroke, by 25% in smokers and only 8% in non-smoking patients [32]. Certainly, such observations set a certain dilemma for specialists and require more in-depth research into this direction.

The problem of aspirin resistance development depending on gender is controversial. According to a number of authors, women are more predisposed to the development of HRPR on the background of antiplatelet therapy [12]. Currently, there are no clear answers to this question, but it is assumed that there is a gender difference in the basic platelet reactivity, possibly due to differences in the functioning of neurohumoral mechanisms of vascular tone regulation and neurotransmitter synthesis.

# CONCLUSION

The problem of antiplatelet drug's efficacy is widely and actively discussed in the scientific papers. The development of resistance to both ASA and P2Y12 inhibitors is quite prevalent. The factors that lead to the development of resistance can be divided into modifiable and nonmodifiable. Apparently, antiplatelet drugs resistance can also be considered in terms of the avoidable and unavoidable, which requires further study and systematization. The emergence of new methods for studying the mechanisms of HRPR development on the background of the use of antiplatelets may provide new tools in therapy personalization.

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# **CONFLICT OF INTERESTS**

The authors declare no obvious and potential conflicts of interest related to the publication of this paper.

# AUTHORS CONTRIBUTION

Kantemirova B.I. — design and writing of the manuscript, Zhidovinov A.A. — methodological and consulting help, Chernysheva E.N. — methodological and consulting help in writing the manuscript, Abdullaev M.A. — collection of reference literature, Orlova E.A. — structure of review, Sultanova O. analysis of clinical material used in the paper.

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# PREPARATION OF COMPONENTS OF ULTRASONIC EXTRACT OF GINKGO BILOBA, PHYSICO-CHEMICAL AND PHARMACOLOGICAL ANALYSIS AND MOLECULAR DESIGN

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ABSTRACT — The main task arising during the processing of medicinal plant raw materials is the intensification of extraction processes in order to maximize the extraction of groups of biologically active substances. It is of interest to obtain an extract and conduct molecular modeling in order to predict the biological activity of the components of the ginkgo biloba phytocomplex. The range of dosage forms obtained on the basis of dry extract is small, despite the wide range of pharmacological activity. THE AIM OF THE STUDY is to optimize the method of obtaining alcohol extract, with the possibility of including it in various dosage forms. PHYSICO-CHEMICAL ANALYSIS: Confirmation of the alleged pharmacological activity by the method of molecular modeling. MATERIALS AND METHODS: Ultrasonic extraction, spectrophotometry in the ultraviolet region. Pharmacological studies by modeling cerebral ischemia using simultaneous bilateral occlusion of the common carotid arteries. Changing the speed of cerebral blood flow by Dopplerography. RESULTS AND DISCUSSION. Liquid extract of ginkgo bilobar leaves was obtained by ultrasonic extraction. The calculation of the electronic structure and quantum-chemical descriptors of ginkgolide B. was carried out. The assessment of specific pharmacological activity was carried out. CONCLUSION: The ultrasonic method of extraction of ginkgo biloba leaves was applied. The predicted biological activity of the obtained phytocomplex was confirmed by methods of molecular modeling and experimentally.

KEYWORDS — ultrasonic extraction, UV spectrometry, ginkgo biloba, ginkgolide B, flavonoids, molecular modeling.

# INTRODUCTION

One of the main tasks that arise in the processing of medicinal plant raw materials is to intensify the extraction of groups of biologically active substances to increase the yield of extractive substances. A large number of studies have been devoted to the study of the pharmacological properties of preparations based on plants of the birch family growing on the territory of Russia, however, the products of processing of these plants still have a significant medical potential. Another of the phytoobjects, the raw material base of which is successfully developing, is Ginkgo biloba [1]. The range of known types of biological action is very wide [2]. However, the range of medicines obtained on the basis of dry Ginkgo biloba extract has few positions. Dry extract from the leaves of Ginkgo (Ginkgo biloba L.), is widely used in the manufacture of medicinal preparations. It is produced by extraction with a established optimal extractant followed by purification with organic solvents (chloroform, acetone, ethyl alcohol). This control is subject to pharmaceutical substances and excipients, as well as drugs, regardless of the method of their use, if organic solvents are used in their preparation or purification. In this regard, the rejection of traditional chloroform extraction and the transition to high-performance ultrasonic extraction with ethyl alcohol is justified. However, the use of US does not always lead to positive results. Sometimes in plant cells, wall rupture and a change in the physicochemical properties of some components occur. Therefore, in each individual case, it is necessary to carefully study the effect of ultrasound on specific substances and under specific conditions.

Substances of different chemical groups, characterized by diverse pharmacotherapeutic activity, are isolated from Ginkgo leaves. They are mainly represented by diterpenes, sesquiterpenes and flavonoids. In this regard, the range of application of this object is very wide: it is a therapy of cerebral ischemia and chronic cerebrovascular insufficiency, normalization of microcirculation and providing a powerful general antioxidant effect [2-4]. The positive effect of G. biloba extract on the rheological properties of blood is also known. However, the number of dosage forms of ginkgo is small. Medicinal products of ginkgo leaves, which include dry extract, are widely used (Tanakan, Bilobil, Memoplant, Ginkor Fort, Ginkor Gel, etc.).Therefore, the creation of various dosage forms based on these plant objects with a sufficient raw material base is quite an urgent task. But obtaining any phytocomposition of varying degrees of technological complexity always begins with the extraction process; it is the central and dominant process in the technology of all, without exception, plant-based preparations. [5].

#### Materials and Methods

The use of ultrasound is much more effective in comparison with mixing, as well as the use of high temperatures and pressures. With the help of ultrasound, almost any substance can be extracted from plant materials [6]. The use of ultrasound not only increases the speed of the process, but also provides an increase in the yield of the target product in comparison with other extraction methods [7,8].

A ginkgo biloba leaf was poured into an ultrasonic extractor NO-230.00P, filled with 70% ethyl alcohol, and thoroughly mixed with a built-in stirrer to remove air. The lid of the extractor was closed and extraction was carried out, cooling the system with cold water supplied to the casing of the apparatus. Thus, the extraction lasted 120 minutes.Next, the optical density of the samples obtained during ultrasound extraction of G. biloba extract was studied by UV spectrometry on an Ecros PE-5400UF spectrophotometer (OOO Ecros-Analytics, Russia, St. Petersburg) at the maximum light absorption at a wavelength 415 nm in a cell with a layer thickness of 10 mm. 2 ml of the sample was placed in a volumetric flask with a capacity of 50 ml and brought up to 70% with ethyl alcohol (solution A). 2 ml of solution A was placed in a volumetric flask with a capacity of 25 ml, 2 ml of a 2% solution of aluminum chloride in 96% ethanol and 0.1 ml of a solution of acetic acid diluted were added. The volume of the solution was adjusted to the mark with the same alcohol (solution B) and left for 40 minutes. The optical density of the solution was measured at the maximum light absorption at a wavelength of 415 nm in a cell with a layer thickness of 10 mm. As a comparison solution, a solution consisting of 2 ml of extraction, 0.1 ml of a solution of diluted acetic acid and 70% ethyl alcohol added to the mark in a 25 ml volumetric flask was used. In parallel, the optical density of the reference standard (RS) of rutin solution prepared analogously to the test solution was measured [5].

Molecular Docking

The calculation of the electronic structure and quantum chemical descriptors of ginkgolide B was the second stage of theoretical research. Molecular descriptors obtained using the publicly available programs MOPAC, DRAGON and GAMESS were used. The assessment of the specific pharmacological activity of the developed dosage forms of Ginkgo biloba was performed on 24 male rabbits of the "California" breed weighing 2.5-3.0 kg, obtained from the laboratory animal nursery "Rappolovo" (Leningrad Region). Before the study, the animals were kept in quarantine conditions for 14 days. During the direct conduct of the experiment, the rabbits were kept in a vivarium under controlled climatic conditions: at an air temperature of 20±2°C, a relative humidity of 60±5% and a 12-hour change of the daily cycle in mesh metal cages equipped with a drip drinker and a feed supply tank. The number of species in one cell was four. The animals' access to food and water was not restricted. The study of the cerebrotropic activity of the developed dosage forms of Ginkgo biloba was carried out on a model of bilateral occlusion of the common carotid arteries. The standardized extract of Ginkgo biloba (EGB 761), obtained from Hunan Warrant Pharmaceuticals (PRC), was used as a comparison drug. The studied dosage forms and the reference drug were administered in a therapeutic mode after modeling brain ischemia once a day for 3 weeks. The comparison drug was administered orally at a dose of 35 mg / kg [2], the analyzed dosage forms (drops, sodium alginate-based gel and chitosanbased gel) were administered intranasally at a dose equivalent to that of the comparison drug. During the study, changes in neurological deficits were determined according to the McGraw scale (the initial indicator, as well as that on the 3rd, 7th, 14th and 21st days of the experiment), the average systolic velocity of cerebral blood flow (on the 3rd, 7th, 14th and 21st days of the experiment) and the pro/antioxidant balance in the hippocampus (on the 21st day of the study) [9,10].

Results and Discussion The calculation of the electronic structure and quantum chemical descriptors of ginkgolide B was carried out. This calculation was performed by us for the first time, data on the analysis of such structures were found by us in only one report by Chinese scientists [11], however, exact quantum chemical calculations were not performed. The calculation was carried out in the HyperChem 8.0 chemical package (license number HC80SA-4-1BBF6). Visualization of the structure demonstrates its steric hindrance.



To determine the chemically active part of the molecule, we first performed the calculation of the energy of the boundary orbitals (namely, the upper occupied molecular orbital) by the AM1 method and the subsequent computer simulation (electron density is shown in blue and green).(Fig 1.)An analysis of the image shows that despite the presence of several potential active centers, the ginkgolide B molecule has only one active center, and it is apparently responsible for the interaction of the molecule with platelet activating factor (PAF)

(Fig. 2. ).The conducted complex of studies allowed us to establish that in conditions of experimental cerebral ischemia modeled by simultaneous occlusion of the common carotid arteries in large laboratory animals (rabbits), the use of the obtained extract contributed to a decrease in the severity of neurological deficit, restoration of cerebral hemodynamics and pro/antioxidant balance in the hippocampus.

# CONCLUSION

Thus, based on the theoretical results and experimental data obtained, it can be assumed that the ginkgo biloba extract obtained by ultrasound extraction may be a promising means of correcting chronic cerebral circulatory disorders with an antioxidant mechanism of action and therapeutic potential superior to the existing, standardized ginkgo biloba extract — EGB 761.

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Fig. 1. Formula and three-dimensional structure of ginkolide B



*Fig. 2.* Computer simulation of the highest occupied molecular orbital of ainkqolide B

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# CAUSES OF MORTALITY IN NEONATES WITH EXTREMELY LOW AND VERY LOW WEIGHT

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**ABSTRACT** — The new methods that have been used to preserve pregnancy have reduced the frequency of premature birth. However, in this case, there is still a high mortality rate among neonates.

AIM: The aim of the study was to assess the main causes of mortality in neonates with extremely low and low body weight.

RESULTS: The largest proportion of deaths among newborn babies with extremely low and low body weight was recorded during the gestation period of 25-26 weeks – 76.9%, at the gestation period of 27-28 weeks, deaths were 36.8%. The leading cause of death of premature newborns in the neonatal period is massive intracranial hemorrhages (45.5%). Intrauterine infection of various etiologies occupies three times the place of causes of mortality of premature newborns and occurs in 24.2%.

CONCLUSION: Among newborns with extremely low and low body weight, mortality is present in every fifth case, the causes of which were: intracranial hemorrhages, intrauterine infection, respiratory distress with cider.

**KEYWORDS** — premature birth, extremely premature baby, perinatal mortality, intracranial hemorrhage, intrauterine infection, singleton births.

### INTRODUCTION

Premature birth is an acute medical problem, as it causes high perinatal mortality [1, 2]. Preterm birth accounts for approximately 11% of births worldwide [3]. About 85% of infants born before 37 weeks are moderate or late premature (32–36 weeks), 10% are very premature (28–31 weeks) and 5% are considered as extremely premature (<28 weeks) [4].

Despite the high level of development of obstetric and gynecological care worldwide, the frequency of premature births over the past 10 yearshasn't decline. And, among premature newborns, there is still a mortality rate for about 60-70% [5]. Moreover, in premature infants with extremely low and low body weight, the incidence much higher. Therefore, the analysis of the causes of mortality in newborn babies with extremely low and low body weight is an urgent task of modern medicine.

Aim

This paper aims to assess the leading causes of mortality in neonates with extremely low and low body weight.

#### METHODS

The study included 152 women with a singleton pregnancy and with premature birth at 25–32 weeks gestation. The criteria for exclusion from the study are extremely premature newborns with a gestation period of 22–24 weeks.

In each case of observation, we assessed the gestation period at birth, the weight of newborns, and the cause of mortality.

Gestation periods at birth (n=152) were: in 13 (8.5%) — 25–26 weeks, in 19 (12.5%) — 27–28 weeks, in 43 (28.3%) — 29–30 weeks and in 77 (50.7%) — 31–32 weeks. The birth weight of newborns was as follows: with extremely low birth weight (up to 1000 g) — 28 (18.4%) children, with very low birth weight (1000–1499 g) — 57 (37.5%), more than 1500 g — 67 (44.1%) children.

All children (n=152) in the early neonatal period were in the neonatal intensive care unit, where they underwent supportive and forced ventilation of the lungs, as well as therapy aimed at treating the underlying disease, cardiovascular and respiratory system, metabolism.

We observed early neonatal death in the pediatric intensive care unit in 13 (8.5%) premature newborns born with extremely low and low body weight. The remaining children (n=139) were transferred to the second stage of nursing in clinical hospitals. At the second stage of nursing, 21 (13.8%) children died. In total, mortality among newborns with extremely low and low body weight was 21.9% (n=34). The maximum mortality (61.7%) in low birthweight newborns was noted during the second week of life.

The statistical analysis was performed using spreadsheets "EXCEL" and "STATISTICA 8.0". The significance of differences between quantitative indicators was assessed using the Mann–Whitney test. Differences were considered significant at p <0.05.

### RESULTS

The mortality rate of premature newborns with extremely low and low body weight at various gestation periods is shown in Fig. 1. A large proportion of deaths among this category of children was at 25-26 weeks of gestation — 76.9%, every third child who died was at 27-28 weeks of gestation.



Fig. 1. Mortality of premature newborns with extremely low and low body weight at different gestation periods

vere Neonates' respiratory distress syndrome (NRDS), which subsequently led to a fatal outcome. We believe that an insignificant percentage of NRDS in the mor-



*Fig. 2.* The dependence of deaths on body weight at birth in the gestation period of 25–32 weeks

The dependence of deaths on the body weight of newborns is shown in Fig.2. The average weight of dead children during single pregnancy was 1247 ± 17 g.

We have recorded the inverse dependence of deaths on the weight of a premature newborn. The leading cause of death of children in the neonatal period is massive intracranial hemorrhages. A total of 45.5% of premature newborns died from this pathology. In the second place in the structure of the causes of mortality of premature newborns is intrauterine infection of various etiologies — 24.2%. 9.1% developed setality structure of premature newborns is associated with the presence of special respiratory equipment, the introduction of surfactant, wait-and-see tactics for preterm labor, the appointment of glucocorticoids. Severe hemolytic disease of the newborn, multiple fetal malformations, asphyxia, necrotic enterocolitis were the cause of death in low-weight newborns with approximately the same frequency: 6%, 6,1%, 6,1%, 3% accordingly.

#### DISCUSSION

Newborns with low and extremely low body weight account for the majority of perinatal losses. Childbirth with a premature fetus is 10 times more likely to end in the death of a newborn compared to timely delivery [5]. The lethality of newborns is influenced by many factors: the quality of prenatal care, the method of delivery, fetal weight, intrauterine infections, gestational age, birth defects, etc.

According to Barfield WD, the death of infants born <32 weeks of pregnancy was 52% due to disorders of the nervous system [6].

In a recent retrospective study, it was shown that 75% of deaths occurred in all premature infants (n=72) with a gestational age of 23–25–31 weeks [1]. The most common causes of mortality in this category of children were: NRDS (95.4%), patent ductus arteriosus (81.3%), sepsis (55.7%), intraventricular hemorrhage (34.4%), retinopathy of prematurity (21.9%) and necrotic enterocolitis (10.9%) [1].

Fetal weight at birth is a predictor of perinatal mortality. Thus, the probability of perinatal death among children with low birth weight was approximately 9.6 times higher than in children with normal birth weight (OR = 9.6; 95% CI, 6.12-15.02) [7].

Due to this study the leading cause of death in neonates with extremely low and low body weight have been considered massive intracranial hemorrhages caused by the peculiarities of the development of brain vessels characteristic in premature newborns. The frequency of massive intracranial hemorrhages is inversely proportional to the gestation period and the birth weight of the fetus, while the frequency of other causes of death inneonates (intrauterine infection, respiratory distress syndrome) does not depend on these indicators.

### CONCLUSION

Mortality among newborns with extremely low and low body weight is present in every fifth case. To date, the leading causes of mortality in premature babies born before 32 weeks of gestation are intracranial hemorrhages, intrauterine infection, NRDS. Consequently, neonates who have suffered from intrauterine hypoxia, severe asphyxia, with massive intracranial hemorrhages can be attributed to a high-risk group, due to the increased possibility of death.

Thus, the analysis of mortality in newborns with extremely low and low body weight will effectively direct the efforts of intensive therapy to improve the results of nursing newborn babies of this category.

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# ACUTE TUBULOINTERSTITIAL NEPHRITIS WITH UNDERLYING UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE. A CLINICAL CASE STUDY

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ABSTRACT — Acute tubulointerstitial nephritis (ATIN) is an acute kidney disease that can develop under the influence of various exogenous and endogenous factors and is manifested by inflammatory changes in the tubulointerstitial tissue of the kidneys, often accompanied by the development of acute renal kidney damage (AKI). Approximately 3-19% of all AKI cases are due to ATIN nephrobiopsy data, which indicates a difficult non-invasive diagnosis of this disease. Complaints of patients with ATIN are few and are associated with manifestations of acute renal damage: a decrease in urine volume, an increase in blood pressure (BP). Important in the diagnosis of ATIN is urinary syndrome, manifested by proteinuria less than 1 gram per day, erythrocyturia, leukocyturia, including eosinophiluria. In patients with suspected ATIN, a full physical examination is performed, attention is drawn to the appearance of pain on palpation of the kidneys, blood pressure is measured, diuresis, and the presence of edema are assessed. In laboratory diagnostics, it is necessary to investigate the level of creatinine, blood urea, general urine analysis, with instrumental — ultrasound examination of the kidneys, if indicated, a kidney biopsy is performed. Treatment is aimed at immediate cessation of the effect of the etiological factor, maintenance of waterelectrolyte balance and correction of violations of acidbase balance, blood pressure. In this regard, it is possible to use crystalloid solutions, loop diuretics (furosemide, torasemide), antihypertensive drugs in accordance with the general principles of management of patients with AKI, immunosuppressive therapy for ATIN immune genesis, with ATIN drug genesis — glucocorticoids. In the presence of appropriate indications, renal replacement therapy is performed. The prognosis of the disease often depends on timely diagnosis and appropriate treatment. The paper presents the clinical case of a female patient affected with acute tubulointerstitial nephritis.

**KEYWORDS** — acute tubulointerstitial nephritis, diagnosis, treatment, undifferentiated connective tissue disease.

# INTRODUCTION

Acute tubulointerstitial nephritis (ATIN) is an acute kidney disease that occurs as a result of exposure to various exogenous and endogenous factors, manifests in the form inflammatory processes in the tubulointerstitial tissue and compromises the functioning of the organ [1]. Renal biopsy detects ATIN in 2.3% to 9% of all cases, whereas its chronic counterpart has a 1.8% to 2.5% occurrence rate. Given that no biopsy is taken in most clinical cases, we could assume medical professionals actually face this disease far more frequently in their work [2].

ATIN is mainly caused by bacterial or viral infections, medications, various metabolic disorders, systemic diseases, etc. [3]. Non-steroidal anti-inflammatory drugs (NSAIDs) cause 45% to 70% of all ATIN cases, with another 30% to 45% attributable to antibiotics [4].

Immune system response plays the key role in the mechanism of this disease. Direct exposure of tubule membranes and renal interstitium to the etiological factor triggers the production of antigenic complexes [5]. Immune complexes are produced in response and become fixed in the interstitium and in the tubule wall, which causes an inflammatory response and interstitial edema. This further causes renal tissue ischemia and epithelial dystrophy of the tubules and vessels. Clinical manifestations of the disease occur [6].

The core manifestations are headache, lumbar pain, arthralgia, rash, fever, drowsiness, adynamia, and nausea. Acute renal failure is common, manifesting as dysuric disorders, mainly as polyuria and nocturia; oliguria and anuria may occur as well, a sign of severe organ damage [7].

When diagnosing the disease, the focus is made on the intake of nephrotoxic substances in the history; a matching clinical picture; urinary syndrome signs in general urine test, which manifests as moderate proteinuria (< 1 g/day), aseptic leukocyturia, hematuria, cylindruria, and reduced relative density of the urine [8]. Blood biochemistry reveals increased creatinine, urea, and electrolyte disorders. Clinical blood tests show eosinophilia, leukocytosis, and increase ESR. Renal ultrasound detects enlarged kidneys with a more echogenic parenchyma. In case the diagnosis is difficult, morphological study of the renal tissue is carried out [9].

Treatment seeks to address the cause, maintain water-electrolyte balance, and adjust the acid-base balance. Glucocorticosteroidscan be used especially effectively when treating ATIN associated with systemic diseases [10]. Renal replacement therapy is used if there are indications. Timely diagnosis and appropriate treatment affect the prognosis.

The goal hereof is to present a clinical case of acute tubulointerstitial nephritis with underlying undifferentiated connective tissue disease.

### MATERIALS AND METHODS

The paper overviews state-of-the-art approaches to the diagnosis and treatment of ATIN as discussed in literature; it also analyzes the clinical case of a patient.

#### RESULTS

Patient G, 22, admitted to the Nephrology Unit of a public hospital in Tver Oblast, the Regional Clinical Hospital in Tver, with complaints of moderate asthenia, frequent headaches, pain in the ankle joints and calf muscles at rest, aggravated by exertion.

Medical history revealed that in June 2020, the patient had survived a laboratory-confirmed coronavirus infection complicated by moderate bilateral polysegmental pneumonia. The patient underwent inpatient treatment at a specialized clinic; her therapy consisted of 1000 mg of azithromycin per day for 7 days, 2.0 g of ceftriaxone per day for 7 days, 5 mg of apixaban per day for 2 weeks, and peroral paracetamol. Discharged from the hospital two weeks later, as X-ray confirmed full recovery from pneumonia.

For several months, she continued to exhibit moderate asthenia and subfebrile temperatures; pain spread across small joints in feet and calf muscles; the patient also reported all-body muscle tremor. For that reason, the patient visited a rheumatologist. The doctor initiated an examination to find a rheumatological disease. The patient was screened for markers of systemic lupus erythematosus, vasculites, rheumatoid arthritis, and other connective tissue diseases that could affect joints and muscles alike. However, all the laboratory markers only showed an increase in the antinuclear factor to 1:160. Thus, undifferentiated connective tissue disease was suspected. For primary therapy, the patient was prescribed 4 mg of methylprednisolone per day (she continues this treatment as of today), which had a positive effect as it alleviated joint pain and eliminated muscle tremor. Therapeutic plasmapheresis was recommended as well. To that end, the patient was admitted to an inpatient clinic.

Anamnesis vitæ showed the patient was a schoolteacher, had no concomitant chronic diseases, bad habits, or allergies to medicines. No burdened family history, no prior surgeries.

General condition was satisfactory as of the time of admission. Normal physique. Normally colored skin of normal humidity, the exposed mucous membranes pink. Peripheral lymph nodes not enlarged, not adhering to the adjacent tissue, palpation painless. Thyroid not enlarged, no peripheral edemas. No visible musculoskeletal pathologies. 18 respiratory movements per minute. Clear pulmonary sound in percussive testing above the lungs. Rattling-free vesicular breathing. The boundaries of relative cardiac dullness unchanged. 80 heartbeats per minute, satisfactory volume, rhythmic. Blood pressure of 130/80 mmHg. Rhythmic and sonorous heat tones. Soft abdomen, no palpation pain in any compartment. Peritoneal irritation symptoms negative. Liver and spleen not enlarged. Regular and formed stool. Kidneys are not palpable. 1.6 l diuresis. Hand joints not swollen, painless, fully motile. Hand strength sufficient. Transverse compression symptom negative. Muscle palpation painless, no muscle asthenia.

The patient went on to undergo inpatient examination. Clinical blood test results were as follows: leukocytes –  $9.48 \cdot 10^9/l$  (mild leukocytosis),erythrocytes –  $4.04 \cdot 10^{12}/l$ , hemoglobin — 122 g/l, erythrocyte sedimentation rate (Westergren) — 8 mm/h, leukocyte formula: 72.2% neutrophils, 22.4% lymphocytes, 4.3% monocytes, 0.4% eosinophils, 0.4% basophils, 0.3% immature granulocytes, total leukocytes: 100.0%; neutrophils —  $6.84 \cdot 10^9/l$ , lymphocytes —  $2.12 \cdot 10^9/l$ ; monocytes —  $0.41 \cdot 10^9/l$ , cosinophils —  $0.04 \cdot 10^9/l$ , basophils —  $0.04 \cdot 10^9/l$ ; immature granulocytes —  $0.03 \cdot 10^9/l$ .

General urine test showed a low specific weight of  $1004 \text{ g/cm}^3$ , some turbidity, a light-yellow color, acidic reaction, 2-5 of squamous epithelium in the field of view, 0-1-2 leukocytes in the field of view.

Bacteriological urine testing for flora and antibiotic sensitivity (by seeding): negative.

Blood biochemistry returned normal readings: potassium — 4.00 mmol/l, sodium — 141.0 mmol/l, venous glucose — 5 mmol/l, total bilirubin — 12.0  $\mu$ M, direct bilirubin — 1.0  $\mu$ M, aspartate aminotransferase — 18.4 U/l, alanine aminotransferase — 25.0 U/l, total cholesterol — 4.77 mM, high-density lipoproteins — 1.39 mM, low-density lipoproteins — 2.78 mM, triglycerides — 0.67 mM, protein — 66 g/l, urea — 4.58 mM, creatinine — 74.4  $\mu$ M, glomerular filtration rate of 99.55 ml/min, uric acid — 299  $\mu$ M, albumin — 43 g/l, phosphorus — 2.27 mmol/l. The kidneys retained their nitrogen excretion function. Zimnitsky urine test showed concentration failure (hyposthenuria, specific urine weight fluctuating between 1004 and 1009 g/cm<sup>3</sup>), polyuria (3.6 l of daily diuresis), and nocturia.

Electrocardiography registered a sinus rhythm at 78 bpm, vertical electrical axis, and signs of sinistroventricular overload.

Kidney ultrasound showed the right kidney to be lowered, as its upper pole was projected 50–55 mm below the diaphragm in lateral recumbent position on the right side. Noteworthy is the increased kidney mobility when changing the body position. Kidney sized 127 mm in length, 43 mm in width. Kidney boundaries clear, with a smooth outline. Traceable 14 to 17 mm thick parenchyma of increased echogenicity. No renal cavity dilations, no concrements detected. Satisfactory acoustic access to the left kidney. Left kidney shape unaltered, lowered slightly less than the contralateral kidney. Kidney sized 128 mm in length, 46 mm in width. Kidney boundaries clear, with a smooth outline. Parenchyma of increased echogenicity and finely granular echostructure, 13 to 16 mm thick. Left-kidney cavities not dilated. No concrements found in the projection of the renal sinus.

Ankle joint X-ray revealed no pathologies. Due to the pandemic, examination by a rheumatologist in the inpatient setting was not an option. The patient was advised to visit the rheumatologist at an outpatient facility after discharge.

With this data in mind, the patient was diagnosed with: Mild tubulointerstitial nephritis as the primary diagnosis. Undifferentiated connective tissue as the secondary diagnosis. Dextral first-degree nephroptosis.

Based on the diagnosis, the patient started a therapy: four sessions of therapeutic plasmapheresis, 4 mg ofmethylprednisolone daily (oral intake), 20 mg of omeprazole twice daily 30 minutes before meals (oral intake).

Treatment continued for 10 days and had a positive effect on the patient: general asthenia decreased, headaches arrested, ankle-joint and calf-muscle pain eliminated. General urine tests showed relative density to have increased to 1018 g/cm<sup>3</sup>, a sign of normalized concentration ability of the kidneys. The patient was discharged and advised to continue to take Canephron, an herbal medication, two pills thrice daily for a month (oral intake) and to be followed by outpatient nephrologist and rheumatologist.

### DISCUSSION

In this clinical case, the patient likely survived ATIN caused by undifferentiated systemic connective tissue disease. This diagnosis was reinforced by the acute concentration disorder that the patient had on top of undifferentiated connective tissue disease without bacteriuria. Interestingly, the patient had no pronounced clinical manifestations of nephritis, and the nitrogen excretion function was preserved, i.e., creatinine and urea in blood were within the normal range. Besides, the patient had lower specific urine weight (hyposthenuria, nocturia), which is characteristic of ATIN, but no proteinuria, no altered urinary sediment in urine tests. We can assume that methylprednisolone intake as prescribed due to undifferentiated joint disease contributed to the absence of typical clinical signs of ATIN; moreover, the same medication is effective in pathogenetic ATIN treatment.

We cannot be certain, however, whether coronavirus and two courses of antibiotics that the patient had to take due to her bilateral pneumonia contributed to the damage of the renal tubulointerstitial system. Undoubtedly, the patient has to be thoroughly examined by a rheumatologist; dynamic follow-up and monitoring of test results are now crucial, as they might help differentiate the connective tissue disease.

In general, timely diagnosis and early treatment helped recover from ATIN. This clinical case is an example of atypical ATIN progression, and it shows how a concomitant pathology, and its treatment could affect the clinical signs of the kidney disease.

We assume this report to be of use for doctors in any field, especially for those in primary care.

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# POLYNEUROPATHY IN PATIENTS WITH CHRONIC BRUCELLOSIS. CASE STUDY

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ABSTRACT — Brucellosis is one of the most common infections that belongs to the group of specifically dangerous zoonoses, which account for a significant share of infectious pathologies affecting humans. The pathogenesis of chronic brucellosis relies on intracellular parasitization of brucella with anti-lysozyme activity. The socio-economic effect of brucellosis problem is due to the specific features of the course that the infection takes, frequently developing into chronic forms, resulting in long-term loss, or even permanent disability. Physically capable population is the group that is affected the most, whereas thew reasons behind this include both professional and social ones. The rate of clinical manifestations pointing at a damage to the nervous system wrought by brucellosis lies within the range of 25% - 90%. This paper presents a clinical case focusing on the nature of the damage chronic neurobrucellosis causes to the peripheral nervous system. We used the MRC, NDS scales as well as electromyography with the identification of the standard conduction parameters for the median, tibial and calf nerves.

**KEYWORDS** — chronic brucellosis, nerve conduction, polyneuropathy, electromyography, diagnosis.

## INTRODUCTION

Brucellosis is a zoonotic infectious disease caused by bacteria known under the common name of *Brucella*, which reveal a high potential for turning chronic and working systemic damage to organs and systems, affecting predominantly the musculoskeletal, the nervous, and the reproductive systems. The epidemiological situation in Russia, in terms of brucellosis prevalence, has remained unfavorable for a long time and can be accounted for by persistent epizootics of brucellosis to be found in small and great cattle, which is the main sources of the brucellosis agent infecting humans. Brucellosis has long been ranked first among occupational diseases of infectious and parasitic etiology. Loss of working capacity or disability in this case explain the socio-economic meaning and relevance of this infection. Another issue is early identification of brucellosis in humans, this being due to a reduced number of laboratory screenings aimed at detecting brucellosis in those who are associated professionally with the risk of contracting brucellosis, as well as due to an increase in the share of cases observed among those who have no association with cattle breeding. A timely diagnosis, though, as well as proper treatment, helps avoid the chronization of the infection and persistent disability [1–4].

The lack of a unified classification for brucellosis nowadays poses a serious obstacle to verifying the diagnosis and studying the disease progress, which is subject to great diversity. Nevertheless, most researchers point at a potentially blurred, low-symptom onset of the disease, where patients seek assistance from various medical experts at a stage, which involves multiple advanced pathologies, all this explaining the relevance of enhancing medical specialists' competence in diagnosing brucellosis [5]. One of the systems involved frequently in the pathological process in case of brucellosis is the nervous system. Neurobrucellosis (NB) is one of the manifestations of general brucellosis, and includes all types of specific damage to the nervous system (NS), all being successive links of a single infectious process affecting the entire body [14]. The frequency of clinically significant manifestations of NB, as different authors note, varies greatly (from 25 to 90%) [6, 8]. Note to be made here that diagnosing NB is a complicated issue due to a number of reasons: lack of pathognomonic symptoms; a wide variety of lesions affecting the NS and its mechanisms. Besides, the diagnosis can be set in case of observing a neurological presentation that is not to be explained by any other neurological health issue [9].

Lesions affecting NS in case of brucellosis can be primary or secondary. The former ones are associated with the direct impact on the tissues that Brucella or products of immune (including immunopathological) responses entail, and is manifested through diffuse encephalopathy and meningoencephalitis; inflammatory peripheral neuropathy and radiculopathy; inflammatory demyelinating syndromes; the optic nerve disc edema or papillitis with no other focal manifestations; meningomyelitis; posterior cranial fossa syndrome (atactic or stem); neuropsychic syndromes. The secondary type of NB includes effects that earlier chronic brucellosis inflammation has on other organs and systems, and include compression myelopathy and radiculopathy, developing against damage to the osteoarticular system and adjacent soft tissues, as well as cerebral vascular syndromes, which develop on the background of damage to the heart or cerebral vessels [14]. A combination of clinical manifestations of various NB types are a rather frequent phenomenon.

NB is primarily characterized by a damage to the peripheral nervous system (PNS), which is a common development in case of chronic brucellosis (CB), yet has an acute onset and is typically accompanied by the intoxication syndrome (fever, chills, sweating, headache, etc.) [10]. It is to be noted that the use of instrumental methods, in particular electro-neuromyography, as well as clinical and electrophysiological analysis of the peripheral nerve's functional status, allows increasing the level of PNS lesion verification in patients with CB. An in-depth neurological study [7], for instance, revealed the pathology of the PNS in 86% of patients with CB, while a notable thing was that the polyneuropathies or polyradio-neuropathies developing in those patients were caused by a mixed axonal-demyelinating lesion of the motor and sensory branches of peripheral nerves, involving predominantly the pathological process of the axial cylinder of nerves. This was accompanied by a decrease in the motor response amplitude and evoked potentials, as well as emerging axonal blocks at large joints, which occurred against moderate demyelination, and manifested through a slowdown in the conduction of impulses, including at the level of the spinal cord roots.

There is clinical proof available showing that CB, in its progress from active to inactive, features an increase in the depth of pathological changes involving peripheral nerves; axonal blocks to be found in the elbow and knee joints in almost 100% of cases; a decrease in the impulse speed, which is more significant at the level of the lumbosacral spine; a critical decrease in the amplitude of the evoked potentials of nerve sensory branches down to an undetectable level.

The PNS pathology severity often correlates with disorders affecting the regional blood circulation. Yu.N. Linkova [7] in her work, for instance, points at a significant decrease in the pulse blood filling the forearms (2.2 times) and lower thighs (2.8 times) in patients with CB (if compared to similar indicators in healthy individuals), with significant asymmetry of blood supply, increased vascular tone of large caliber, and venous congestion. Disturbed regional blood flow was at its maximum in patients with inactive CB, in case of which, unlike with its active type, the symptoms of impeded venous outflow were aggravated by a drop in the tone of small vessels.

Given the hematogenic, lymphogenic, as well as perineural ways of spreading brucella in the human body, as well as the role that immunopathological processes play in the development of organ pathology in case of brucellosis, the genesis of damage affecting organs and tissues, including peripheral nerves in each case still remains unclear. The value of this understanding, however, is of extreme importance, when it comes to administering proper therapy. Assistance in clarifying the major mechanism of peripheral nerve damage can be found in an additional instrumental study, which can be inferred from the case presented below.

#### CASE STUDY

Patient P., 54 y.o.; a veterinarian; admitted for inpatient treatment at the occupational diseases clinic (August, 2019); complained of moderate pain in limb large joints, spine, weakness and weight loss in the limbs, a feeling of numbness in the hands and feet. The diagnosis of chronic brucellosis affecting the musculoskeletal system, vegetative and cardiovascular system, was set in 2016 when the patient was seeking medical help for organ lesions, positive serological test results (Wright's test, Heddlson's reaction; RPGA in the titer – 1:320) based on his professional contact with farm animals. Following the treatment, periodic moderate pains in the knee, elbow and wrist joints persisted. The pain worsened under physical strain in the affected joints and at hypothermia. About two years ago, the patient developed weakness and gradual loss of mass in the limbs, which affected the legs more, as well as a feeling of numbness in the hands and feet. For various reasons, did not seek help from doctors.

The current health deterioration has been there for the last two weeks, when, following physical overload, the patient noted intense, stable pain and sharp restriction of movement in the lumbar spine, in the joints (more — in the elbows and knees). Selfadministered Ibuprofen, ensured a short-term effect. Furter contacted a local Neurologist who referred him to hospital for treatment.

The specific points that drew attention through the examination were excess weight (BMI - 30.3); skin moisture; pain at palpation along the spinous processes of the spine at the cervical and lumbar sections with restricted movements in the lumbar region and neck; painful palpation and restricted movements in the elbow and knee joints; extended heart boundaries to the left (the left limit is in the intercostal space 1.2 cm inside of *l. mediaclavicularis*) with muffled heart tones and the second tone accent above the aorta; high blood pressure (150 and 90 mmHg).

The patient had an examined with a GP, a surgeon, a neurologist, and underwent certain instrumental (ECG, elbow and knee joint radiography, lumbosacral spine MRI, echocardiography, rheovasography of the upper and lower extremities), and laboratory, tests (general blood test, biochemical blood test, general urine test), and the analysis of the outcomes, given the respective clinical manifestations, allowed defining the diagnosis. Major: chronic brucellosis, combined type with damage to the musculoskeletal system, the vegetative nervous system, the peripheral nervous system and the cardiovascular system. Polyosteoarthrosis involving the elbow joints (radiologically — Stage 1; function disturbance — 0-1), knee joints (radiologically — Stage 1–2; function disturbance — 1). Polyneuropathy of the upper and lower extremities, chronic lumbosacral radiculopathy. Infectious myocarditis in history. Relative insufficiency of AV valves. Minor: arterial hypertension — Stage 3; risk — 4. Complication: circulatory deficiency 1 (functional class 2). The clinical presentation of the patient with a peripheral form of NB was assessed relying on the topographic features of the hypotrophy and their severity (see Table. 1), the level of muscle weakness (MRC scale) (see Table. 2), changed reflexes and sensitivity based on the neurological disorders Neuropathy Disability Score (NDS) scale (see Table 3). The hypotrophy was assessed based on a 2-point subjective scale: 0 points — no hypotrophy; 1 point — minor degree; 2 points — significant hypotrophy.

Table 1. To	pographic	features of li	imb muscle l	iypotrop	ohy

Museles heine tested	Side		Average core
muscles being tested	<b>Right side</b>	Left side	Average score
Muscles of the upper limbs			
M. abductor pollicis brevis	1	0	
M. abductor digiti minimi	1	1	
M. flexor digitorum superficialis	1	1	
M. biceps brachii	0	1	0.275
M. triceps brachii	0	0	0.375
M. deltoideus	0	0	
M. trapezius	0	0	
M. petoralis major	0	0	
Muscles of the lower extremities			
M. rectus femoris	1	0	
M. adductor femorris magnus	1	0	
M. tibialis antreior	1	2	1
M. gastrocnemius	1	1	
M. extensor digitorum brevis	2	2	

As Table 1 shows, the typical signs with the patient in question include a proximal/distal distribution of muscular hypotrophies (with the lower extremities dominating); another notable issue is the asymmetric distribution of their severity.

Besides, there is also a notable decrease in lower extremities strength, the distal parts showing greater severity.

The study of sensitivity issues and reflex changes revealed a moderate degree of sensorimotor polyneuropathy (the patient had an NDS index of 13 points).

To objectify the lesion to the peripheral nerves' motor and sensory fibers, an electromyographic study (EMG) was carried out with an EBNeuro Nemus (Italy) electromyograph following the standard technique. The nerve conduction velocity (NCV), the distal latency (DL), the motor response amplitude (MRA) of the main nerves (median, tibial), and the sensory response amplitude (SRA) of the sural nerve on both sides were evaluated. Needle EMG of the calf muscles was performed this aiming to identify the spontaneous activity, as well as the denervation/reinnervation intensity. The patient was found to have (Table 4) a decrease in NCV along motor and sensory fibers, an increase in DL, which was associated with axon demyelination. The severity of the amplitude decrease in the M-response was associated with the level of fiber conduction slowing, which also serves another proof of the lesion's primary demyelinating nature.

The spontaneous activity manifested as single potentials of acute waves and fibrillation potentials

Table 2. Muscle weakness (average score, MRC)

Fastura	Side		
reature	Right side	Left side	
Elbow extension	5	5	
Elbow flexion	5	4	
Finger flexion	5	5	
Wrist bending	5	5	
Wrist undending	5	5	
Opposable thumb	4	4	
Spreading fingers	4	4	
Hip flexion	5	5	
Knee flexion	4	5	
Knee extension	4	4	
Foot flexion	4	3	
Foot extension	3	3	

Sensitivity/reflex test	Right, score	Left, score	Total score
Knee reflex	1	0	r
Achilles reflex	2	2	S
Temperature sensitivity	2	2	0
Pain sensitivity	2	2	8

in the calf muscles is proof to the denervation of muscle fibers, whereas the restructuring of motor units towards an increase in their amplitude and duration confirms the chronic nature of the process.

#### DISCUSSION

The pathogenesis of the PNS lesion in case of brucellosis is yet to be studied. Analysis of the respective literature data suggests possible both axonal [11, 12] and demyelinating [13] damage to peripheral nerves in this zoonosis. An assumption can be made that the nature of the injury depends on the type of exposure — brucella and their endotoxins invading the peripheral nerve directly, in case of axonal polyneuropathy, or through immuno-mediated mechanisms of demyelination [14, 15, 16].

## CONCLUSION

The medical history described above shows that the clinical nature of neurobrucellosis is of chronic, slowly progressing course. In our case, the effect of a mechanical damage – as a result of the musculoskeletal system pathology, occurring at an earlier stage of the disease – cannot be excluded.

The EMG study allows an objective assessment of the nature, the degree and the prevalence of the peripheral nervous system damage, which makes it a good choice not only to set the diagnosis and opt for a treatment tactics, yet also to assess the dynamics in view of the therapy underway.

Special attention should also be paid to patients with neurological manifestations who live or come from a brucellosis-vulnerable area, so as not to overlook a possible case of neurobrucellosis.

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#### Table 4. EMG outcomes

FMC index	Side		
EMG INDEX	Right	Left	
Average MRA, n. medianus	4.25	4.15	
Average MRA, n. tibialis	1.7	1.75	
DL, M-response, n. medianus	4.6	4.3	
DL, M-response, n. tibialis	5.2	4.3	
NCV, n. medianus	45	44.8	
NCV, n. tibialis	31.8	33.2	
SRA, n. suralis	0.4	0.6	
NCV, n. suralis	30.1	32.2	
M. rectus femoris	1	0	
M. adductor femorris magnus	1	0	
M. tibialis antreior	1	2	
M. gastrocnemius	1	1	
M. extensor digitorum brevis	2	2	

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# SYNDROM OF SENILE ASTHENIA AS A COMORBID STATE IN A MULTISPECIALITY HOSPITAL

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ABSTRACT — Among one of age-associated diseases, the syndrome of senile asthenia is increasingly common. The massive spread of senile asthenia syndrome among elderly patients forces us to look for new approaches to the treatment and diagnosis of this syndrome and other pathologies of organs and systems. The purpose of this study is: to determine the incidence and structure of comorbid pathology in patients with senile asthenia syndrome followed by the study of the clinical significance in the development of adverse complications in this category of patients.

According to a retrospective analysis of hospitalized patients with senile asthenia syndrome and various comorbid conditions, it was revealed that in the structure of chronic non-infectious diseases, arterial hypertension took the first place among cardiovascular diseases — 130 (100%). The second place among comorbid pathology was taken by chronic heart failure — 84% of cases. Ischemic heart disease was detected in 97 people (74%). Also, a significant place in the structure was taken by chronic kidney disease — 54 (41.5%), degenerative-dystrophic changes in the joints in 123 (94%) cases.

Thus, in the course of the study, it was revealed that senile asthenia syndrome is highly common among comorbid elderly patients. In addition, there is a certain relationship between senile asthenia syndrome and other age-related conditions, which undoubtedly affects the life expectancy and quality of life.

**KEYWORDS** — geriatrics, elderly age, geriatric patients, senile asthenia syndrome, comorbid conditions.

## INTRODUCTION

Today, it is easy to notice the global aging trend and, as a result, an increase in the proportion of elderly people among the general population. This trend is due to the fact that the global aging of the population more and more covers various countries and states all over the world. According to the analysis of data from the Federal State Statistics Service, the population over 60 years old in Russia as of January 1, 2020 is more than 45% among people of all age groups. In addition, one more trend has recently become noted — this is an increase in life expectancy. All over the world, the work of medical organizations strives to increase the life expectancy of patients and improve their quality of life [1, 2].

Among the patients who seek medical care on an outpatient or inpatient basis, the majority are elderly patients. In this regard, in recent years, such a field of medicine as geriatrics has been developing. Among the patients who seek medical help, it is possible to note patients with various pathologies of organs and systems, including those with age-associated diseases. Among one of these age-associated diseases, the syndrome of senile asthenia is increasingly common.

The British Geriatric Society in the 2014 consensus defines senile asthenia as a special health condition associated with the aging process, in which several body systems gradually lose their reserve capacities[8].

The massive spread of senile asthenia syndrome among elderly and senile patients forces us to look for new approaches to the treatment and diagnosis of this syndrome and other pathologies of organs and systems. The syndrome of senile asthenia can often aggravate the course of underlying conditions.

Currently, among patients of elderly age, cardiovascular pathology undoubtedly occupies a leading position. According to Rosstat (Russia), mortality from diseases of the cardiovascular system (CVD) in the Russian Federation in 2017 amounted to 587.6 cases per 100 thousand of the population with the initial registration of 4 million 706 thousand patients with diseases of the circulatory system[7].

Often, the severity of the process is not determined by the process itself, but by various accompanying changes in the body. One of such changes, aggravating the course of various diseases of organs and systems, is precisely the syndrome of senile asthenia. Against the background of aging processes in the body, various functional disorders occur, which can lead to the development of severe pathology. Thus, it can affect patients' life expectancy and their quality of life.

The syndrome of senile asthenia entails a decrease in physical activity, impaired functional activity, a change in the compensatory and restorative

THERAPY

reserve of the body, increases the risk of adverse complications and disasters. Against this background, the number of hospitalizations of patients for inpatient treatment more than doubles, and the risk of death increases [9].

In connection with the increase in patients with comorbid pathology in combination with the syndrome of senile asthenia, it is necessary to timely identify functional disorders in the body and predictors of the development of adverse complications. This will help optimize the approach to treatment and diagnosis among patients of this category and, accordingly, provide timely medical care. It is important at the initial contact between the doctor and the patient to identify the presence of senile asthenia syndrome, which, as mentioned above, can aggravate the course of any existing or developing pathology in the body [3, 5, 6].

The aim of the study: to determine the incidence and structure of comorbid pathology in patients with senile asthenia syndrome, followed by the study of the clinical significance in the development of adverse complications in this category of patients.

### MATERIAL AND METHODS

The study included 130 patients who underwent inpatient treatment in the department of therapeutic profile at G.A. Zakharyin Clinical Hospital No. 6 (Penza, Russia) in 2019–2020. The study was retrospective, was carried out at the Department of Internal Diseases, Penza State University and consisted in the study of patient histories. The study complies with ethical standards, data on individual patients are not covered.

When analyzing the case histories, the following data were taken into account: age (over 65 years old), gender (male or female), the presence of senile asthenia syndrome, a history of arrhythmias, laboratory and instrumental diagnostics data during hospitalization (clinical blood test, lipid profile, creatinine level, glucose, blood electrolytes, blood pressure, electrocardiogram, Holter ECG monitoring, echocardiography). The above criteria made it possible to judge the presence of chronic non-communicable diseases. They also took into account the data on the intake of drugs, taking into account age, the presence of concomitant pathology, which made it possible to assess the treatment regimen and patient adherence to treatment. The diagnosis of cardiac arrhythmias in patients was established on the basis of anamnestic data, according to the results of clinical and instrumental studies. Screening of the syndrome of senile asthenia was carried out using the questionnaire "Age is not a hindrance". (Table 1).

Table 1. Questionnaire "Age is not a hindrance"

N⁰	Question	Answer
1	Have you lost 5 kg or more in the last 6 months?	yes/not
2	Do you have any limitations in your daily life due to decreased vision or hearing?	yes/not
3	Over the past year, have you had any fall-related injuries or non-injured falls?	yes/not
4	Have you been feeling depressed, sad, or anxious over the past weeks?	yes/not
5	Do you have problems with memory, understanding, orientation or planning ability?	yes/not
6	Do you suffer from urinary incontinence?	yes/not
7	Do you have difficulty getting around the house or outside? (Walking up to 100 meters or climbing 1 flight of stairs)	yes/not

Note: for each answer "Yes" 1 point is awarded

The interpretation of the results is based on the scores received for all the answers: 5 or more points — a high probability of the diagnosis of senile asthenia syndrome; 3-4 points — the likelihood of senile asthenia syndrome; 0-2 points — low probability of diagnosis of senile asthenia syndrome. Patients with scores of 3 or more underwent a more detailed examination based on the use of a geriatric card, which includes a short battery of tests of physical functioning (The Short Physical Performance Battery, SPPB), dynamometry, Mini-Cog test.

The maximum score for this test is 12 points. A result of  $\leq$  7 points is a criterion for diagnosing senile asthenia syndrome. (Fig. 1) [4].

Dynamometry is a method that allows you to determine the symmetry (or the degree of asymmetry) of the muscular system. Dynamometry is carried out using an electronic or mechanical dynamometer. The last test that has been used among patients with senile asthenia syndrome is the Mini-Cog test. This test is highly sensitive and informative and is used to detect cognitive impairments. (Table 2).

Interpretation of the results obtained: if the patient scored less than 3 points, the likelihood of cognitive impairment is high.

Comorbidity in patients with senile asthenia syndrome was assessed using the Charloson comorbidity index. The Charloson Index calculates the risk of mortality in the next 10 years. According to the comorbidity index of 1 point, the 10-year survival rate is 99%, 2 points — 96%, 3 points — 90%, 4 points — 77%, 5 points — 53%, 6 points — 21%. (Table 3).

The results obtained in the course of the study were formed into a database in Microsoft Excel 10.0.



Fig 1. The Short Physical Performance Battery (SPPB)

Tabl	le 2.	Min	i-Ko	a test

Step	Action	Points
1.	Tell the patient: "Listen to me carefully. Now I will name 3 words, and you will need to repeat them after me and remember." Later I will ask them from you. "Pronounce 3 words clearly: key, lemon, flag. If the patient has not repeated all 3 words, from the words again. If the patient cannot repeat all 3 words after 3 attempts, refer to Step 2.	Not accrued
2.	Tell the patient: «Next, I want you to draw a round clock. Arrange all the numbers that should be on the dial» Upon completion, ask the patient to adjust the clock to show the time at 11 hours and 10 minutes.	Correctly drawn clock - 2 points. A correctly drawn clock contains all the necessary numbers in the correct sequence without dupli- cation. The numbers 12, 3, 6, 9 are located in the corresponding places. The arrows point to the numbers 11 and 2 (11:10). The length of the arrows is not in- cluded. Failure to draw the clock correctly or failure = 0 points
3.	Ask the patient to recall 3 words from Step 1.	For each word played in Step 3, the patient receives 1 point. If you did not remember 1 word – 0 points

Table 3. Charlson Comorbidity Index

Points	Diseases
1	myocardial infarction congestive heart failure peripheral arterial disease cerebrovascular disease dementia COPD connective tissue disease peptic ulcer mild liver damage diabetes
2	hemiplegia CKD diet with organ damage malignant tumor without metastases leukemia lymphomas
3	moderate to severe liver damage
6	metastatic malignant tumors AIDS
	+ 1 point is added for every 10 years of life after 40 (40- 49 years - 1 point, 50-59 - 2 points, etc.)

The analysis of the data obtained during the study was carried out using the StatSoftStatistica 10 program.

## RESULTS

Patients (130 people) who were included in the research work were distributed according to gender — 57 male patients (43.8%), 73 female patients (56.2%) (Fig. 2). The median age of the subjects was 76 (65; 92) years.

According to the comprehensive geriatric assessment (which also includes the questionnaire Age is not a hindrance, a short battery of tests of physical functioning, dynamometry, the Mini-Kog test), all patients were divided into two main groups: the first group — patients with senile asthenia syndrome — 121 people (93%), the second group included patients with preasthenia — 9 people (7%). (Table 4).

As a result of the analysis of the case histories of patients with senile asthenia syndrome, diseases of the cardiovascular system took the first place among comorbid pathologies. The most common disease among CVS was arterial hypertension, which was detected in all patients (100%), which is a significant factor in the onset of chronic and acute forms of ischemic heart disease. Chronic heart failure (CHF) occurred in 84% of cases (110 patients). Next in terms of the frequency of



Fig. 2. Distribution of patients by gender

 Table 4. CGA parameters in comorbid patients with senile asthenia

 syndrome

Indicator	Patients ( $n = 130$ )	Р
Questionnaire "Age is not a hin- drance", points	4 (2;5)	<0,001
Brief Battery of Physical Functioning Tests, Points	4 (2;5)	<0,001
Mini-Kog test, points	2 (1;4)	<0,001

Note: the results are presented as Me (25%; 75%)

occurrence was ischemic heart disease in 97 people (74%). Postinfarctioncardiosclerosis was diagnosed in 39 people (30%). Angina pectoris was present in 52 patients (40%) (Fig. 3).



*Fig. 3.* Distribution of patients by morbidity combined with senile asthenia syndrome

When assessing the lipid profile, namely, the following indicators were taken into account: total cholesterol, triglycerides, high-density lipoproteins, low-density lipoproteins, atherogenic coefficient, the incidence of dyslipidemia was 44 (39.3%) among the men, 68 (60.7%) among the women.

As a result of cardiac remodeling in IHD and AH, 81 patients (62.3%) had rhythm disturbances manifested in the form of a permanent and paroxysmal form of atrial fibrillation. Supraventricular and ventricular extrasystoles were somewhat less common.

Among the diseases of the endocrine system, type 2 diabetes mellitus (DM), when using the data of anamnesis and laboratory research methods, there were 43 people (33%). When assessing the glomerular filtration rate using the CKD-EPI formula, chronic kidney disease was detected in 54 patients (41.5%), in most patients it was stage 3–4.

Degenerative-dystrophic changes in the joints, namely osteoarthritis, occurred in 123 (94%) cases. Iron deficiency anemia occupied a significant place among blood diseases.

The treatment prescribed to patients was, in most cases, multicomponent. Women with comorbid pathology received on average 5 drugs, men 7. Analyzing the prescriptions, it was revealed that all drugs were focused on the correction of all concomitant diseases. In this regard, it is necessary to take into account drug-drug interactions that affect the kinetics of drugs. Adherence in this study was 40% for men and 60% for women.

The Charloson comorbidity index among patients with senile asthenia syndrome averaged 5.8 points, which corresponds to 10-year survival in 21% of patients (Table 5). Among men, on average, the index was 5.6 points, among women — 5.2 points.

#### CONCLUSION

1. In the study group, among patients with comorbid conditions in combination with senile asthenia syndrome, female patients predominated — 73 (56.2%).

2. In the structure of chronic non-infectious diseases, the first place among cardiovascular diseases was taken by arterial hypertension — 130 (100%). The second place among comorbid pathology was taken by chronic heart failure, which accounts for 84% of cases. Ischemic heart disease occurred in 97 people (74%), which is a significant share in the structure of concomitant diseases.

3. Also, a significant place in the structure was taken by chronic kidney disease — 54 (41.5%), degenerative-dystrophic changes in the joints in 123 (94%) cases.

4. In patients with senile asthenia syndrome, the comorbidity index averaged 5.8 points, which corresponds to 10 — year survival in 21% of patients. The presence of comorbid pathology in patients with senile asthenia syndrome aggravates the course of the underlying disease, which undoubtedly affects its outcome.

**Table 5.** Evaluation of the prognosis according to the Charlson comorbidity scale

Points total	10-year survival rate,%
0	99
1	96
2	90
3	77
4	53
5	21

Thus, in the course of the study, it was revealed that senile asthenia syndrome is highly common among comorbid elderly patients. In addition, there is a certain relationship between the syndrome of senile asthenia and other age-associated conditions, which undoubtedly affects the life expectancy and quality of life of patients. It is necessary to timely identify geriatric syndromes among patients over 65 years of age, which in turn will help to provide proper medical care and optimize approaches to the diagnosis and treatment of various diseases.

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# METHOD FOR INGUINAL HERNIA TREATMENT WITH XENOPERICARDIUM

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**ABSTRACT** — Our experimental study shows the possibility of using a xenopericardial plate as a prosthesis in patients with inguinal hernias.

The method of hernioplasty proposed by us is tension-free prosthetic technique.

The advantage of the proposed method is the low probability of recurrence of a hernia in the area of the inner inguinal ring by strengthening both the posterior and anterior walls of the inguinal canal. Due to the fact that the spermatic cord, m. transversus abdominis and m. obliquus internus abdominis are in contact with the smooth antiadhesive surface of the xenopericardial plate, there is no formation of rough cicatricial fusion and no dysfunction of these structures. As an experiment, this method was tested on thirty Wistar rats with implantation of a prosthesis in the tissue of the anterior abdominal wall. Morphological and morphometric assessment of the tissue in the area of implantation shows that the formation of connective tissue around the implanted hernioprosthesis is very active. The final stage of the experiment (after 3 months) has revealed that the rough side of xenopericardial plate is tightly fixed to the underlying tissues. The xenopericardial plate contacting the tissues with the smooth side does not cause the formation of connective tissue, which protects this area from adhesions in the postoperative period.

**KEYWORDS** — pericardium, inguinal hernia, tension-free prosthetic technique, morphological reaction.

## INTRODUCTION

Despite the fact that the basic principles of the treatment of inguinal hernias have been known since the 19<sup>th</sup> century the improvement of these methods of treatment is a relevant topic of scientific research. Inguinal hernia is diagnosed in about 5% of the male working-age population. This circumstance testifies to the economic losses of the state and gives the problem a social orientation [1, 2].

Initially, techniques based on the use of the patient's own tissues for hernia repair were proposed and widely used. The basis for a large number of hernia repair methods is the Bassini technique. Analyzing the complications that develop after this operation, a large percentage of hernia recurrences was noted. The cause of recurrence is the tension of the tissues sutured during plastic surgery, as well as their morpho-functional inferiority [3].

At present, the use of tension-free prosthetic techniques is considered optimal [4]. These methods involve the use of hernia prosthetic materials. A positive point is the absence of tension between the sutured tissues and ischemia in the plastic zone as a result. Nevertheless, a new group of so-called *prosthesis-associated* complications was identified during the process of gaining experience in the use of synthetic implants

A large number of currently used techniques demonstrate the need to find an optimal material for hernia repair. This material should have the already known advantages of the implant and should be free of the disadvantages associated with foreign body reactions.

## MATERIAL AND METHODS

The team of Penza State University Department of Surgery developed a method for hernia repair of the inguinal canal using a xenopericardial plate (patent RU 2392 874 C1).

Technically, the proposed method is most similar to the repair of the inguinal canal according to Lichtenstein. The method consists in the formation of the posterior wall of the inguinal canal with a polypropylene mesh, which is attached to the inguinal and Cooper's ligaments and to the common aponeurosis of the internal oblique and transverse abdominal muscles. A special hole is created in the polypropylene mesh for the passage of the spermatic cord. The edges of the hole are subsequently sutured to the inguinal ligament.

Despite its great popularity, the Lichtenstein method is not ideal and has a number of disadvantages. One of them is the formation of a rough scar at the junction of the prosthesis with the surrounding tissues. Also, due to the presence of a hole in the mesh, a recurrence of a hernia with compression of the spermatic cord and the development of testicular atrophy and subsequent infertility is possible. The operation in such cases is complicated by the separation of the elements of the spermatic cord from the prosthetic mesh, since due to their close proximity, fusion occurs with subsequent deformation and disruption of the functioning of the vas deferens and testicular vessels. The developed method is carried out as follows. First, hernia repair is performed according to generally accepted requirements. An 8 cm incision is made 2-2.5 cm higher and parallel to the inguinal ligament. Upon completion of manipulations with the hernia sac, the transverse fascia is visualized and the space behind the transverse abdominal muscle is prepared, separating the latter from the transverse fascia to a depth of 2.5-3 cm, for the location of the first leaf of the endoprosthesis. Then the xenopericardial plate, 15 by 15 cm in size, is bent in half to form two sheets of 7.5 by 15 cm so that the smooth surface of the implant faces the inside of the bent implant sheet.

The first implant leaf is modeled over the formed space behind the transverse muscle. Two ligatures are fixed along the upper edge of the modeled first implant leaf. Ligatures are passed through the transverse and internal oblique muscles from back to front along the upper edge of the prepared space to the anterior surface of the internal oblique muscle and tied. This ensures that the top edge of the first leaf is secured. After that, a hole is formed in the first sheet of the implant. The hole must match the inner opening of the inguinal canal through which the spermatic cord is passed. Then the lower edge common for both sheets (fold zone) is fixed with single interrupted sutures to the groin and, partially, to the Cooper's ligament. At the same time, the medial edge of the first leaf overlaps the area of the pubic tubercle, entering the anterior wall of the sheath of the rectus abdominis muscle, to which it is fixed with additional sutures.

Then the upper edge of the second sheet of the implant is fixed to the aponeurosis of the external oblique muscle of the abdomen from the inside with single interrupted sutures, passing the threads from the inside to the outside. At the end of the reconstruction, the dissected aponeurosis of the external oblique abdominal muscle is sutured over the second sheet of the implant, forming the external opening of the inguinal canal according to generally accepted requirements (Fig. 1–4).

The advantage of the proposed method is the low probability of recurrence of a hernia in the area of the inner inguinal ring by strengthening both the posterior and anterior walls of the inguinal canal. Due to the fact that the spermatic cord, m. transversus abdominis and m. obliquus internus abdominis are in contact with the smooth antiadhesive surface of the xenopericardial plate, there is no formation of rough cicatricial fusion and no dysfunction of these structures. As an experiment, this method was tested on thirty Wistar rats with implantation of a prosthesis in the tissue of the anterior abdominal wall. The studies were carried out in accordance with the requirements of the *European Convention for the Protection of Vertebrate Animals, used*  *for experiments or other scientific purposes* (Strasbourg, 1986). Permission was obtained from the local Ethics Committee of the Medical Institute of Penza State University.

There were no complications in the postoperative period in rats.

Animals were removed from the experiment after 2 weeks, 1 month and 3 months after the start of the study. Conducted morphological and morphometric assessment of the state of tissue in the area of implantation of the prosthesis.

## **RESULTS AND DISCUSSION**

The study showed that the xenopericardial plate leads to the development of a sufficiently pronounced inflammatory response in the tissues of the abdominal wall.

In the early stages — 2 weeks after surgery, inflammatory infiltration is mainly detected in the area of the prothesis, then lymphocytes and neutrophilic leukocytes spread into the thickness of the xenopericardial plate. A month after the start of the experiment, inflammation in the area of operation reaches its maximum intensity, then its regular decrease occurs.

The formation of connective tissue around the implanted hernioprosthesis is very active. Initially, a large number of fibroblasts and, accordingly, connective tissue fibers are formed at the border of the intrinsic tissues of the abdominal wall and the prothesis (Table 1).

Then the fibers and capillaries of the granulation tissue grow into the mesh cells, approaching the xenopericardial plate. The development of the inflammatory reaction and the growth of connective tissue around the combined prosthesis has a number of features compared to separately used mesh implants.

The final stage of the experiment (after 3 months) shows that the rough side of xenopericardial plate is tightly fixed to the underlying tissues.

The xenopericardial plate facing the tissues with the smooth side does not cause the formation of connective tissue, which protects this area from adhesions in the postoperative period.

## CONCLUSION

Thus, the data of experimental studies allow us to conclude that the proposed method for the treatment of inguinal hernias using a xenopericardial plate makes it possible to strengthen both walls of the inguinal canal. This method minimizes the incidence of recurrent hernia. The antiadhesive side of the prosthesis facing the spermatic cord prevents the formation of rough cicatricial adhesions between the elements of the spermatic cord and the implant, thereby preventing the risk of impairment of its trophism and function.



Fig. 1. Figure of carved out endoprosthesis



**Fig. 4.** The final view of the operation. New inguinal canal is formed: 1 inguinal ligament; 2 — ligature fixing the endoprosthesis to the inguinal ligament; 3 — ligature on the aponeurosis of the external oblique abdominal muscle; 4 — anterior leaflet of the endoprosthesis; 5 — spermatic cord; 6 — ligature fixing the anterior leaflet of the endoprosthesis; 7 — ligature fixing the posterior leaf of the endoprosthesis; 8 — posterior leaf of the endoprosthesis; 9 — fascia transversalis; 10 — internal oblique and transverse abdominal muscles



**Fig. 2.** Scheme of fixation of the posterior leaflet of the endoprosthesis: 1 — inguinal ligament; 2 — endoprosthesis; 3 — fixing ligature; 4 — aponeurosis of the external oblique muscle of the abdominal wall; 5 — internal oblique and transverse muscles; 6 — fascia transversalis



**Fig. 3.** Scheme of fixation of the endoprosthesis to the inguinal ligament: 1 — inguinal ligament; 2 endoprosthesis; 3 — ligature fixing the endoprosthesis to the inguinal ligament; 4 — spermatic cord; 5 aponeurosis of the external oblique muscle; 6 — ligature fixing the posterior leaf of the endoprosthesis

**Table 1.** The number of connective tissue cells in the area of implantation of the xenopericardial plate (cells in the field of view)

	3 month		
	Min	Max	M±m
Fibroblasts	130	172	151,01±9,67
Fibrocytes	74	93	79,43±5,32
The ratio of fibroblasts and fibrocytes			1,9

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# CLINICAL EXPERIENCE OF APPLYING A MODIFIED FILAC PROCEDURE FOR TREATMENT OF COMPLEX ANAL FISTULAS

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ABSTRACT — Surgical treatment of complicated anal fistulas remains one of the most difficult issues of coloproctology. In this study we used a modification of Fistula Laser Closure procedure in complex treatment of patients with anal fistulas.

The purpose of our study was to assess the short-term and remote results of applying the modified FiLaC procedure in patients with complex anal fistulas and compare these results with conventional fistulectomy.

The patients with complex transsphincteric and extrasphincteric anal fistulas were prospectively divided into FiLaC and conventional fistulectomy groups. The operative duration was longer, by 31% (p<0.05), in the FiLaC group compared to the control group. The healing of fistulas was faster by 42% (p<0.05)in the FiLaC group  $(7.3 \pm 0.5 \text{ weeks versus } 12.6 \pm 0.7 \text{ weeks})$ . The Wexner Incontinence scale scores were significantly lower (p < 0.05) in the FiLaC group. The recurrence of rectal fistula after the surgery was observed in 37.2% in the control group versus 17.5% in the FiLaC group (p<0.05) (median follow up period — 13 months). The pressure parameters of the anal sphincter were significantly higher (p<0.05) in the longterm follow-up period in patients of the FiLaC group and continence was maintained in 92.5% of the FiLaC group. Thus, the study has shown that the modified FiLaC procedure accelerates the healing time of the fistula by 42% (p<0.05), reduces the number of fistula recurrences from 37.2% to 17.5% (p<0.05), and has minimal negative effects on anal continence.

KEYWORDS — FiLaC, anal fistula, laser treatment.

### INTRODUCTION

Surgical treatment of transsphincteric and extrasphincteric anal fistulas remains one of the most difficult issues of coloproctology. This problem is accompanied by a high level of the disease recurrence, severity of the pain syndrome in the early postoperative period, long disability, and a high incidence of anal incontinence in the distant postoperative period [1, 2, 3]. A promising development of minimally invasive surgery is the emergence of FiLaC technology (Fistula Laser Closure) [4, 5, 6].

The aim of the study

was to compare the short term and long terms results of FiLaC with historical, standard fistulectomy, controls in the management of transsphincteric and extrasphincteric anal fistulas.

## MATERIALS AND METHODS

Clinical charts of patients with transsphincteric and extrasphincteric anal fistulas were analyzed and then divided into two groups: the FiLaCgroup (n=40) and the control group (n=43). Modified FiLaC procedure was used for treatment of fistulas in the FiLaC group. Standard fistulectomy with excision of the fistula's inner opening into the lumen of the anal canal and excision of cicatricial and purulent-inflammatory perineal tissue was used in the control group. 43 patients of the control group were operated from 2008 till 2012 and 40 patients of the FiLaC group were operated from 2012 till 2016.

The preoperative examination methods included a digital rectal examination, colonoscopy, fistuloradiography, sphincteromanometry with Peritrondevice (Australia), endorectal ultrasound, pelvic MRI, and perineal examination in order to locate the external and internal openings of fistula and the area of cicatricial and inflammatory changes in the perirectal space and on the perineum.

In FiLaC group the operation was performed in lithotomy position with general anesthesia and muscle relaxants. The operation began with the injection of contrasting liquid into the fistulous tract (brilliant green solution), and then the external opening was excised by the fringing incision (incision that surrounds the external fistulous opening, O-shaped), the main fistula tract was detected in the operating wound and transected at a distance of 0,5 cm from the entrance to the anal sphincter mass. Additional fistulous tracts and purulent cavities were drained by separate point incisions through every 2 cm taking into account the data of endorectal ultrasound and MRI (Fig. 1). Latex drains were placed through the point incisions. The fistula was catheterized by the laser fiber FiLaC Fistula Probe (Fig. 2, 3). Then laser coagulation of the sphincter portion of the fistula by the laser with a wavelength of 1470 nm, 12 W power, in a continuous wave mode, with a total energy of 100 Jper cm was performed, achieving ablation and decontamination of the fistula, without damaging the anal sphincter and fibrous sheath of the fistula. The internal opening was sewn with interrupted stitches with Vicryl 2.0.



Fig.1. MRI of the fistula tract



Fig. 2. Catheterization of fistula by FiLaC Fistula Probe

In the control group, the operation was performed in lithotomy position with general anesthesia. Then the external opening was excised by the fringing



Fig. 3. Catheterization of fistula by FiLaC Fistula Probe



*Fig. 4.* Fibrous capsule of the fistula after the exposure of laser with a 12 W power, 100 J/cm energy. X400. Hematoxylin-eosin. 1 — coagulation edema and defibration of structures of the internal part of the fistulous tract

2 — the external part of the fistulous tract remains intact

incision, continuing the access perianally along the entire extent of the cicatricial-inflammatory tissues of the perineum using mono- and bipolar coagulation, then removing all additional fistula tracts and excising the internal aperture of the fistula tract into the lumen of the anal canal. The internal opening was closed by Z-shaped absorbable suture.

When the fistula was spread through the puborectal muscle, a silicon filament loop Ethicon 1.1 was additionally inserted through the fistulous tract to the internal opening and tightened after dissecting its mucosa below the inner fistula opening saving a deep portion of the anal sphincter and the puborectal muscle. The cutaneous edges of the perineal wound were sewn to the underlying tissues by Vicryl 1.0 filament, leaving the wound open for the secondary healing in a form of a triangle or trapezium facing the perineum. Tamponing of the wound was not used, as we preferred frequent baths, irrigation with antiseptics, ultrasonic cavitation of the wound.

Table 1. Initial characteristic of patients in both clinical groups.

Index	FiLaC group (n=40)	Control group (n=43)
Men, abs. (%)	31 (77.5%)	30 (70%)
Women, abs. (%)	9 (22.5%)	13 (30%)
Age, years (M $\pm$ m)	44.5±1.8	47.6±2.1
Type of fistula: – complextranssphincteric – extrasphincteric III grade of complexity – extrasphincteric IV grade of complexity	9 (22.5%) 26 (65%) 5 (12.5%)	11 (25.6%) 28 (65.1%) 4 (9.3%)
Number of previously operated patients, abs. (%)	25 (62.5%)	22 (51.2%)
Diabetes mellitus, abs. (%)	7 (17.5%)	6 (14%)
Obesity, abs. (%)	9 (22.5%)	10 (23.3%)
Initial results of sphincterotonometry, mmwg. • at rest – operated previously – non-operated previously – summary • when straining – operated previously – non-operated previously – summary	49.3±1.6 65.2±2.3 57.6±2.0 77.5±1.9 109.4±1.5 83.6±1.1	48.2±1.8 63.1±2.7 59.4±2.2 76.2±2.4 104.7±1.3 89.5±1.4
ScoresontheWexnerscale: – operated previously – non-operated previously – summary Eacal incontinence (operated previously patients)	7.3±0.3 2.1±0.6 5.2±0.5	8.1±0.4 2.0±0.2 5.4±0.4
1 stage, abs. (%) 2 stage, abs. (%)	2 (5%) 1 (2.5%)	2 (4.7%) -

The general characteristics of patients in clinical groups are presented in Table 1.

Patients of the FiLaCand control groups by age, sex, severity of the underlying disease, type and complexity of rectal fistulas, concomitant pathology, and previous surgical interventions did not differsignificantly (p > 0.05).

The duration of follow-up of patients was 6-28 months (mean 14.3  $\pm$  2.6 months) in the FiLaC group, 10–36 months (an average of 14.3  $\pm$  2.6 months) in the control group. Short- and long-term results of treatment in the FiLaC and control group were compared to each other using the Mann-Whitney test while assessing the quantitative indices and the Pearson criterion with the Yates correction for continuity while comparing qualitative parameters with the Statistica 10.0 program.

### **RESULTS AND DISCUSSION**

Characteristics of the intraoperative and early postoperative period in patients of both clinical groups are presented in Table 2. Fig. 5, 6, and 7 demonstrate the appearance of postoperative wound at 1, 2 and 6 months after the surgery, respectively.

The Wexner Incontinence scale scores were significantly lower (p <0.05) in the Fi-LaCgroup (Table 3). This fact evidences that the usage of the FiLaC technique allows keeping anal sphincter muscles intact, avoiding incontinence. The parameters of anometry had recovered up to the initial value in the patients of the FiLaC group in the long-term period. At the same time, in the control group these parameters decreased in comparison with the initial values (Fig. 8). In 92.5%, continence was preserved in the FiLaC group. In the control group 6 previously operated patients noticed deterioration of the anal continence.

As witnessed by recent publications minimally invasive methods of anal fistula treatment have been rapidly adopted by proctologists. However, long-term results have showed a high incidence of fistula recurrence, up to 40–50%. Due to the convoluted fistulous tract, the need to remove additional fistulous tracts and cicatrical-inflammatory changes of perineal tissues, minimally invasive methods of treatment are limitedly used in grade III–IV anal fistulas.

Despite of advanced multiple methods of surgical treatment for rectal fistulas as fistulotomy, fistulectomy, cutting seton, advanced flap, minimally invasive methods with the use of fibrin glue, collagen implant ("Fistula plug"), isolating biomaterials, VAAFT and so on, not a single treatment has been found satisfactory. Minimally invasive methods are expensive and do not exclude relapses in the longterm postoperative period [7, 8].

Currently, endorectal advanced mucosal-submucosal flap continues to be a method of choice for the treatment of complex (transsphincteric, extrasphincteric and suprasphincteric) fistulas, supplemented in some cases by setons. Necrosis of the flap, anal incontinence, and fistula recurrence of 30–40% are risks of the flap repair [9, 10, 11].

In our series, the FiLaCoperation duration was greater than the control by 31%(p<0.05), the patients took non-opioid analgesics less time on average ,the healing of fistulas was faster in the FiLaC group compared with the control group. The frequency of bleeding

Index	Statistic value	FiLaC group (n=40)	Control group (n=43)	р	
Operation duration, min	M±m	42.9±2.4	32.7±2.9	-0.05	
	[Min-Max]	25-65	20-80	<0.05	
Duration of analgesics course in the postoperative	M±m	2.3±0.4	7.2±0.5	<0.001	
period, days	[Min-Max]	0-10	3-30	<0.001	
Duration of fistula healing, weeks	M±m	7.3±0.5	12.6±0.7	<0.001	
	[Min-Max]	4-15	8-20		
	Total number	1	2	> 0.05	
Bleeding in early postoperative period (0-5 days)	%	2.5	4.7	>0.05	
Bleeding in the remoteperiod (6-30 days)	Total number	-	3		
	%	-	7.0	]-	
Total number of bleedings	Total number	1	5	. 0.05	
5	%	2.5	11.7	>0.05	
	Total number	5	7	> 0.05	
	%	12.5	16.3	>0.05	

Table 2. Characteristics of intraoperative and early postoperative period in patients of both clinical groups



*Fig. 5.* The appearance of postoperative wound in a month after the operative intervention



*Fig. 7.* The appearance of postoperative wound in 6 months after the operation



*Fig. 6.* The appearance of postoperative wound in 2 months after the operation

and septic conditions did not differ in the two groups at the postoperative stage. The relapse of rectal fistula after the surgery was observed in 37.2% in the control group versus 17.5% in the Fi-LaC group. The pressure parameters of the anal sphincter were significantly higher in the long-term follow-up period in patients of the FiLaC group than in the control group, both in previously operated and non-operated patients, at rest and under straining.

With the use of the FiLaC technique, patients can be treated in an outpatient setting. Due to the absence of damage of the anal mucosa, the technique does not cause pain, rectal bleeding and stricture of the anal canal in the postoperative period. The lack of an individual approach to the choice of the laser energy densities can lead not to ablation of the fistulous tract only, but also to the destruction of its fibrous capsule, which can hinder the formation of a reliable scar in the area of the internal fistula outlet, and cause a relapse of the disease [12].

The use of the described technique does not make performing the operation more complicated. But at



**Fig. 8.** Changes in the parameters of sphincterometry of the rectum in the remote postoperative period in comparison with the baseline values before surgery in patients of the FiLaC and control groups at rest and with straining effort.

\* — significant differences in comparison with the initial values for p <0.05

method enables to avoid postoperative rectal bleeding, does not affect the function of anal sphincter and accelerates the fistula healing time by 42% compared to the control group with the traditional operating technique. A reduced frequency of relapses in the FiLaC group — 17.5% versus 37.2% in the control group evidences the relevance of the technique.

In some cases, the main technical difficulties arise in case of a narrow fistulous tract when searching for the main tract at the site of perforation of the anal sphincter, as well as its catheterization with a laser light guide. We encountered such a situation in 6 cases, relapses of fistula were observed in 5 patients.

## CONCLUSION

This study of short-term and long-term results of treatment of III–IV complexity grade transsphincteric and extrasphincteric fistulas using modified FiLaC technology suggests it may have advantages over standard fistulectomy.

# **CONFLICT OF INTEREST**

The authors declare no conflict of interest.

Index	Statistic value	FiLaC group (n=40)	Control group (n=43)	р	
The Wexner scale scores: – operated previously – non-operated previously – summary	M±m	7.5±0.4 2.2±0.3 5.3±0.6	10.6±0.5 5.4±0.1 8.9±0.4	<0,05 >0.05 <0,05	
Relapse of rectal fistula (6–36 months after	Total number	7	16	<0.0E	
surgery)	%	17.5	37.2	<0,05	
Initial results of sphincterotonometry, mmwg. • at rest – operated previously – non-operated previously – summary • when straining – operated previously – non-operated previously – summary	M±m	47.1±1.6 63.2±2.5 55.9±1.8 74.3±2.3 107.4±2.7 80.2±2.1	30,1±1.5 51,6±2.8 42,6±2.0 51.1±1.9 89.3±2.2 65.7±2.6	<0,05 <0,05 <0,05 <0,05 <0,05 <0,05 <0,05	
Absence of fecal incontinence	Total number	37	35	N 05	
	%	92.5	81.3	/0.05	
Fecal incontinencestage 1	Total number	2	6	> 0.05	
	%	5.0	14.0	/0.03	
Eacol incontinence stage 2	Total number	1	2	> 0.05	
i ccai incontinence staye z	%	2.5	4.7	~0.03	

Table 3. Characteristics of the remote postoperative period in patients of both clinical groups

the same time, it prolongs the operation time and requires the expensive laser equipment and radial laser fibers. The analysis of the short-term and long-term treatment re-sults in the FiLaC group shows that the

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# MODERN ASPECTS OF DIAGNOSIS AND SURGICAL TREATMENT OF HIATAL HERNIAS: LITERATURE REVIEW

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ABSTRACT — Laparoscopic correction is the main method of treating hiatal hernias. However, despite more than thirty years of experience, many issues remain controversial and require compilation and standardization. The authors have analyzed the latest scientific studies and recommendations on the treatment of hiatal hernias with a high level of evidence, which is presented in the form of a review with a comparison of their own experience in surgical treatment of 171 patients operated on for hiatal hernias. The risk of transition of an asymptomatic hiatal hernia to a clinically significant one is 1% per year, while observation, rather than active surgical tactics, is indicated. Only symptomatic hernias are subject to surgical treatment. Surgical intervention should include the following mandatory steps: dissection of the esophagealdiaphragmatic ligament with excision of the hernial sac while protecting the branches of the vagus nerve; dissection of both crura of diaphragm, transhiatal mobilization of the esophagus in the mediastinum to achieve the length of its intraabdominal segment of 2-3 cm; if a short esophagus is suspected, a mandatory step is to perform Collis gastroplasty; mobilization of the gastric fundus by dividing gastrointestinal ligament and short gastric arteries; creation of a fundoplication cuff on a calibration probe of at least 30-36 Fr. The choice of the fundoplication and cruroraphia methods did not significantly affect the long-term results of treatment. Laparoscopic interventions are the most effective way to treat patients with hiatal hernias, due to their safety, low trauma, low complication rate and the possibility of rapid rehabilitation of patients. The technique of surgical intervention needs a clarified standardization.

**KEYWORDS** — hiatal hernia; fundoplication; recurrence; surgical mesh; symptom assessment; treatment failure; laparoscopic correction; diagnosis.

## INTRODUCTION

Hiatal hernia is a disease characterized by displacement through the esophageal orifice of the diaphragm into the thoracic cavity of the abdominal esophagus, cardia, upper stomach, and sometimes intestinal loops [1]. Hiatal hernia is a fairly common disease and can often be diagnosed during examinations for a completely different pathology, since in most cases it is absolutely asymptomatic. According to various authors, the detectability of this pathology among the adult population can reach 20-30% [2]. However, the long-term existence of hiatal hernia and the associated trouble of anatomical and functional relationships in the cardioesophageal zone, as a rule, over time leads to the onset of clinical symptoms, primarily associated with the development of gastroesophageal reflux, sometimes dramatically worsening the quality of life of the patient and requiring treatment. The only method of treatment that allows to eliminate the existing hiatal hernia complicated by gastroesophageal reflux disease (GERD), is surgical. The laparoscopic method is currently the gold standard in the treatment of hiatal hernia and GERD [3].

However, despite the almost thirty years of experience with laparoscopic interventions, a number of issues still remains relevant. Such as: whether to operate hiatal hernia and GERD or to treat conservatively, determining the optimal volume and technique of the surgical aid, choosing the method of cruroraphia, the need to use a mesh or biological graft to close a hernial defect or strengthen sutures during plastic surgery of a hiatal hernia, the need to complement plastic surgery of esophageal hiatus by fundoplication or gastropexy [4]. The widespread introduction of laparoscopic techniques and the emergence of a large number of surgical methods for correcting hiatal hernia have not led to the development of a unified approach to the diagnosis and surgical treatment of patients with this pathology.

#### MATERIAL AND METHODS

The present study analyzes the latest published studies and recommendations on the surgical treatment of hiatal hernia with a high level of evidence, which is presented in the form of a review with a comparison of data from our own retrospective analysis in surgical treatment of 171 patients operated for hiatal hernias for the period 2009–2018. Indications for surgical treatment were:

— clinically, radiologically and endoscopically confirmed hiatal hernia;

— inefficiency of conservative therapy of gastroesophageal reflux during more than 3 months;

— the presence of clinically significant extraesophageal (cardiac or bronchopulmonary) manifestations of hiatal hernia and associated GERD.

All patients were operated in the scope of laparoscopic cruroraphia with fundoplication. There were 69 men (40.4%) and 102 women (59.6%). The age of the patients ranged from 25 to 74 years, the average age was  $54.2\pm 6.1$  years. Nissen fundoplication was used in 109 cases, Toupet fundoplication was used in 62 patients. In 29 patients with a hernia defect size of 5 cm and larger, suture cruroraphia was supplemented with alloplasty.

Statistical analysis was carried out using the R Studio program Version 1.2.1335© 2009–2019 R Studio, Inc., GPL. Quantitative variables are presented in the form of mean and standard deviation, since they all had a normal distribution (Shapiro-Wilk test). When comparing two independent groups with quantitative variables, the Student's T-test was used. Nominal and ordinal variables are represented as percentages. To compare the nominal scales, the Pearson criterion was applied if no more than 20% of the expected frequencies were less than 5, otherwise the exact Fisher criterion was applied.

#### LITERATURE REVIEW

The formation of approaches to the treatment of patients suffering from hiatal hernia had several stages. Initially, most surgeons adhered to active surgical tactics when detecting hiatal hernia, justifying the need for surgical intervention by prevention ofsevere complications associated with ischemia in the hernial sac. However, in 2002, the publication of the Stylopoulosstudy[5] showed that when choosing the tactics of monitoring patients with this pathology, the frequency of theneed for urgent intervention was 1.1%, and the quality of life was lower in the group of routinely operated hiatal hernias compared with the observation group. At the same time, a fairly large number of publications appeared in the literature on repeated surgical interventions performed for complications after plastic surgery of hiatal hernia. The appearance and widespread use of drugs of the proton pump inhibitor group allowed to improve the quality of life of patients with hiatal hernia and gastroesophageal reflux as a leading symptom, also at some stage reducing the number of surgical interventions for this

pathology [6]. And yet, the results of studiesshowed that despite the high cost, laparoscopic hernia plastic surgery with fundoplication had the best indicators of quality of life, especially in the group of patients refractory to antisecretory drugs. All of the above was the reason to make a note in the recommendations of the Association of Gastrointestinal and Endoscopic Surgeons of America (SAGES) that absolutely forbids to operate on patients with sliding (type I) hiatal hernia in the absence of a gastroesophageal reflux manifestations [7]. For paraesophageal hernias, it was noted that when using observational tactics, despite the low percentage of urgent operations (less than 2%), the risk of transformation of an asymptomatic hernia into a symptomatic one is up to 14% per year[8]. Therefore, surgical intervention in fully asymptomatic paraesophageal hernias can be considered individually, taking into account age, concomitant pathology, the risk of surgery and the experience of the operating surgeon. All experts unanimously agree that surgical treatment is indicated for all patients with symptomatic hiatal hernia 9.

Surgical intervention for hiatal hernia includes the following mandatory steps: moving the contents of the hernia into the abdominal cavity, isolation and excision of the hernial sac, mobilization of the lower third of the esophagus in the mediastinum in order to achieve a sufficient length of the esophagus, closure of the esophageal hiatus defect, formation of a fundoplication cuff. The literature describes several variants of cardioesophageal junction mobilization [10, 11]. Some surgeons prefer to start mobilization from the left crus of diaphragm, arguing that with large hernias, the right gastric artery and vein may be located in the hernial sac, which, in case of mobilization from the right crus, may be injured. However, we prefer to start the operation by dissecting the gastro-hepatic ligament and mobilizing the right crus of the diaphragm.When dissecting the gastro-hepatic ligament, in 10–15%, an additional hepatic artery may be found, which, especially in overweight patients, may be quite large, and with a rapid dissection can cause massive bleeding. Regardless of the diameter, this vessel must be coagulated and dissected; attempts to preserve the latter will not allow adequate access to the gastroesophageal junction and will create technical difficulties at the stage of formation of the fundoplication cuff.In no case did the dissection of the accessory hepatic artery affect the course of the postoperative period. Next, one of the tools captures the bottom of the hernial sac and performs traction towards the abdominal cavity. The peritoneum is dissected along the border of the hernial sac along the edge of the esophageal hiatus and then the incision is extended circularly, separating the

left crus of the diaphragm. After the mobilization of the diaphragm crura, usually in a "blunt" way, a tunnel is formed behind the esophagus, into which Penrose drainage or a thin gauze cloth is inserted to carry out traction during further mobilization of the esophagus in the mediastinum. At the same time, during the mobilization of the left semicircle of the esophagus, traction for drainage is carried out towards the right crus of the diaphragm and, accordingly, vice versa. During the mobilization of the esophagus, the diaphragmatic nerves should be identified and traced in order to avoid their trauma [12, 13].

A clear definition of the required length of esophageal mobilization is not described in the literature, it is generally understood that mobilization is carried out until the length of the intraabdominal segment of the esophagus, devoid of tension, is at least 2-3 cm. In order to achieve the required length of the esophagus, some authors cite the length of the esophagus mobilized in the mediastinum from 5 to 10-12cm, other authors consider it necessary to mobilize it to the level of the lower pulmonary vein. The isolation of the esophagus in the mediastinum should be carried out as close as possible to its adventitious membrane; in this case, the probability of the pleura oozing or injury during mobilization is minimal. Nevertheless, one of the most unpleasant intraoperative complications is the dissection of the esophageal muscle membrane or its perforation at the stage of mobilization [14].

One of the main problems after laparoscopic hiatal hernia surgery is the high frequency of recurrence which ranges from 10% to 40%. In order to improve long-term results, some surgeons, by analogy with the plasty of hernias of the anterior abdominal wall, suggested using mesh prostheses for the plasty of large defects of esophageal hiatus, especially in cases where the closure of the hiatal opening without tension has certain difficulties. The multitude of various materials used for both synthetic and biological transplants and methods of their fixation make certain difficulties in developing a universal protocol for surgical intervention. Almost all meta-analyses published to date note the advantage of using mesh implants in comparison with suture plasty. The largest in the last few years are Tam et al. [15] (2016) who analyzed 13 studies, 1194 patients: 673 with mesh plastic surgery and 521 with suture plastic surgery. The recurrence rate was 13% in the mesh plastic surgery group versus 24% in suture plastic surgery group (HR 0.51, 95%; CI 0.30-0.87; p=0.014). In a published study by Zhang et al. [16] (2017), where the results of treatment of 719 patients using a mesh implant and 755 with primary suture surgery were analyzed, the recurrence rate was 2.6% vs. 9.4%, respectively (OR 0.23, 95% CI 0.14-0.39,

p=0.00001). In a meta-analysis by Sathasivamet al.[17] (2019), the results of treatment of 942 patients were analyzed (mesh plastic surgery — 517 patients, suture microplasty — 425 patients), where the advantage of mesh implant plastic surgery was also noted (OR 0.48, 95% CI:0.32–0.73, p<0.05). In all the above studies, there was no significant difference in the frequency of intraoperative and postoperative complications.

## OUR EXPERIENCE AND DISCUSSION

We conducted a retrospective analysis of the results of surgical treatment of 98 patients operated for hiatal hernia, with a hernial defect size of 5 cm or larger for the period 2009–2016. Depending on the method of plastic surgery of the esophageal orifice of the diaphragm, patients were divided into 2 comparison groups. The first group included 69 patients who had hernial defect plastic surgery performed by suture method. The second group included patients who underwent plastic surgery of hiatal hernia using a mesh allograft (29 patients). In the group of cruroraphia with alloplasty, the crura of the diaphragm during stitching were strengthened from the side of the abdominal cavity with a mesh graft, which was located in a V-shape. Analysis of long-term results 5 years after the study showed no advantage of using a mesh graft for plastic surgery of large hiatal hernias in comparison with standard suture plastic surgery both in terms of recurrence rate -4(13.8%) vs. 14 (20.3%), CI: 0.19–2.1, p=0.44, and in assessing the quality of life according to the GERD-HRQL questionnaire. Therefore, taking into account the likelihood of complications associated with alloplasty, in particular mesh erosion into the esophagus and dysphagia, do not allow us to recommend this method for routine use. Nevertheless, in the case of using the alloplasty technique, we, like most authors, prefer lightweight composite prostheses, preferably with an adhesive coating [18]. We do not recommend the circular arrangement of the mesh around the esophagus, as well as the use of a tension-free option, closing the esophageal orifice defect only by the mesh. In order to reduce the likelihood of complications associated with the implantation of a mesh implant, the latter should be located only behind the esophagus in the area of the stitched crura of the diaphragm. We did not note any cases when we bring the crura together and close esophageal orifice in our practice.

Despite the opinion of some authors who question the need for the formation of a fundoplication cuff, we consider this stage mandatory for plastic surgery of hiatal hernia. Indeed, to date, there is no convincing evidence in the literature in favor of the need for the use of fundoplication in plastic surgery of hiatal hernia. According to some authors, the very formation of the fundoplication cuff, especially when the latter is fixed to the wall of the esophagus and the crura of the diaphragm, creates an additional obstacle to the herniation of the stomach into the mediastinum.There are practically no works in the literature assessing the influence of both the fundoplication cuff itself and the method of its formation on the frequency of relapse in the long-term period. Only some studies provide data in favor of reducing the incidence of pathological reflux in patients with a formed fundoplication cuff. According to our data, 89% of patients with symptomatic hiatal hernia have clinical or endoscopic manifestations of pathological gastroesophageal reflux of varying severity, which dictates the need to perform an antireflux procedure.

The most commonly used antireflux procedure is Nissen fundoplication, which we also prefer to routine use. In its standard form, this technique involves wrapping the gastric fundus around the esophagus by 360°, while the formation of the cuff itself is carried out at the expense of the anterior and posterior walls of the gastric fundus. To do this, the posterior wall of the previously mobilized gastric fundus is captured with a soft clamp from the side of the right crus through the retroesophageal canal, and pulled in the direction of the right crus. The anterior and posterior walls are sewn together in front of the esophagus with 3-4 separate seams with a braided non-absorbable "Ethibond" thread 2–0 or 3–0 for up to 3 cm. In order to prevent dysphagia, the fundoplication cuff should be formed on a thick gastric tube 30-36 Fr. To prevent the formed cuff from slipping off, the anterior semicircle of the esophagus should be caught in two seams.Some authors consider it necessary to fix the upper edge of the fundoplication cuff, as a rule, to the right crus in its upper part. Many surgeons use a variation of this operation described by Rohr S. et al. [19] in 1992 as Floppy Nissen or Nissen-Rosetti in the literature, in which the fundoplication cuff is formed only at the expense of the anterior wall of the stomach without dissecting the gastrosplenic ligament ligament. Initially, this technique assumed the formation of a fundoplication cuff for a length of 4 to 6 cm. Currently, a length of up to 2 cm is considered sufficient, which in the literature has acquired the term Short Floppy Nissen. Despite the results of the meta-analyses conducted by Khatri et al. [20] and Markar et al. [21], which did not reveal significant differences between the above methods in functional results, we are of the opinion that restriction of the mobility of the gastric fundus can cause the formation of a fundoplication cuff with tension and increase the risk of dysphagia or "gas-bloat" syndrome in the long term, which is shown in the meta-analysis

by Engsrom et al.[22], and therefore is not used in our routine practice.

The method competing in the frequency of use with the fundoplication technique is the Toupetmethod, in which the formed fundoplication cuff envelops the posterior semicircle of the esophagus by 270°, leaving its anterior wall free. One of the latest metaanalyses published by XingDu et al. [23] and comparing the effectiveness of both methods of fundoplication included 1201 patients (8 randomized trials), laparoscopic Nissen fundoplication was performed in 625 patients, Toupet method — in 567 patients. The study showed no differences between the methods in terms of the duration of hospitalization, the frequency of postoperative complications, patient satisfaction with the operation, postoperative heartburn, regurgitation, esophagitis. When performing Nissen fundoplication, a shorter operation time and a higher pressure of the lower esophageal sphincter were noted, and the frequency of dysphagia, gas-bloat syndrome and the frequency of reoperations was higher. However, in the same study, when conducting a subgroup analysis, it was noted that the differences between the methods for dysphagia and gas-bloat syndrome disappeared with an increase in the observation period in the study.

We conducted a retrospective analysis of the results of surgical treatment of 171 patients operated on for hiatal hernia associated with GERD. Depending on the method of fundoplication, patients are divided into 2 groups. The first group consisted of 109 patients, where Nissen fundoplication was used. The second group consisted of 62 patients who had Toupetfundoplication. A comparative analysis of the results of the use of various antirefluxtechniques showed their equal effectiveness in the short and long term. The choice of the fundoplication method did not affect the duration of surgery, the frequency of intra- and postoperative complications; the proportion of functional dysphagia was 24 (22%) vs. 8 (12.9%), p=0.14; the number of unsatisfactory results, in particular, relapse, was 19 (17.4%) vs. 15 (24.2%), p=0.48, and of dysphagia – 8 (7.3%) vs. 2 (3.2%), p=0.27.

Of particular interest is the appearance of an increasing number of publications devoted to the effectiveness of the use of partial anterior Dor fundoplication (which consists in fixing the anterior wall of the gastric fundus to the anterior semicircle of the esophagus and the crura of the diaphragm) compared with the widespread Nissen and Toupetfundoplications in the aspect of use in hiatal hernia plastic surgery.Broeders et al., in a meta-analysis of surgical treatment of 458 patients, showed the same reflux control with a lower frequency of postoperative dysphagia when performing anterior Dor fundoplication compared with Nissen fundoplication [24]. A retrospective cohort study that was conducted by Trepanier et al. showed that the use of Dor and Nissen fundoplications is equivalent in the effectiveness of reflux control in the plastics of large paraesophageal hernias [25].

The frequency of occurrence of a short esophagus according to the literature varies from 0 to 60%, averaging from 5% to 20%. Thus, Madan et al. [26], citing the experience of 628 patients operated on in the scope of fundoplication, of which 351 patients were operated on for hiatal hernia, noted the absence of the need for esophageal elongation procedures. Nason et al. [[27,28,29], citing the results of surgical treatment of 795 hiatal hernias, performed Collis gastroplasty in 454 (57%) patients.

Early destruction of the fundoplication cuff or the eruption of sutures on the crura of the diaphragm with the development of early recurrence of hiatal hernia is extremely rare and, as a rule, is due to a sharp increase in intra-abdominal pressure caused by vomiting or coughing during the patient's recovery from anesthesia. To prevent these complications, massive antibiotic therapy should be carried out. If the patient has concomitant pulmonary pathology, the cough reflex should also be suppressed. Given the probability of developing postoperative dysphagia of a functional nature, which according to our data and literature data can reach 20-30%, it is generally accepted to gradually switch from liquid to solid food within 4-6 weeks. Many authors do not recommend performing routine radiopaque examinations for patients who do not have any clinical manifestations. We are of the opinion that such a survey is necessary at least once a year.

## CONCLUSION

Laparoscopic interventions are the most effective way to treat patients with hiatal hernia complicated by GERD, due to their safety, low trauma, low complication rate and the possibility of rapid rehabilitation of patients. Prevention and reduction of the frequency of complications is possible with the surgeon's clear understanding and knowledge of the subtleties of the surgical intervention. Further generalization and analysis of surgical technique options will allow to create a unified protocol of the surgical intervention and, thereby, improve the outcome in patients with hiatal hernia.

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# SURGICAL TREATMENT FOR CYSTIC LESIONS OF THE PANCREAS

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ABSTRACT — During the period 2011–2021, 45 patients with pancreatic cysts were treated at the Alexander-Mariinsky Regional Clinical Hospital in Astrakhan. All patients were divided into 2 groups. 20 patients of the first group (45%) underwent external drainage of cysts, 7 out of them underwent obliteration of residual cavities by the method developed by us. To do this, the drug Povidone - Iodine 10% was used. The second group included 25 (55%) patients with internal drainage of cysts: in 5 patients (11%) pancreacystogastrostomy was performed; in 9 patients (20%) — pancreatocystoejunostomy; in 5 patients (11%) — pancreatic drainage; in 5 (11%) — laparoscopic cystectomy; and open echinococcectomy was performed in 1 patient (2%). Clinical, laboratory, instrumental and statistical research methods were carried out. A comparative evaluation of two methods of drainage operations for pancreatic cysts showed the advantage of internal drainage over external. 7 (16%) patients had a variety of complications. The recurrence of cysts was 4 (9%) cases. All the patients recovered. There were no cases of lethality.

**KEYWORDS** — pancreatic cyst, surgical treatment, internal drainage, pancreatocystogastrostomy, pancreatocystoejunostomy.

### INTRODUCTION

To date, the number of patients with pancreatic cysts (PC) has increased. This is due both to the effective treatment of destructive forms of acute and chronic pancreatitis, and the widespread introduction of modern instrumental diagnostic methods [7, 8]. A large percentage of this disease falls on the able-bodied part of the population, due to which this problem is socially significant [8]. The main method of treatment of this pathology is surgical [1, 4, 7, 9]. Currently, there are a large number of methods for surgical treatment of pancreatic cysts, which are constantly being improved [1, 2, 3, 4, 5, 6, 8, 9, 11]. The choice of the method of surgical treatment is influenced by many factors — this is the localization of pancreatic cysts, the connection of the cystic cavity with the ductal system of the pancreas, the nearby location of organs

and vascular structures [1, 2, 9, 10]. In this regard, the choice of the method of surgical treatment of pancreatic cysts is an urgent problem [1, 10].

#### The aim of the research:

to evaluate the results of surgical treatment methods in patients with pancreatic cysts.

## MATERIALS AND METHODS

Within the period 2011–2021, 45 patients with PC were operated on. Among them, there were 26 males (58%) and 19 females (42%). The inclusion criterion was patients with chronic PC, and the exclusion criterion was patients with cysts of tumor etiology.

By localization, head cysts were found in 22 (49%) patients, head–body cysts in 6 (13%) patients, body cysts in 9 (21%) cases, body and tail cysts in 3(7%), tail — 4(9%) and in 1(2%) case, the cyst occupied the entire gland. The sizes of cysts ranged from 5 to 10 cm in diameter -31 (69%)patients, more than 10 cm - 13 (29%). According to the nature of surgical interventions, the patients were divided into 2 groups. Patients from group 1 with cysts larger than 10 cm in diameter underwent surgery — external drainage (ED) - 20, 7 of which obliteration of residual cavities (ORC) was performed using the method developed by us RF Patent No. 2551189 "Method of treatment of residual cavity after marsupialization and open echinococcectomy" [4]. Patients from group 2 with cysts ranging in size from 5 to 10 cm underwent operations — internal drainage (ID) - 25.

Laboratory and instrumental research methods were used within the pre- and postoperative periods. These are biochemical blood tests, ultrasound of the abdominal cavity and retroperitoneal space, EGD (fiberopticgastroduodenoscopy), CT (computer tomography). In addition, the contents of the cyst were examined for amylase levels and bacteriological, cytological and histological studies were carried out.

# STATISTICS

For statistical analysis of the data obtained, the Statistica 12.0 program was used. (StatSoft, USA). Median (Me) and percentiles (5 and 95) were calculated for each indicator. The Mann-Whitney U criterion was used when conducting intergroup comparisons in the two study groups. The level of critical statistical significance was assumed  $p \le 0.05$ . When conducting

SURGERY

intergroup comparisons in three or more groups, the Kraskel-Wallis criterion was used.

### **RESULTS AND DISCUSSION**

The number of male patients is one and a half times higher than the number of female patients. This is mainly due to the social status of the population. Despite the obvious superiority of male patients over female ones suffering from this disease, no significant differences were found when comparing by gender, depending on the attitude to a particular age group.

Depending on the forms of cysts, their localization, degree of maturity and connection with the ductal system, all this determined an individual approach to choosing the volume and nature of surgical interventions. ED was performed in 20 patients. The indications were unformed PC; as well as cysts not associated with the ductal system of the pancreas, as the first stage in infected cysts for subsequent more radical operations. There were 20 patients in 13 patients, simple ED cysts with cavity tamponade were performed. In 7 patients for ORC, we used a method developed by us, which consisted in 2-fold washing of the cystic cavity with a 10% povidone-iodine solution with an exposure of 15 minutes [4].

ID was performed in 25 patients. Indications were mature single cysts with their localization in the area of the head and body of the pancreas, as well as their communication with the ductal system of the pancreas.

Pancreatocystogastrostomy (PCG) was performed in 5 patients. RF Patent No. 2571711 "Method of surgical treatment of pancreatic head cysts" [5]. Pancreatocystoejunostomy (PCE) — performed in 9 patients on a disconnected loop.

Extrapancreatic location of cysts, with small sizes, retention cysts, and cysts not associated with the ductal system of the pancreas, were indications for cystectomy (CE). These operations were performed in 6 patients, of which in one case — by means of laparoscopic method.

In one case with large-sized pancreatic head echinococcosis, an open echinococcectomy was performed with drainage of the choledochus by Ker.

The indication for endoscopic transgastric drainage of pancreatic cysts was a single-chamber cyst of the pancreatic body, intimately fused with the posterior wall of the stomach. Such operations were performed in 5 patients.

The length of stay of patients in the hospital with ED with tamponade was — 24 = 4.5 bed days; with ED with ORC — 12.5 = 1.2 bed days. The length of stay of patients in the hospital with ID was 10.6 = 1.1 bed-days, with CE — 15 = 4.4 bed-days, with transgastric drainage (TGD) of PC — 10 bed days.

In the postoperative period, 7 (16%) patients had complications. ID operations turned out to be on the first place — 3 operations (23%) in patients with cyst suppuration. PCE operations were on the second place — 2 (22%) patients, with a case of bleeding in 1 patientand 1 case of sutures failure in the area of anastomosis. A relapse of the cyst occurred in 1 patient with TGD of PC. In other cases, there were no complications and no fatality cases.

There was no presence of cyst at the time of discharge in 45 patients after surgery, 41 (91%), and 4 (9%) still had a residual cavity. Among them, with external drainage with tamponade, a residual cavity was present in 3 patients, with endoscopic TGD — in 1 patient. 1 year after surgery, 38 (84.4%) patients were in satisfactory condition, there were no dyspeptic phenomena and pain syndrome, exocrine and endocrine disorders were absent. Residual cystic cavities and infiltrative changes in the pancreatic zone were not detected. 2 (4.5%) of the total number of operated patients had no cyst, but there were manifestations of chronic pancreatitis. Cyst recurrence was detected in 3 (6.6%) patients, and the residual cavity was preserved in 2 (4.5%) patients.

Within ED with obliteration of the cavity according to the developed method, the average bed days were two times less than with ED with tamponade of the cyst cavity. With endoscopic TGD, the indicators of the period of hospitalization were better, due to the low traumatism of this method and early rehabilitation, in comparison with other methods of surgical treatment. However, 1 month after the operation, a relapse of the disease occurred. In the late postoperative period, the same indicators in the internal drainage group were better than in the other group of patients.

Summing up the analysis of the results of PC treatment, we can say that the ED operations performed, although were less traumatic; however some disadvantages suchas long healing of residual cavities and a high incidence of pancreatic and purulent fistulas were observed. The use of the developed method of ORC guarantees the prevention of complications and ensures rapid healing of the residual cavity.

### CONCLUS ION

1. The choice of surgical intervention should be decided individually in each particular case.

2. Drainage operations are safe if there is an optimal ORC method.

3. With small-sized cysts, cystectomy is indicated.

4. With large and giant cysts, preference should be given to drainage operations.

Table 1. The number of patients and type of operations performed on pancreatic cysts

Type of Operation	Patients (n)	%	Average hospital stay, day,
			Me (5.95 percentiles)
ED (external drainage)	13	33	24 [18; 30]
Cystectomy — laparoscopically-open echinococcectomy and drainage of the choledochus by Keru	6 (5) (1)	8	16 [10; 21] p <sub>1</sub> <0,001
ED with ORC (extarnal drainage operations with obliteration of residual cavities)	7	18	13 [11; 15] p <sub>1</sub> <0,001; p <sub>2</sub> =0,035
Endoscopictransgastricdrainage (TGD)ofpancreaticcysts (PC)	5	13	11 [9; 15] p <sub>1</sub> <0,001; p <sub>2</sub> =0,011; p <sub>3</sub> =0,019
ID (internal drainage): Pancreatocystogastrostomy pancreatocystoejunostomy	5 9	13 23	9 [7; 13] $p_1 < 0,001$ $p_2 = 0,002;$ $p_3 < 0,001;$ $p_4 = 0,004$
In total	45	100	

**Note:** p1 is the level of statistical significance of differences compared with ED; p2 is the level of statistical significance of differences compared with cystectomy; p3 is the level of statistical significance of differences compared with ED with ORC; p4 is the level of statistical significance of differences compared with endoscopic trans-ventricular drainage of pancreatic cysts. The Kruskal Wallis criterion was x2=32.429, df=4, p<0.001.

#### Table 2. Long-term results in various operations

Type of operation	Patients (n)	%	Long-term results
	2	15,5	the presence of complaints and recurrence of the cyst
ED (outornal drainage)	3	23	the presence of complaints and residual cavity
ED (external drainage)	2	15,5	the presence of complaints, no cyst to be found
	6	46	No complaints and no cyst to be found
ED with ORC (external drainage operations with obliteration of residual cavities)	7	100	No complaints and no cyst to be found
Pancreatocystogastrostomy	5	100	No complaints and no cyst to be found
Pancreatocystoejunostomy	9	100	No complaints and no cyst to be found
Cystectomy	6	100	No complaints and no cyst to be found
	1	20	No complaints and no cyst to be found
Endoscopic transgastric drainage (IGD) of pancre- atic cysts (PC)	1	20	No complaints , the signs of residual cavity
	3	60	No complaints and no cyst to be found
In total	45		

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# OPTIMIZATION OF SURGICAL TACTICS BASED ON MORPHOLOGICAL CRITERIA FOR READINESS OF BURN WOUNDS FOR AUTODERMOPLASTY

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ABSTRACT — With the permission of the Ethics Committee of the Far Eastern Federal University and in accordance with Russian legislation and the Declaration of Helsinki (2013), immunohistochemical studies were carried out and morphological criteria were developed for the readiness of burn wounds for autodermoplasty with predicted efficacy. The aim of the study was to optimize active surgical tactics in the treatment of burns with the development of morphological criteria for determining the timing of effective autodermotransplantation. The analysis of the material in 4 groups of patients was carried out: group 1 with autodermotransplantation in the first 7 days (32 patients); 2nd group — after 7 to 14 days (24) and after 14 days due to the insufficient number of Lonor sites (4), as well as with the final covering of wounds even at a later date due to rejection and microbial contamination in the wound after 21 days (2 patients). It was found that the optimal time for complete covering of burn wounds is 7–8 days after thermal injury. On the 9–14<sup>th</sup> day, the conditions for autodermoplasty are preserved, but in the wounds the phenomena of scar tissue formation and vascular hardening occur. In terms later than 14 days after the injury, the conditions for autodermoplasty worsen, the effectiveness of treatment decreases and is accompanied by the healing of the tissue defect with scarring. Autodermoplasty after 2 weeks is accompanied by a decrease in reparative processes with the induction of pathological angiogenesis, an aggressive reaction of immunocompetent cells with non-infectious destruction and lysis of the graft, which requires significant correction of therapeutic measures.

**KEYWORDS** — skin, burns, regeneration, immunocytes/ phagocytes, restitution, autodermoplasty, active surgical tactics.

## RELEVANCE

Severe thermal injuries at the present stage remain one of the most difficult problems of clinical medicine, occupying the 3rd place in the general structure of injuries, and patients account for more than 10% of those injured in peacetime [1]. Burn size, accounting for more than 60% of the total area of the burned body surface, is associated with risks and mortality [2]. Improper initial treatment or delaying treatment may adversely affect subsequent outcomes. Major burn treatments and approaches include dressings, antimicrobials, fluid resuscitation, burn wound excision, skin grafts, and the use of skin substitutes [3]. With extensive severe and deep damage to the skin, along with detoxification and correction of metabolic disorders, immunocorrection and autodermotransplantation are necessary. [4].With deep second-degree and third-degree burns, the epidermis and appendages of the skin are destroyed, so that healing can only occur with severe scarring. In these cases, necrectomy and skin grafting are recommended [5]. The prognosis of the effectiveness of therapeutic measures depends on the chosen strategy and tactics for managing burn patients, based on determining the optimal surgical tactics and timely autodermoplasty [6, 7]. For successful healing and regeneration, stabilization of blood circulation is necessary, intensive infusion therapy. To eliminate the risk of infection, early necrectomy and skin grafts with exfoliation are performed. In addition, the success of treatment depends on other factors. The key issue is to determine the readiness of not only the burn wound for graft transplantation, but also the possibility of re-sampling of material from the donor site [8, 9]. An effective response to extensive burns requires well-coordinated institutional efforts and preparation for treatment with predictable results based on objective indicators [10], which determined the direction of our research.

#### The aim of the study

was to develop morphological criteria for the readiness of a burn wound for autodermotransplantation and a donor site for repeated sampling of material within the framework of modern standards and innovations for active surgical tactics in the treatment of burns.

# MATERIAL AND METHODS

With the permission of the Ethics Committee of the Far Eastern Federal University, studies were carried out on 62 patients aged 18 to 60 years with thermal burns who were treated at the Primorsky Burn Department of Far Eastern Regional Medical Center" (Russia) in the period from 2007 to 2016. The inclusion criteria were the presence of IIIA-IIIB burns with an area of 10 to 20% of the body surface, as well as deep IV degree burns, in accordance with the requirements of the Ministry of Healthcare of the Russian Federation dated 04.29.94 No. 82 and according to the nomenclature of clinical laboratory studies of the Ministry of Health of the Russian Federation (Order No. 64 of 02/21/2000 y.) taking into account the provisions of the Helsinki Declaration (2000–2013). The exclusion criteria were the presence of a large area of superficial I and II degree burns in the victims. Also used 16 biopsies of cadaveric material of the skin of patients without pathology. To study the dynamics of morphological changes in all patients, after obtaining a written voluntary consent, a biopsy material was taken from burn wounds under local anesthesia in the dynamics of healing during treatment of wounds according to clinical indications. The size of biopsies was no more than 1–2 mm<sup>3</sup>. Depending on the objectives of the study, the material was collected at different times. Depending on the timing of covering the burn wounds, all patients were divided into 4 groups: the first included victims who underwent the final stage of autodermoplasty in the first 7 days (32); Group 2 — after 7 to 14 days (24) and after 14 days due to the insufficient number of Lonor sites (4), and with the final covering of wounds even later after 21 days (2 patients). Potential homogeneous subgroups of dermal biopsies were investigated using cluster analysis in accordance with the principles of evidence-based medicine. A classical morphological research method was used with staining of sections with hematoxylin and eosin, followed by analysis of the obtained illustrative material. To quantify the regenerative potential of burn wound tissues, the expression of the Ki-67 gene was studied using a panel of mono- and polyclonal antibodies to this antigen, followed by staining with hematoxylin. Immunohistochemical identification of immunocompetent cells (Langerhans cells, macrophages, CD-4, CD-8) was carried out according to the same scheme, despite the different localization of the antigen in cellular structures: membranes, lysosomes, nuclei, Golgi complex. Retrospective assessment of the lesions was carried out according to the morphological features observed using the Olympus Bx 52 microscope. All patients received standardized treatment: infusion, antibiotic therapy, drugs for the prevention

of acute stress ulcers of the upper gastrointestinal tract, disseminated intravascular coagulation. In local treatment, an active surgical approach was followed in order to remove necrotic tissue as early as possible. Thus, surgical necrectomy was performed in 55 (88.7%) patients, necrolyticnecrectomy was performed in 5 (8.1%) patients, spontaneous rejection of a scab of some small wounds occurred in 33 (53.2%) burned patients. The data obtained were statistically processed on a PC using Excel 2010 for Windows 10.

### **RESEARCH RESULTS**

With extensive wounds (Fig. 1) against the background of an open skin defect, partially replaced by subcutaneous fatty tissue, healing occurs with the formation of fibrinous-purulent exudate. Suppuration should be considered as a process of biological cleansing of damaged tissue with the participation of bacterial proteases and macrophage hydrolases [11]. In burn wounds covered up to 7-9 days, the content of macrophages and Langerhans cells in biopsies obtained on border of autodermotransplant and intact skin. It was found that in the case of complete engraftment of the autodermotransplant, the content of Langerhans cells increases sharply starting from the first day after autodermoplasty, reaches a maximum value on the 3<sup>rd</sup> day and remains at a high level until the 7<sup>th</sup> day, which corresponds to the deployment of active processes of angiogenesis and engraftment of the skin graft. After the completion of the processes of formation of a single vascular network of the wound bed and autodermotransplant, the number of these cells decreases sharply and corresponds to those in normal skin. These data indicate the restoration of the barrier properties of the epidermis and a decrease in the number of antigen-presenting cells. The number of cells of the macrophage pool also decreases, which corresponds to the formation of a viable skin flap and a decrease in the number of contaminating microorganisms on the surface of the epidermis and necrotic cells that need to be utilized. It is noted that the success and effectiveness of the treatment are dependent on the timing of the treatment with autodermoplasty (Table 1; Fig. 2).

Re-autodermoplasty was successful after preparation of the wound surface and removal of granulations.

At the same time, it was noted that from the first to 7 days in the infiltrate and under the scab there is a high regenerative potential of keratinocytes, as well as a high content of CD4+ and macrophages expressing CD68. From 7 to 14 days, their number stabilizes, and, starting from the  $14^{th}$  day, decreases, which indicates the depletion of the regenerative potential. In the donor site, after taking the autodermotransplant, the high regenerative potential does not correspond to the



**Figure 1.** Patient on the  $2^{nd}$  day after admission; extensive burn wounds after severe thermal injury. Limited ability to take donor material. The need to re-take autodermotransplant from donor sites



Fig. 2. 10 days after admission to the hospital and treatment with active surgical tactics with necrectomy and autodermoplasty and early terms

<b>Table 1.</b> Ch	aracteristics	of the results of	f treatment of	deep burns de	epending or	n the timing of	<sup>c</sup> autodermopla:	sty
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Terms of the final stage	Complete engraftment of the graft		Partial lysis of the graft		Complete lysis of the graft	
of ADP (days)	Abs.	%	Abs.	%	Abs.	%
up to 7	32	81,3	2	12,5	1	6,3
9–14	23	76,9	2	15,4	1	7,7
Later 14 to 21 days	5	65,6	3	9,4	8	25
After 21 days	0	50	1	50	1	50

\*ADP — autodermoplasty

restoration of the barrier properties of the epithelium, therefore, the best indicators for re-sampling of the material reach on the  $9-10^{\text{th}}$  day.

## CONCLUSION

Adequate treatment of burn injuries, taking into account the data obtained and the recommendations developed on their basis, improves the outcome of thermal injury for patients. The rational introduction of methods for treating burn wounds using morphological criteria for the readiness of burn wounds for autodermotransplantation is recommended. Timely active surgical tactics can speed up the healing of burn wounds and increase the efficiency of autodermoplastat engraftment.

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# TO THE QUESTION OF CONNECTIVE TISSUE DISORDERS IN CHILDREN AND ADOLESCENTS WITH ORTHOPEDIC PATHOLOGY

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ABSTRACT — Clinical and histological changes were studied in 96 adolescents with knee pathology of non-traumatic genesis, with signs of connective tissue disease (CTD). The detection of connective tissue dysplasia was carried out according to the data of a clinical examination, functional and radiation diagnostic methods in accordance with the Russian recommendations for algorithms for the diagnosis and treatment of children with connective tissue disease (2015). Serial sections stained with hematoxylin and eosin were examined on an Olympus CX-41 microscope at a magnification of ×100, ×200, ×400. Some of the preparations were additionally stained with picrofuchsin according to van Gieson. Signs of a pronounced diffuse pathological process of a degenerative-dystrophic nature were revealed, caused by hypoxic and metabolic disorders, which led to the development of pain syndrome and became a reason for subsequent surgical intervention.

**KEYWORDS** — connective tissue disease, morphological changes, collagen fibers, chondrocytes.

### INTRODUCTION

The formation of surgical diseases in childhood is based on complex pathogenetic mechanisms associated with mesenchymal disorders. The clinical picture of these disorders often comes to the fore and determines the prognosis of the underlying disease[1, 3].

Modern studies of hereditary, congenital and some acquired diseases of the skeletal system have shown that most of them are based on violations of the molecular structure of a number of organic substances that make up the connective tissue. A systemic defect determines structural and functional disorders at the tissue level, which leads to pathological changes in various organs and systems of the body. The most common signs of dysmorphogenesis in CTD are changes in the skeleton, muscles and periarticular tissues. For many variants of CTD, a decrease in muscle mass and the size of muscle fibers of striated muscles is characteristic, which indirectly indicates atrophy of muscle tissue. Against the background of developmental anomalies of the lower extremities, systemic skeletal pathology and connective tissue disease, changes in the structures of the knee joint are noted in children and adolescents.

Previous histological studies of bone tissue in children with the syndrome of undifferentiated connective tissue disease revealed the predominance of osteocyticresorption and compensatory replacement of it with fibrous elements [6]. At the same time, local manifestations of lymphocytic infiltration of tendons and perimysiumwere accompanied mainly by osteoclasticresorption with compensatory osteogenesis in the endosteum. A direct dependence of the strength and function of connective tissue on the inflammatory and reparative process in collagen and elastin of tendons, muscles, bones and blood vessels has been established [2, 4].

Damage to the menisci of the knee joint is quite common in comparison with the entire pathology of the knee joint [5]. In the available literature, we did not find data on the relationship between the development of pathological processes in the knee joint in children and adolescents with variants of impaired connective tissue stability. Considering the fact that the number of detected dysplastic changes in the musculoskeletal system in childhood is growing annually in the world, this problem is becoming more and more important.

#### The aim of the study

was to assess morphological changes in the structure of connective tissue in children and adolescents with diseases of the knee joint of non-traumatic genesis.

#### MATERIAL AND METHODS

Biopsy material obtained intraoperatively during arthroscopy in 96 children and adolescents with phenotypic manifestations of connective tissue dysplasia of varying severity was studied. The selection criterion for the study was the presence of pathological changes in the knee joint in the form of pain syndrome, dam-

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age to the meniscus and anterior cruciate ligament of non-traumatic genesis against the background of signs of CTD. There were no syndromic forms of CTD of the type of Marfan, Ehlers-Danlos, etc. in the study group of patients. The severity of CTD manifestations was assessed according to the classification of T.I. Kadurina and V.N. Gorbunova. The age of children ranged from 11 to 17 years, girls — 51 (53.1%), boys — 45 (46.9%). There were no statistically significant gender and age differences.

Fragments of cartilaginous and fibrous tissue obtained intraoperatively were fixed in 10% buffered formalin solution, followed by histological wiring according to the standard technique and embedded in paraffin blocks. Serial sections stained with hematoxylin and eosin were examined on an Olympus CX-41 microscope at a magnification of  $\times 100$ ,  $\times 200$ ,  $\times 400$ . Some of the preparations were additionally stained with picrofuchsin according to van Gieson. We studied the morphological structure of the tissue, assessed the presence of hemodynamic disorders, inflammatory infiltration and dystrophic changes, as well as the number of solitary cells and the number of isogenic groups per unit area of unchanged cartilage tissue of the sections studied.

## **RESEARCH RESULTS**

Among the patients, mild severity of CTD was detected in 7 (7.3%) people, moderate severity — in 75 (78.1%), severe — in 14 (14.6%). There were no pronounced connective tissue disorders in patients with mild severity. In patients with severe manifestations of DST, morphological changes on the part of the connective tissue structure were manifested by a sharp thickening of collagen fibers with a chaotic arrangement and a violation of the architectonics of fibrillar structures in the form of pronounced sharp changes in shape and orientation, the appearance of spirally curved and fragmented areas with irregular outlines on transverse sections (Fig. 1).

Microscopy in all observations showed the usual structure of the articular cartilage with a well-visualized outer zone, with single flattened spindle-shaped chondroblasts located in the cartilaginous matrix, and a zone of young cartilage passing without a clear border into the zone of mature cartilage. In the middle and basal zones, chondrocytes were located in isogenic groups in the form of chains of rounded cells oriented perpendicular to the articular surface. In some fields of vision, uneven contours and areas of destruction of the articular surface were revealed, under which the structure of the cartilaginous tissue was distinguished by poorly distinguishable stratification and heterogeneity. Areas of thinning of the surface zone were noted. In the zone of young cartilage, against the background of the predominant intercellular substance, there were areas with a chaotic arrangement of cell nests of chondrocytes, some of which were enclosed in gaps (Fig. 2).

Cartilaginous cells were characterized by an uneven distribution of nuclei with symptoms of karyopycnosis and karyorrhexis. In the deeper layers, there was a proliferation of connective tissue with infiltration with single histiocytes, macrophages and lymphocytes, and a pronounced edema of the intercellular substance with the formation of cracks (Fig. 3). In areas of sclerosis, collagen fibers were colored most intensely. In some observations, against the background of disorganization of collagen fibers of the basic substance of cartilage, among collagen fibers with unevenly expressed tinctorial properties, foci of petrification in the form of polygonal basophilic deposits of calcium salts were noted. The revealed morphological changes are signs of degenerative-dystrophic processes accompanied by an inflammatory reaction.



**Fig. 1.** Biopsy of the connective tissue of the knee joint.Van Gieson staining with picrofuchsin, ×400. Violation of the architectonics of fibrillar structures

In normal articular cartilage, the processes of destruction and repair of tissues occur rather slowly, are strictly controlled, are in equilibrium and are the basis of physiological remodeling. Against the background of inflammatory and degenerative-dystrophic processes in the joint, there is a qualitative and quantitative change in the cells and intercellular matrix of the cartilage. The proliferative activity of chondrocytes decreases, the number of cells decreases, the production of proteoglycans practically stops, which entails the loss of water, degradation of the matrix and blocks regeneration.


*Fig. 2. Fibrous hyaline cartilage. Staining with hematoxylin and eosin,* ×200. *Chondrocyte nests separated by bundles of collagen fibers. Inhomogeneity of tinctorial properties of the extracellular matrix* 



**Fig. 3.** The synovial tissue of the knee joint. Staining with hematoxylin and eosin,  $\times 200$ . Edema and inflammatory infiltration of the intermediate substance



*Fig. 4.* The synovial tissue of the knee joint. Staining with hematoxylin and eosin, ×200.Petrification in the extracellular matrix

# CONCLUSION

The changes in the structure of the connective tissue of the knee joint in children with clinical manifestations of connective tissue disease indicate the presence of a pronounced diffuse pathological process of a degenerative-dystrophic nature caused by hypoxic and metabolic disorders resulting in pain syndrome and a subsequent surgical intervention.

CTD is a polysystemic pathology, which is based on defects in the synthesis and/or catabolism of the components of the extracellular matrix. The use of an integrated approach at the stage of surgical correction, taking into account the severity of CTD, allows not only to reduce the number of postoperative complications and relapses of the disease, but also to outline ways for the further development of approaches in the treatment of this pathology in childhood.

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# SPORTS AND MOVEMENT THERAPY FOR PATIENTS WITH TRAUMATIC EXPERIENCES

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ABSTRACT — RELEVANCE: Sport and movement therapies are indicated for patients of practically all specialties and can be defined as follows: the therapy is based on biological laws and comprises the elements of educational, psychological and social therapy methods and aimed at raising the patent's competence in preserving health. This paper deals with a novel method for treatment and rehabilitation of a number of diseases — boxing therapy. AIM: The paper provides evidence for effectiveness of using boxing therapy at such conditions as: burnout syndrome/stress, emotionally unstable personality disorder, depression, addictive disorders, anger, explosive personality disorder, Alzheimer's disease, Parkinson's disease and other conditions.

RESULTS: There is medical evidence for positive outcomes due to use of boxing therapy for such conditions as: perceptual disorders, anxiety, burnout syndrome/stress, listlessness, depression, addictive disorders, bilateral hemispheric stimulation for processing experiences of violence, increasing frustration tolerance, improvement of stamina, inner tension, for people with traumatic experiences.

Positive experiences are observed:

- With patients in forensic psychiatry,

- Patients with depression;

- Patients with borderline personality disorder;
- as an anti-aggression training with adolescents, etc.
- CONTRAINDICATIONS OF THE BOXING THERAPY ARE:
- Bipolar disorder in the manic phase
- Borderliner, self-injured, questionable...
- Eating disorders, anorexia, bulimia questionable...
- Osteoporosis
- Rheumatic diseases in acute phases
- CONCLUSION:

1. Boxing therapy unites both physical and psychological training. Boxing therapy noticeably boosts and

strengthens movement coordination, cognitive, motor and concentration functions, enables a better command over the body.

2. Further studies on the effectiveness of boxing therapy are required.

3. Boxing therapy should be widely used for such conditions where its effectiveness is substantiated.

4. Specialists for work as box therapists should be trained.

**KEYWORDS** — sport therapy, box therapy, depression, antiaggression training, rehabilitation.

# GRUNDLAGEN

Die Sporttherapie hat in den letzten 20 Jahren eine bemerkenswerte Entwicklung genommen. Das ist sicher auch der Tatsache geschuldet, das Ende der 1990er Jahre eine Ausbildung zum Sporttherapeuten in Deutschland eingeführt wurde, welche Interessenten ansprach, die bereits erfolgreich ein sportwissenschaftliches Studium absolviert hatten. [1, 2]

Leider wird der Begriff Sporttherapie oft noch falsch interpretiert und zwar dahingehend, dass man meint dabei werden Sportler therapiert. Das ist aber bei der Sportphysiotherapie so.

Die Sporttherapie wendet sich an alle Patienten fast aller medizinischen Fachgebiete und definiert sich wie folgt:

"Sporttherapie ist eine bewegungstherapeutische Maßnahme, die mit geeigneten Mitteln des Sports gestörte körperliche, psychische und soziale Funktionen kompensiert, regeneriert, Sekundärschäden vorbeugt und gesundheitlich orientiertes Verhalten fördert. Sie beruht auf biologischen Gesetzmäßigkeiten und bezieht besonders Elemente pädagogischer, psychologischer und soziotherapeutischer Verfahren ein und versucht, eine überdauernde Gesundheitskompetenz zu erzielen." (Deutscher Verband für Gesundheitssport und Sporttherapie 1992). [3, 4]



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In der konkreten Durchführung von sporttherapeutischen Therapieverfahren, ist es so das der Sporttherapeut entsprechend der ärztlichen Diagnosestellung bestimmte Übungen meist aus den sportlichen Training von entsprechend geeigneten Sportarten auswählt und daraus ein sporttherapeutischen Konzept entwickelt, es mit dem Arzt abstimmt und mit dem betreffenden Patient(en) in der Einzel — oder Gruppentherapie umsetzt [5, 6].

Elemente aus dem sportlichen Training folgender beispielhafter Sportarten kommen häufig zur Anwendung:

- Kraftsport als Medizinische Trainingstherapie (MTT)
- Klettern als Therapeutisches Klettern
- Aquafitness als Medizinische Aquatherapie (MAT)
- Gymnastik als Krankengymnastik (KG)
- Schwimmen als Therapeutisches Schwimmen
- Boxen als Therapeutisches Boxen

Bei dem letztgenannten Beispiel, Therapeutisches Boxen hat sich erfahrungsgemäß bei deren Einführung an der Medizinischen Hochschule Hannover, folgendes gezeigt: Das Therapeutische Boxen hatte gerade bei Patientinnen und Patienten mit psychomatischen Diagnosen eine besonders gute Therapiewirkung. Das ergab sich schon bei dem Beginn dieser für die allermeisten Patienten neuen Therapieform. Eine besondere Fazination hat dabei offensichtlich der Boxhandschuh selber ausgeübt. Denn kaum war dieser übergestreift konnte man förmlich eine Veränderung bei fast allen Teilnehmern verspüren. Sie fühlten sich nicht mehr als Patienenten, sondern als "Sportler" in diesem fall als "Boxsportler". Auch Patienten, zu denen man sonst schwer einen Zugangang fand da sie sehr introvertiert oder depressiv waren, gingen aus sich raus begannen zu erzählen, dass sie früher oft Boxen im TV geschaut haben oder fingen an im Boxerstil zu tänzeln. Somit war natürlich auch eine sehr gute Ausgangsposition für das nachfolgende Training gegeben.

Die Resonanz auf die Einführung des Therapeutischen Boxens an der MHH war so überwältigend, dass Peter Klug, Sportwissenschaftler & Sporttherapeut, auf dessen Initiative das Therapeutische Boxen an der MHH eingeführt wurd, beauftragt wurde eine Fortbildung, mit Ärzten und Therapeuten der Klinik für Rehabilitationsmedizin der MHH, zum Thema Therapeutisches Boxen durchzuführen. Diese Veranstaltung wurde so gut bewertet und angenommen, das sie wiederholt werden musst und ein entsprechender Artikel im Fachmaganzin der Medizinischen Hochschule Hannover (MHH) MHH-Info 06/2020 publiziert wurde. Ein Grund für diesen großenartigen Erfolg ist natürlich auch die solide Ausbildung der MHH Boxcoaches im PITT Institut Hannover durch Ulrike Angermann.

Ein weiterer Grund ist sicherlich das, gerade beim Therapeutischen Boxen alle motorischen Grundeigenschaften, wie Kraft, Schnelligkeit, Ausdauer, Beweglichkeit und die Koordination mit dem sicherlich wichtigsten Einfluss, abgefordert und damit natürlich auch trainiert und ausgebildet werden. Nicht zu vergessen die Myokine, welche bei jedem sportlichen Training ausgeschüttet werden, sie sind Botenstoffe, die der Körper vermehrt bei intensiver Muskelbeanspruchung ausschüttet. Sie stoppen beispielsweise Entzündungen und regulieren die Immunabwehr und haben auch positiv regulierende Eigenschaften beim Glykogenstoffwechsel und Lipidstoffwechsel [7–13].

Es kommt generell bei einem sportlichen Training von circa 30 bis 60 Minuten zu einer Verbesserung der Durchblutung in der Muskulatur, aber auch ein deutlicher Anstieg der Durchblutung im Gehirn. [14, 15, 16, 17] Dabei wird vermehrt eine Vielzahl von Botenstoffen im Gehirn gebildet sowie ausgeschüttet und hat dadurch den psychologischen Effekt einer stimmungsaufhellenden und schmerzdämpfenden Wirkung. Das betrifft wichtige Neurotransmitter wie Noradrenalin, Serotonin und Dopamin. Es werden darüber hinaus vermehrt bestimmte Proteine gebildet, die in einigen Hirnteilen das Aussprossen von Nervenzellen (Neuroplastizität) und die Bildung kleinster Blutgefäße (Kapillarisierung) fördern. [18, 19, 20, 21, 2]

Für das Gedächtnis, aber auch der Konzentrations- und Aufmerksamkeitsleistung ist der Teil des Gehirns, der Hippocampus, wichtig. In verschiedenen experimentellen und klinischen Studien konnte gezeigt werden, dass körperliches Training eine Vergrößerung des Hippocampus bewirken kann. Diese Größenzunahme stand statistisch mit einer Besserung der Symptomatik bei Patienten, die unter einer Erkrankung des schizophrenen Formenkreis litten, in Zusammenhang. Beim Sport werden zudem Endorphine (Endogene Morphine), die sogenannte Glückshormone, ausgeschüttet und auchkörpereigene Angsthemmer, wie das Peptid ANP (auch B-type natriuretic Peptide oder natriuretisches Peptid Typ B genannt) [23, 24, 25].

## TRAININGSSTEUERUNG

Der Trainingsteuerung beim therapeutischen Boxen obliegt eine besondere Betrachtung, welche sich vom Trainingsziel ableitet! Generell folgt jede Bewegungstherapie in ihren Prinzipien der Trainingslehre und der Sportwissenschaft bzw. der Sporttherapie, welche sich ja, wie der Name schon sagt, mit Elementen aus verschiedenen Sportarten und deren speziellen Trainingsinhalten bedient und therapeutisch nutzt.

Beim therapeutischen Boxen sollte man deshalb diagnosebezogen 3 Gruppen unterscheiden. Patient\*innen/Klient\*innen mit psychiatrischen und psychosomatischen Diagnosen als eine Gruppe und Patient\*innen mit anderen Diagnosen z.B. aus den Bereichen Orthopädie, Rheumatologie, Traumatologie oder Neurologie als eine zweite Gruppe. Klient\*innen, die therapeutisches Boxen als Prävention betreiben, sind dann einer 3. Gruppe zuzuordnen.

Während man in den Gruppen 1 und 2 zunächst mit Bewegungs- und Anbahnungstraining beginnen sollte, können in Gruppe 3 gleich überschwellige Belastungsreize zur Leistungssteigerung in der Superkompensation (ist jene Anpassungsreaktion der belasteten Struktur mit einer Leistungssteigerung die in der Wiederherstellungsphase auf überschwellige Trainings- oder Belastungsreize erfolgt.

Entscheidend ist aber bei jedweden therapeutischem Boxen, die richtige Dosierung des Belastungsumfanges und der Belastungsintensität und natürlich auch die gut aufeinander abgestimmte Auswahl der Trainingselemente, denn hier liegen schon sehr entscheidende Punkte für den Erfolg des Trainings/Therapie oder im schlimmsten Fall auch des Misserfolges zum Beispiel das Überfordern (Gefahr von Verletzungen) oder das Unterfordern (Ausbleiben von Trainingserfolgen). Beides hätte sicher einen Motivationsrückgang der Trainierenden zur Folge und sollte unbedingt vermieden werden. Deshalb sollten wir beim therapeutischen Boxen zunächst bei Beginn des Trainings/Therapie, den Bereich der moderaten Trainingsreize verwenden und dann später den Bereich der günstigen Trainingsreize verwenden und die optimalen Trainingsreize dem Wettkampf- und Leistungssport überlassen, da hier wie die folgende Abbildung zeigt der Grat zum Übertraining sehr schmal ist.

Um die gerade beschriebene Fehlsteuerung (Über oder- Unterforderung) im Training zu vermeiden, sollte man das jeweilige Leistungsniveau des oder der Trainierenden kennen oder entsprechend testen. Dazu eignet sich sehr gut ein Stufentest auf einem Fahrradergometer oder andere Ausdauertests mit der Selbsteinschätzung über die Borg Skala. Mit der Borg Skala kann man sogar über die Pulskontrolle die Objektivität bewerten.

Wobei die Basis für jede boxtherapeutische Intervention zunächst eine eindeutige Diagnose der zugrunde liegenden Störung sein muss. Ebenso sollte die entsprechende Eignung für das therapeutische Boxen vorhanden sein, sowohl physisch als auch mental, hier sind auch alle vorhandenen Kontraindikationen abzuklären! (siehe Kapitel Kontraindikationen)

Das therapeutische Boxen hat nicht das Ziel boxsportliche Fähigkeiten zu entwickeln und zu perfektionieren sondern mit ausgewählten Elementen aus dem Repertoire des Boxtrainings, genau die Elemente anzuwenden, die dem Erreichen des Trainings bzw. Therapieziel am sinnvollsten erscheinen. Hierbei hat der jeweilige Kursleiter bzw. Therapeut eine sehr hohe Verantwortung der er am ehesten gerecht werden kann je höher seine Fachwissen auf dem Gebiet des therapeutischen Boxens ist. Ebenso spielt eine hohe Sozialkompetenz eine große Rolle bei der Trainingsgestaltung also der Umsetzung der Trainingsplanung (siehe Anhang, beispielhafter Rahmentrainingsplan für das therapeutische Boxen). Wobei man hier wieder unterscheiden sollte ob man Patient\*innen in einer Klinik trainiert, die nur eine bestimmte Zeit z.B. 10 Wochen zu trainieren sind. In diesem Fall sollte ein Rahmentrainingsplan für diesen Zeitraum erarbeitet und entsprechend umgesetzt werden. Anders sieht die Trainingsplanung für Trainierende z.B. in der Nachsorge oder in der Prävention aus, die ein oder mehre Jahre zum Training kommen. Hier sollte dann schon eine Zyklisierung bzw. Jahresperiodisierung des Trainings erfolgen,

Nähe-Distanz-Verhalten. Das Therapeutische Boxen kann auch eine Alternative zu selbstverletzendem Verhalten sein. Beim therapeutischen Boxen boxen die Klient\*innen nicht gegeneinander, sondern mit Materialien, wie z.B. Doppelendbällen, Boxsack, Wandschlagkissen oder Pratzen. Es wird mit auf Krankheitsbildern / Beschwerden wird mit den entsprechenden Materialien gearbeitet.

Beim therapeutischen Boxen wird das Augenmerk auf das Erleben gerichtet, nicht auf die bloße Umsetzung der Technik. Es geht nicht um sportliche Leistung, sondern um Erleben, Wahrnehmung und persönliche Entwicklung.

Sinn des therapeutischen Boxens ist es, den Zusammenhang des persönlichen Themas zu entdecken. Die Frage lautet also: was haben die Erfahrungen in der Boxübung mit meinem persönlichen Thema zu tun? Wichtig ist hier, dass die Klient\*innen selbst den Zusammenhang erkennen.

Für wen ist das therapeutische Boxen geeignet? Das therapeutische Boxen ist u.a. für Klient\*innen mit folgenden Krankheitsbildern / Beschwerden geeignet:

- Burnout-Syndrom / Stress
- Emotional-instabile Personlichkeitsstörung
- Depressionen
- Suchterkrankungen
- Wut
- Explosive Persönlichkeitsstörung
- Alzheimer

— Parkinson

- Sinnvolle boxtherapeutische Intervention (Indikationen) bei:
- Wahrnehmungsstörungen
- Angst
- Stress/Burnout
- Antriebslosigkeit
- -Depressionen
- Verarbeitung von Gewalterfahrungen
- Verarbeitung von Wuterfahrungen
- Erhöhung der Frustrationstoleranz
- Verbesserung des Durchhaltevermögens
- Innere Anspannung
- Für Menschen mit traumatischen Erfahrungen
- Suchterkrankungen
- Bilaterale Hemisphärenstimulation

## Positive Erfahrungen:

- mit Patienten in der forensischen Psychiatrie
- Patienten mit Depressonen
- Patienten mit Borderline Persönlichkeitsstörung
- als Anti -Aggressionstraining mit Jugendlichen, etc.

## Kontraindikationen

- Bipolare Störung in der manischen Phase
- Borderliner, Selbstverletzter, fraglich...
- Eßstörungen, Anorexie, Bulemie fraglich...
- -Osteoporose
- Rheumatische Erkrankungen im akuten Schub
- Mit aktuell wahnhaften Patient\*innen sollte nicht gearbeitet werden, da hier eine Reizüberflutung droht.

Das therapeutische Boxen hat sich vor allem bei Klient\*innen mit Depressionen und Borderline-Persönlichkeitsstörungen bewährt. Es eignet sich für Patient\*innen mit Suchterkrankungen, Posttraumatischen Belastungsstörungen (PTBS) und als Wutbewältigung mit Jugendlichen und Erwachsenen. Schon im Kindesalter wird uns beigebracht, Wut nicht auszuleben. Das kann zu Depressionen führen. Wut auszuleben ist wichtig, doch es gilt, das richtige Maß zu finden. Ein depressiver Klient fühlt sich antriebslos, hat wenig Durchhaltevermögen. Die Bewegungen sind verlangsamt, der Muskeltonus ist herabgesetzt, sodass die nötige Spannung zur inneren und äußeren Aufrichtung fehlt. Bei Patient\*innen mit einer Borderline Persönlichkeitsstörung treten veränderte (Körper-) Wahrnehmungen auf, wie z.B. eine verminderte Schmerzwahrnehmung unter bestimmten

Umständen. Ziele des therapeutischen Boxens sind deshalb, den Körper zu aktivieren, die innere Anspannung zu reduzieren, die Körperwahrnehmung zu verbessern sowie Affekte und Gefühle besser wahrzunehmen und zu steuern, sofern der Patient stabil genug ist und sich darauf einlassen kann.

# FAZIT

- Beim Boxtraining handelt es sich sowohl um ein physisches als auch um ein psychisches Training. Das Boxtraining fördert und stärkt insbesondere beim therapeutischen Boxen:
- die Bewegungskoordination
- -kognitive Fähigkeiten
- Leistungs- und Konzentrationsfähigkeit
- motorische Abläufe
- Körperbeherrschung
- die Kondition
- 2. Die Forschung über die Auswirkungen der Boxtherapie auf Krankheiten sollte fortgesetzt werden.
- Die Boxentherapie sollte bei den Erkrankungen, bei denen sie sich als wirksam erwiesen hat, in größerem Umfang eingeführt werden.
- 4. Die Ausbildung von Fachleuten in der Boxentherapie sollte eingeleitet werden.

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# A COMBINATION TREATMENT FOR CHRONIC PERIODONTITIS ASSOCIATED WITH DYSBIOSIS OF ORAL MICROBIOTA AND ASSESSMENT OF ITS EFFECTIVENESS

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ABSTRACT — The high virulence of periodontal pathogenic bacteria, progression of chronic periodontitis in patients with comorbidities not always treated efficiently with conventional therapies, may result in oral dysbiosis. In this connection, the development of new pathogenetically oriented treatment methods and their improvement is of both theoretical and practical interest to the dental community. AIM: to improve the algorithms for the treatment of periodontitis associated with comorbidities and to assess its effectiveness using an immobilized synbiotic developed by the authors. METHODS: clinical, microbiological, analytical, and statistical methods were used in our study. The study included clinical examination and treatment of 93 patients of both genders (37 female and 56 male patients) between 18 and 65 years old with moderate generalized chronic periodontitis. The results confirm the effectiveness of adding the proposed symbiotic to the treatment of chronic periodontitis with underlying gastrointestinal, endocrine and cardiovascular diseases in oral administration to restore the gut microbiota as well as applied locally in the periodontal pocket.

**KEYWORDS** — periodontitis, microbiocenosis, dysbiosis, probiotics.

# INTRODUCTION

Periodontal diseases are the most common dental diseases in any age group: they occur in 40% of young dental patients, and 90% and 100% of middle-aged and elderly patients, respectively [1]. The inflammation of tissues is characterized by remaining undetected at early stages, developing chronically, having short remission periods and frequent relapses, progressing rapidly, and being difficult to treat [2, 3]. In recent

years, periodontal diseases have often developed in patients with comorbidities, thus exacerbating the underlying condition which in turn accelerates tooth loss, causing significant morphofunctional changes of the mastication apparatus [4, 12–14]. Periodontal pathogens of red and orange complexes, characterized by an invasive growth process, form complex relationships with each other inside the microbiota and affect the immune system, causing systemic inflammatory and degenerative processes [5-7]. Because of that, the existing options for the treatment of periodontitis with underlying pathology are not always efficient as they do not take into account the pathogenesis of diseases. This is why the development of new pathogenetically-oriented methods for the treatment of periodontitis with underlying pathology and dysbiosis is a critical task, and the development of means for determining oral microbiota composition is a promising area of dentistry.

## The objective of the study

is to improve the algorithms of the combination treatment of periodontitis in patients with comorbidities.

## MATERIALS AND METHODS

The study included the clinical examination and treatment of 93 patients of both genders (37 female and 56 male patients) between 18 and 65 years old with moderate generalized chronic periodontitis. The patients were divided into 2 groups according to the treatment regimen: the first group (control group) included 32 patients of both genders (15 female and 17 male patients) between 18 and 65 years old with moderate generalized chronic periodontitis and underlying chronic pathology (gastrointestinal, endocrine and cardiovascular diseases) who received only the basic treatment, including desensitizing, non-steroidal anti-inflammatory drugs and general tonics; the second group (treatment group) included 61 patients (25 female and 34 male patients) with moderate generalized chronic periodontitis, with similar age, gender and comorbidity distribution, who received not only the basic treatment but also the proprietary immobilized multistrain synbiotic "LB-complex L"

(Patent No. 2441907, priority date: July 29, 2010, Certificate of State Registration No. RU.77.99.88.003 .E.002.522.06.18) — both for oral administration and local application.

"LB-complex L" is a fourth-generation probiotic supplement — a consortium of living antagonistic active strains of bifidobacteria (3 strains) and lactobacilli (3 strains) immobilized on zeolite (an enterosorbent). Zeolite is volcanic sediment and a unique mineral sorbent. In "LB-complex L", microorganisms and zeolite particles are in direct contact with each other, with bacteria forming biofilms on the crystal surface. The microorganisms are released in the intestine, with the sorbent acting as a detoxicating agent. The probiotics were administered orally, with a dosage of 10 ml/day in one or two doses for 25 days, and locally — injected into a periodontal pocket with a dosage of 0,1–0,2 ml and then covered with a Diplen-denta film, for 14 days.

The clinical examination and treatment of patients were based at Dentistry Department, Privolzhsky Research Medical University. The quantitative and qualitative analysis of gut and periodontal pocket microbiota was carried out at the Laboratory of Microbiome Analysis and Restoration, Academician Blokhin Research Institute of Epidemiology and Microbiology (Nizhny Novgorod, Russia).

#### *Research methods:*

clinical, microbiological, analytical, and statistical methods.

The examination of a periodontal patient included standard examination with a periodontal probe, assessment of periodontal indices, and filling the patient's medical record. Experts assessed the periodontitis condition before the treatment, immediately after the treatment course, and 6 months later.

Oral hygiene was assessed using the simplified oral hygiene index (Green-Vermillion, 1964). Bleeding was measured using the Muhlemann-Son Sulcus Bleeding Index (SBI) which is based on assessing bleeding from the gingival sulcus on probing. The degree of inflammation was visualized by calculating the associated periodontal index (API). The API is designed by the study authors and is based on assessing the following factors: gum inflammation, sulcus bleeding on probing, the depth of periodontal pockets, the degree of tooth mobility, and gum recession.

The quantitative and qualitative assessment of the gut biocenosis was conducted using the unified methodology of colon microbiota assessment and evaluation [10, 11].

The quantitative and qualitative assessment of the periodontal pocket microbiocenosis was conducted

according to the following procedure: No oral hygiene procedures were conducted before the sampling. The material was sampled from the periodontal pocket using a single-use polystyrene sterile inoculating loop No. 2 in the volume of 1  $\mu$ l (0.001 ml) and a needle produced by Nuova Aptaca SRL, Italy. After that, the material was suspended in Eppendorf tubes with 0.09 ml of Haenel buffer solution for obtaining a  $10^{-2}$ dilution, and the loop was placed into a sterile polymer test tube with an anaerobic transport medium (Stuart medium, China). The material was delivered to a laboratory within 2 hours of being taken. The 10<sup>-2</sup> solution was used for inoculation on plating media: chocolate agar, Endo-GRM agar, Enterococcus Agar, Sabouraud agar No. 2 produced by State Research Center for Applied Microbiology and Biotechnology, Obolensk, Russia.

The inoculation was performed according to the following procedure: the material was spread with a 3 mm loop in the A sector, then the loop was flamed, and four linear streaks were made from sector A to sector I. The same method with loop flaming was used for re-inoculation from sector I to sector II, and from sector II to sector III [8].

The inoculants were incubated aerobically at  $37\pm1^{\circ}$  C for 24–48 hours.

The same method was used for the inoculation of the 10<sup>-2</sup> solution on Schaedler agar (BBLTM Schaedler agar, Becton Dickison, USA), Clostridial agar (M497 HiMedia Laboratories Pvt. Limited, India) and agar MRS-4 (Pharmacotherapy Research and Development Center, Saint Petersburg). Specimens were inoculated from the anaerobic transport medium to a bile esculin plating medium with the introduction of a selective supplement for anaerobic bacteria — Bacteroides Bile Esculin Agar (M805; FD062 HiMedia Laboratories Pvt. Limited, India), Schaedler agar, Clostridial agar, and MRS-4. The inoculants were incubated anaerobically at  $37\pm1^{\circ}$  C for 72-96 hours. Incubation was performed using the GasPak Anaerobe Gas Generation Pouch System with Indicator (Becton Dickinson, USA).

After the incubation, the number of bacteria colonies was counted in each sector, with the identification of 4–5 colonies of each species. For bacteria identification, a Bruker Autoflex speed MALDI-TOF mass spectrometer was used with Biotyper software. The preparation of daily culture samples was conducted according to the standard direct deposition method presented in the user manual: a sample was applied to three target cells, a matrix solution was deposited ( $\alpha$ -CHCA)) and dried up, and then combined mass spectra were obtained automatically for each cell. The mass spectra

were identified, recorded, processed, and analyzed using the BioTyper RTC software. The reliability of identification was determined by the score values (2,000– 3,000 — species identification, 1,999–1,700 — genus identification, 1,699–0 — not reliable identification) and consistency categories (A — species consistency, B — genus consistency, C — no consistency.

The number of identified microorganisms of each species was counted according to Table 1.

Table	<b>1.</b> A	lssessment	oftl	he mi	crot	oial	content of	period	ontal	pock	ets
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Number of colon ganism species i	Amount of each type of microorganism in 1 ml of separable gingi- val pocket, CFU/ml			
A	I	ll	III	
1–6	-	-	-	< 104
8–20	-	-	-	$3\cdot 10^4$
20-30	-	-	-	5 · 10 <sup>4</sup>
30–60	-	-	-	1 · 10 <sup>5</sup>
70–80	-	-	-	5 · 10 <sup>5</sup>
100-150	5–10	-	-	1 · 10 <sup>6</sup>
Can't count	20-30	-	-	5 · 10 <sup>6</sup>
Can't count	40-60	-	-	1 · 10 <sup>7</sup>

The quantitative and qualitative characteristics and the dysbiosis of periodontal pocket microbiocenosis were assessed according to an article by N.A. Sakharuk [9].

The treatment included the removal of supragingival and subgingival calculus, oral hygiene instruction and control, gingival curettage (if medically required), the correction of traumatic occlusion, the splinting of mobile teeth, and antiseptic treatment (using chlorhexidine 0.05% antiseptic solution).

## RESULTS

The clinical examination and index assessment showed poor oral hygiene, high Muhlemann-Son Sulcus Bleeding Index, and API index in 98% of patients with moderate generalized chronic periodontitis.

The pre-treatment analysis of oral hygiene assessment in patients with moderate generalized chronic periodontitis showed mineralized and nonmineralized dental plaque. The oral hygiene index was  $3.8\pm0.08$  points for the control group patients, and  $4.1\pm0.06$  points for the treatment group patients, which indicates poor oral hygiene in all patients. Immediately after the periodontitis treatment, oral hygiene instruction and control, the oral hygiene of patients in both groups improved significantly — to  $0.6\pm0.07$  points in group 1 and  $0.8\pm0.07$  in group 2, which indicates good oral hygiene. The check-up examination 6 months after the treatment showed a slight worsening of the oral hygiene level. Still, the average oral hygiene level of the treatment group patients is considered good even though it is close to the satisfactory level ( $1.2\pm0.04$  points), and the level of the control group patients is considered satisfactory ( $1.6\pm0.03$  points).

Hygiene index

Diagram 1. Comparative assessment of the hygiene index

The condition of periodontal tissue improved, including a reduction in bleeding determined by the Muhlemann-Son Sulcus Bleeding Index. Before the treatment, the treatment group patients showed bleeding of high severity —  $2.1\pm0.04$  points and the control group patients had bleeding of moderate severity —  $1.9\pm0.03$  points. After the periodontal treatment, the level of bleeding decreased in both groups: to  $1.1\pm0.04$ points in group 1 and  $1.3\pm0.02$  points in group 2, which indicates bleeding of moderate severity. The check-up examination after 6 months indicated good tissue condition among the treatment group patients —  $0.8\pm0.05$  points, and bleeding of moderate severity among the control group patients —  $1.3\pm0.04$  points.



**Diagram 2.** Comparative assessment of the Muhlemann-Son Sulcus Bleeding Index

The pre-treatment associated periodontal index was  $8.7\pm0.09$  in the first group and  $9.2\pm0.12$  points in the second group, which indicates moderate severity of periodontal disease, although getting closer to high severity in the second group. After the treatment, the API decreased to  $7.6\pm0.08$  points in the first group and  $7.9\pm0.10$  in the second group. Six months later, the API in both groups decreased — to  $7.1\pm0.11$  points in the control group and to  $6.6\pm0.09$  in the treatment group which indicates moderate periodontitis. However, the fact that the average API in the treatment group is closer to the lower boundary of moderate severity, can be considered as a sign that there is no inflammation or at least that it has decreased significantly.



Diagram 3. Comparative assessment of the associated periodontal index

Before the treatment, bifidobacteria were present in the fecal microbiota of 100% of patients from both groups, with 37.5% of patients having a low level of bifidobacteria: 10<sup>6</sup>–10<sup>7</sup> CFU/ml. The most prevalent species were B.longum (75%), B.adolescentis (62.5%), and B.bifidum (33.3%). B.dentium, B.pseudocatenulatum, B.animalis, B.catenulatum, B.angulatum were detected in individual cases. Bacteria of the Lactobacillaceae family were detected only in 70.8% of patients, with a concentration of less than 107 CFU/ml in 29.1% of patients. 21% of patients had no lactobacilli in their colon microbiota. Most often, the following species were detected in fecal microbiota: L.gasseri (45.8%), L.paracasei и L. vaginalis (29.1%) L.oris (25%), L.crispatus and L.salivarius (20.8%). Bacteria of other genera and species were detected in individual cases. The quantity Bacteroides spp. was low in 91.6% of patients, at the level of 10<sup>8</sup> CFU/ml — in 41,6%. B. uniformis and B.ovatus (33.3%), B.vulgatus and B.thetaiotaomicron (25%) were the most prevalent species. E.coli was detected in all patients, with a low concentration of 106 CFU/ml and less in 41.6% of patients. Lactose-negative coliform bacteria were detected in 4.2% of patients. Enterococci were

detected in 50% of patients (10<sup>5</sup>–10<sup>8</sup> CFU/ml). Most often, E.faecalis (33.3%) and E.faecium (16.6%) were detected in fecal microbiota. Various species of the Clostridium genus were identified in 52.6% of patients at concentrations within 10 CFU/ml which is considered normal. In individual cases, higher concentrations of C.innocuum (10<sup>6</sup> CFU/ml) and C.perfringens (10<sup>7</sup> CFU/ml) were identified. S.aureus was identified in 12.5% of patients. Coagulase-negative staphylococci were found in 41.2% of patients, with a concentration of over 10<sup>5</sup> CFU/ml in 12.5% of patients. Significant levels of opportunistic pathogenic Enterobacterales  $(>10^{5} \text{ CFU/ml})$  were identified in 45.8% of patients, most often — Enterobacter cloaceae (16.6%) and Klebsiella pneumoniae (12.5%). Proteus mirabilis, M.morganii, Raoultella ornithinolytica, and Citrobacter freundii were detected less often and in lower quantities. Yeast-like fungi of the Candida genus were identified in the colon microbiota of 70.8% of patients. The most prevalent species (with concentrations of  $10^{5}$ – $10^{7}$  CFU/ml) were C.kefyr and C.lusitaniae. C.albicans was identified more often — in 54.2% of patients but at lower levels of  $10^2 - 10^4$  CFU/ml. C.crusei, C.tropicalis, C.guillermondii, C.parapsilosis, C.dublinensis, and C.glabrata were identified in individual cases. Non-fermenting gram-negative bacilli were detected in significant quantities (>10<sup>5</sup> CFU/ml) in individual cases, including P.aeruginosa, Acinetobacter lwoffii, and Comamonas testosteroni. The following Streptococcus species were detected in significant quantities (10<sup>6</sup>–10<sup>7</sup> CFU/ml): S.lutetiensis, S.pleomorphus, S.salivarius, S.sanguinis, S.gallolyticus, S.vestibularis, and S.parasanguinis, as well as Collinsella aerofaciens, Eggerthella lenta, and Streptomyces lavendulae. It should be noted that although the above-mentioned Streptococcus species were only identified in individual cases, some species of Streptococcus bacteria were detected in 45.8% of patients. Pre-treatment assessment of the overall colon microbiota condition showed grade I dysbiotic disorders in 50% of patients, grade II disorders in 33.3% of patients, grade III disorders in 8.3% of patients, and normal microbiocenosis in 8.3% of patients.

After the treatment, control group patients did not show any positive dynamics in restoring the microbiocenosis. Having undergone the combination treatment, the treatment group patients showed an increase in bifidobacteria and lactobacilli in colon microbiota to  $10^8-10^9$  CFU/ml in 94.7% and 100% cases, respectively. Bacteroides spp. was detected in 100% of patients, at the level of 108 CFU/ml — in 73.6% of patients. Opportunistic microorganisms of the Enterobacterales order and Staphylococcaceae family were detected in significant quantities (>10<sup>5</sup> CFU/ml) in 15.7% of the treatment group patients and 45.8% of the control group patients. After the treatment, yeastlike fungi of the Candida genus were only identified in 47.3% of the treatment group patients, while no such positive dynamics were observed in the control group (70.8%). After the treatment, microbiocenosis recovered in 87.5% of the treatment group patients, with improvements in the condition of the remaining 12.5%: pronounced grade III and II dysbiosis disorders improved to mild grade I disorders.

Pre-treatment bacteriological examination of the periodontal pocket showed that S.aureus was detected in the quantities of  $10^3 - 10^6$  CFU/ml in 16.6% of patients of both groups. Coagulase-negative staphylococci were found in 66.6% of patients. The most common bacterium is S.epidermidis (37,5%), the ones present in the largest quantity (105-106)CFU/ml) were S.epidermidis, S.warneri, S.xylosus, and S.felis. Neisseria were detected in 87.5% of patients in the amount of  $10^3$ – $10^6$  CFU/ml. The most prevalent of the 12 identified Neisseria species were N.mucosa (33.3%), N.flavescens and N.elongata (29.1%), as well as N.macacae (25%). The genus represented by the largest number of species was Streptococcus, with 21 species identified. In most cases, S.oralis (83.3%), S.sanguinis (66.6%), S.vestibularis (62.5%), S.pneumoniae (58.3%), S.anginosus (54.1%), and S.salivarius (50%) were identified. S.sanguinis, S.cristatus, S.psudopneumoniae, and S.gordonii were detected in the largest quantities  $(10^7 \text{ CFU/ml})$ . Bacteria of the Lactobacillaceae family (17 species) were mostly detected at the level of  $10^3$  CFU/ml. In most cases, L.gasseri (25%), L.paracasei (16.6%), and L.oris (12.5%) were identified. Haemophilus bacteria were detected in 16.6% of patients in the amount of  $10^4$ – $10^7$  CFU/ml. Yeast-like fungi of the Candida genus were identified in 25% of patients. C.albicans, C.lambica, C. lusitaniae, and C.kefyr were detected equally often in the quantities of 105–107 CFU/ ml. Bacteria of the Veillonella genus were detected in 95.8% of patients. V.parvula was identified in 66.6% of patients, V.atypica — in 29,2% of patients. Two-thirds of the Veillonella spp. identified in the periodontal pocket were present in the quantities of 10–10<sup>4</sup> CFU/ml. 12 species of the Prevotella genus were detected, with P.nigrescens, P.oralis, and P.denticola present in the quantities of 10<sup>5</sup> CFU/ ml. The quantity of other Prevotella species was in the range between 10 and 10<sup>3</sup> CFU/ml. Among the Actinomyces genus bacteria, the most common species were A.naeslundii (37.5%), A.odontolyticus (29.2%), and A.oris (25%), with a wide range of quantity between 10 and 107 CFU/ml. 45.8% of specimens contained Fusobacterium nucleatum in the

quantity of 10<sup>3</sup>–10<sup>5</sup> CFU/ml. Also, Selenomonas spp. was identified in 25% of patients, mostly in the form of S.noxia and in the amount of 105 CFU/ml; single Clostridium spp. cells — in 20.8% of patients; Rothia mucilaginosa in the quantities of 10<sup>3</sup>–10<sup>5</sup> CFU/ml — in 16.6% of patients, and Capnocytophaga spp. in the quantities between 10 and 105 CFU/ml — in 16.6% of patients. Other bacteria (over 40 genera, each including between one and four species) were detected in individual patients, forming their individual microbiota profiles.

Pre-treatment assessment of the overall periodontal pocket microbiota condition showed grade I dysbiotic disorders in 29.2% of patients, grade II disorders in 45.8% of patients, and grade III disorders in 25% of patients.

After the basic treatment, 15.7% of the control group patients showed normal microbiota condition, 59.2% — grade I dysbiotic disorders, and 25% grade II dysbiotic disorders, with no patients having grade III dysbiotic disorders.

After the treatment, the number of treatment group patients with staphylococci decreased. S.aureus was identified in 10.5% of patients, with its concentration not exceeding 104 CFU/ml. The number of coagulase-negative staphylococci decreased, with only S.capitis and S.epidermidis detected in the quantities of 10<sup>3</sup>–10<sup>4</sup> CFU/ml. The most common Neisseria species were N.flavescens (42.1%), N.mucosa (26.3%), and N.elongata (26.3%). The occurrence of Streptococci slightly decreased: S.oralis was identified in 73.6% of patients, S.pneumoniae — in 68.4% of patients, S.salivarius and S.vestibularis — in 63.1% of patients, S.anginosus — in 47.3% of patients, and S.sanguinis — in 42.1% of patients. Streptococcus species were identified in various quantities in the range between 10 and 10<sup>6</sup> CFU/ml. The number of Lactobacilli species identified in the periodontal pocket in the quantities of 10<sup>5</sup>–10<sup>6</sup> CFU/ml increased. L.gasseri, L.paracasei, L.rhamnosus, L.plantarum, L.oris, L.amylovorus, L.frumentii, and L.fermentum were detected with such titers. Haemophylus parainfluenzae was identified rarer (5.2%) and in lower quantities (10<sup>3</sup> CFU/ml). After the treatment, the substrate of only 5.2% of patients showed single C.albicans cells. Other species of the Candida genus were not detected. The occurrence, quantities, and species composition of the identified Veillonella and Prevotella remained almost the same. After the treatment, the most common Actinomyces species was A.oris (36.8), with A.naeslundii detected only in 10.5% of patients. The quantity of identified Actinomyces did not exceed 10<sup>6</sup> CFU/ml. After the treatment, Selenomonas spp. was identified in 42.1% of patients in the quantity of  $10^5$ – $10^7$  CFU/ml. The

occurrences and quantities of Capnocytophaga spp. also decreased after the treatment. Post-treatment assessment of the overall periodontal pocket microbiota condition showed grade I dysbiotic disorders only in 26.3% of the treatment group, with normal microbiological indicators in all the other patients in that group (73.7%).

After the treatment, the periodontal pocket microbiocenosis became normal in 73.7% of the treatment group patients, with the microbiota condition also improved in the remaining 26.3% of patients from grade I and II dysbiosis to compensated dysbiosis.

Before the treatment, combined intestinal and periodontal pocket dysbiosis was identified in 83.3% of patients, with 16.6% showing periodontal pocket dysbiosis and normal intestinal microbiota. After the treatment, only 15.7% of the control group patients showed normalization of the intestinal and periodontal pocket microbiocenosis, compared to 73.7% of the treatment group patients. The treatment groups also showed positive dynamics of microbiocenosis recovery in the remaining 26.3% of cases.



N+N – normalization of the intestinal and periodontal pocket microbiocenosis

D+D – the dysbiosis of the intestinal and periodontal pocket microbiota

**Fig. 1.** The post-treatment condition of the intestinal and periodontal pocket microbiota in patients with generalized chronic periodontitis and comorbidities (in two groups)

# CONCLUSION

When added to the diet as part of the combination basic treatment of patients with moderate generalized chronic periodontitis and comorbidities, the proprietary immobilized synbiotic "LB-complex L" allowed to achieve sustained periodontal disease remission, to counterbalance the effect of inflammation on the development of periodontitis, and to restore the gut microbiocenosis.

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# A MODIFIED METHOD FOR RAPID PALATAL EXPANSION ANCHORED ON MINI-IMPLANTS

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ABSTRACT — In modern orthodontic practice, a narrow upper jaw is often corrected using teeth-anchored expanders. As a result of skeletal expansion, dental orthodontic appliances have an adverse effect both on the teeth and on the supporting tissues. An analysis of the issues associated with dental fixation devices, as well as the results of combined orthodontic & surgical treatment with Surgically Assisted Rapid Palatal Expansion (SARPE), has allowed us to develop a palatal expander anchored on miniimplants. This method has been tested through the upper jaw expansion in patients in their post-pubertal period. The article offers a view at the changes in the skeletal and dental parameters during rapid maxillary expansion with the proposed expander. Skeletal expansion of the upper dentition in this case is achieved with minor changes in the lateral teeth inclination, thus allowing to minimize the risk of side effects typical for teeth-anchored expanders: root resorption, alveolar bone buccal thickness reduction, marginal bone reduction, and gum recession. The method proposed for upper jaw skeletal narrowing treatment with a palatal expander supported by mini-implants improves the upper airway.

**KEYWORDS** — orthodontics, upper jaw rapid expansion, expander with bone fixation, mini-implants, microosteoperforation, upper respiratory tract.

## INTRODUCTION

Elimination of the upper jaw skeletal narrowing is one of the most complicated issues faced by practicing orthodontists. The diagnosis of *narrowing upper and lower jaw dentition* is one of the most common in daily orthodontic practice, while the prevalence of mesial occlusion within the structure of dental anomalies reaches 8-16% [1]. The upper jaw transversal plane narrowing is quite widespread — 8-23% among children and adolescents, and under 10% among adults. This anomaly is not subject to self-regulation through age [2–5].

The high need for combined treatment through puberty and at the end of the skeletal growth is due to the patient's underestimation of the role played by timely modification of the jaw and maxillofacial region soft tissue growth. Scientific literature presents contradictory data on the validity and possible relapse associated with combined treatment of the upper jaw narrowing, given the change dynamics in the position of the teeth, the tongue, the head, the temporomandibular joint heads, the respiratory tract size, the soft palate uvula [6-11]. The authors prove in this article that a <37% narrowing of the upper jaw apical base, and a >5 mm narrowing of the dental alveolar arch will take opening the interdigital suture through non-removable expanding orthodontic devices, while palatal dilators with intraosseous support would lead to a more significant effect of the lateral teeth body movement thus contributing to relapse prevention [12].

Patients whose physical growth is still underway are treated with orthodontic appliances anchored on teeth. However, there is bone suture calcification and interdigitation occurring over age. Given that, the device counteracts the anatomical resistance from the mid-palatal suture, the alveolar-zygomatic counterforce [13, 14]. SARPE (Surgically Assisted Rapid Palatal Expansion), therefore, offers an option to be used in such cases. Lately, an alternative to this method of treatment has been employed — a modified method of Miniscrew Assisted Rapid Palatal Expansion (MARPE), which is a way to expand the upper jaw with no major osteotomy, and which allows arriving at orthopedic changes affecting the middle third of the face in patients in their post-puberty period. This method allows minimizing such unfavorable effects as the lateral teeth inclination, the root and bone tissue resorption, the gum recession, reduced buccal bone thickness, and loss of the marginal bone. This is also the main feature, as well as an advantage over devices with teeth fixation [15-17].

The upper jaw deficient bone tissue often entails serious effects, one of them being a decrease in the

nasal cavity volume, which leads to obstructive sleep apnea syndrome [18, 19]. As a result, a narrow and high palate is shaped, along with a curved septum and deformed bottom of the nasal cavity, which together disturb respiratory function [20, 21].

## Aim of study:

to increase the effectiveness of combined orthodontic & surgical treatment offered to patients with narrowed upper jaws using a modified palatal expander with onbone fixation.

# MATERIALS AND METHODS

The study involved 5 patients of both sexes (3 males and 2 females) with severe narrowed upper jaws and anomalies affecting the position of certain teeth (Fig. 1).



Fig. 1. Tooth position disturbance and upper jaw narrowing

The degree of narrowing was identified based on Pont's Index diagnostic models. The patients' age fell within the range of 14–16. For cases involving the upper jaw expansion, a palatal plate device with a screw was proposed, which was tailor-made following the palate topography (Fig. 2).

The device was fixed on the heads of orthodontic mini-implants with composite material, while 4 mini-implants (diameter -1.5 mm; length -6-8 mm) are included in the design as supports. When removing the screw, the device, given the bilateral skeletal support, transmits pressure to the bone tissue. The installation of mini-implants was carried out in an outpatient setting, under bilateral infiltration anesthetic (articaine anesthetics with vasoconstrictors, since the installation area features a good blood supply) at the large palatal and incisor openings, as well as in the transitional fold on the vestibular side. The correct



Fig. 2. Palatal plate device with a screw

positioning of the mini-implants was ensured through a surgical template (Fig. 3).



Fig. 3. Mini-implant installation with a 3D template

To reduce the anatomical resistance at the midpalatal suture and the alveolar-zygomatic counterforce, micro-osteoperforations were made with a 1-mm-diameter drill. 6-mm-long mini-implants were installed in the T-zone [22], whereas 8-mm-long ones — on the palatal surface of the alveolar process between the second premolar and the first molar, on both sides (Fig. 4).

The device is activated by unwinding the screw up until complete immobility. Further activation of the device was done according to the following procedure — three activations per day for a quarter turn of the screw. This scheme of the upper jaw skeletal expansion by bone-supported devices is optimal. This protocol



Fig. 4. Appliance fixed on mini-implants

is believed to stimulate the adaptation process in the nasal-maxillary complex, reducing the risk of relapse through post-retention. The median palatal suture opening occurred on Days 14–21. Activation was carried out prior to the cross-bite removal. After the activation was completed, the devices were kept for 6 months as retentions. On the day the devices were installed, all patients were prescribed nonsteroidal anti-inflammatory drugs and rinsing with antiseptic solutions. The expander localization at the palate vault leads to a short-term alteration involving speech, as well as difficulty when eating solid food. Adjustment takes a few days. Patients with a significant thickness of the submucosal layer of the palate had the hemostatic drug Dicynone<sup>®</sup> prescribed to prevent bleeding (250 mg, 2 times a day, oral intake).

The narrowing degree was identified based on diagnostic models subject to Pont's Index. The patients' age ranged from 14 to 16. The expansion dynamics was evaluated relying on the CBCT data before, and after, applying the Yonsei Transverse Index (YTI) calculation method (Fig. 5).

The skeletal expansion values were measured by CBCT between the first premolars (P1) and the first molars (M1) in all patients for each pair of teeth.

Changed inclination of teeth was, too, calculated by the patients' CBCT data. The inclination angles of the premolars and the first molars to the sagittal plane, before and straight after the expansion, were identified. For this purpose, lines were drawn through the buccal tubercles and the root tip (mesial-buccal for the molars; buccal for the first premolars). The measurement difference showed a change in the inclination through treatment. The alveoli vestibular plate thickness was checked on the CBCT coronal sections in the center of the examined teeth roots. The thickness was measured 4 mm apical of the enamel-cement border (Fig. 6).

The level of the marginal bone was measured on the CBCT coronal sections in the center of the examined teeth crowns. The level was measured from the top of the tooth buccal tubercle to the available level of the marginal bone in the center of the tooth root (Fig. 7).

The patients within the study underwent a 4-week clinical observation, whereas the results of the expansion were assessed relying on the patients' CBCT data, prior to, and following the appliance activation. The statistical processing was carried out with the Statistica 6.0 and Microsoft Excel 2000 software packages. The Student's t-test and a two-sample t-test with the same dispersion, were used, while the qualitative parameters were analyzed following Pearson's  $\chi^2$  criterion. The quantitative indicators are presented as an average value  $\pm$  standard error (M  $\pm$  m). The differences between the parameters under examination were admitted as significant at P<0.05.

# **RESULTS AND DISCUSSION**

In all cases, sufficient expansion of the upper jaw was achieved in patients with no complete upper jaw osteotomy. When applying the method to all the cases, there was a diastema observed (Fig. 8).

Table 1 offers a view at the results of the maxillary skeletal expansion in the patients, taking into account the YTI.

The seam opens up in a pyramidal shape, with a wide base in the nasal direction. The analysis of the CBCT data before and after the treatment showed revealed the median palatal suture opening, which had a positive effect in terms of eliminating occlusion anomalies in the transversal plane. The resulting expansion along the alveolar arch reached 6.2-10.4 mm at the first premolars, and 5.6-9.6 mm — at the first molars. Through the entire course of treatment, two patients complained of soreness and discomfort at the hard palate during the first week. An examination showed that the mucous membrane in the area of the installed mini-implants was of pale pink coloring, with no pathological changes. There was no change observed in the periodontium and alveoli.

The course of treatment also involves the dentition expansion, which is associated with the buccal inclination of the lateral teeth. The assessment of the changes in the upper jaw lateral teeth inclination was performed on CBCT sections. The teeth inclination angles towards the sagittal plane were measured before the treatment and immediately after upper jaw active



*Fig. 5.* Cone-beam computed tomography; patient A., 16 y.o., with the upper jaw skeletal narrowing: a, b, c — panoramic reconstruction; d — axial projection; e, f — sagittal projection with the airways volume analysis; g — frontal projection with marks for YTI identification

*Fig. 6.* The boundaries of identifying the alveoli vestibular plate thickness

- *Fig. 7.* The boundaries of identifying the alveoli marginal bone thickness
- Fig. 8. The skeletal expansion effect after 3 weeks

Table 1. Dynamics of the upper dentition width increase before and after active expansion, in view of the YTI, (mm)

Patient	Maxilla, CR width 16–26 pretreatment / post treat- ment	Maxilla width difference. CR 16–CR 26	Maxilla, CR width 14–24 pretreatment / post treat- ment	Maxilla width difference. CR 14–CR 24
Patient 1, girl, 14 years old	34,2/40,9	6,7	27,0/34,2	6,2
Patient 2, girl, 15 years old	35,1/40,7	5,6	28,2/35,2	7,0
Patient 3, man, 15 years old	39,3/46,8	7,5	30,1/38,2	8,1
Patient 4, man, 15 years old	36,5/45,1	9,6	23,3/33,7	10,4
Patient 5, man, 16 years old	38,4/47,9	9,5	29,0/38,1	9,1

expansion was completed. Table 2 shows the change in the teeth inclination.

Using a palatal expander with a fixation on bones ensures the dentition expansion, which is

due to expanding the upper jaw skeleton, while the change in the dental component size is insignificant. A change in the teeth inclination during the expansion is obvious, however, and is caused by the out**Table 2.** The lateral teeth inclination angle change in patients after completing the active expansion of the upper jaw (M = m), (°),  $(p \le 0.05)$ 

Tooth topography	Change options:
P1 (14) Rincl	3,08 ± 0,49
M1 (16) Rincl	3,91 ± 1,47
P1 (24) Lincl	1,07 ± 0,23
M1 (26) Lincl	2,59 ± 0,54

ward movement (bending) of the alveolar processes themselves.

Rapid expansion may also be accompanied with some changes involving the periodontal tissues of the upper jaw lateral teeth, which reveals itself through resorption of the alveolar process bone. Table 3 shows the measurements of the vestibular plate thickness in the alveolar process at the examined teeth.

**Table 3.** Thickness parameters of the alveolar process vestibular plate before and after active expansion  $(M\pm m)$ , (mm),  $(p \le 0.05)$ 

Tooth topography	Dimensional quantities:				
	Before treatment	After active expansion			
P1 (14,24) buccal	0,78 ± 0,07	0,78 ± 0,09			
M1 (16,26) buccal	2,06 ± 0,37	1,89 ± 0,26			

Following the evaluation of the treatment with a palatal bone-fixed expander, there were no statistically significant changes found in the thickness of the alveolar process vestibular plate.

The marginal bone level measurements at the examined teeth can be seen in Table 4.

**Table 4.** Marginal bone thickness before and after active expansion (M=m), (m),  $(p \le 0.05)$ 

Tooth topography	Dimensional quantities:				
	Before treatment	After active expansion			
P1 (14,24) buccal	9,78 ± 0,27	9,91 ± 0,22			
M1 (16,26) buccal	8,06 ± 0,34	8,43 ± 0,41			

The assessment of the treatment with a palatal expander involving bone fixation, revealed no statistically significant changes in the marginal bone level.

The devices relying on bone support, therefore, allow the upper jaw expansion while keeping the tooth supporting tissues almost unchanged. Figure 9 shows the assessment results for the upper jaw skeletal expansion using a palatal expander with bone fixation, combined with micro-osteoperforation, in patients with the upper jaw narrowing based on CBCT data.

Further orthodontic treatment using braces allowed improving the dentition occlusion, ensuring multiple fissure-tubercle contacts, restoring the face symmetry and proportion, improving the middle face area volume, normalizing the incisional lines of the dental arches, eliminating palatal occlusion and dysocclusion in the vertical and sagittal directions, improving certain teeth position, and eliminating the discrepancy in the dental arch size of the upper and the lower jaw (Fig. 10).

Subjectively, all patients reported relieved breathing. This could be attributed to an increase in the nasal cavity width. MARPE may have increased the airway (the short-term observation data). One patient's parents reported significantly improved sleep with improved respiratory function and no longer observed snoring. Respiratory tests and rhinopneumometry in patients before and after the maxillary dilation revealed an improvement in the upper respiratory tract capacity (40% to 53%; Fig. 11), proof to that being the data to be found in respective scientific literature [23].

## CONCLUSION

1. Miniscrew Assisted Rapid Palatal Expansion (MARPE), when combined with micro-osteoperforation, is mainly a consequence of the upper jaw skeletal expansion with minimal effect from the dental component. The buccal inclination of the lateral teeth, which occurs during the expansion, is insignificant.

2. The change in the lateral teeth inclination is mainly due to the outward (vestibular) bending of the alveolar processes.

3. The advantage of upper jaw dental alveolar arch intensive expansion with respective devices fixed on bones (MARPE), as well as of the developed protocol, if compared with Surgically Assisted Rapid Palatal Expansion (SARPE), is its lower invasiveness, as well as potential to be used both during the bite replacement in adolescents, and when dealing with adult patients featuring a completely shaped bite.

4. A palatal expander with bone fixation, if used for the upper mandible rapid expansion in orthodontic practice, will help avoid such undesirable changes affecting teeth and their supporting tissues as root resorption, reduced buccal bone thickness, loss of marginal bone, and gum recession, observed typically in case of using expanders relying on teeth.

5. There is a need for improving the treatment algorithm, based on respective analysis of clinical and



*Fig. 9.* Computed tomogram, patient A., 16 y.o., with upper jaw severe narrowing before (a) and after (b) using a palatal expander with bone fixation.



*Fig. 10.* Virtual diagnostic Set-Up model (ORAPIX 3Txer 2.5.0 file (Japan); patient A., 16 y.o., with the upper jaw severe narrowing before (a) and after (b) combined orthodontic & surgical treatment



*Fig. 11.* Increased volume of the respiratory tract (CBCT data) before (a, b) and after (c, d) combined orthodontic & surgical treatment

radiological data, depending on the median palatal suture ossification, the bone biotype, the degree of the upper jaw narrowing, and the lateral teeth inclination, which, in turn, will allow arriving at both functional and aesthetically qualitative outcome of combined orthodontic & surgical treatment.

6. In case of combined orthodontic & surgical treatment used to treat patients with the upper jaw narrowing, there is an expansion of the middle face and an improved respiratory function of the nose. Further studies in this area, involving a larger pool of patients, would allow substantiating the clinical effectiveness of this method when treating obstructive sleep apnea.

7. Upon activating the device, there is a recommendation to carry out additional research methods (CBCT, X-ray of the hard palate, teleroentgenography in direct projection) to assess the maxillary expansion. Physiological regeneration of bone tissue following the upper jaw expansion, a bone supported palatal expander is recommended to be kept as a retention device for at least 6 months.

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# CLINICAL TYPES OF HARD PALATAL VAULT IN PEOPLE WITH VARIOUS GNATHIC DENTAL ARCHES WITHIN PHYSIOLOGICALLY OPTIMAL NORM

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ABSTRACT — The study is based on an analysis of conebeam computed tomograms and biometric examination of jaw cast models obtained from 68 people aged 21-35 with permanent teeth physiological occlusion. The findings were used to identify the relationship between the morphometric values (height, depth) of the palatal vault, and the linear parameters (length, width) of dental arches. In patients with mesognathic dental arches, the palatal vault index, taken as a ratio between the palate height to the alveolar part width, was 41.14  $\pm$  2.87%, whereas the width indicators exceeded (by 2.43 times on average) the hard palate vault depth parameters. People with dolichognathic dental arches had the value of the palatal vault index reaching  $51.75 \pm 2.57\%$ , while the width indicators exceeded the depth parameters of the hard palate vault by 1.93 times on average. In patients with brachygnathic dental arches, the palatal vault index was  $28.29 \pm 2.62\%$ , with the width indicators exceeding the depth parameters by 3.53 times on average. There is evidence showing that mesognathic dental arches have mesopalatal (proportional) palatal vault matching them, while in case of dolichognathic dental arches, the match is dolichopalatal (high and narrow) type of vault. As for brachygnathic dental arches, then the match is brachypalatal, i.e. a low and wide vault. The obtained data can be used in clinical orthodontics, orthopedic dentistry, as well as maxillofacial surgery to assess the hard palate parameters, to diagnose palatal vault pathologies, and to select respective treatment approaches in view of the dental arches shape and size anomalies.

**KEYWORDS** — dental system; hard palate; cone-beam computed tomography; physiological occlusion; gnathic types of dental arches; biometrics of jaw cast models.

# INTRODUCTION

Modern achievements in applied anatomy, focusing on the organ structure and their topography in normal cases as well as in pathologies, which serving the interest of various areas of clinical medicine, rely on advanced technologies for intravital study of various morphological structures belonging to the human support & motor system [6, 9, 15, 20, 29, 43, 55].

Methods employed for visualizing the face bonebased skeleton and its soft frame, especially in dentistry and maxillofacial surgery, have been given a specific development impetus [7, 14, 19, 24, 28, 34, 53].

Highly reliable, safe, non-invasive methods of X-ray diagnostics, which involve computer software, allow identifying the individual variability patterns within the structure of the facial skull bones [2, 10, 16, 30, 36, 45].

Continuous improvement of research technologies in this field contributes to enhancing the knowledge when applied to studying various aspects of the skull clinical anatomy, this entire activity facilitating the activities of dentists, maxillofacial surgeons, neurosurgeons, otorhinolaryngologists, ophthalmologists, etc. [3, 8, 11, 21, 37, 44, 54, 56].

One of the fundamental problems of morphology, which is of applied value, is a comprehensive study of the individual typological variability of the structures of the skull facial and cerebral parts, as well as the interconnection patterns of individual components in the skull system as a whole [12, 18, 23, 31, 38].

A detailed and thorough study of the facial and cerebral skull morphology, in view of individual typological features, will allow significant expansion of the scientific knowledge concerning the patterns pertaining to the structure of the craniofacial complex and its components, while obtaining valuable information related to variant anatomy [1, 4, 17, 22, 27, 33, 46].

The hard palate, which is a bone wall separating the oral cavity from the nasal cavity, is both the roof of the oral cavity and the bottom of the nasal cavity. The front section of the hard palate includes the palatal processes of the maxillary bones, whereas the posterior (distal) part is shaped by the horizontal plates of the palatal bones. The mucous membrane covering the hard palate is fused tightly with the periosteum, whereas there is a bone suture running along the hard palate middle line. The configuration of the palatal vault, depending on the individual typological variability, features significant variability [5, 25, 41, 48].

As far as measuring the hard palate is concerned, there were various devices and research methods proposed — from the classical symmetrograph of Korkhaus to computer 3D diagnostics. The proposed programs allow not only identifying the main parameters of the palatal vault, yet also matching them versus the average values falling within the norm, as well as archiving the study outcomes [13, 47].

Following expert recommendations, the length of the palatal vault is measured from the apex of the interstitial papilla to the line connecting the first permanent molars' distal surfaces. Vertically, the distance is measured from the deepest point (between the second premolars and the first molars) to the line connecting the interdental papillae. The transversal dimensions (the width of the palatal vault) are measured at the same spot. As for a criterion to evaluating the palate parameters, the authors here propose the palate height index, which is to be calculated as a ratio of the palate depth (height) to the palate width. The value of the index in question has been found to be 31–32% at a young age. Notable is that this study was caried out without taking into account the gnathic and the dental types of dental arches, which determine the major morphometric features of the dental system [26, 42, 49]. There is reliable data showing that people belonging to the brachygnathic type, have their upper dental arches wider transversally and shorter sagittally, if compared with mesognathic dental arches [35, 40, 50, 52, 58]. People with dolichognathic types, however, revealed something completely opposite — upper dental arches shorter in the transversal, and longer in the sagittal, plane, if matched against mesognathic dental arches [32, 39, 51, 57].

The available literature offers no data on the variability of the hard palate parameters for different types of dental arches, which explains the aim of this study.

#### *Aim of study:*

to identify the main parameters of the hard palate vault in people with different genetic types of dental arches within the physiologically optimal norm.

## MATERIALS AND METHODS

A stratified, as well as a retrospective study was conducted focusing on the examination of cast models and CBCT images of 68 patients within their first adulthood stage (age - 21-35). All the patients were registered as featuring the physiological occlusal norm, and they were divided into 3 groups in view of the gnathic type their dental arches belonged to, namely, mesognathic (25 patients), dolichognathic (21 patients) and brachygnathic (22 patients). The type of the dental arch was identified relying on the ratio of the transversal measurement of the dental arch distal part (the width between the second molars' distal tubercles at the vestibular and occlusal surfaces border) to the sum of the crown width of 14 teeth (the dental arch length). Mesognathic arches included those where the arch index varied from 0.52 to 0.56. The gnathic index of the dental arch under 0.52 was considered typical of the dolichognathic type of dental arches, and that exceeding 0.56 — of the brachygnathic one (Fig. 1).

The position of the highest point of the hard palate vault in the sagittal plane (passing between the medial upper incisors) was identified based on the respective CBCT data, whereas the horizontal palatal line passed through the incisor papilla apex. The palatal vault height was measured from the top height to the horizontal papillary line. These landmarks were used to measure the palate width in the CBCT direct projection, as well as in the occlusal norm projection. As a rule, the deepest point was located between the second premolar and the first molar, which reflects respective data reported by most researchers (Fig. 2).

Apart from the CBCT analysis, these parameters were measured on jaw cast models. The measuring points were similar to the CBCT marks. The obtained linear parameters allowe1d identifying the *palatal vault index* as a ratio of the palate height (depth) to the width of the alveolar part. The index allowed selecting three groups — at an index of 35% to 45%, the palatal vault was attributed to the mesopalatal type. An increase in the index pointed at a palatal vault belonging to the deep (dolichopalatal) type, while a decrease in the index was indicative of the low (brachypalatal) type. In addition to the palatal vault index, the indicators of the palatal vault module were evaluated, taken as half the sum of the palate height and the width of its alveolar part.

The statistical processing of the obtained data was performed with Microsoft Excel 2013 software as well as the SPSS Statistics (Version 22) statistical software package. The critical level of a possible null statistical hypothesis was set at 0.05.

# **RESULTS AND DISCUSSION**

A biometric study of jaw cast models revealed that the main parameters of dental arches and the palatal vault arch are determined by the gnathic types of dental arches (Table 1).



Fig. 1. The major shape of dental arches: mesognathic (a), brachygnathic (b), dolichognathic (c)



Fig. 2. Reference marks for measuring the depth and the width of the hard palate vault on CBCT slices

*Table 1.* Outcomes of a biometric study focusing on dental arch parameters and on the hard palate vault, jaw cast models ( $M \pm m$ ) ( $p \le 0.05$ )

Parameters	Size and index of dental arch					
	mesognathic	dolichognathic	brachygnathic			
Arch length (mm)	112.72±1.25	113.23±1.59	109.05±1.96			
Arch width (mm)	59.08±1.27	55.05±1.86	63.09±1.89			
Palate width (mm)	39.14±1.18	36.61±1.32	43.12±1.25			
Palate depth (mm)	15.24±0.21	19.36±0.48	12.53±0.19			
Palatal vault index (%)	38.94±1.42	52.88±1.57	29.06±1.23			
Palatal vault module (mm)	27.19±1.18	27.98±1.39	27.82±1.37			

DENTISTRY

The gnathic type of dental arches was identified based on their length and width dimension parameters. The ratio of the transversal size between the second molars to the dental arch length in the mesognathic type of arches was  $0.52 \pm 0.02$ ; in case of the dolichognathic type —  $0.49 \pm 0.02$ , whereas for the brachygnathic type the value was  $0.58 \pm 0.02$ , which fell well within the ranges to be found in respective research literature.

The transversal dimensions of the hard palate, as combined with its height (depth) served to identify the indices that characterized the type of the palatal vault as *deep*, *medium* or *low* (Fig. 3). According to the CBCT data, patients with *meso-gnathic dental arches* had a palate width of 38.04±1.29 mm; the *palate depth* value was 15.65±1.01 mm; the *palatal vault index* was 41.14±2.87 %, the *palatal vault module* being 26.85±0.85 mm.

For patients with the *dolichognathic dental arches*, the palate transversal dimensions were  $36.85\pm1.17$  mm; the vertical parameters were  $19.07\pm1.12$ , the *palatal vault index* reached  $51.75\pm2.57$  %, with the palatal vault module being  $27.96\pm1.12$  mm. An analysis of coronal tomograms obtained from patients with *dolichognathic dental arches* shows that the palatal vault dome is visualized as high and narrow (Fig. 4).



Fig. 3. Cast models for cases of mesognathic (a), dolichognathic (b) and brachygnathic (c) dental arches

As the biometric study of jaw cast models show, patients with *mesognathic dental arches* have a palate width of  $39.14 \pm 1.18$  mm; a depth of  $15.24 \pm 0.21$  mm, the value of the *palatal vault index* being  $38.94 \pm 1.42\%$ , and the *palatal vault module* —  $27.19 \pm 1.18$  mm.

For patients with *dolichognathic dental arches*, the palate transversal dimensions were  $36.61\pm1.32$  mm; the vertical parameters were  $19.36\pm0.48$ ; the *palatal vault index* was  $52.88\pm1.57$  %, while the *palatal vault module* was  $27.98\pm1.39$  mm. The *palatal vault index* in this category was found to feature statistically significant prevalence of such indicators over similar ones in people with mesognathic dental arches (p<0.05).

In patients with the *brachygnathic type of dental arches*, the width of the palate was  $43.12\pm1.25$  mm; the palate depth was  $12.53\pm0.19$  mm; the palatal vault index was  $29.06\pm1.23$  %, with the palatal vault module being  $27.82\pm1.37$  mm. The study revealed that in this category, the palatal vault index was reliably lower than similar parameters in people with *mesognathic* and *dolichognathic* type of dental arches (p<0.05).

An analysis of CBCT indicators revealed that the main parameters of the hard palate vault were close to the dimensions obtained through studying the jaw cast models, and were also determined by the types of dental arches (Table 2). In people with brachygnathic dental arches, as the CBCT showed, the palate width was  $43.16\pm1.32$  mm; the depth was  $12.21\pm0.85$  mm; the palatal vault index was  $28.29\pm2.62$  %, while the palatal vault module was  $27.68\pm1.11$  mm. When visualizing coronal tomograms of patients with brachygnathic dental arches, it was obvious that the palatal vault dome visualized as *low* and *wide* (Fig. 4).

It is important to note that the hard palate vault module in patients with various genetic types of dental arches is stable, the limits of variability being not statistically significant ( $p \ge 0.05$ ).

This means that the morphometric parameters of the hard palate vault obtained through biometric study of jaw cast models and cone-beam computed tomograms reveal no statistically significant differences ( $p \le 0.05$ ), and can be used in orthopedic dentistry and orthodontics for diagnostics, as well as for selecting tactics when dealing with patients featuring dental anomalies, and for evaluating the effectiveness of dental treatment.

## CONCLUSION

1. CBCT data shows that patients with *meso*gnathic dental arches have palatal vault index of 41.14  $\pm$  2.87%, while the width indicators exceed the hard palate depth parameters — by 2.43 times on average.

Parameters	Size and index of palatal vault at the following dental arches:					
	Mesognathic	dolichognathic	brachygnathic			
Palate width (mm)	38.04±1.29	36.85±1.17	43.16±1.32			
Palate depth (mm)	15.65±1.01	19.07±1.12	12.21±0.85			
Palatal vault index (%)	41.14±2.87	51.75±2.57	28.29±2.62			
Palatal vault module (mm)	26 85+0 85	27 96+1 12	27 68+1 11			

*Table 2.* Parameters of hard palate vault based on CBCT data ( $M \pm m$ ) ( $p \le 0.05$ )



Fig. 4. CBCT of patients with mesognathic (a), dolichognathic (b) and brachygnathic (c) dental arches

2. People with *dolichognathic dental arches*, according to CBCT data, have the palatal vault index reaching  $51.75 \pm 2.57\%$ , while the width indicators are an average of 1.93 times those of the hard palate depth parameters, while a decrease in the hard palate vault width is accompanied by an increase in the height indicators.

3. CBCT data reveals that patients with *brach-ygnathic type of dental arches* have a value of the palatal vault index of  $28.29 \pm 2.62\%$ , while the width indicators exceed the depth parameters of the hard palate vault by 3.53 times on average, whereas an increase in the palatal vault width comes combined with a decrease in the height indicators.

4. The palatal vault module, taken as the ratio of its height (depth) parameters half-sum to the width of the alveolar part, as is obvious from the respective CBCT data, is a constant value and: with *mesognathic* dental arches is  $26.85 \pm 0.85$  mm, with *dolichognathic* dental arches is  $27.96 \pm 1.12$  mm, while with *brachygnathic* dental arches it is  $27.68 \pm 1.11$  mm.

5. When visualizing coronal tomograms at the second premolars level in patients with the *brachyg-nathic* type of dental arch, the palatal vault dome is visualized as *low* and *wide*, whereas in patients with the dolichognathic dental arches it is *high* and *narrow*.

6. The outcome of the individual-typological variability study focusing on the cranio-facial structures with physiologically normal occlusion, is identifying the relationships (patterns) between morphometric values (height, depth) of the palatal vault and the linear parameters (length, width) of dental arches. Patients with *mesognathic* dental arches correspond to the *mesopalatal* (proportional) type of the vault; those featuring the *dolichognathic* type of dental arches — to the *dolichopalatal* (high and narrow) type of the vault, whereas patients with *brachygnathic* dental arches matched the *brachygnalatal* (low and wide) type of the palatal vault.

7. Cone-beam computed tomography, which is part of the standard X-ray examination protocol provides the most complete diagnostic information on the cranio-facial bone structures. Improving visualization algorithms of cranio-facial bone structures in regard to age, sex and individual variability facilitates standardization of dental research methods used for objective diagnostics of patients with congenital issues (cleft lip, alveolar process, hard and soft palate, dysplastic disorders), as well as occlusion anomalies and deformities in the sagittal and transversal planes.

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# STUDY OF THE ACTIVITY OF THE ANTIOXIDANT SYSTEM IN EXPERIMENTAL PERIODONTITIS

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**ABSTRACT** — The aim of this study was to evaluate the activity of the antioxidant system when creating a model of periodontitis in an experiment in rats. We made a model of periodontitis in rats (n = 10) by ligating the first two molars with a ligature. The control group consisted of intact rats (n = 10). In all animals, we determined the level of activity of catalase, superoxide dismutase and free hydroxyproline in blood plasma on the  $3^{rd}$ ,  $7^{th}$ ,  $25^{th}$  days. As a result, we revealed a significant decrease in the activity of enzymes of the antioxidant system in the main group compared with the control (p <0.001). Also, the rats of the main group had a negative correlation between the level of catalase (r = -0.84), and superoxide dismutase (r = -0.79) in relation to the parameters of free hydroxyproline.

CONCLUSION: Low antioxidant status in rats with periodontitis leads to destruction of collagen structures in periodontal tissues.

**KEYWORDS** — periodontitis, oxidative stress, periodontal diseases, catalase, superoxide dismutase, collagen.

## INTRODUCTION

Periodontitis is a chronic inflammation of the tooth-supporting tissues [1]. Almost every adult faces periodontitis, at least once in a lifetime. Due to chronic inflammation in the periodontal tissues, neutrophils and lymphocytes are activated enabling synthesis of cytokines and prostaglandins [2]. Long-term chronic inflammation in tissues leads to an increase in reactive oxygen species (ROS), and an imbalance in the antioxidant system [3, 4]. The long-term chronic inflammation is known to facilitate destruction of tissues supporting teeth, including the gums, periodontal ligament, and alveolar bone [5]. Also, chronic periodontitis is the main cause of tooth loss, which significantly impairs quality of life in such patients. Therefore, assessment of oxidative processes, identification of the

correlation between activity of the antioxidant system and destruction of collagen structures of periodontal tissues is an urgent issue of modern dentistry.

Aim:

To assess the activity of the antioxidant system when creating a model of experimental periodontitis in rats.

## MATERIAL AND METHODS

The experiments were performed on 20 healthy outbred rats aged 12 to 16 weeks and weighing 180 to 225 g. All procedures with animals were performed according to the rules of the Guide for the care and use of laboratory animals. We randomly assigned the rats into two groups:

— control group (n = 10) — animals that were not manipulated

— the main group (n = 10) — animals for which a model of periodontitis was created.

We carried out all the manipulations in animals under general anesthesia (0.03 ml/m). To create a model of periodontitis, we applied a ligature (Vicryl 5.0) between the two molars, while we tried to suture the interdental papilla between the first and second molars of the upper jaw on the left. This ligature acted as an irritant to the gums and caused accumulation of bacterial plaque, followed by the development of periodontitis after 30 days.

Further, we evaluated the intensity of oxidative stress and investigated the key enzymes of the antioxidant system — catalase and superoxide dismutase in blood plasma. We determined the activity of the above enzymes in both groups of animals using kits for spectrophotometric analysis. We determined the degree of collagen destruction by the change in the level of free hydroxyproline (mg/l). Oxyproline is one of the essential amino acids in collagen. Consequently, fluctuations in the level of this indicator indicate the intensity of the degradation of collagen structures. We determined the oxyproline of blood serum by the colorimetric method.

The results were monitored after modeling periodontitis and removing the ligature on days 3, 7 and 25. During the observation, all animals were kept in the same conditions and were fed soft food. Statistical processing was carried out with the calculation of arithmetic mean values (M) and their errors (m). The reliability of differences in the groups was calculated using the Mann-Whitney test. The differences were considered significant if p < 0.05.

# RESULTS

The indicators of the activity of the antioxidant system before the start of the study did not significantly differ between the main and control groups of animals. After creating a model of periodontitis, throughout the observation period, the indicators of catalase and superoxide dismutase activity in blood serum significantly differed between the groups (Table 1, 2).

Table 1. Indicators of catalase activity (mmol / I) in blood plasma of animals of both groups

Research days Animal groups	Before the research	3 <sup>rd</sup> day	7 <sup>th</sup> day	25 <sup>th</sup> day
Control group (n=10)	1,17±0,05	1,16±0,04	1,19±0,03	1,15±0,03
Main group (n=10)	1,15±0,02	0,51±0,02	0,44±0,04	0,40±0,03
р	p>0,05	p <0,001	p <0,001	p <0,001

**Table 2.** Indicators of the level of superoxide dismutase (U / mI) in the blood plasma of animals of both groups

Research days Animal groups	Before the research	3rd day	7th day	25th day
Control group(n=10)	1,30±0,04	1,31±0,02	1,29±0,03	1,32±0,04
Main group (n=10)	1,31±0,03	0,45±0,04	0,48±0,05	0,52±0,06
р	p>0,05	p <0,001	p <0,001	p <0,001

The level of free hydroxyproline in rats of the main group was significantly higher than in the control (p <0.001), which indicates a high metabolic activity of collagen-containing structures of connective tissue in periodontitis (Fig. 1).



Fig. 1. Dynamics of changes in the level of free hydroxyproline (mg/l) in animals of both groups

At the end of the experiment, we found that we found a negative relationship between the level of free hydroxyproline and catalase in blood plasma (r=-0.84), and superoxide dismutase (r=-0.79).

# DISCUSSION

Periodontal diseases cause not only inflammation of the gums and periodontal ligament but also an imbalance in the regulation of redox processes. Many authors point out that oxidative stress is an important factor in the etiology and pathogenesis of diseases of the oral cavity and teeth [3, 6]. Some studies indicate that neutrophils, lymphocytes, bacteria, smoking, diseases of the cardiovascular system, diabetes mellitus contribute to the formation of reactive oxygen species and provoke the development of oxidative stress in periodontitis. Research by Yang P.S. et al. showed that an increase in superoxide dismutase activity is positively associated with the severity of periodontitis [6]. German researchers have revealed a significant increase in the level of catalase activity when creating a model of hypoxia and inflammation in vitro (p < 0.001) [2]. The authors believe that prolonged inflammation causes a decrease in catalase activity, which indicates the formation of an imbalance in the antioxidant defense system, an increase in reactive oxygen species, and the progression of inflammatory diseases of the oral cavity [2]. Also, Oktay S et.al. recorded a high activity of catalase and superoxide dismutase was significantly higher in rats with generalized periodontitis (p <0.001) [7]. Our study showed that catalase and superoxide dismutase activity significantly changes in rats with periodontitis against the background of oxidative stress, which negatively affects the metabolism of collagen in the supporting tissues of the tooth.

# CONCLUSION

In rats with periodontitis, the antioxidant defense system is impaired, which is manifested in a decrease in

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the activity of the key enzymes of the antioxidant defense activity: catalase and superoxide dismutase. Moreover, the longer the inflammation persists (over three weeks), the lower the catalase activity becomes. Inhibition of the antioxidant system leads to impaired collagen formation and damage to periodontal tissues.

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# IMPROVEMENT OF ALGORITHMS FOR THE TREATMENT<br/>OF PATIENTS WITH COMBINED ENT AND DENTAL<br/>PATHOLOGY DURING MINIMALLY<br/>INVASIVE SIMULTANEOUS OPERATIONSReceived 24 November 2021;<br/>Received in revised form 18 December 2021;<br/>Accepted 20 December 2021;<br/>Accepted 20 December 2021;

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ABSTRACT — The aim of the study was to assess the effect of pathogenic microflora on the postoperative period of simultaneous surgical intervention in patients with chronic maxillary sinusitis and partial absence of teeth in the distal parts of the maxilla in 49 patients (25 to 65 years old), who were divided into 2 groups (I — with identified pathogenic microflora, II — with normal microflora). Simultaneous surgical intervention included endonasal endoscopic maxillofacial surgery in combination with subantral plastic surgery and/or dental implantation, if necessary, with correction of intra-nasal structures. According to the results of clinical, hardware and laboratory research methods, it was noted that the proposed algorithm of examination and simultaneous surgical intervention in combination with conservative therapy allows for such treatment in patients with pathological flora in the maxillary sinus.

**KEYWORDS** — simultaneous surgery, ENT doctor, dentist, dental implant, chronic maxillary sinusitis, pathogenic microflora.

# INTRODUCTION

A long-term partial absence of teeth in the maxilla leads to atrophy of the alveolar process, which significantly limits the possibilities of treating patients using dental implants. To solve the problem of replenishing the bone base in the vertical direction, oral surgeons perform an operation — subantral plastic surgery using osteoplastic materials of various origins [1-6].

Despite the developed protocol of subantral plastic surgery, both intraoperative and postoperative complications are often possible. The most significant intraoperative complications that occur with a frequency of up to 40% of cases are perforation of the Schneider membrane, migration of osteoplastic material into the maxillary sinus cavity and, as a consequence, the development of odontogenic maxillary sinusitis [7].

An unfavorable factor for the development of postoperative inflammatory complications is the already existing chronic maxillary sinusitis (CMS) [8-12]. Therefore, before performing subantral plastic surgery in the designated group of patients, a preoperative assessment of the condition of the maxillary sinus (MS) is necessary in order to diagnose inflammatory changes and prevent postoperative complications.

In international practice, a classification based on an X-ray conclusion on the thickness of the mucous membrane of the MS is actively used, which makes it possible to judge the severity of the inflammatory process and choose an adequate tactics of preoperative preparation. One of the contraindications to dental implantation is the thickness of the mucous membrane of the bottom of the MS more than 6 mm and, caused by this change, the block of the natural anastomosis [13–15]. This category of patients traditionally receives two-stage treatment: the first stage is a sanitizing intervention (functional surgery — FESS); then, after 3–4 months, the second stage is subantral plastic surgery [16]. Currently, the possibilities of combining these two stages into one or a simultaneous surgical approach are of particular interest.

There is an opinion that CMS is supported by immunopathological changes, which are based on the features of the microbial landscape [17, 18]. Thus, it was shown that in the group of patients with CMS there is a high infection with Staphylococcus aureus with a decrease in the proportion or absence of other cultures of microorganisms. Huvenne W. et al. (2013) [19] showed the role of the environment in the formation of dysbiosis, when one or more bacterial species occupy a dominant position in the microbial landscape of the nose, suppressing normal microflora. Staphylococcus aureus is often combined with streptococci and pneumococci, forming microbial associations. In one of the latest studies, Velasquez N. et al. (2021) found in chronic sinusitis the presence of normoflora in 56%, hemophilic bacillus in 13%, and Pseudomonas aeruginosa in 6.5% of cases. The authors concluded that microbial aggression and a defect in the epithelial barrier of the nasal sinus mucosa play a key role in the development of CMS [20].

The purpose of this study is to assess the effect of pathogenic microflora on the course of the postoperative period of simultaneous surgical intervention in patients with CMS and partial absence of teeth in the distal parts of the maxilla.

## MATERIALS AND METHODS

The study involved 49 patients diagnosed with partial absence of teeth in the distal parts of the maxilla, CMS. The age of the patients ranged from 25 to 65 years.

Initially, patients planned to be treated only by a dentist in order to make up for a defect in the dentition of the distal upper jaw using dental implants, however, during a preoperative examination (computed tomography of the paranasal sinuses — CT PS), CMS was detected, which required FESS.

Inclusion criteria — patients with combined pathology: partial absence of teeth in the distal part of the maxilla, signs of CMS — retention cystic changes occupying up to <sup>3</sup>/<sub>3</sub> of the maxillary sinus, hypertrophy of the mucous membrane in the alveolar bay, circularly thickened mucous membrane with a block of natural anastomosis (Fig. 1, 2). nose, CT PS, and bacteriological examination of the contents of the nasal cavity were performed. Endoscopic evaluation was performed on the 10<sup>th</sup> and 90<sup>th</sup> days after surgical treatment, CT PS and microbiological evaluation — 90 days after surgery.

To assess the microflora of the nasal mucosa before surgical treatment, seeding of the discharge was carried out on nutrient differential diagnostic media (KA, ZHSA, Endo, enterococcus agar). When taking samples of pathological material from the nasal mucosa and transporting it for further research, sterile tupfers with Ames commercial transport medium were used. Sowing was carried out by the sector method. Incubated in a thermostat at 37° C for 24 hours. For normal values of microbial flora, digital indicators up to 10<sup>6</sup>, Neisseria spp were taken for Streptococcus spp. — up to 10<sup>4</sup>, Staphylococcus spp. — up to 10<sup>4</sup>, Haemophilus spp — up to 10<sup>2</sup> [21].

Depending on the detected microflora (pathogenic/non-pathogenic), patients were divided into 2 groups. Group I included 24 patients with detected pathogenic microflora, group II — 25 patients with normal microflora.

The operation consisted of simultaneous surgical intervention: endonasal endoscopic maxillofacial surgery in combination with subantral plastic surgery and/or dental implantation, if necessary, the intervention was supplemented with correction of intra-nasal structures — septoplasty, vasotomy of the lower nasal



Fig. 1. Reformat of cone-beam computed tomography of a patient diagnosed with the presence of a foreign body in the maxillary sinus

The criteria for non-inclusion were: allergic rhinitis, acute rhinosinusitis, polypous sinusitis, pregnancy and lactation.

Anamnesis was collected in all patients at the preoperative stage, an endoscopic examination of the

concha, partial resection of bullous-altered middle nasal concha. Unilateral treatment was performed in 43 patients (87.8%), bilateral — in 6 patients (12.2%).

In order to prevent the exacerbation of CMS in the postoperative period, no nasal cavity tamponing 104



Fig. 2. Reformat of cone-beam computed tomography of a patient who has been diagnosed a cyst of the maxillary sinus

was performed, limiting the placement of a hemostatic sponge in the middle nasal passage for 2 hours. Vasotomy was performed with a Surgitron device, and the nasal septum was splinted with silicone splints.

The data of endoscopic examination of the nasal cavity before and after surgical treatment were interpreted using the Lund–Kennedy scale (1995), adapted to the designated purpose of the study. Attention at the preoperative stage was fixed on the presence of swelling of the nasal mucosa and the nature of the discharge. Since the characteristics of the airflow are affected by the deviation of the nasal septum and the pathology of the structures of the ostiomeatal complex (OMC), their presence was included in the assessment (0 — no sign, 2 — there is a sign) [22, 23].

In the postoperative period, attention was paid to the severity of reactive mucosal edema, the appearance and nature of the discharge, the formation of crusts (0-2), fibrin (0-2), postoperative complications (perforation, severity of sinusitis, etc.), where 0 — there is no sign, 2 — the sign is well expressed [24, 25].

The assessment of changes on CT PS scans before and after surgical treatment was carried out using the Lund–Mackay scale (1993) [26], where total sinus darkening was estimated at 2 points, parietal darkening — 1 point, aplasia — 1 point, absence of darkening — 0 points; blockade of the middle nasal passage — 2 points, its absence — 1 point, changes from the ostiomeatal complex — 2 points. The maximum number of points corresponded to 24, the right and left halves of the nose were evaluated separately.

All patients were prescribed ceftriaxone 2.0 intravenously 30 minutes before the operation. In the postoperative period, anti-inflammatory (INGX mometasone fuorate 400 mcg/day for 14 days) and local vasoconstrictive therapy (decongestants no more than 5–7 days) were performed. The choice of an antibacterial drug depended on the results of a microbiological study.

Statistical data processing was carried out on a personal computer using the SPSS version 17.0 program. When comparing the two groups, the Student's T-test was used for independent samples. The signs analyzed in the study were qualitative (ordinal or alternative), therefore, to assess the reliability of different frequencies of detection of individual signs in the compared groups of patients, the exact Fisher criterion was used, the values were considered significantly different at  $\phi^2 > 1.64$  for p=0.05. The normality of the samples was confirmed using the Shapiro–Wilk criterion, followed by the application of the Mann-Whitney criterion with a significance level of 0.05 for nonparametric data.

# RESULTS

According to the results of microbiological studies in the preoperative period in patients of the first group, the most frequently isolated pathogenic microbial culture was Haemophilus influenzae (1), Str. Pyogenes (2), Moraxella catarrhalis (3), Streptococcus pneumoniae (4) in combination with Staphylococcus aureus (5) and Staphylococcus epidermis (6). In 10 patients, a combination of 1-4 (41.7%), 2-3-4 — in 5 patients (20.8%), a combination of 3-5 — in 2 patients (8.3%), 2-4 — in 7 patients (29.2%).

In patients who made up group II, Staphylococcus aureus in 10 patients (40%) and Staphylococcus epidermis in 5 patients (20%) and in microbial association in 10 patients (40%) were determined in isolation.

The sensitivity of the identified flora was determined to amoxicillin clavulanate, levofloxacin, ceftriaxone, ciprofloxacin. The regimens of the drugs used of the drug, then the transition to oral administration: for amoxicillin clavulanate 875 + 125 mg 2 r/d, for levofloxacin — 500 mg 1 r/d, for ceftriaxone 1.0 g 2 r/d, for ciprofloxacin — 500 mg 2 r/d. The duration of antibacterial therapy in all cases was at least 10 days.

Endoscopic assessment of the condition of the nasal cavity 10 days after surgical treatment showed an increase in the frequency of mucosal edema and discharge in both groups. Unilateral edema was diagnosed in group I in 8 (33.3%), in II — in 9 (36.0%) patients, bilateral — in 11 (44.0%) and 10 (40.0%) cases, respectively. Separation on one side occurred in 5 (20.8%) and 7 (28.0%) patients, on

The pathology revealed during the examination is reflected in Table 1.

	1				1		
Sign		Before the operation	on	10 days after th	e operation	After 90 days	
		Group 1 n=24	Group 2 n=25	Group 1 n=24	Group 2 n=25	Group 1 n=24	Group 2 n=25
	d/s	5	6	8*	9*	0*	0*
Edema	d+s	3	5	11*	10*	0*	0*
	absent	16	14	5*	6*	24	25
	d/s	4	5	5	7	0*	0*
exudate	d+s	6	7	3	4	0*	0*
Edema exudate ostiomeatal complex curvature of the nasal septum Crusts	absent	14	13	16	14	24	25
	d/s	6	7				
ostiomeatal complex	d+s	7	6				
	absent	11	12				
curvature of the nasal septum		18	15				
	d/s			5	4	0	0
Crusts	d+s			3	5	0	0
	absent			16	16	24	25
Fibrin	d/s			1	0	0	0
	d+s			2	1	0	0
	absent			21	24	24	25
Perforation of the nasal septum				0	1	0	1

*Table 1.* The frequency of diagnosed changes in the state of the nasal cavity during endoscopy

\**p*<0.05 (before and after surgery in the group) is the confidence value in the group when comparing data 10 days and 90 days after surgery. The differences obtained were statistically significant (*p*<0.05)

At the preoperative stage, unilateral edema of the nasal mucosa was detected in group I in 5 (20.8%), in II — in 6 (24.0%) patients, respectively; bilateral edema — in 3 (12.5%) and 5 (20.0%) patients. Nasal discharge was observed on one side in 4 (16.7%) and 5 (20.0%) patients, on both sides — in 6 (25%) and 7 (28%) patients, respectively. There was also no statistical difference. Features of OMC in patients of the first group were revealed on the one hand in 6 (25.0%) cases, on the two sides — in 7 (29.2%), in group II patients — in 7 (28.0%) and 6 (24.0%) cases, respectively. At the same time, there was no statistical difference in the frequency of detection of edema (8/11,  $\phi^2$ =0.73), nasal cavity discharge (10/12,  $\phi^2$ =0.444), OMC pathology (13/13,  $\phi^2$ =0.154) between groups I/II.

both sides — in 3 (12.5%) and 4 (16.0%) patients, respectively.

Moreover, the increase in reactive changes was significant in both unilateral and bilateral manifestations (p<0.05). In addition to reactive edema and discharge, the formation of crusts was noted — unilateral in 5 (20.8%), bilateral in 3 (12.5%) patients, and in 4 (16.0%) and 5 (20.0%) patients, respectively, groups. There was no statistical difference in the frequency of formation of nasal mucosal edema (19/19,  $\phi^2$ =0.266), discharge (8/11,  $\phi^2$ =0.773) and crusts (8/9,  $\phi^2$ =0.199) between patients of group I/II.

A distinctive feature of the postoperative period was the deposition of fibrin: on the one hand — in 1 (4.2%) and on both sides — in 2 (8.3%) patients of group I, in group II fibrin was detected only in 1 (4.0%) patient on both sides. A complication of surgical treatment (perforation of the nasal septum) was recorded in one case (2.0%) in a patient of group I.

A control examination 3 months after the operation confirmed the presence of a perforation detected on the 10th day after surgical treatment. No other complications were detected, mucosal edema and discharge were no longer recorded 90 days after surgery.

The endoscopic evaluation of the results on the Lund–Kennedy scale is presented in Table 2.

treatment, regardless of its volume, led to a significant positive result, which affected the indicators.

The frequency and types of pathological changes in the maxillary sinuses according to CT PS at the preoperative stage are presented in Table 3.

Retention cysts occupying  $\frac{2}{3}$  of the sinus volume were most common — unilateral cysts were recorded in 9 (37.5%) and 8 (32.0%) patients, bilateral — in 2 (8.3%) and 3 (12.0%) cases, respectively, groups. Unilateral hypertrophy of the MS mucosa in group I patients was detected in 6 (25.0%) cases, in II — in

Sign	points	Before surgery		10 days after surgery		90 days after surgery	
		Group 1 n=24	Group 2 n=25	Group 1 n=24	Group 2 n=25	Group 1 n=24	Group 2 n=25
Edema	0	11	10	11	14	23	23
	1	7	8	4	3	1	2
	2	6	7	8	8		
		p>0,05		p>0,05		p>0,05	
Exudate	0	15	18	19	19	23	22
	1	6	3	2	1	1	3
	2	3	4	3	5		
		p>0,05		p>0,05		p>0,05	
ostiomeatal complex	0	13	17			·	
	1	8	5				
	2	3	3				
curvature of the nasal septum	2	22	21	-			
		p>0,05					
Crusts	2			19	20		
				p>0,05			
Fibrin	2			5	2		
				p>0,05			
Perforation	2				2		1
Total points for all patients/average number of points per patient		89/3,7	86/3,4	77/3,2	76/3,0	2/0,08	6/0,24

#### Table 2. Endoscopic assessment of the nasal cavity on the Lund-Kennedy scale

\**p*<0.05 — the values are reliable

The score before and 10 days after the operation showed that the groups were not different from each other according to the identified endoscopic signs (p>0.05). The performed surgical treatment led to a significant decrease in the sum of points / average score in both groups after 10 days (p<0.05), however, the analysis shows that this decrease occurred due to the correction of OMC structures, the assessment after 90 days showed that the performed surgical 8 (32.0%) cases, bilateral changes were noted in 3 (12.5%) and 2 (8.0%) cases, respectively. Circular thickening of the mucous membrane of the MS on one and two sides was noted in 2 cases in group I, in group II patients — in 3 (12.0%) and 1 (4.0%) cases, respectively.

In addition to the pathology of MS, intra-nasal changes were also detected at the preoperative stage: curvature of the nasal septum in group I in 22 patients
	Group 1 (n=24)		Group 2 (n=25)	
	d/s	d+s	d/s	d+s
Retention cyst, occupying more than 2/3 of the volume	9 (37,5%)	2 (8,3%)	8 (32,0%)	3 (12,0%)
Hypertrophy of the mucous membrane of the alveolar bay	6 (25,0%)	3 (12,5%)	8 (32,0%)	2 (8,0%)
Circular thickening of the mucosa with a block	2 (8,3%)	2 (8,0%)	3 (12,0%)	1 (4,0%)
Total:	17 (70,8%)	7 (29,2%)	19 (76,0%)	6 (24,0%)
	24 (100%)		25 (100%)	

Table 3. The frequency and types of pathology of the maxillary sinus according to CT PS

d — right side; s — left side

(92.0%), in II — in 21 patients (84.0%), and hypertrophic rhinitis — in 23 (92.0%) and 22 cases (88.0%), respectively.

According to the severity of pathology, according to the Lund–Mackay scale, the overall assessment before surgical treatment was 7.3±3.5 for group I patients, 6.9±3.7 for group II patients. Although the assessment value in group I (combination of CVS with the presence of pathogenic flora) was higher, however, this excess was not statistically significant compared to the same indicator in group II, where microbial carrier was absent (p>0.05). Evaluation of the results of CT PS in patients of groups I/II 3 months after simultaneous surgery showed that the values obtained, according to the Lund–Mackay scale, were 1.9±1.3 and 2.1±1.5, respectively, which is significantly lower than the indicators of the preoperative stage (p < 0.05). It should be noted that there were no differences between the groups according to CT PS data during all the survey periods (p>0.05).

## CONCLUSION

1. Preoperative microbiological analysis of a smear from the nasal mucosa in patients with partial absence of teeth in the distal part of maxilla and CMS revealed a high incidence of pathogenic microflora in almost half of the examined patients (48.9%).

2. Preoperative antibacterial therapy corresponding to the identified microflora allowed simultaneous treatment and prevented the development of odontogenic postoperative complications.

3. Thus, the algorithm used for the management of patients with partial absence of teeth in the distal parts of the maxilla and CMS, combined with pathogenic microflora, made it possible to combine two diverse operations into a single surgical intervention, reduce the number of anesthesia, reduce hospital stay and duration of rehabilitation, increase patient compliance and cost-effectiveness of treatment.

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# IMPROVEMENT OF PERIODONTAL TREATMENT METHODS IN PATIENTS WITH DENTAL IMPLANTS

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**ABSTRACT** — In connection with the increase in the number of dental implants installed, there is an increase in the number of inflammatory processes — mucositis and peri-implantitis, which rank first among the complications after dental implantation. Our study confirmed the high clinical effectiveness of the GBT protocol combined with the use of a brush for reciprocating rotation with pulsation in the complex of supportive periodontal therapy. Hence, we can recommend this complex not only for patients at risk (with a history of inflammatory periodontal diseases), but also for other patients with dental implants. This protocol of maintenance therapy is a simple and cost-effective way to prevent inflammatory complications after dental implantation.

KEYWORDS — periodontal diseases, dental implants, Guided Biofilm Therapy (GBT) protocol.

### INTRODUCTION

Today, dental implantation is widely used all over the world to replace missing teeth. In this regard, there is an increase in the number of cases of inflammation of the surrounding tissues — mucositis and peri-implantitis. The frequency of inflammatory complications ranges from 54-77% — mucositis and peri-implantitis — 16-22% [1,2,3].

It has been proven that the main etiological factor in the occurrence of inflammatory complications in the area of implants — mucositis and peri-implantitis is a biofilm [6, 7, 8, 9]. Studies have shown a significant correlation between poor oral hygiene and peri-implantitis [10, 11], and the role of existing periodontitis as a risk factor for mucositis and peri-implantitis is also noted [12, 13]. Those implants placed in patients with a history of periodontitis are associated with a higher incidence of biological complications and lower rates of success and engraftment than in periodontically healthy patients. High rates of implant loss are associated with severe forms of periodontal disease [14]. Biofilm-related infections are known to be resistant to antimicrobial therapy [15] if the biofilm is not mechanically disrupted [16].

Due to the peculiarities of the implant surface and limited access to the biofilm, surgical access may be required more often and at an earlier stage in the treatment of peri-implantitis than in periodontal therapy [10]. Thus, intervention in biofilm formation is a universal measure for the prevention of oral diseases [17].

Since inflammatory complications not only lead to destruction of bone tissue around implants and the risk of their loss, but also have a negative effect on general health, supportive peri-implant therapy (SPIT) should be an integral part of implant treatment [4]. To ensure a favorable long-term result of implantation, it is necessary to take all measures for the prevention and timely treatment of mucositis and peri-implantitis [5].

The basic principle of operation of a hygiene product — a toothbrush, the regularity and correctness of its use can affect the results of individual oral hygiene and the prevention of caries and periodontal diseases [18, 19, 20, 21], there are few data in the literature on the influence of the method of individual oral hygiene in patients with dental implants at risk for the result of maintenance therapy.

#### Purpose:

to improve the methods of peri-implant therapy for dental implantation.

## MATERIALS AND METHODS

85 patients with supportive periodontal therapy (SPT) aged 24 to 52 years with concomitant initial and moderate (mild to moderate) generalized periodontitis in remission were under observation (see Table: Classification of periodontal diseases and conditions and peri-implant tissues, 2018) [22, 23], in equal proportions formed the study group, which underwent dental implantation according to a two-stage protocol (153 implants), within 1, 3, 6 months after the installation of the orthopedic constructions.

Depending on the method of individual oral hygiene and the protocol of professional oral hygiene, the patients were divided into three groups. SPIT patients of the first group (I, n = 30) and the third (III, n = 25) 109

group were carried out according to the Guided Biofilm Therapy (GBT) protocol aimed at controlling biofilm, which is of great importance in patients at risk — with periodontitis, including stages in the following sequence (Fig. 1): (Fig. 1e) with erythritol powder (Air-Flow Master Piezon, Air-Flow Plus powder, 14 µm, EMS) [24],

5. Hardware ultrasonic method for removing mineralized dental plaque (Air-Flow Master Piezon, EMS), instrument PS in the area of teeth, PI instru-



Fig. 1 (a, b, c, d, e, f, g, h, i). Stages of professional hygiene of oral cavity according to the Biofilm Guided Therapy

1. examination, diagnosis (Fig. 1a);

2. indication of biofilm of different maturity with a three-tone dye (GC TriPlaque ID Gel) (Fig.1b),

Fig. 1 (a, b, c, d, e, f, g, h, i).Stages of professional oral hygiene according to the Guided Biofilm Therapy protocol.

Fig. 1 (a, b, c, d, e, f, g, h, i).Stages of professional hygiene of oral cavity according to the Biofilm Guided Therapy.

3. motivation of the patient, training in rational oral hygiene with the correction of manual hygiene skills and the selection of individual hygiene products, taking into account the identified zones of presence of mature biofilm;

4. air polishing to remove biofilm sub- and supragingivally (Fig. 1c, d), from the oral mucosa

ment in the area of implants with maximum irrigation flow aimed at the visualized areas after removing biofilm (Fig. 1f)

6. quality control of professional oral hygiene (Fig. 1g),

7. rational individual hygiene and supportive therapy through individually set periods with hygiene control (Fig. 1h — control after a week, Fig. 1i — after a month).

Patients of the second (II, n = 30) group underwent professional oral hygiene according to the *classical* protocol — diagnosis, removal of mineralized deposits by ultrasound, biofilms above the gums — air polishing with sodium bicarbonate powder (Air-Flow Classic, EMS, 65 µm), under gum and in the area of implants — glycine (Air-Flow Plerio, EMS, 23 µm) [25].

All patients were recommended (prescribed): methods of interdental hygiene (brushing and flossing), an irrigator. In group I, patients cleaned their teeth with a manual toothbrush, the rest — with an electric one: in group II — a brush brush for reciprocating rotation (7600 rotation movements per minute) (Oral-B Vitality), in group III — a brush with reciprocating rotary pulsating movements (up to 10,500 reciprocating-rotational and up to 48,000 pulsating movements per minute) and Bluetooth for feedback and optimization of the efficiency of the teeth cleaning process through a mobile application by processing data received from the front camera of a smartphone during the procedure (Oral-B Genius). The movements of the brush for reciprocating rotation with pulsation determine its effect on the biofilm: the pulsating movements destroy, and the reciprocating movements remove it from the surface of the teeth and orthopedic structures. In the application, individual settings were entered for patients with an increase in the recommended cleaning time in the area of implants, and the application also generates a reminder to the patient about the need for hygiene procedures, monitors their compliance (including interdental hygiene with the use of additional means), encourages for correct implementation, gives comments. reference data, records the collected information, generates a statistical report on the quality of the patient's personal hygiene and sends it to the doctor's (assistant's, administrator's) e-mail.

The effectiveness of SPIT was assessed based on the analysis of clinical parameters (objective examination) and indicators of periodontal and hygienic indices: the index of quantitative determination of plaque in the gingival area Silness-Loe (SL), the index of plaque interdental spaces API, the index of bleeding PBI (papilla bleeding index) (Muhllemann -Sukser), PMA index, subjective pain sensations were recorded according to the visual analogue scale (VAS), the timing of the manipulations performed according to each of the protocols was carried out, the patients were questioned twice.

## **RESEARCH RESULTS**

Indicators of hygienic and periodontal indices before hygiene measures were: S-L — in group I  $1.8\pm0.1$ ; in II —  $1.7\pm0.1$ ; in III —  $1.8\pm0.1$ ; API — 40, 38 and 43%; PBI —  $1.3\pm0.3$ ;  $1.2\pm0.1$ ;  $1.3\pm0.1$ ; PMA  $13.7\pm1.2$ ;  $13.2\pm1.3$ ;  $15.6\pm1.1$  in groups I, II and III, respectively. After professional oral hygiene, motivation and correction of hygiene skills in the second visit (after 3 months), varying degrees of improvement were recorded in most patients.

With approximately the same initial data in group II, on average, there was no negative dynamics,

in groups I and III — positive dynamics in hygiene indices and periodontal indices during the entire observation period, with a statistically significant superiority in group III. Thus, the reduction of the index of gingival plaque S-L in group III after 3 months was 3 times higher (p < 0.01) than in group II, 5.5 times (p < 0.01) than in group II; the API index is 1.6 times (p < 0.05) higher than in group I, 1.9 times higher than in group II (p < 0.01). The dynamics of periodontal indices was noted in direct correlation with changes in the level of hygiene indices (Fig. 2a).

Fig.2 (a, b). Dynamics of hygienic and periodontal indices after 3 and 6 months from the initial level,%.

Fig. 2 (a, b). Dynamics of hygienic and periodontal indices in 3 and 6 months from the initial level,%.

After 6 months, against the background of professional hygiene within the SPIT and hygiene recommendations, an even more pronounced difference in hygienic and periodontal status was observed in the study groups: and to the data obtained after 3 months, then in group II they remained stable compared to the level after 3 months or even returned to the initial value (Fig. 3b).

The timing showed a lower time spent on professional oral hygiene according to the Guided Biofilm Therapy protocol (in patients of groups I and III) by an average of  $14.3\pm5.6\%$  (p < 0.05) at a visit after 3 months and by 21,  $1\pm7.8\%$  (p <0.01) after 6 months than in group II. The assessment of subjective pain sensations during the SPIT procedure according to VAS showed in the GBT group 2.8 (p < 0.01) and 3.4 times (p <0.01) (first and second procedures) lower Picures compared to the group, where professional hygiene was carried out according to the classical scheme. When answering the questionnaires, more than 80% of respondents from groups I and III (GBT) noted the visualization of biofilm on the surface of teeth during staining as an important motivating factor for hygiene; increased sensitivity of teeth after professional hygiene in these groups was noted 3.3 times less patients than in group II. 96% of patients in group III indicated an increase in responsibility for observing individual oral hygiene, noting the analogy of reports sent by a mobile application with a doctor's constant monitoring of compliance with prescriptions.

Thus, without the indication and visualization of biofilm and the patient's motivation to correct the existing shortcomings in individual hygiene, the use of an electric toothbrush (group II — the classic PGPR protocol, Oral-B Vitality brush) did not give any advantages over group I (GBT protocol, manual brush ).

The use of the GBT protocol showed better clinical results in both groups (I and III) in comparison 117



Fig. 2 (a,b). Dynamics of hygienic and periodontal indices in 3 and 6 months from the initial level, %

with the group with the classical protocol; in addition, a decrease in the doctor's time for carrying out a maintenance procedure was recorded on average by 18.3%. The absence of unpleasant sensations during the procedure and the phenomena of hyperesthesia after it in these groups make it possible to count on a large proportion of patients *return* to supportive therapy and adherence to its terms.

### CONCLUSION

The study showed both the high clinical effectiveness of the combined inclusion of the GBT protocol and the use of a brush with the technology of reciprocating rotational movements with pulsation and feedback through a mobile application in a complex of maintenance periodontal therapy, which statistically significantly surpasses the control group according to the index score, and economic efficiency and allows recommend this complex not only for patients at risk (with a history of inflammatory periodontal disease), but also for other patients with dental implants.

Biofilm control through clinically validated personal hygiene and Guided Biofilm Therapy as part of maintenance therapy is a simple and cost-effective way to prevent inflammatory complications after dental implantation and to ensure long-term stable performance of implant-supported prostheses.

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# CLINICAL AND LABORATORY EVALUATION OF A NOVEL DENTAL GEL FOR TREATMENT OF CHRONIC CATARRHAL GINGIVITIS

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**ABSTRACT** — This article presents the study of a dental gel developed by us, containing, as an active ingredient, sanguitrithrin and oil extract from calendula flowers and yarrow grass. As a result of our studies of the dental gel on 1,844 children and adolescents, we revealed that it has anti-inflammatory and wound-healing activities and produces anti-inflammatory, reparative, hemostatic and trophic effects. The results of the study make it possible to use the dental gel in clinical practice for treatment of inflammatory periodontal diseases in children. We substantiated the prospects of using the phytocomplex in the form of a dental gel and proved it as effective and safe. Besides, its dosage form is convenient for use in dental practice and even provides advantages over known domestic analogues.

**KEYWORDS** — plant-based (phyto) dental gel, periodontal diseases, anti-inflammatory effect.

### INTRODUCTION

An analysis of the results of epidemiological studies conducted in various countries and regions indicates a high prevalence of inflammatory periodontal diseases in people of all age groups, including children and adolescents (4, 7, 8, 11).

The high prevalence of inflammatory diseases is due to inadequate diagnosis, the course of inflammatory periodontal diseases is particularly resistant to treatment, which determines the importance and urgency of this problem in modern dentistry (5, 6). The initial manifestations of inflammatory periodontal diseases occur in children with temporary bite, with age, the prevalence increases and their severity worsens, while undiagnosed catarrhal gingivitis without appropriate local and general therapy can turn into a more severe form - periodontitis (9, 10).

In modern dentistry, many options for therapeutic effects are considered using well-known methods and means, while the use of alternative methods is also relevant, including various natural components herbal remedies that reduce the possibility of imbalance in the normal flora (1, 2, 3, 12). This served as the basis for the development of our composition in the form of a dental gel based on the phytocomplex and evaluation of its effectiveness in the treatment of chronic catarrhal gingivitis.

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#### The aim of the study

was to evaluate the effectiveness of the treatment of chronic catarrhal gingivitis using a phytocomplex in the form of a dental gel.

## MATERIALS AND METHODS

A comprehensive dental examination was carried out in 1,844 children and adolescents, including 625 children at the age of 6: 610 adolescents at the age of 12 and 609 adolescents at the age of 15. The next step was the development of the technology and composition of a dental gel based on a phytocomplex containing an oil extract from calendula flowers and yarrow herb and sanguirithrin in a 1: 1 ratio. (Pupykina K.A., I shmakova Z.P., Shikova Yu.V., Averyanov S.V. (2016) Dental Gel with plant extract for treatment of inflammatory diseases of periodontium and oral mucosa. Patent RF, 2621297, May 4, 2016). Then, the effectiveness of the treatment of chronic catarrhal gingivitis was evaluated.

Statistical processing of the obtained data was performed using the STATISTICA software package for Windows 10.0. and Microsoft Excel. Methods of parametric and nonparametric statistics were used. The arithmetic mean (M), the arithmetic mean error (m), the reliability criterion (t), and the standard deviation were calculated.

## RESULTS

An epidemiological examination of 1844 patients — children aged 6 years and adolescents 12, 15 years old — revealed a high prevalence of chronic catarrhal gingivitis (K05.1 according to ICD-10) in 1344 children, which amounted to 72.88  $\pm$  1.21% of cases. An intact periodontium was found in 27.12% (500) of the examined 6-year-old children and adolescents aged 12, 15 years.

Depending on age, inflammatory periodontal diseases were noted in  $53.44 \pm 2.85\%$  (334) cases in 6-year-old children, in  $80.28 \pm 3.45\%$  (490) — in

12-year-old adolescents and in 85 38 ± 3.68% (520) in 15-year-olds.

The intensity of lesions of the periodontal tissues in the examined children according to the indicators of the complex periodontal index KPI (Leus P.A., 1988) also had a tendency to a gradual increase in the indicator depending on age. Thus, in 6-year-old children it was  $1.21 \pm 0.02$ , in 12-year-old adolescents  $-1.56 \pm 0.03$  points, and in 15-year-old adolescents it reached  $1.74 \pm 0.01$  points.

When assessing the PMA index in children aged 6 years, a mild degree of in-flammation in the periodontal tissues was revealed in  $43.24 \pm 2.71\%$  of cases, and in  $10.2 \pm 1.66\%$  of cases — an average degree of inflammation. In adolescents aged 12 and 15 years, a mild degree of inflammation according to the PMA index was diagnosed in  $65.26 \pm 2.15\%$  and  $66.0 \pm 2.08\%$ , respectively, the average degree was diagnosed in  $15.02 \pm 1$ , 64% and  $19.38 \pm 1.73\%$  of adolescents, respectively.

Thus, when assessing the dental status and condition of periodontal tissues, among the main dental diseases in the examined children, chronic catarrhal gingivitis (K05.1, according to ICD-10) prevailed in  $63.3 \pm 1.33\%$  of cases.

## DEVELOPMENT OF A DENTAL GEL CONTAINING PHYTOCOMPLEX

The proposed method of application of the dental gel used for the treatment of chronic catarrhal gingivitis, showed that the dental gel was reliably fixed on the area of chronic catarrhal gingivitis and had high manipulation characteristics.

The composition of the dental gel provided a drug with a high therapeutic activity and prolonged action. At the third stage, as a result of a preclinical study of the phytocomplex with a known proportion of individual components, the anti-inflammatory activity of the dental gel was established — the inflammation index was  $36.14\pm1.32$  (p<0.05).

In a laboratory study of the antimicrobial activity of the original dental gel, the largest value of the diameter of the zone of inhibition of the growth of microorganisms was established for a 0.5 solution of sanguirithrin (20 mm). The lowest antimicrobial activity was found in the oil extract of calendula petals (Calendula officinalis) and herbaceous herb (Herba Millefolii) (3 mm).

Analysis of the data of the study on antimicrobial activity revealed that a mixture of a solution of sanguirithrin, an oil extract of calendula officinalis and a herb of yarrow, and has the greatest antibacterial activity against gram-positive bacteria and fungi.

## EFFECT OF THE DENTAL GEL ON THE CONDITION PERIODONTAL TISSUES

For the clinical assessment of the effectiveness of local treatment of chronic catarrhal gingivitis in children of 6 years old and adolescents aged 12, 15 years, an examination was carried out before and after treatment. Patients' complaints were studied and the data of objective examination, index assessment, microbiological research in dynamics were compared before and after the treatment in 14 days, 6 months, 12 months.

The scheme of complex treatment of inflammatory periodontal diseases included the phytocomplex developed by us in the form of a dental gel containing sanguirithrin and an oil extract from calendula flowers and yarrow herb as an active component. At the same time, the choice of the drug in the prognostic aspect turned out to be pathogenetically justified and promising. During the clinical stage of the study, we assessed the state of periodontal tissues in children of 6 years old and adolescents 12, 15 years old according to all criteria, which characterizes the level of inflammation in patients of the studied groups in the presence of chronic catarrhal gingivitis.

Patient K., 15 years old, complained of bleeding gums when brushing teeth. Denies somatic pathology, allergic history is not burdened. The analysis of the hygienic index revealed an unsatisfactory level of oral hygiene, the study of the CPI and PMA indices showed the presence of gingivitis, according to the PMA index — corresponds to moderate severity, the GI index corresponds to moderate gingivitis, when studying the PBI index, bleeding was noted when probing along the edge of the apex of the papilla. Diagnosis: chronic catarrhal gingivitis (K05.1) (Fig. 1, 2, 3, 4).

The assessment of the hygienic and periodontal status was carried out after 6 months in dynamics. When determining the hygiene status, a good level of oral hygiene was noted.

## CONCLUSION

The results of our study substantiate the pathogenetic mechanism and indications for the use of the dental gel based on sanguinethrin and oil extract of calendula flowers and yarrow herb in the treatment of chronic catarrhal gingivitis in children and adolescents. The prospects for the use of the phytogel of the specified composition were observed as an effective and safe, with a convenient dosage form for the use in dental practice. The use of the gel provides advantages over known domestic analogues.

The obvious advantages of the dental gel of the proposed composition are its relative cheapness, ease



*Fig. 1.* Patient K., 15 years old. Diagnosis: chronic catarrhal gingivitis (K05.1) initial situation



*Fig. 3.* Patient K., 15 years old. Periodontal condition 6 months after starting treatment with the dental gel



Fig. 2. Patient K., 15 years old with applied dental gel

of use by a dentist, good handling characteristics. It is fundamentally important that all components of the phytogel are included in the list of the Russian State Pharmacopoeia.

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*Fig. 4.* Patient K., 15 years old. Periodontal condition 12 months after treatment with the dental gel

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117

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# IDENTIFICATION OF ORAL HYGIENE LIVEL IN HEARING-IMPAIRED COLLEGE STUDENTS IN PENZA REGION (RUSSIA)

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ABSTRACT — THE AIM OF THE STUDY is to compare the level of oral hygiene practices among students with hearing disabilities and well-hearing university students. MATERIALS AND METHODS. The level of hygienic knowledge was studied using the sociological research method (questionnaire) among students with hearing disabilities at Penza Medical College, specialty "Orthopedic Dentistry" and their peers — students of Dentistry Department at the Penza State University. 60 students took part in the study. The average age of the subjects was 19.5±0.85 years.

RESULTS AND DISCUSSION. The results of the study indicate a weak motivation to preserve dental health, insufficient awareness of the means and methods of oral hygiene among hearing-impaired students compared with their peers. In the university students all the survey indicators were 1.5–2 times higher than in the hearing-impaired college students. This indicates an insufficient specialized education and awareness as a consequence of hearing limitations.

CONCLUSION. It is necessary to strengthen dental education in students with hearing impairments, taking into account the specifics of communication and the worldview of this population. This can be achieved through educational videos and options for free preventive dental services.

**KEYWORDS** — dental health, hearing disabilities, oral hygiene.

## INTRODUCTION

The dental health of the Russian population has a steady tendency to deteriorate [1, 4, 5, 8]. The high level of dental morbidity in various social groups is the result not only of the conditions and lifestyle, but also of the system of organization of outpatient dental care for certain categories of the population [2, 3, 7, 13]. One of the problems of modern dentistry is the improvement of dental care for deaf-mute patients.

Diseases of the hearing organs currently occupy far from the last place in the list of socially significant diseases. Hearing loss and deafness not only worsen the formation of intelligence, but can also lead to a change in the personality of an individual. This may lead to lower social adaptability and disability in a person with hearing impairments. [2, 8, 10].

Dental health in the hearing impaired, as well as for healthy people, is part of general health. Many authors have proved that the state of the oral cavity of each person affects not only his health, but also physical and socio-psychological functioning [1, 5, 10, 11].

The special medical and social status makes this population particularly vulnerable in matters of dental education, which entails a low level of knowledge on dental hygiene, as well as insufficient motivation to preserve and strengthen oral health. The above indicates the need to solve the urgent problem of rational organization of outpatient dental care for the hearing impaired in order to increase its accessibility and quality [1, 6, 8, 12].

### **METHODS**

60 students took part in our study. The subjects of the study were 30 students with hearing disabilities from Penza Medical College, specialty "Orthopedic Dentistry" and 30 healthy students of the Dentistry Department at Penza State University (Penza, Russia). The average age of the examined was  $19.5 \pm 0.85$ years. The study of the level of hygienic knowledge was carried out using a sociological research method (questionnaire). In the course of the work, 60 questionnaires were filled out and processed, consisting of 21 questions, starting with the general information and reflecting the attitude of the respondents to problems of oral hygiene. Statistical processing of the obtained data was carried out using the Statistica 8.0 for Windows application software packages.

## **RESULTS AND DISCUSSION**

Analysis of the results of the survey of patients with hearing disabilities showed that 23% of the surveyed contingent visit a dentist once a year, rarely — 20%, and on symptoms — 57%. Thus, it can be concluded that this group of the population is poorly informed about the frequency of visits to the dentist.

Among the examined deaf students, 74% do not use oral hygiene aids, while 82% of the surveyed have a desire to receive professional recommendations on oral hygiene. 69% of respondents do not know how often they need to change their toothbrush. They select basic oral hygiene products mainly according to their choice (93%). On the question of knowledge about the need to visit a dentist for professional oral hygiene, 79% of respondents answered that they do not know about professional hygiene, and only 21% know about this procedure. Thus, it can be concluded that this group of the contingent has a weak idea of additional hygiene products, the importance of professional hygiene and the rules of oral hygiene.

According to the analysis of the survey data of the university students, 67% of the surveyed contingent go to the dentist 1 time a year, rarely — 10%, and if necessary — 23%.

24% of the university students do not use oral hygiene aids, while 82% of the surveyed have a desire to receive professional recommendations on oral hygiene. 21% of respondents do not know how often they need to change their toothbrush. They select basic oral hygiene products mainly according to their choice (78%). On the question of knowledge about the need to visit a dentist for professional oral hygiene, they answered that they did not know about professional hygiene — 18% of respondents and only 82% knew about this procedure. Thus, it can be concluded that this group of the contingent is not well informed about additional hygiene products, about the importance of professional hygiene and the rules of oral hygiene.

The results of the study indicate a weak motivation to preserve dental health, insufficient awareness of the means and methods of oral hygiene of hearingimpaired people compared with healthy students of the Penza State University.

## CONCLUSION

The results obtained indicate insufficient promotion of the prevention of dental diseases and oral hygiene lessons.

It is necessary to develop comprehensive approaches to dental education of the hearing impaired, taking into account the specifics of communication and the worldview of this medical and social group. Integrated approaches include video teaching materials, hygiene lessons. It is also important to work with a psychologist so that hearing impaired people are not afraid to go to the dentist.

To strengthen the motivation of hearingimpaired people to preserve dental health and visit a dentist, Dentists, together with sign language interpreters, need to conduct oral hygiene lessons, conversations about oral hygiene aids and products, about the possibility of free treatment in urban dental clinics and the need for professional oral hygiene.

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# EVALUATION OF ENDODONTIC TREATMENT IN THE PRACTICE OF THERAPEUTIC DENTISTRY

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**ABSTRACT** — AIM OF THE STUDY is to study the need for a qualitative diagnosis before endodontic treatment, as well as methods for determining additional root canals, ways of passing the root system of the tooth, irrigation and obturation methods and the frequency of possible complications during endodontic treatment.

MATERIALS AND METHOD: The quality of endodontic treatment was studied using the social research method (questionnaire) among dentists from Penza and Penza Region (Russia). 140 practicing doctors participated in the study.

RESULTS AND DISCUSSION: According to the results of the survey, most doctors note a favorable result of endodontic treatment and associate this with the use of X-ray imaging, especially computed tomography, which greatly contributes to the qualitative and accurate mapping of the root system and the surrounding bone structure.

CONCLUSION: After the conducted research, we can assume that in the near future no intervention in the root system will be complete without preliminary X-ray diagnosis and without means of magnification.

**KEYWORDS** — endodontic treatment, dentist, X-ray diagnosis, root canal.

## INTRODUCTION

Endodontic treatment is a complex of manipulations, the purpose of which is to depulpate an infected tooth, giving a shape to the root canal based on the chosen obturation technique [2, 3, 6, 9].

Each stage of endodontic treatment requires special attention, knowledge and skills of the dentist, especially at the diagnostic stage [5, 7]. It is precisely due to neglecting this stage that complications most often occur, therefore, it is important to identify the number of root canals, their shape, structure and all possible variations of the anatomical structure of the maxillary system, which is observed both on the upper and lower jaw [1, 8]. In 1971, Professor Walter Hess proved to the whole world the diversity and complexity of the morphology of root canals, which is difficult for full-fledged cleaning and obturation [4, 10, 11].

Particular attention should be paid to the first molar of the upper jaw, because it is in this tooth that the number of root canals varies and can reach eight [6, 7, 10].

Such a clinical case was described in 2011 by Kottor J. In Portugal, during endodontic treatment in a 30–year-old Indian patient, eight root canals were identified, namely: three root canals were identified in the mesial-buccal and distal-buccal roots, and two canals in the palatine root [5].

## MATERIALS AND METHODS

The subjects of the study were dentists of Faculty of Dentistry at Penza State University, as well as dentists of Penza and the Penza region. 140 doctors took part in the study, of which 72 dentists have up to 5 years of work experience, 34 dentists — 5-10 years, 30 doctors — 11-15 years and 4 dentists — above 15 years. 108 doctors work at private institutions and 32 dentists — at public institutions.

The evaluation of the quality of endodontic treatment was carried out using a sociological research method (questionnaire). In the course of the work, 140 questionnaires consisting of 25 questions were filled out and processed, taking into account the specialist's work experience, diagnostic methods, treatment stages and materials used. Statistical processing of the received data was carried out using the Statistics 8.0 application software packages for Windows.

### **RESULTS AND DISCUSSION**

According to the results of the survey, diagnostic X-ray examination before the start of endodontic manipulations is carried out; always — 51% of doctors who took part in the survey, 33% — often, 11% — rarely and only 5% — never resort to this diagnostic method. They also use CT quite often in their practice, namely, 12% of doctors absolutely always conduct an X-ray examination for patients with 3D, 40% — quite often, 20% — rarely and, unfortunately, a considerable part, namely 28% — never use CT in their practice.

Accordingly, 70% of the surveyed doctors noted a positive result in endodontic treatment using X-ray diagnosis. Additional methods of magnification (binoculars, microscope) are used in their practice by only 20 out of 140 interviewed doctors, even taking into account the fact that they significantly increase the quality of the manipulations performed.

Most of the practicing dentists, namely 93% (130 people) recorded the occurrence of additional root canals in their practice, and special attention was paid to the first molar on the upper jaw, where the root canal system is the most variable and unpredictable (Fig. 1, 2).



Fig. 1. Options for the location of root canals



Fig. 2. Selection of the technique of instrumental treatment of root canals

The majority of the surveyed doctors — 84% use endodontic tips, which indicates the high technical equipment of doctors.

One of the aspects of high-quality endodontic treatment is the choice of a means for washing root canals. The results of the survey showed that sodium hypochlorite solution is mainly used (105 people -75%), which has the most pronounced antimicrobial effect, and 25% — a combination of solutions.

Drying of root canals is an equally important stage, if neglected, complications may arise, for example, the development of an air embolism when drying the canals with air. Questionnaire data showed that doctors make a choice in favor of paper pins -67%, cotton wool -20% and the remaining 13% use a combination of the above-mentioned means.

The most commonly used material for obturation of root canals are preparations based on zinc oxide and eugenol -71%,

zinc-phosphate + resorcinol formaldehyde — 6%, materials based on epoxy resins — 15%, resorcinol-formalin + zinc oxide eugenol — 8%.

For obturation of the root canal system 95% of dentists use in my practice gutta-percha pins, which ensures a reliable seal, and only 5% disregard their use.

Questionnaire data showed that 90% of doctors perform root canal fillings up to the physiological apex, 5% — up to the anatomical apex, 5% — are removed beyond the apex.

X-ray diagnosis is an integral part of the work of any modern dentistry [1]. So, a large number of doctors in their practice widely use both extraoral research methods such as computed tomography, orthopantomography, and intraoral methods — sighting. Based on this, it was found that almost all doctors — 75% always carry out a control scan to identify the quality of obturation, 20% — often, 5% — rarely.

Every practicing dentist has faced complications after the treatment. This is associated with a number of reasons, and the most common of them is the destruction of anatomical (physiological) narrowing, which was found in practice in 48% of the respondents, a missed root canal -17%, a fracture of the instrument in the root canal -6%, perforation of the root walls -2%, due to infection -27%.

The above reasons lead to complications such as changes in periapical tissues 57%, residual pulpitis 10%, post-sealing pain — 33%.

In the structure of the reasons for the irregular use of additional diagnostic tools, the first place belongs to the problem of the lack of necessary equipment in clinics for X-ray diagnostics and the need to refer patients to specialized institutions. Further, there are a number of reasons for the lack of financial capabilities of patients, since conducting 3D diagnostics additionally requires costs. The third reason was the inability of the doctor to decipher and describe CT scans.

## CONCLUSION

The results of the survey showed that carrying out diagnostic measures, such as X-ray examination, during endodontic treatment significantly reduces the risk of complications, which is associated with the detailing of the root system on a CT scan and predicts a favorable outcome of the dentist's intervention. Also, 14% of the respondents noted the high quality of treatment when using additional means of magnification, which contributes to better visualization of the working field. Based on the above, we can assume that in the near future no intervention in the root system will be complete without preliminary diagnosis on an X-ray machine and without means of magnification.

It was noted that sodium hypochlorite is the actual preparation for irrigation, and paper pins are the best way to dry the channels, as noted by most of the interviewed doctors, so we suggest using them in practice.

In the issue of obturation, more than 90% of dentists preferred gutta-percha pins and filling to the physiological tip, which indicates the relevance of using this method of filling and its effectiveness?

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# STUDY OF CHANGES IN THE DENTAL SYSTEM DURING REPETITIVE PHYSICAL LOADING

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ABSTRACT — THE AIM OF THE STUDY is to assess the impact of professional physical activity on the dental status of cheerleaders with constantly recurring physical load. At the moment, the impact of serious physical load on individual organs, tissues of the human body and on dental health has not been studied enough. Physical exercises with weights affect the condition of the hard tissues of the teeth, periodontal and temporomandibular joint. MATERIALS AND METHODS: The studies were carried out by the method of clinical examination, the prevalence of pathological changes in the temporomandibular joint, damage to the tongue, teeth erasability were evaluated. **RESULTS AND DISCUSSION:** The results of studies on the prevalence of tooth abrasion, tongue damage and pathological changes in the temporomandibular joint in cheerleader athletes with professional sports experience of more than 5 years are worse than in cheerleader athletes with professional sports experience of 2 to 5 years. CONCLUSION: All the results show that a professional sport has a significant impact on the dental system, contributes to the development of pathological changes. It is necessary to develop tools and materials for the effective prevention of teeth erasure, tongue damage and pathological changes in the temporomandibular joint in order to avoid possible consequences.

**KEYWORDS** — cheerleader athletes, teeth erasability, temporomandibular joint, tongue, dental status, dentistry.

## INTRODUCTION

The last century was a century of rapid development of sports. Cheerleading is one of the newly emerged sports. To date, it is impossible to achieve success in cheerleading without having a sufficiently high level of flexibility, endurance, and coordination abilities [3, 9, 13].

It is known that regular physical exercises are of great importance for strengthening health, increasing the stability and resistance of the body [1, 5–7]. However, excessive physical exertion can contribute to an increase in the morbidity of athletes (including dental) [11]. In B. Reid studies, the prevalence of untreated caries and oral pain among 9620 athletes

of Special Olympics was estimated. The prevalence of oral pain and untreated caries was 13.5% and 30.4%, respectively [10]. Thus, athletes are more likely than their non-sports peers to have anomalies of teeth and jaws, the prevalence and intensity of caries, dental injuries and maxillofacial injuries are higher [2, 4]. A feature of the physical exertion of cheerleader athletes is the constant jumping from a height, in which there is a strong compression of the jaws, the load on the temporomandibular joint. With constant jumps, accidental injury to the tongue is also possible. More often under the influence of physical activity among athletes cheerleaders determine the presence of pathological changes in the temporomandibular joint (looseness of the temporomandibular joint, "clicky" jaw pain dysfunction syndrome of the temporomandibular joint), occlusion, dental abrasion (proximal and occlusal abrasion, professional teeth grinding), periodontal disease (gingivitis, periodontitis), tooth decay, tongue damage [10–12].

## MATERIALS AND METHODS

Our study was conducted by the method of clinical examination of cheerleader athletes who experience constantly recurring physical activity. The study involved 30 people.

The criteria for inclusion in this study were: constant physical professional activity for more than 2 years, the presence of voluntary informed consent. The exclusion criteria for this study were: constant physical professional activity for less than 2 years, refusal to participate in the survey.

According to their professional sports experience, the subjects were divided into 2 groups (15 people each): Group 1 – cheerleader athletes performing from 2 years to 5 years; group 2 — cheerleader athletes who performed above 5 years.

Before determining the indicators necessary for the study, a standard examination of the dental patient was carried out. During the clinical examination, the configuration of the face, skin color, and the presence of pathological formations on it were evaluated. Regional lymph nodes were palpated: mandibular, chin, occipital, cervical. The degree of mouth opening and temporomandibular joint (TMJ) were evaluated, namely: symmetry, smoothness of movements, to determine the deviation of the lower jaw. Next, the vestibule of the oral cavity was examined (mucosa, ducts of the salivary glands, frenulum of the lips, depth of the vestibule) and occlusions were evaluated. Then an examination of the oral cavity itself: the oral cavity and the tongue. During the examination of the dentition and teeth, probing and percussion of the teeth were performed.

Directly for this clinical study, it was necessary to assess the prevalence of tooth abrasion, tongue damage and pathological changes in the temporomandibular joint.

## **RESULTS AND DISCUSSION**

When analyzing the prevalence of tongue injuries in cheerleaders: in group 1 (15 people) -20% of the prevalence of tongue injuries; in group 2 (15 people) -53.3%.

According to the results of a clinical examination of the prevalence of pathological changes in the temporomandibular joint in cheerleaders, it was found that in group 1 (15 people) -13.3% of the prevalence of pathological changes in the temporomandibular joint; in group 2 (15 people) -46.6%.

The analysis of the clinical examination of the prevalence of tooth erasure in cheerleader athletes was carried out and it was found that in 15 people from group 1, the prevalence of tooth erasure was 26.6%; from group 2 (15 people) — 60%.

All these results prove that with constant physical exertion for more than 5 years, the prevalence of tooth abrasion, changes in the temporomandibular joint and damage to the tongue is greater than that of cheerleader athletes who have a professional sports experience of 2 to 5 years.



*Fig. 1.* Prevalence of pathological changes in the dentofacial region in cheerleader athletes

## CONCLUSION

1. The results obtained indicate a high rate of increase in the prevalence of pathological changes in the dental system, such as tooth abrasion, dysfunction of the temporomandibular joint, tongue damage, in cheerleaders due to an increase in sports professional experience.

2. Cheerleader athletes with 2 to 5 years of professional sports experience have significantly bet-

ter prevalence rates of pathological changes in the maxillofacial region than cheerleader athletes with more than 5 years of professional sports experience. From this it follows that it is necessary to develop tools and materials for the effective prevention of damage to the tongue and pathological changes in the temporomandibular joint in order to avoid possible consequences.

3. It is necessary to introduce wearing a protective mouthguard by cheerleader athletes on both jaws during physical load, preventive examinations by a dentist every 3 months, to have a dental cleaning every 6 months or, if necessary, to teach cheerleaders proper oral hygiene. If the recommendations are followed, the likelihood of any pathological changes due to constant physical exertion decreases.

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