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# CONTENTS

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# EDITORIAL

*Dear colleagues,*

Here is the first issue of the year 2020. This year is very important for the journal, its editorial board and authors: starting from this year the journal becomes a quarterly.

In addition, new thematic sections have appeared, contributing to multidisciplinary perspective and internationality.

Another important task of the editorial board is to improve quality of papers and assert new guidelines for preparation of the manuscript. Adhering to the requirements is important for the rating of the journal.

Thanks to active work of the editorial board the amount of papers and their level has significantly increased, which promotes indexing and the recognition of the journal. A special thanks goes to Prof. Vladimir Astashov (Moscow), Prof. Alexey Zhidovinov and Prof. Dmitry Domenyuk (Stavropol), who were consulting and instructing the authors. Without their constant and rigorous work the preparation of the issues would be impossible.

Nowadays the world has entered a very dangerous phase, when an increased responsibility for the health of people in their counties was laid upon medical professionals. Our colleagues in practical medicine do heroic work, putting at risk their health and life. Medical researchers are doing their best to support their colleagues and provide them with necessary information and materials to fight the outbreak of coronavirus.

There are lots of challenges on this way but now medical specialists influence political and economic decision-making. Hope is dawning that when coronavirus is defeated, understanding of priority of health will emerge. Other spheres become secondary, when industry, politics and prosperity depend on the health of the population.

Dear colleagues, I wish all of us that the pandemic eventually comes to an end and life returns to normal.

Looking forward to your reports on latest research and studies!

Yours,

*Editor-in-Chief*
***Dr. Georg Tyminski***

*Dear clinicians, research fellows, colleagues and friends!*

On the modern stage of the development the world medicine as a system of scientific knowledge and practical approaches aimed at identifying, treatment and prevention of diseases has been rapidly developing. New discoveries are being made entitled to improve the healthcare and to help the patients. The key priority for strategic development of medical science worldwide is to develop and introduce modern technologies based on latest innovative methods, which are going to safeguard health in all age groups.

During last decade the theme of precision medicine has been widely debated by the scientific and medical community. The primary goal of the precision medicine is to optimize and to personalize the prevention and treatment, to avoid side effects due to detection of individual specifics of the body. Evidently based scientific-practical interests are determined by a huge, earlier unrealized potential of a *patient-oriented approach*, which is based on the possibility to use individual indicators for planning therapeutic measures to each individual patient.

The volume of published research works, dedicated to various aspects of introduction of personalized methods into clinical practice, has been constantly growing. This confirms not only presence of growing interest but also arising questions, which have to be solved by researchers and practical doctors.

The constitutional anatomy dealing with structural and functional characteristics of the human body, his organs and systems and being viewed from the point of individual typological approach based on constitutional diagnostics has received the recognition of leading medical specialists. The constitutional-anatomical approach evaluates the influence of form-basing factors on body structures, typological features of reactivity, the higher nervous system, functioning of sensor systems, qualitative and quantitative features of muscle activities, etc. The impact of constitutional-typological features on the specifics and such processes as immunological, biochemical, neurohumoral and adaptational ones have been evidently proved. Integrating somatotypological and dermatoglyfic approaches complementing each other in the context of morphological studies, seems to be a productive field of research.

In the current issue you may read about the results of applied researches focusing on the issues of individual variability of human morphological structures. This will empower your professional competence, to widen the concept of the human somatype as a structural, genetically determined expression of the constitution. Constitutional-anatomic data in the context of personalized medicine is going to facilitate the transition from group schemes of prevention and treatment to individual typological schemes. Introduction of such data into practice will enable to accomplish critical indicators for treatment, prioritizing individual health and to improve the health of the population in all age groups.

*Executive Editor*
***Prof. Dmitry Domenyuk***

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# PUBLIC HEALTH AND AIR POLLUTION IN THE CONTEXT OF SUSTAINABLE URBAN DEVELOPMENT

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**ABSTRACT** — The results of the study of the impact of polluted air on the health of the population in the zone of influence of industrial enterprises of oil refining, as well as urban planning factors and natural and climatic conditions that lead to the strengthening of this impact within the limits of the environmental laws of development are presented.

**KEYWORDS** — public health, air pollution, urban planning factors, natural and climatic conditions, environmental laws of development, sustainable urban development.

The outcome document of the Rio+20 Conference, in the context of sustainable development of cities and human settlements, notes the importance of supporting adequate air quality as air pollution has a negative impact on human health [1]. According to the World Health Organization (WHO), air pollution represents a significant environmental risk to public health. Globally, this risk accounts for 7 million premature deaths annually and more than 0.5 million in the WHO European Region [2]. Due to increased risk of respiratory and cardiovascular diseases, as well as lung cancer, the negative impact of air pollution reduces life expectancy in the WHO European Region by an average of 1 year [3]. The costs associated with disability due to air pollution in 2010 in the WHO European Region were about $1.6 trillion; and the annual economic loss of 2015 due to morbidity and premature mortality caused by air pollution in 44 of the 48 countries of the WHO European Region was estimated to be equivalent to 1% of their gross domestic product [4]. Subsequently, the WHO resolution *Health and Environment: Addressing the Effects of Air Pollution on Health* recognized the right to clean air as a fundamental human right [5].

Industry, transport and energy make the greatest contribution to air pollution. In EU countries, fuel combustion was the main source of benzopyrene and some heavy metals emissions in 2015 [6]. At present 55% of the world population lives in cities that are directly connected with the development of industry, energy and transport, and by the middle of the XXI century this indicator will reach 68% [7]. Therefore, among the effective measures to reduce the negative impact of polluted air on public health the UN and WHO materials note the measures in the field of urban development [4, 6, 8].

In 2016, the age-standardized mortality rate attributed to indoor and outdoor air pollution (per 100,000 population) is almost 35 in the WHO European Region, 15 in Germany, 50 in the Russian Federation and 70 in Ukraine [6]. Thus, the problem of clean air, public health and sustainable urban development is also relevant for Ukraine, where about 70% of the population is urban.

### *Purpose of the study*

The purpose of the study was to identify the impact of polluted air on the health of the population in the zone of influence of the northern industrial hub of the city of Kremenchuk (Kremenchuk agglomeration ranks 18th out of 23 agglomerations in Ukraine), as well as the factors and conditions that contribute to the strengthening of this impact.

## MATERIALS AND METHODS

The objects of the study were air and soil pollution (which accumulates this pollution) in the zone of influence of the northern industrial hub of the city of Kremenchuk and the health condition of residents of the Molodizhnyi district with which the industrial hub borders. In addition, the natural and climatic conditions (seasonal and regional features of the natural and climatic potential of the atmosphere dispersion) and urban planning factors (the mutual location of the industrial hub and residential development) were considered, the joint action of which contributes to the accumulation of pollution in the air.

The choice of these territories is motivated by the fact that since 2016 the number of complaints received from residents of the Molodizhnyi district to the Kremenchuk City Council regarding air pollution by enterprises of the northern industrial hub, in particular, the unpleasant smell of petroleum products and deteriorating health has increased significantly. In order to determine the composition and concentrations of air pollutants and the main sources of their emissions,

in 2017 the specialists of the State Institution *Marzeev Institute of Public Health of the National Academy of Medical Sciences of Ukraine* in the zone of influence of the northern industrial hub of Kremenchuk (in particular, 4 of its powerful enterprises: Oil Refinery Ukrtatnafta, Kremenchuk Plant of Technical Carbon; Kahamlyk Washing and Steaming Station (WSS) and Kremenchuk Thermal Power Plant (TPP)) studied the state of air and soil pollution. The concomitant consideration of natural climatic and urban planning factors is motivated by the fact that the majority of complaints fall on the period of summer — from the end of May to September.

The work uses a systematic approach, methods of population survey, comparative, field and statistical analysis. The content of heavy metal (HM) compounds and benzopyrene in soil and atmospheric air was determined by instrumental and atomic absorption spectral analysis method. The determination of polycyclic aromatic hydrocarbons (PAHs) in air samples was based on low-temperature spectral luminescence analysis; the determination of PAHs in soil samples was carried out by gas chromatographic method; the concentration of the sum of saturated hydrocarbons $C_{12}$–$C_{19}$ and the mass concentration of petrol — by chromatographic method.

### *Starting position*

The technologies of Kremenchuk TPP use natural gas and fuel oil; Kremenchuk Plant of Technical Carbon — coke-chemical and oil raw materials; Ukrtatnafta Oil Refinery specializes in oil processing; Kahamlyk WSS provides preparation of tank cars for oil products loading. The closest residential development to the north industrial hub is in the Molodizhnyi district. Sampling of atmospheric air in the area of the industrial hub was carried out in February, May, August and September 2017. The analysis of population morbidity was made on the basis of the data received from the Health Department of the Kremenchuk City Council Executive Committee.

## RESULTS AND DISCUSSION

In February, the measured concentrations of PAHs and HMs in the atmospheric air of the Molodizhnyi district did not exceed the established maximum permissible concentrations (MPC). On the other hand, snow samples on the territory of the industrial zone revealed the presence of some PAHs and vanadium (0.175 mg/dm$^3$), which indicates the presence of these substances in the atmospheric air as well.

In May, August and September on the territory of the industrial hub and residential development sampling of atmospheric air and soil showed excess content of pollutants, in particular: benzopyrene, benzanthracene, vanadium, cadmium, gasoline and saturated hydrocarbons $C_{12}$–$C_{19}$ (Tables 1, 2, 3).

***On the impact of air pollution on public health and self-assessment***. The analysis of prevalence of diseases of the adult population of Kremenchuk in the period from 2012 to 2016 established the growth of indicators of the population morbidity with allergic rhinitis in 1.1 times, chronic bronchitis in 1.3 times, bronchial asthma in 1.3 times. Bronchial asthma was 1.3% higher than the regional rate and obstructive lung diseases was 4.7% higher. The analysis of the levels of adult population primary morbidity, compared to 2012, found a gradual increase in allergic rhinitis by 1.3 times and chronic bronchitis by 12 times; excess of the average region indicator for allergic rhinitis by 3.3%, chronic bronchitis by 6.1%, bronchial asthma by 0.7%, obstructive lung diseases by 6.3%. Between 2012 and 2015, there was also a 3-fold increase in the incidence of chronic bronchitis and an 11-fold increase in allergic rhinitis among children.

Taking into account the fact that the city population is not sufficiently covered by preventive medical examinations and does not always seek medical help before clinical manifestations of a disease, the self-assessment of health and attitudes to the factors that form it were investigated (according to the questionnaire survey of the population). Analysis of the survey data made it possible to establish common features inherent to all age groups: the overwhelming majority of respondents, regardless of gender, are concerned about the environmental situation in the city (Fig. 1A). As for concerns about the environmental situation, it was found that the greatest degree of eco-anxiety is typical for the residents of the Molodizhnyi district (Fig. 1A, B). The majority of respondents of all age groups noted the presence of discomfort from industrial facilities functioning in the city, and the main reason for discomfort was the presence of a constant unpleasant smell (Fig. 2).

The survey revealed the features of subjective assessment of the health status of respondents of different ages and sex (Fig. 3, 4).

Almost half of young people (under 35 years of age) are characterized by *good* assessment of their own health (43% of men and 54% of women). In persons with existing chronic pathology, allergic diseases and diseases of the respiratory system prevailed in the disease structure. One in six male and one in two female respondents, who have no chronic diseases, have noticed deterioration of health status in the recent period and complained about fatigue and drowsiness — 20%, headache — 22%, breathing heaviness — 16%.

Respondents of middle age (from 36 to 46 years) were characterized by *satisfactory* assessment

***Table 1.*** *Content of pollutants in the air and soil in the impact zone of the northern industrial hub of Kremenchuk in May 2017*

| Distance from emission source, (m) | Substance | Concentration | MPC |
|---|---|---|---|
| In the atmospheric air of | | | |
| industrial area | | | |
| 380 | benzopyrene | 0.51 | 0.1 μg per 100 $m^3$ |
| | vanadium | 0.007 | 0.002 mg/$m^3$ |
| residential development | | | |
| 1500 | benzopyrene | 0.53 | 0.1 μg per 100 $m^3$ |
| | vanadium | 0.004 | 0.002 mg/$m^3$ |
| 2170 | benzopyrene | 0.45 | 0.1 μg per 100 $m^3$ |
| | vanadium | 0.003 | 0.002 mg/$m^3$ |
| 2800 | benzopyrene | 0.43 | 0.1 μg per 100 $m^3$ |
| | vanadium | 0.002 | 0.002 mg/$m^3$ |
| In the soil of residential development | | | |
| Distance from emission source, (m) | Substance | Concentration | MPC of benzopyreney in soil, (mg/kg) |
| 380 | benzopyrene | 0.049 | 0.02 mg/kg |
| 2160 | benzopyrene | 0.036 | 0.02 mg/kg |

***Table 2.*** *Content of pollutants in the air and soil in the impact zone of the northern industrial hub of Kremenchuk in August 2017*

| Distance from emission source, (m) | Substance | Concentration | MPC |
|---|---|---|---|
| In the atmospheric air (August, 16$^{th}$) of | | | |
| residential development | | | |
| 1400 | benzopyrene | 0.52 | 0.1 μg per 100 $m^3$ |
| | benzanthracene* | 0.015 | 0.005 mg/$m^3$ for working area (!) |
| In the atmospheric air (August, 29–30$^{th}$) of | | | |
| industrial area | | | |
| 500 | benzopyrene | 0.31 | 0.1 μg per 100 $m^3$ |
| | benzanthracene* | 0.023 | 0.005 mg/$m^3$ for working area (!) |
| residential development | | | |
| 3000 | benzopyrene | 0.35 | 0.1 μg per 100 $m^3$ |
| 2300 | benzopyrene | 0.45 | 0.1 μg per 100 $m^3$ |
| In the soil of industrial area (August, 29–30$^{th}$) | | | |
| near Kahamlyk WSS | vanadium | 193,9 | 150 mg/$dm^3$ |
| | cadmium | 2.44 | 1.5 mg/$dm^3$ |

***Note:*** *the benzanthracene concentration, which is contained in coal tars, which are raw materials of the Plant of Technical Carbon, significantly exceeds the MPC of this substance for the working area (!), while the sampling took place outside the sanitary protection zone (SPZ) of the enterprises of this industrial hub, which is 1000 m.*

***Table 3.*** *Content of pollutants in the air in the impact zone of the northern industrial hub of Kremenchuk in September 2017*

| Distance from emission source, (m) | Substance | Concentration | MPC |
|---|---|---|---|
| industrial area | | | |
| near Oil Refinery | petrol | 28 | 5 mg/$m^3$ |
| | saturated hydrocarbons C12-C19 | 30 | 1 mg/$m^3$ |
| 1100 (beyond the SPZ of Oil Refinery) | petrol | 8 | 5 mg/$m^3$ |
| | saturated hydrocarbons C12-C19 | 25 | 1 mg/$m^3$ |

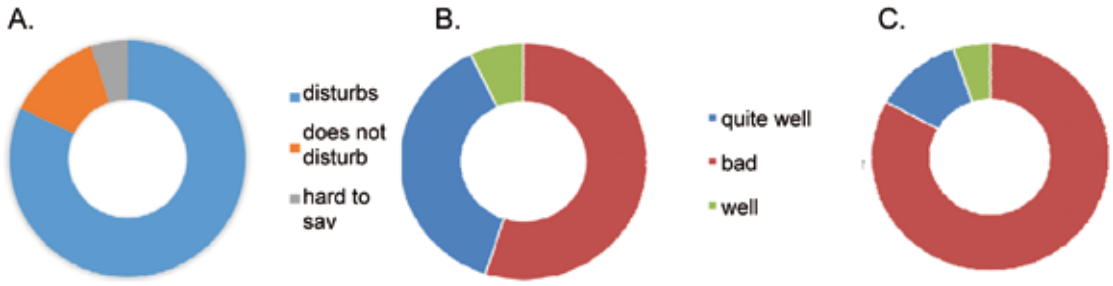


***Fig. 1.*** *Population assessment of environmental situation (A) and comparative assessment of environmental wellbeing of Kremenchuk (B) and the Molodizhnyi district (C)*

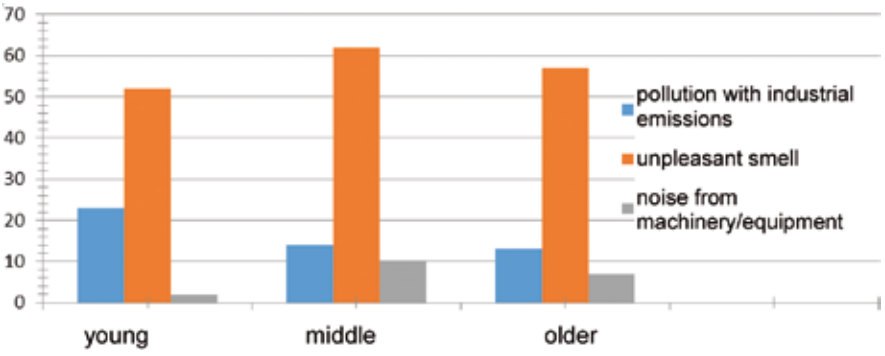


***Fig. 2.*** *Main reasons for discomfort as indicated by the population of three age categories (%)*

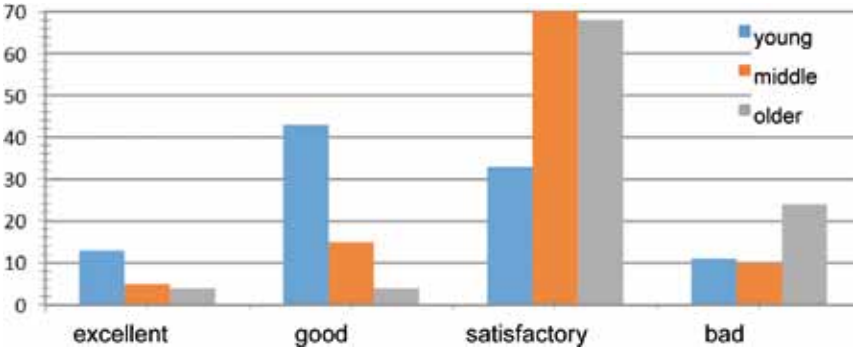


***Fig. 3.*** *Distribution of respondents of different ages (male) by subjective health assessment, (%)*

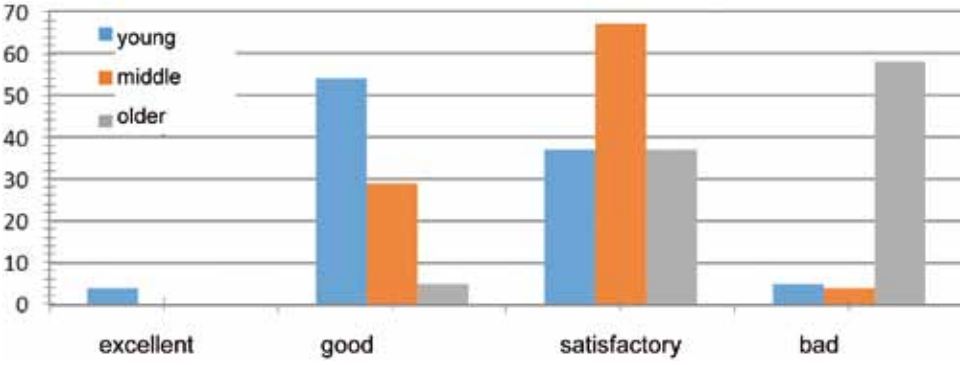


***Fig. 4.*** *Distribution of respondents of different ages (female) by subjective health assessment, (%)*

of their own health, the presence of chronic diseases in most men and a third of women, and deteriorating health regardless of gender. Only 16% of men and 8% of women indicated the presence of occupational diseases. Complaints of fatigue and drowsiness — 25% and breathing heaviness — 19% (regardless of gender) were typical.

The older age group (over 47 years) was characterized by *satisfactory* assessment of the health status of men and mainly *bad* assessment of women; growth of the proportion of people with chronic pathology (diseases of the respiratory and digestive organs, circulatory system and musculoskeletal system); deterioration of health. The typical complaints of respondents in this age group were breathing heaviness (22%), fatigue and drowsiness (21%) and joint pain (21%) (regardless of gender).

***On the impact of meteorological conditions on air pollution status***. Naturally, air pollution depends on industrial emissions (see Tables 1–3). However, meteorological conditions also contribute to the accumulation (transport, dispersion and washing out of the atmosphere) of pollutants. During 1971–2010 in some regions of Ukraine deterioration of favorable conditions for dispersion of harmful impurities in the air has been revealed. This manifestation of climate change has led to significant changes in meteorological conditions in the country since the mid-1990s, which affect the ability of the atmosphere to purify itself [9]. It is established that Kremenchuk is located in natural and climatic conditions, the combined effect of which contributes to accumulating in the air industrial emissions harmful to public health. Firstly, the city is located in an area with a high potential for air pollution (determined by the recurrence of surface temperature inversion, the presence of days with precipitation and wind speeds < 1 m/s); secondly, in a region with a limited climatic potential for self-cleaning of the atmosphere (determined by the presence of days with precipitation and wind speeds ≥ 6 m/s); thirdly, in a region with seasonal features of atmospheric self-cleaning (in July the conditions of pollutants' removal are characterized as limitedly favorable; in August-October — as unfavorable [9]).

***On the impact of urban planning factors.*** The distance from the territory of the surveyed enterprises to the development of the Molodizhnyi district is: Oil Refinery Ukrtatnafta — 2000 m; Kremenchuk Plant of Technical Carbon — 2000 m; Kremenchuk TPP — 2400 m; Kahamlyk WSS — 700 m. According to the cl. 5.5 of *State sanitary rules for planning and development of settlements*, the specified distances not only correspond to requirements of sizes of a sanitary-protective zone, established for this promuzla (1000 m), but also in 2 and more times exceed them (for Kahamlyk WSS — in 14 times, its SPZ — 50 m) [10]. However, natural studies have identified cases where concentrations of harmful impurities in the atmospheric air and soil at the outer boundary of the SPZ facing residential buildings and far beyond were significantly above the maximum permissible concentrations (see Tables 1–3). That is for the enterprises of the northern industrial hub of Kremenchuk normative sizes of sanitary protection zones can be considered as insufficient.

For the Molodizhnyi district, taking into account average annual and seasonal (summer, winter) rose of winds in Kremenchuk [11], the current design standards are practically complied with — regarding the location of residential areas from the windward side for winds prevailing towards industrial enterprises (hubs) with technological processes that are sources of air pollution, harmful, and have an unpleasant odor of chemicals (cl. 5.3, 5.4); the requirements for landscaping sanitary protection zone (cl. 5.13) are also complied with [10]. However, despite this, the inhabitants negatively assess the living conditions in the neighborhood and attribute this assessment to the negative impact of industrial facilities (see Fig. 1).

***On the impact of environmental laws of development***. By the fact that *norms do not work*, one can see the effect of a number of environmental laws [12] and, above all, the law of *ecosystem self-regulation*. According to this law, the rejection of pollution created by humans from biosphere cycles is a manifestation of environmental resistance; strengthening of the negative feedback mechanism and an ultimatum of the environment, a manifestation of which are changes in the gas composition of the atmosphere and climate [13]. The aggregate effect of these factors is aimed at reducing anthropogenic pressure on the natural environment in order to maintain ecological equilibrium through depopulation. The species which is growing numerically, including the species *homo sapiens*, worsens its environment, which, in turn, does not have time to recover and becomes less suitable for normal life of the species (see Fig. 1–4). In an ecologically balanced system, all byproducts of one species are eliminated by others; if the balance is disturbed, pollution accumulates (see Tables 1–3).

## CONCLUSIONS

1. Air pollution, as a form of environmental degradation, is an indicator of an imbalanced ecosystem. Air pollution is caused by the accumulation of harmful substances in the atmosphere as a result of anthropogenic activities and climate change. It currently acts as an ultimatum feedback

factor in the *population* ↔ *environment* system, which tends to increase the rate of air pollution.
2. Due to climate change, some regions of Ukraine have experienced significant changes in meteorological conditions since mid-1990s, affecting the atmosphere's self-cleaning ability. This increases the negative impact of polluted air on human health. Deterioration of natural conditions of atmospheric dispersion of pollutants in the region, especially in July–October, is felt by the population of Kremenchuk and causes numerous complaints of people, the climax falls exactly on the summer period (for Kyiv the climax falls on September–October).
3. Approaches to placing the industrial enterprises and rationing of the sizes of their sanitary-protective zones, the majority of which has been drawn up till the middle 90$^{th}$ years of the XX century, need revision. At designing of inhabited objects it is necessary to consider presence of tendencies to growth of negative influence of industrial clusters on adjoining territories.

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# INCIDENCE OF OSTEONECROSIS OF THE JAW DUE TO BISPHOSPHONATE TREATMENT IN THE CITY OF CRAIOVA

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**ABSTRACT** — Bisphosphonates have been used for many years worldwide for the treatment of osteoporosis, Paget's disease, but especially for the treatment of various bone density disorders such as tumour formations, bone metastases associated with osteolysis and hypercalcemia. The effects of bisphosphonates on the bones are due to their action on osteoclasts by inhibiting them. Although the existence of the risk of osteonecrosis of the jaw in patients undergoing bisphosphonate treatment is known, this pathology has been considered very rare for a long period and many times the risk of its occurrence has been ignored. Since the use of bisphosphonates is becoming more prevalent and the duration of such treatment is steadily increasing, the incidence of osteonecroses associated with this treatment is also increasing.

OBJECTIVE. The objective of this study is to highlight the fact that the incidence of cases of bisphosphonate-related osteonecrosis of the jaw has been increasing in recent years.

METHODS. We have carried out a search and analysis of all cases with *osteonecrosis* as main diagnosis in the Oral Maxillo-Facial Surgery Clinic during the period from January 2009 and December 2018.

RESULTS. We found 84 patients with osteonecrosis of the jaw following bisphosphonate treatment. Of these, 37 were men and 47 women with an average age of 67 and 59 respectively. There were 26 cases (31%) with incidence in the jaw, 52 cases (62%) with incidence in the mandible, and 6 patients (7%) manifested bilateral osteonecrosis of the jaw. Of these, 20% were on the left side, 36% on the right side and 44% on the median line.

CONCLUSIONS. The incidence of bisphosphonate-related osteonecrosis of the jaw is steadily increasing due to the more frequent use of a class of bisphosphonates with a strong impact on the oro-facial bone system.

**KEYWORDS** — Medication-related osteonecrosis of the jaw, osteonecrosis, Bisphosphonates, Tooth extraction, Side effect, oral and maxillofacial surgery, anti-angiogenic.

## INTRODUCTION

Bone metastases are a serious and frequent complication of cancer. Their incidence varies greatly depending on the type of tumour and its location. Thus, the incidence in the case of multiple myeloma is 70–95% [1], while in prostate and breast cancer it is 65–75% [2] and in lung cancer 30–40%. The occurrence of bone metastases in other types of tumours is very low [3].

***Bone metastases*** are osteolytic in multiple myeloma, lung cancer and melanomas, osteocondensed in prostate cancer and mixed in breast cancer [3].

The tumour cell migration process from the primary tumour to the bone marrow resulting in the occurrence of bone metastases occurs in several successive stages. Initially, the tumour cells are separated from the primary tumour by migrating through the blood or lymphatic vessels to stop in the capillaries of the target organ, namely the bone marrow. Once in the marrow, tumour cells can enter into a latent state, becoming active many years later, or being able to adapt to the local micro-environment (osteomimicry).

The occurrence of bone metastases results both in the impairment of the osteoclast and osteoblast function resulting in a change in normal equilibrium between the new bone formation and the bone resorption. Thus, the bone-derived growth factors and calcium ($Ca^{2+}$) are eliminated from the bone which, in turn, promotes tumour growth [4].

***Bisphosphonates*** are inhibitors of bone demineralization for which reason they are used in the treatment of diseases that associate or cause bone resorption. Bisphosphonates are generally administered per os in osteoporosis and intravenously in patients with bone metastases (secondary to prostate, lung, kidney or breast tumours), as well as in various osteolytic bone pathologies (Paget's disease, multiple myeloma) [3, 5].

Bisphosphonates enter the bone with the help of osteoclasts, for which they have an increased affinity and can remain in the bone for more than 15 years and can be released only with bone destruction during the physiological turnover [6, 7].

Some studies suggest that bisphosphonates, in addition to inhibiting osteolysis, could prevent both the occurrence of bone metastases and the survival of latent tumour cells in the bone marrow. The fact that bisphosphonates may have direct antitumour effects in combination with chemotherapy is not yet scientifically proven [8].

Besides to reducing the risk of bone fracture by inhibiting the osteoclastic activity, other benefits of bisphosphonate treatment include pain reduction in cases of bone metastases and reduction in mortality rates [9].

Side effects of bisphosphonates include atypical femoral fractures, osteonecrosis of the jaw, atrial fibrillation as well as various diseases of the gastrointestinal system (oesophageal ulcer, dysphagia, gastroesophageal reflux, xerostomia, dyspepsia) [9].

The American Association of Oral and Maxillofacial Surgeons (AMOMS) has defined bisphosphonate-induced osteonecrosis as the presence of non-cured maxillary or mandibular bone, exposed to the oral cavity environment, with a lack of healing tendency and persisting for more than eight weeks in patients who were administered treatment with bisphosphonates but who did not have metastases in the maxillary bones and did not receive radiotherapy in this area [10].

Diagnosis is generally clinically put by drawing a thorough anamnesis (which should reveal the presence of the bisphosphonate treatment in antecedents) associated with evidence of bone exposed to the oral environment, generally recommending an orthopantomography (OPG) for a radiological confirmation. It is important to note that in the incipient stages no suggestive radiological changes can be visualized in order to guide the practitioner to a precise diagnosis) [11].

AAOMS has proposed the medication-related osteonecrosis of the jaw (MROJ) as follows:

- Stage 0: Patient who was administered bisphosphonate treatment and without exposed, necrotic bone but with discreet radiological changes.
- Stage 1: exposed, necrotic bone, but without the presence of a symptomatology or infection.
- Stage 2: exposed, necrotic bone, with the presence of a painful symptomatology, erythema with or without the presence of purulent secretions.
- Stage 3: exposed, necrotic bone with the presence of a painful symptomatology and local infection, and the extension of bone necrosis to the basilar edge of the mandible or maxillary sinus, possibly leading to pathological fractures, cutaneous fistulas, oro-nasal or oro-antral (oro-sinusal) communications [12].

The conservative treatment seems to give favourable results in the first stages of the ailment [13].

The osteonecrosis of the jaws is a severe complication of the treatment with bisphosphonates and other resorbable agents [5].

Of the many theories on how osteonecrosis onsets following bisphosphonate administration, there are basically two main theories.

The first relates to the inhibition of bone remodelling by direct action on osteoclasts, and the second theory is based on the inhibition of angiogenesis, in both cases leading to the involution and even loss of blood vessels following the development of the avascular bone necrosis.

Although bisphosphonates and anti-angiogenesis agents increase the risk of occurrence of the osteonecrosis of the jaw, the exact mechanism is not yet known. It is also worth mentioning the fact that the number of elderly people requiring this type of treatment is steadily increasing [14].

### *Effects of bisphosphonates on osteoclasts*

Recent studies have shown that the prevalence and incidence of bisphosphonate-related osteonecrosis (OB) are low [7, 14].

Bisphosphonates remain for prolonged periods in the bone, more precisely in osteoclasts where they inhibit their activity, leading indirectly to anti-resorptive effects. Also, nitrogen-containing bisphosphonates are known to have much stronger resorptive bone effects [7].

Recent studies have concluded that bisphosphonates, once attached to the bone, can inhibit the growth of cells in the covering mucous membrane [15] as well as the fact that they can induce osteoclast apoptosis by inhibiting pyrophosphate synthase [16]. Thus, it was suggested that this apoptosis could be directly involved in the occurrence of osteonecrosis [17, 18].

Hence, by their effect on osteoclasts, it will result in the bone inability to adapt to local trauma and implicitly in their susceptibility to developing infections and micro-fractures [19,20, 21].

It has also been shown that the presence of unhealed micro-cracks in the bones of patients undergoing bisphosphonate treatment is associated to the onset of osteonecrosis [18, 22, 23].

Several studies have described the presence of infection in bisphosphonate-related osteonecrosis, suggesting the possibility of its participation in the onset and development of osteonecrosis [24, 25, 26].

A recent study has found the presence of anaerobic bacteria specific to the periodontal space microflora in the necrotic bone, also suggesting that an oral cavity infection in association with bisphosphonate treatment could be responsible for the osteonecrosis onset [27].

Thus, Fusobacterium, Actinomyces, Bacillus, Streptococcus, Staphylococcus, Selemonas, Treponema and Candida, were observed to be frequently present in the osteonecrosis of the jaw, [28] these bacteria being detectable at the bone level prior to its necrosis [29].

For patients being administered bisphosphonate treatment, it is advisable to avoid as much as possible dental extractions or any other intervention on the bone, as many studies show the close relationship between dental extraction and the onset of osteonecrosis [30, 31].

In these patients, it is recommended that treatment administration should be discontinued, whenever possible, for approximately 3 months, before any bone surgery. This interruption is performed strictly by the patient's attending oncologist/endocrinologist upon referral and in collaboration with the surgeon [30].

Although the most optimal time between treatment discontinuation and surgery is not known, it is necessary to assess the benefit/risk ratio for each individual patient. The minimum recommended discontinuation period is 3 months [30].

Since bisphosphonates remain in the bone for a long time (more than 3 months), a discontinuation of treatment for several months would not significantly influence the amount of bisphosphonates in the bone but may positively influence the healing of the area subjected to surgical intervention by avoiding the anti-angiogenic effect of the treatment, thus allowing for healing [30].

In a meta-based study carried out on 1,389 cases and 569,620 examinations, there was find there is a close correlation between the bisphosphonate treatment of cancer patients and the onset of osteonecrosis of the jaw. In this study, the risk of onset of this pathology was 4 times higher in the case of intravenous bisphosphonate treatment versus per os administration [30].

### *Anti-angiogenic effect of bisphosphonates*

Angiogenesis is a physiological process by which occurrence of new blood vessels takes place out of existing ones [32].

In addition to the effect in bones, several articles have brought up the ability of bisphosphonates to inhibit angiogenesis [33], as well as the possible involvement of this effect in the pathogenesis of the osteonecrosis of the jaw [17, 34, 35].

Thus, following in vitro experiments, direct inhibition of osteogenesis and angiogenesis by bisphosphonates administered in high concentrations in the plasma sampled from various patients was observed [15, 36, 37].

Recently, various articles revealed the role of osteoclasts in angiogenesis [17, 38, 39, 40].

Thus, it can be speculated that the anti-angiogenesis effect of bisphosphonates would be an (indirect) consequence of inhibition of osteoclast activity [41].

Moreover, in an in vivo study, the ability of a bisphosphonate (zoledronate) to inhibit PDGF-BB preosteoclasts has been shown to suppress angiogenesis and osteogenesis [42].

Numerous studies have highlighted the role of osteoblasts in stimulating both osteogenesis and angiogenesis [32, 43, 44, 45, 46].

Thus, the suppression of the generation of angiogenic factors of osteoblasts by bisphosphonates may partially explain the occurrence of osteonecroses of the jaw, [47] since angiogenesis plays a fundamental role both in bone production and remodelling as well as in the occurrence of tumour metastases and osteonecrosis. [48] Compromising angiogenesis also has a negative effect on local healing after surgical intervention [17].

Another study in animals treated with anti-resorptives showed the presence of a reduced vascular network with the occurrence of apoptosis, oxidative stress and hypoxia at the outbreak of the osteonecrosis [49].

### *Risk factors associated with osteonecrosis onset*

Risk factors that can negatively influence bone metabolism, favouring the occurrence of bisphosphonate-related osteonecrosis include: local or general infections, advanced age, various bone traumas, dental extraction and concomitant use of anti-angiogenic medication or radio-chemotherapy administration. Of all these factors, most commonly involved in initiating an osteonecrosis outbreak is bone trauma in the form of a dental extraction [8].

Of the local risk factors, the extraction of a single tooth or root, the bone loss, the presence of increased mobility teeth and the lack of healing of a bone exposed wound were associated with a higher risk of occurrence of osteonecrosis [50].

Although osteonecrosis of the jaw may also occur in patients undergoing angiogenesis inhibitor treatment, the most documented cases are those related to treatment for osteoporosis and bone metastases, denusumab and bisphosphonates, respectively. The risk of occurrence increases with duration, dose and frequency of treatment [31, 51, 52].

In the scholarly literature, many other risk factors have been reported in the occurrence and worsening of osteonecrosis, such as: dental or periodontal infections, anaemia, corticosteroids, diabetes, smoking, low immunity and poor oral hygiene [31, 53, 54, 55, 56].

## MATERIALS AND METHODS

We have searched for all cases of *osteonecrosis* as main diagnosis at the Oral and Maxillofacial Surgery Clinic diagnosed between January 2009 and Decem-

ber 2018. All patients who had osteonecrosis without a history of bisphosphonate treatment confirmation were excluded from the study.

## RESULTS AND DISCUSSIONS

In this study, we analysed 84 patients with osteonecrosis of the jaw following bisphosphonate treatment. Of these, 37 were men and 47 women with an average age of 62. The group of men was found older (67 average age) compared to the group of women (59 average age). (Table. 1) (Fig. 1) A number of 52 patients came from the urban area, and 32 from the rural area. (Fig. 2)

***Table 1.*** *Mean age of men vs women*

| Age | Women | Men |
|---|---|---|
| Sample size | 47 | 37 |
| Arithmetic mean | 59.1915 | 67.6216 |
| 95% CI for the mean | 55.7693 to 62,6137 | 64.7747 to 70.4685 |
| Variance | 135.8538 | 72.9084 |
| Standard deviation | 11.6556 | 8.5386 |
| Standard error of the mean | 1.7001 | 1.4037 |
| F-test for equal variances | P = 0.056 | |

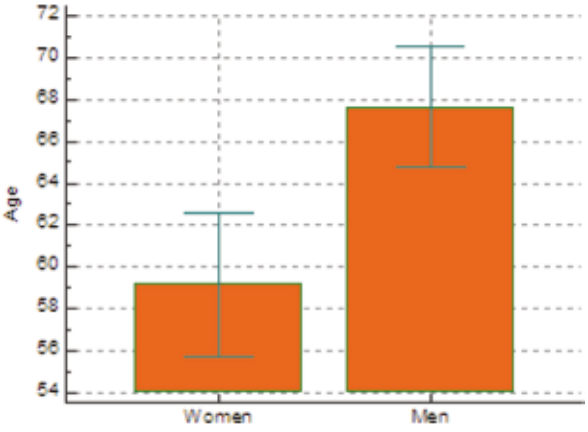


***Fig. 1.*** *Women vs Men age*

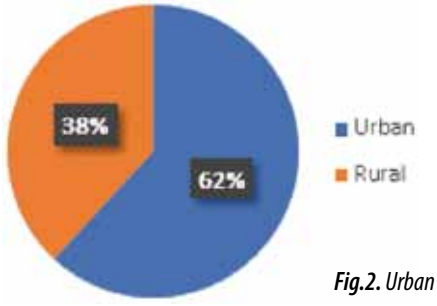


***Fig.2.*** *Urban vs Rural*

There were 26 (31%) cases of osteonecrosis of the jaw, while 52 (62%) cases of osteonecrosis of the mandible and 6 (7%) patients had bilateral osteonecrosis of the jaw. (Fig. 3) Of these, 20% were on the left side, 36% on the right side and 44% on the median line. (Fig. 4)

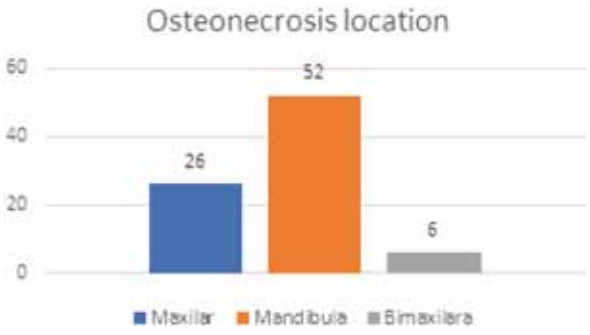


***Fig.3.*** *Jaw, Mandible, Bilateral jaw*

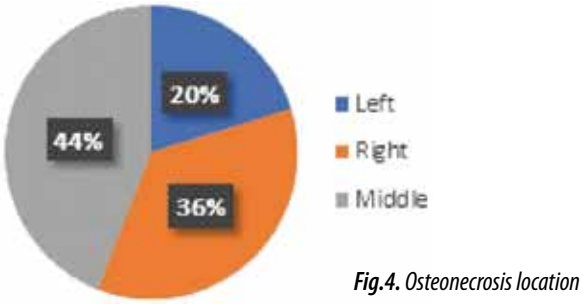


***Fig.4.*** *Osteonecrosis location*

The main symptomatology that caused patients to come to the doctor was local pain, followed by local changes (denuded bone), as well as physiological disorders caused by oedema and swelling due to the penetration of the germs from the oral environment to the bone left denuded. The patient's delay in presenting to medical examination may lead, in the absence of adequate treatment, to local overinfection, with the appearance of purulent secretions.

The treatment of osteonecrosis included the administration of antibiotics and anti-inflammatory drugs, the local toilette with chlorhexidine and antialgic medication, where needed. Surgery was performed by removing bone seizure only in patients who had a minimum period of 3 months since the last bisphosphonate administration.

In this study, there was an exponential increase in the incidence of the osteonecrosis of the jaw, thus: from 1 new case to 291 admissions, respectively 5 new cases/year in 2010 to 1 new case to 47 admissions, respectively 19 new cases/year in 2018. (Fig. 5)

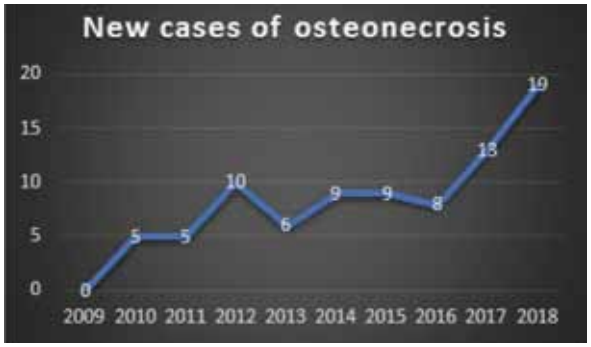


***Fig.5*** *Incidence of new cases*

From a clinical point of view, the patients presented in the OMF Policlinic, being or not being guided here by the dentist, due to the presence of a post-extraction (gingival) injury that did not heal in time, leaving the post-extraction alveolus exposed to the germs in the oral environment. The gum is erythematous, inflamed and associated with local pain, and the underlying bone is exposed, grey, dull, necrotic, with or without local purulent secretions.

Although secondary impairment of the upper gastrointestinal system is considered to be the most common adverse reaction, the bisphosphonate-related osteonecrosis is a condition that once appeared greatly affects the quality of patient's life.

Its incidence is reported in a study to less than 1 in 1,000 patients under per os bisphosphonate treatment [57] and approximately 5% of patients under intravenous treatment to develop osteonecrosis [58], this ailment being very difficult to treat and greatly affecting the quality of patient's life.

Other studies reported an incidence of 0.01–0.06% occurrence of osteonecrosis in patients with per os bisphosphonate administration and 0.8–12% in patients with intravenous bisphosphonate administration [28], thus arguing that the risk of occurrence increases in the case of the intravenous treatment [59].

This was also found in our paper, as most patients were under injectable treatment.

The pathogenesis of osteonecrosis is not yet fully understood, the multiple effects of bisphosphonates on cells could also increase the susceptibility of occurrence of infections and affect the healing of mucous membranes [58], thus leading to the non-closure of the post-extraction alveolus and increasing the risk of germs in the oral cavity infiltrating the bone.

In the current study, all patients who presented complained of the onset of the symptomatology following a dental extraction without performance of alveolar sutures, and from a clinical point of view the post-extraction site was unhealed.

However, recent statistics show that there is a much greater chance of curing osteonecrosis through surgical intervention compared to simple medical treatment consisting of local administration or systemic antibiotherapy [60, 61].

This is also highlighted in this paper, as all patients were prepared for surgery resulting in a success of approximately 79.76% while another study showed a 76.7% success rate [62].

It is imperative that a relationship be established between the beneficial role of bisphosphonates and the risks of occurrence of osteonecrosis following this treatment before starting any treatment. Thus, explaining to the patient the benefits and risks and possible measures to prevent them is currently the best way to reduce the incidence of osteonecrosis [63].

There is currently no well-established protocol in the treatment of bisphosphonate-related osteonecrosis of the jaw. It is generally recommended to control possible infection followed by a conservative treatment, before surgical treatment.

The conservative treatment plan seeks to maintain proper oral hygiene, to treat dental injuries and periodontal diseases, and to associate local and/or general antibiotic treatment [56].

Conservative treatment seems to be successful in the majority of cases though it can not necessarily reach a complete cure, but it can improve the patient's symptomatology [54, 64].

This is especially recommended for patients who, for various reasons, cannot undergo surgical treatment, for example, when bisphosphonate therapy cannot be discontinued, or when the patient has a contraindication to general anaesthesia.

Some recent studies suggest that dental extractions can be performed in patients treated with bisphosphonates but only under a minor impact on dento-periodontal tissues and under antibiotic protection, suggesting that the osteonecrosis-initiating factor would rather be local infections [65]. This is consistent with our study, in which patients with osteonecrosis asserted lack of pre- or post-extraction antibiotic treatment.

A study by [6] confirms that prophylactic antibiotic administration prior to surgical intervention, associated with appropriate wound closure, can prevent osteonecrosis onset.

According to recent studies, patients treated with per os administered bisphosphonates for the treatment or prevention of osteoporosis did not experience a decrease in the incidence of osteonecrosis in case of discontinuation of the treatment in order to perform

simple dental extractions [50, 66]. In turn, it was found the presence of a late healing of the post-extraction alveolar wound [67, 68] and it is recommended to carry out the extractions only under the conditions of an antibiotic intravenous treatment and the complete closure of the post-extraction alveolus in order to reduce the possibility of infiltration of the germs at bone level [69].

In this study, a preventive discontinuation of bisphosphonate treatment was chosen for 3 months before any intervention was performed, also noticing a delay in healing.

It is noteworthy that any trauma, either chronic or acute, to a bone with a metabolism already altered due to bisphosphonate treatment will further reduce the vascularization of the respective area and implicitly lead to the occurrence of some avascular bone areas which will necrose and thus the onset of bisphosphonate-related osteonecrosis may be initiated following bone trauma.

## CONCLUSION

Although the pathogenesis of the bisphosphonate-related osteonecrosis of the jaw is not fully understood, it is known that a very important role in its occurrence is played by the impairment of both angiogenesis and osteogenesis.

It is recommended to solve any dental problems before any bisphosphonate treatment is set up, maintaining proper oral hygiene and periodic dental examination for early detection of signs of osteonecrosis as well as for professional hygiene. The aim is to avoid as much as possible a surgical intervention involving the bone.

It is very important that any patient who should be treated with bisphosphonates, either to combat osteoporosis or bone metastases, should be made aware of the potential risk (Altınay, Dagli, Altinay, & Altınay, 2019; Damian, Diac, Iov, Hunea, & Bulgaru Iliescu, 2019; Frunză, 2018; Hosseinpour, 2019) of osteonecrosis of the jaw and be explained the importance of maintaining good oral cavity hygiene in order to prevent the occurrence of this harmful pathology.

It is also important that prior to the application of any dental treatment, the patient informs the physician about bisphosphonate treatment to prevent surgical interventions that may increase the risk of onset of an osteonecrosis outbreak.

The osteonecrosis of the jaws is an ailment secondary to bisphosphonate treatment, but very difficult for both the patient and the physician, which is why it is advisable to prevent this disease occurring before, during and even after the discontinuation of the bisphosphonate treatment.

*Abbreviations*

AAOMS = American Association of Oral and Maxillofacial Surgeons; MROJ = medication-related osteonecrosis of the jaw.

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# KNOWLEDGE AND BEHAVIORS REGARDING THE USE OF ANTIBIOTICS: A DESCRIPTIVE CROSS-SECTIONAL SURVEY IN ROMANIA

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## INTRODUCTION

World Health Organization draws attention upon antibiotic resistance becoming one of the biggest threats to global health, food security, and development today [1]. Moreover, it is recognized that the overuse of antibiotics among patients is one of the main causes of the emergence of resistant bacteria [2]. European Centre for Disease Prevention and Control draws attention that the levels of antimicrobial resistance in Romania in key indicator bacteria from humans are very high and/or rising in comparison to most other EU/EEA countries [3]. For example, in 2015, Romania was ranked the 6th in the world for the consumption of daily doses of antibiotics per inhabitant [4]. More recently, data from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) show that Romania had a total consumption in the community and the hospital sector of 33.3 defined daily doses per thousand inhabitants and per day, the second highest in Europe [5]. As a response to this issue, countries have initiated educational campaigns to stimulate the public in reducing unnecessary use of antibiotics [6]. However, the majority of measures initiated in Romania regarding the rational use of antibiotics were discontinued in 2017 [7].

The aim of this study was to inspect the knowledge regarding the use of antibiotics among general public in Romania. This is considered a first step in raising awareness campaigns about the excessive use which poses a serious threat to public health [8].

## MATERIALS AND METHODS

### *Sources of data*

Data were collected at the end of 2018 using a face-to-face questionnaire by students from the University of Agricultural Sciences and Veterinary Medicine, who were also involved throughout the project. Before the field research they were given explicit instructions about the sampling procedure and filling in the data. Data were analyzed using the SPSS version 18 for Microsoft Windows. Response frequencies for the survey questions were determined and displayed in graph and tabular formats.

### *Sample profile*

The total sample reached 500 respondents from 4 Romanian counties in the West region (Arad, Timiș, Caraș-Severin and Hunedoara). There were more male respondents in the sample (58.1% compared to 41.9%). Two thirds of them were living in urban areas (68.5%). Half of the respondents were in the age group 35–54, and one third had university studies

### *Measurements*

The study used the instrument proposed by WHO [9]. The translated version of questionnaire included 30 questions grouped in three dimensions: use of antibiotics, knowledge about antibiotics, and knowledge about antibiotics resistance. Additional information was gathered on gender (male/female), residency (urban/rural), age (16-24, 25-34, 45-54, 55-64, 65+), and education (basic, highschool, higher).

## RESULTS

### *Usage of antibiotics*

#### *How people obtained antibiotics*

One third of respondents surveyed report having taken antibiotics within the past six months (37.6%) and 20.1% during the last year. The administration of medicine appears as a quite responsible behavior, because respondents who reported were having taken antibiotics, when asked how they obtained it, the vast majority (79.1%) report that they got their antibiotics through a prescription. There are little variations around how respondents reported getting their antibiotics. Females respondents are slightly more likely than males to have a prescription (80.1% compared to 77.9%), urban respondents (80.1%) are also slightly more likely than those in rural areas (77.9%) to report having gotten antibiotics through a prescription, and more educated a respondent is, more likely is to adopt a prescription-driven behavior.

### Where people obtained the antibiotics

Almost all surveyed respondents report having obtained the antibiotics they last took from a pharmacy (88.9%) out of which 8.9% without a prescription. Respondents aged 65 and older are more likely to obtain the antibiotics from a pharmacy using a prescription (87.8%) compared with 74.1% of those aged 16–24, 81.5% of those aged 25–34, and 78.5 of those aged 35–54. Similarly, respondents who are more educated are more likely to procure antibiotics from a pharmacy (84.6%), compared to 77% of those with basic education or a highschool degree. Male respondents and those residing in urban areas are slightly more likely to report having received antibiotics from the internet.

## *Knowledge about antibiotics*

### How and when to take antibiotics

Respondents were first asked whether they thought the following statement was true or false: *It's okay to use antibiotics that were given to a friend or family member, as long as they were used to treat the same illness*. Overall, 12% of the survey respondents think this is true, whereas it is in fact a false statement, showing that the majority of them had the correct information. Slightly more male respondents (13.3%) think this statement is true compared to females (10.6%), respondents from rural areas are more likely than those in urban areas to think that this incorrect statement is true, at 14.8% and 10.7% respectively. Also, the more educated a respondent is, the less likely they are to agree with the incorrect statement (8.9% for those with higher education, 10.9 for those with a highschool degree and 22.1% those with basic education).

However, when asked if *It's okay to buy the same antibiotics, or request these from a doctor, if you're sick and they helped you get better when you had the same symptoms before*, more than one quarter (27.2%) thought this statement is true, whereas it is also in fact a false statement. Females are also more likely to correctly indentify this statement as false (58.2%) compared to their male counterparts (48.8%). There is a slight towards older respondents being more likely to correctly identify that the statement is false for the interval 16–54, but after 55 years old, respondents follow a downward trend whereas only 41.2% of the respondents older than 65 correctly indentifying the statement.

### When to stop taking antibiotics

Asked when they think they should stop taking antibiotics once they had begun administration, the majority of respondents answered the entire dosage should be continued as prescribed (65.9%). Even if WHO recommends to follow the health worker's advice when using antibiotics [10], one quarter (27.6%) think it is better to stop administration once the symptoms have ameliorated. There are some notable differences by socio-demographics: younger adults (16–24) and older adults (over 65) are more likely to believe that they should stop administration once they feel better (37.1% and 34.2% respectively) compared to other age groups. The age group 35–54 appeared as the most informed group because 69.7% of them considered continuing the treatment as prescribed. Females are slightly more likely to continue administration of antibiotics as directed (68.7%) compared to males (64.7%). Additionally, respondents in rural areas are slightly more likely than respondents in urban and urban areas to think that they should stop taking antibiotics when they feel better, at 29.5%, compared to 26.8%. There is a clear upward trend in terms of education, thus respondents who are more educated are more likely to continue the treatment as directed. So, 37.3% of respondents with at least compulsory education say that they should stop taking antibiotics when they feel better compared to 32.1% and 16.8% of respondents a highschool degree or higher education respectively.

### Which conditions should antibiotics be used to treat

Asked from a list of medical conditions to say which can be treated with antibiotics, the majority of respondents correctly identified bladder/urinary tract infection (81.9%) and skin/wound infections (61.2%). In contrast, only 32.3% of respondents correctly identified gonorrhea as a condition treatable by antibiotics. Also, more than half of respondents mistakenly thought that viral conditions which do not respond to the use of antibiotics can, nonetheless, be treated with these medicines: 67.7% agree that the use of antibiotics is useful for sore throats while 57.4% agree that the use of these medicines is appropriate for cold/flu (Fig. 1).

We can notice some insteresting differences between the socio-demographic groups' responses to the bladder infection/UTIs, the condition for which the highest rate of accurate identification was obtained. Women are more likely to responde correctly, with 86.6% compared to 78.4% males. Respondents aged 35 and older are more likely to give the correct answer, with 88.3% of respondents over 35 answering that UTIs can be treated with antibiotics, compared with 69.4% of those aged 16–24 and 66.7% of those aged 25–34. Urban respondents are more likely to respond correctly, with 85.4% thinking that UTIs can be treated with antibiotics compared to 73.7% of those in rural areas.

## CONCLUSIONS

The cross-sectional design prevents us from drawing conclusions regarding causal relationships. However, several important conclusions emerged. There are still some misconceptions about the efficacy of antibiotics for different medical conditions. Healthcare professionals have the first responsibility towards responsible antibiotic use by informing the public about the appropriate use of antibiotics for common infections [11]. Access to antibiotics without a prescription is a contributing factor for irrational and excessive use of antibiotics. Even if the majority of our respondents used a prescription from a doctor and a pharmacy to buy them, the procurement via the internet is considered to be a growing problem [12]. Changing habits and increasing awareness [13, 14, 15, 16] of public about antibiotic use is considered as a fundamental early planning to maintain antibiotic potency in the time of growing bacterial resistance [17].

*Declaration of conflicting interests*

The author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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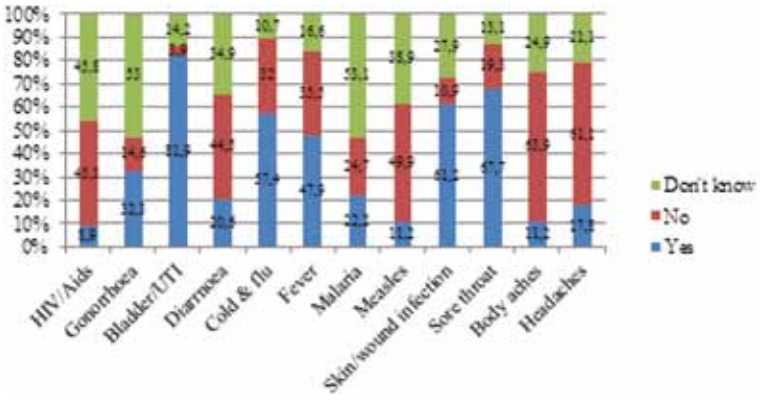


***Fig. 1.*** *Percentage of responses from all respondents to "Do you think these conditions can be treated with antibiotics?"*

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# MANAGING EMPLOYEE TURNOVER INTENTIONS IN JORDANIAN HEALTH SECTOR

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**ABSTRACT** — Employees turnover intentions occur because of many reasons happen together at a certain time so the employees take a serious decision to leave the organization or the firm. Searching for a better workplace conditions and/or bigger salaries could be the main reasons to leave an organization, but also lack of employee effort recognition and respect play a significant reason to employee turnover. Likewise the workplace conditions and the work law of the minorities and the single parents, also the former employees' situations highly affect the turnover rate. So a strategies and plans has to be implemented to motivate the employees each with a suitable way that in a way or another can change the factors which affect the employee's turnover, and this is has to be done by a qualified managers who apply and validate these strategies to get the best from the employee's in the organization in order to achieve the firm or the organizational goals. Employee motivation is one of the policies of managers to increase effectual job management amongst employees in organizations (Shadare et al, 2009). A motivated employee is responsive of the definite goals and objectives he/she must achieve, therefore he/she directs its efforts in that direction. The empirical results revealed that the factors that enhance employee motivation are fair pay, incentives, special allowances, fringe benefits, leadership, encouragement, trust, respect, joint decision making, quality of supervision, adequate working relationships, appreciation, chances for growth, loyalty of organization, identification and fulfillment of their needs, recognition, empowerment, inspiration, importance attached to their job, safe working conditions, training and information availability and communication to perform actions.

**KEYWORDS** — motivation, employees, incentives, organizational goals, employees' turnover.

Health sector in Jordan consider one of the most developed and modern health care in the Middle East, the healthcare system in Jordan divided into three sectors: public, private, donors.

The public sector include the Ministry of health (MOH), University hospitals: Jordan University Hospital in Amman and King Abdullah Hospital in Irbid (north of Jordan), and the center of diabetes, Endocrinology and Genetics and the Royal Medical Services (RMS).

The private sector includes many private hospitals like Farah Hospital and Al-khaldi Hospital and many more other private centers, hospitals and poly clinics, which are very developed and equipped with the latest medical devices.

The international sector provides services through UNRWA clinics for refugees and the UNHCR and the services of King Al-Hussien center for cancer and some charity association clinics.

The Jordanian healthcare sector is characterized regionally and internationally by the high quality of its healthcare services provided due to the presence of internationally qualified and world-class doctors and the presence of accredited hospitals equipped with the latest machinery and equipment leading to a lack of waiting period for treatment.

The attractiveness of the healthcare sector (Çolak, Işik, & Yiğit, 2019; Tomaziu-Todosia, 2019) in Jordan has continued to rise and the country has become a major destination therapeutic tourism (Huidu, 2018).

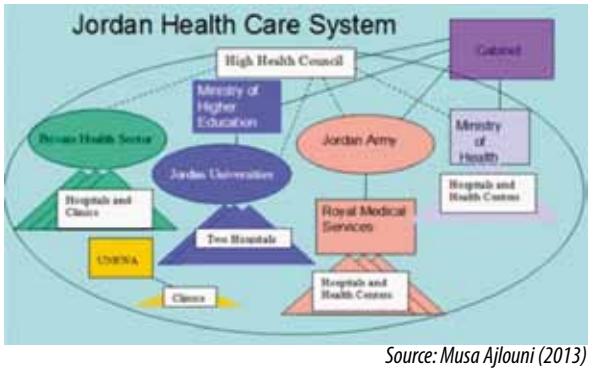
Despite the attractiveness of the sector and the government's effort to strengthen it, it faces many challenges, including the transfer of the talent (Karpov, 2018) from the sector.

The Higher Health Council through the law no.9 of 1999 elaborates the general policy for health sector in Jordan.

According to Health System profile Jordan report published by Regional Health System Observatory(2006, pp.7), "*the main challenges related with health care system in Jordan are problems related to accessibility, equity, duplication of services, poor coordination among major providers, unregulated private sector, low utilization rates in the private sector, limited quality improvement programs, inefficient use of available resources, poor management*".

The Ministry of health hospitals suffers of several limitations in providing a better health care among which the lack of incentives for hospital staff occupied an important place. Ajlouni (2013) presented the scheme of Jordan health care system highlighting the main actors involved in the process of health decision making.

The National health strategy in Jordan has the objective of building a viable health care system utilizing both public and private service providers and improving the quality of health services by implementing a national health services accreditation program.




Source: Musa Ajlouni (2013)

***Fig.1.*** *The scheme of Jordan Health care system*

The health human resources are an essential component of any health system (WHO 2007), as the quality of health services highly depends on the skills, motivation and how enthusiastic is the health system staff, and this is could be the main reasons for providing a qualified, skilled and motivated staff (WHO 2006; Martineau et .al, 2000).

According to the ministry of health in Jordan, the average of the healthcare staff has declined in the last eight years comparing with the population average, (as shown below in Fig. 2 & 3).

source (MOH)

| Job | Average/ 10000 from Population |
|---|---|
| Physicians | 26.52 |
| Dentists | 9.31 |
| Pharmacist | 14.97 |
| Registered Nurses | 23.13 |
| Midwives | 3.44 |
| Assistant Nurses | 9.32 |
| Practical Nurses | 0.0 |
| Associate Degree Nursing | 6.09 |

***Fig. 2.*** *Health personnel 2018 by selected category and health sector in Jordan*

source (MOH)

| Job | Average/ 10000 from Population |
|---|---|
| Physicians | 23.04 |
| Dentists | 7.23 |
| Pharmacist | 13.15 |
| Registered Nurses | 21.86 |
| Midwives | 3.22 |
| Assistant Nurses | 1.92 |
| Practical Nurses | 0.0 |
| Associate Degree Nursing | 5.41 |

***Fig. 3.*** *Health personnel 2018 by selected category and health sector in Jordan*

The studies revealed that there are many reasons affecting the the ability of the health system from providing the best healthcare services; like the size, composition, distribution, training and migration of health personnel, (Kabene, Orchard, Howard, Soriano & Leduc, 2006).

Studies have also pointed out that one of the reasons for the failure of health system reform efforts is the absence of studies which directly related to the promotion of human resources for health system. (Aitken-Kolehmainen, 1998).

## PROBLEM STATEMENT

Measuring the employee turnover rate is very important for the employers to investigate the reasons behind the employee leave and to set the plans to raise the chances of retentions or/ and set future strategies to keep the new employees from leaving an organization. Studies proved that the lack of recognition, incentives which affect the motivation of an employee to continue with the same workplace, which raise the intentions to leave seeking better job chances.

Motivation is literally the level of energy, commitment, and creativity that a company's workers bring to their jobs. Whether the economy is growing or not, employee motivation is always the management concern.

The Vroom's theory has proved its utility in analyzing the motivational factors at the workplace (Regis, Falk & Dias, 2008, Kanfer, 1990, Ghoddousi, Bahrami, Chileshe and Hosseini, 2014). Chiang and Jang (2008) proposed an adapted version of the expectancy theory for the investigation of work motivation.

The most commonly applied motivational theories in empirical studies who investigate the main factors of employees' motivation were Maslow theory, Herzberg theory and Vroom theory. Unlike the first two theories, the vroom theory, a process theory highlights how the motivation occurs (Chiang and Jang, 2008). It based on three elements: expectancy (E), instrumentality (I) and valence (V). According the Chiang and Jang (2008, p. 314), the motivation force can be regarded as the result of following interaction:

$$Motivation\ force = Expectancy \cdot Instrumentality \cdot valence$$

Expectancy (E) is seen as the acquisition that performance could be obtained is the effort is applied. Instrumentality (I) refers to the perspective of rewards when the conditions of performance are achieved. Valence (V) is more related with the rewards (Regis, Falk & Dias 2008). From the three elements of expectancy theory, instrumentality and valence refers to outcomes and therefore they can be considered from intrinsic or extrinsic opinion.

Empirical evidence on the health employee motivation in Jordanian hospitals have been offered by the studies of AbuAlRub and Al-Zaru (2008), AbuAl-Rub(2007), AbuAlRub, Omari and Al-Zaru(2009), Abualrub, Omari, Abu Alrub and Fawzi(2009), Alhusban and Abualrub(2009), Abualrub(2010), Hayajneh, AbuAlRub, Athamneh, Almakhzoomy(2009) and

AbuAlRub, El-Jardali, Jamal and Al-Rub(2016).

AbuAlRub and Al-Zaru (2008) analyzed if the recognition of nurses' performance could be considered as an important factor for retention diminishing the effects of stress, indicating that the recognition of nurses' performance could be considered as an important factor for the intention to stay.

AbuAlRub (2007) pointed out one of the main causes that declined the number of nurses in Jordanian hospitals is the slow increase of nurse wage mentioning that a potential solution for retention could be improving the working conditions and the satisfaction associated with their profession.

AbuAlRub, Omari and Al-Zaru (2009) founded that the higher level of work motivation and the higher intention of nurses stay in private hospitals comparative with public hospitals.

Abualrub, Omari, Abu Alrub and Fawzi(2009) have proved that social support from co-workers and supervisors increase the level of satisfaction for Jordanian nurses, while AbualRub(2010) have shown that female nurses who are mothers, have a full-time job and receive support from co-workers and supervisors tend to have a higher level of retention than others.

Hayajneh, AbuAlRub, Athamneh, Almakhzoomy(2009) determined the rate of nurses turnover in Jordanian hospitals to be 36.6% and also identified significant differences by geographical region, health sector and place of residence pointing out that a further research is need to reveal the cause of these differences.

AbuAlRub, El-Jardali, Jamal and Al-Rub (2016) investigated if there is a potential connection between work environment, job satisfaction and the level of retention using a sample of 330 Jordanian hospitals nurses, the level of job satisfaction and also work environment significantly influenced the level of retention of nurses.

Studies that analyze the job satisfaction and intention of stay at work and other factors related to work motivation for health employees in Jordan take in consideration mostly the perceptions of nurses. The present study aims to investigate the level of work motivation and especially the factors who contribute to motivation for all employees (doctors, nurses, administrative staff, support staff, helpers) and also to reveal potential differences of opinions regarding these factors.

## RESEARCH QUESTIONS

The research aim to answer two main questions.

What make the health employees satisfied with their workplace?

How to motivate them in order to reduce the employee turnover rate?

And whether applying the expectancy theory help to motivate and change the intentions of the employees to leave?

## PURPOSE OF THE STUDY

The main goal of this research is to investigate the rate of the employee turnover in the Jordanian health sector, and to reveal the main reasons of the intentions of the employees to leave, and determine the strategies and the plans which reduce the intentions of the employee turnover.

## RESEARCH METHODS

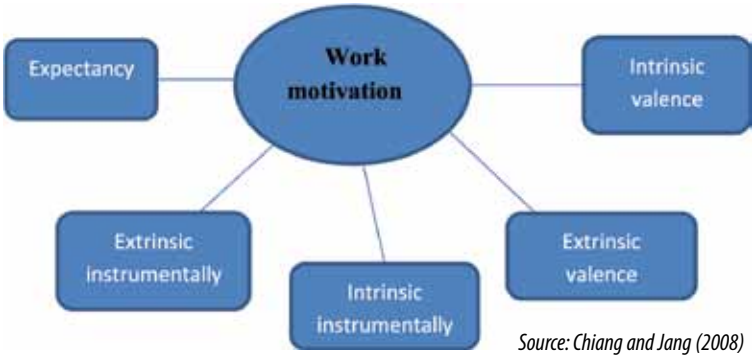
Motivation in hospitals was the study of Chiang and Jang (2008), according to which the expectancy theory was adapted by classifying instrumentality and valence into extrinsic instrumentality, intrinsic instrumentality, extrinsic valence, and intrinsic valence in order to capture the impact of intrinsic/extrinsic components.

The study aims to test the hypotheses that each component-expectancy, extrinsic instrumentality, intrinsic instrumentality, extrinsic valence and intrinsic valence have a positive effect on employee motivation.

In order to test that, the items are rated using a 5 point Likert scale where (1= very dissatisfied) and (5= very satisfied).

From the five component of expectancy theory, expectancy, extrinsic instrumentality, intrinsic instrumentality were measured using four items, while extrinsic and intrinsic valence were measured using five items. For work motivation there were used four items. The items are rated using a 5 point Likert scale where 1=very dissatisfied and 5=very satisfied. In order to analyze the responses of items were used descriptive statistics (mean and standard deviation).Comparisons of work motivation elements following the expectancy theory and the demographic and employment variables were performed using t-test and one-way between-groups analysis of variance (ANOVA). To validate the constructs, we applied CFA (confirmatory factor analysis). Multiple linear regression analysis was conducted to identify the factors associated with work motivation (Cohen &Cohen, 1983). The Statistical Package for Social Sciences version 22.0 (SPSS) was used to analyze the data from the questionnaire.

The data was collected from 325 health workers from six Jordanian hospitals: King Abdullah Hospital public hospital in north of Jordan IRBID city, Amman Specialist Hospital private hospital in Amman, Irbid Specialist Hospital private hospital, Ibn Al-Nafees private hospital in Irbid city, Al-Shona public hospital in the middle area of Jordan, and Princess Basma hospital. The sample is composed by doctors, nurses, helpers, support staff, administrative staff and other health related staff.




Source: Chiang and Jang (2008)

***Fig. 4.*** *The model of the constructs of work motivation*

## FINDINGS

### *Sample profile*

From the sample of respondents that I collected from the Jordanian health system different hospitals, the majority of them are from public hospitals (66.5%), with the largest age group as being the group of 25–35 years old (51.4%). Of the total number of respondents, the majority were male employees (52.9%) and 43.3% have bachelor degree in science. Almost 33.5% of the respondents claimed that they have more than 10 years' experience in the same position and about 51% of them work in therapeutic area.

Regarding the proportions of nurses vs. doctors, only 36% of the respondents declared to be nurses and only 19% are doctors. Heavy workload and health care financing issues were mentioned by the respondents as the main changes that affect the hospitals. The majority declared that they have more than 20 patients per day (62.5%). Regarding the intention to stay, 61.2% of the respondents confirmed the intention of staying.

### *Revealing the determinants of work motivation among Jordanian employees*

The mean scores for the four measures of expectancy ranged from 2.90 to 3.67, and the mean scores of components are extrinsic instrumentality, from 2.87 to 3.00; intrinsic instrumentality, from 3.46 to 3.54; extrinsic valence, from 2.83 to 2.99; intrinsic valence, from 3.43 to 3.59; work motivation, from 3.62 to 3.72.

When respondents evaluated five components of modified expectancy theory, intrinsic valence had the highest scores. Respondents indicated that they would improve their performance if they were highly motivated (Table 1).

A measurement model was estimated with a confirmatory factor analysis to validate the new measures and also to verify its validity, the factor loading for all items was positive, ranging from 0.77 to 0.964. The mean standardized factor loadings for each dimension are: expectancy 0.77, extrinsic instrumentality 0.955, intrinsic instrumentality 0.93, and extrinsic valence 0.95, and intrinsic valence 0.96, work motivation 0.964, suggesting that all items have enough interval consistency to construct a single measure (Table 2).

In order to decide the main determinants of work motivation according to Vroom theory, multiple regression analysis was applied. The dependent variable was worker motivation determined as mean score of the four items of motivation. The independent variables are the mean score of expectancy, extrinsic instrumentality, intrinsic instrumentality, extrinsic valence and intrinsic valence and personal and employment characteristics (Table 3).

Empirical results pointed out the statistical significance of three of five components of Vroom theory-expectancy, extrinsic instrumentality and intrinsic valence and also hospital type, graduation degree, experience in the same position, area of work.

The expectancy manifests a positive impact on work motivation, individuals desiring to be regarded as effective employees, with higher productivity and increasing performance.

Extrinsic instrumentality displayed a negative impact on work motivation at the significance level of 10%, highlighting the fact that financial incentives will not maintain for a long time the level of motivation of employees.

The intrinsic valence manifests an important impact on work motivation, pointing out the need of personal development as a main desire of employees.

While expectancy and intrinsic valence have a positive effect on hospital employee motivation, extrinsic instrumentality showed a negative sign for the relationship with work motivation, infirming the results from literature review and this results have been explained by Chiang and Jang (2008) using what is called to be the suppressor effect which was defined as a variable that increases the predictive validity of another variable (or set of variables) by its inclusion in a regression equation. The negative significance can also be explained by the fact that the greater extrinsic instrumentality means an employee will be less motivated.

The absolute values of coefficients in expectancy and intrinsic valence toward work motivation were greater than those of extrinsic instrumentality suggesting that intrinsic motivation factors are more influential than extrinsic

*Table 1. Descriptive statistics*

| | Mean | Std. Deviation |
|---|---|---|
| Expectancy | 3.49 | 0.8577 |
| If I work very hard, my job performance will significantly improve | 3.66 | 1.078 |
| If I work very hard, I will get a lot more accomplished | 3.43 | 1.119 |
| If I put more effort into my job, my productivity will improve significantly | 3.59 | 1.060 |
| If I put more effort into my job, I will definitely be regarded as an effective employee | 3.28 | 1.188 |
| Extrinsic instrumentality | 2.91 | 1.159 |
| Performing well in my job will definitely result in | | |
| -getting good pay | 2.89 | 1.241 |
| -getting monetary bonuses | 2.87 | 1.227 |
| -getting pay increases | 2.91 | 1.233 |
| -having more opportunities for promotion | 3.00 | 1.239 |
| Intrinsic instrumentality | 3.50 | 1.00 |
| Performing well in my job will definitely result in | | |
| -having more responsibility and control over my job | 3.46 | 1.148 |
| -taking on more challenging work tasks | 3.54 | 1.070 |
| -having feelings of accomplishment | 3.54 | 1.064 |
| -feeling very good about myself | 3.48 | 1.145 |
| Extrinsic valence | 2.90 | 1.08 |
| Performing well in my job will definitely result in | | |
| -Good salary/wage | 2.90 | 1.191 |
| -More monetary bonuses | 2.83 | 1.179 |
| -More pay increases | 2.86 | 1.190 |
| -Interesting work | 2.99 | 1.215 |
| -Opportunities for advancement/promotion | 2.97 | 1.169 |
| Intrinsic valence | 3.53 | 1.04 |
| Performing well in my job will definitely result in | | |
| -More responsibility/control over my job | 3.43 | 1.144 |
| -More challenging work tasks | 3.55 | 1.098 |
| -Full use my skills and abilities | 3.56 | 1.114 |
| -Feelings of accomplishment | 3.59 | 1.084 |
| -Personal growth and development | 3.55 | 1.160 |
| Work motivation | 3.67 | 1.118 |
| When I am highly motivated, I will definitely | 3.67 | 1.186 |
| -expend more effort on the job | | |
| -enhance quality of my job performance | 3.72 | 1.173 |
| -increase productivity on the job | 3.70 | 1.160 |
| -be willing to get involved in my job | 3.62 | 1.189 |

factors for hospital employees. It is worth mentioning that for health employees, the level of responsibility, the challenging work tasks, usage of skills and abilities, feelings of accomplishment and the perception of

*Table 2.*

| Theoretical dimensions | Constructs | Standardized factor loadings | Cronbach Alpha |
|---|---|---|---|
| Expectancy | If I work very hard, my job performance will significantly improve | 1.00 | 0.77 |
| | If I work very hard, I will get a lot more accomplished | 0.67 | |
| | If I put more effort into my job, my productivity will improve significantly | 0.85 | |
| | If I put more effort into my job, I will definitely be regarded as an effective employee | 0.86 | |
| Extrinsic instrumentality | Performing well in my job will definitely result in<br>-getting good pay<br>-getting monetary bonuses<br>-getting pay increases<br>-having more opportunities for promotion | <br>1.17<br>1.18<br>1.17<br>1.30 | 0.955 |
| Intrinsic instrumentality | Performing well in my job will definitely result in<br>-having more responsibility and control over my job<br>-taking on more challenging work tasks<br>-having feelings of accomplishment<br>-feeling very good about myself | <br>1.88<br>1.79<br>1.78<br>1.64 | 0.933 |
| Extrinsic valence | Performing well in my job will definitely result in<br>-Good salary/wage<br>-More monetary bonuses<br>-More pay increases<br>-Interesting work<br>-Opportunities for advancement/promotion | <br>1.30<br>1.30<br>1.40<br>1.41<br>1.37 | 0.951 |
| Intrinsic valence | Performing well in my job will definitely result in<br>-More responsibility/control over my job<br>-More challenging work tasks<br>-Full use my skills and abilities<br>-Feelings of accomplishment<br>-Personal growth and development | <br>2.01<br>2.02<br>2.01<br>1.95<br>2.07 | 0.96 |
| Work motivation | Work motivation<br>When I am highly motivated, I will definitely<br>-expend more effort on the job<br>-enhance quality of my job performance<br>-increase productivity on the job<br>-be willing to get involved in my job | <br><br>1.76<br>1.69<br>1.59<br>1.54 | 0.964 |

personal growth and development are more important than the financial incentives.

Expectancy led hospitals' employees to believe their effort will lead to desired performance. Instrumentality is the belief that if a hospital employee meets performance expectations, he will receive a greater reward.

The employees think they will have accomplishment if they perform well in their job, but they do not think that better pay, monetary bonus, pay increases, or promotion are related with performance expectations. They valorize valence, preferring responsibility over job, using their abilities, and feeling of accomplishment, which are intrinsic valences.

The empirical results of ANOVA analysis pointed out that the model is statistically valid due to the fact that Sig. (F-test) is smaller than 1% (Table 4).

The goodness of fit of the model revealed that the degree of determination in the model is 0.51, pointing out that the influence of all significant variables explains 51.3% of the total variance in work motivation (Table 5).

Analyzing the differences between the main drivers of work motivation according to the expectancy theory and the demographic variables, I can mention the following:

There are statistical differences regarding the level of work motivation and intrinsic valence in public hospitals in comparison with private hospitals, stating that the employees in the public hospitals have a higher level of work motivation and intrinsic valence, individuals valorising more the responsibility of their job, the challenging work tasks, the usage of their skills and abilities and the feeling of accomplishment and also the personal growth.

***Table 3.*** *Coefficients*[a]

| Model | | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | .500 | .502 | | .997 | .320 |
| | expectancy | .209 | .065 | .160 | 3.229 | .001 |
| | extrinsic_instrum | -.112 | .069 | -.116 | -1.632 | .104 |
| | intrinsic_instrum | -.037 | .073 | -.033 | -.506 | .613 |
| | extrinsic_valence | .067 | .071 | .065 | .934 | .351 |
| | intrinsic_valence | .643 | .065 | .598 | 9.936 | .000 |
| | TYPE OF HOSPITAL | .357 | .108 | .151 | 3.322 | .001 |
| | GENDER | .029 | .091 | .013 | .312 | .755 |
| | AGE | -.043 | .053 | -.036 | -.802 | .423 |
| | GRADUATION DEGREE | -.065 | .035 | -.084 | -1.872 | .062 |
| | TIME WORKING IN HOSPITAL | .013 | .042 | .015 | .315 | .753 |
| | YEARS IN THE SAME POSITION | .099 | .042 | .113 | 2.348 | .019 |
| | MARITAL STATUS | -.121 | .100 | -.055 | -1.209 | .228 |
| | POSITION | .025 | .030 | .039 | .833 | .406 |
| | AREA OF WORK | -.104 | .056 | -.090 | -1.850 | .065 |
| | MANAG.POSITION | -.009 | .114 | -.004 | -.076 | .939 |
| | INTENTION_LEAVE | .003 | .098 | .001 | .026 | .980 |
| | ORGANIS_STRUCTURE | .044 | .039 | .052 | 1.125 | .261 |
| | CHANGES AFFECT HOSPITAL | .017 | .039 | .019 | .438 | .662 |

[a] *Dependent Variable: work motivation*

***Table 4.*** *ANOVA*[b]

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 208.154 | 18 | 11.564 | 17.943 | .000a |
| | Residual | 197.219 | 306 | .645 | | |
| | Total | 405.372 | 324 | | | |

[a] *Predictors: (Constant), changes affecting hospital, intrinsic_valence, management position, work experience in the same position, intention to leave, gender, graduation degree, marital status, organizational structure, expectancy, age, type of hospital, position, working experience, area of work, extrinsic_valence, intrinsic_instrum, extrinsic_instrum*
[b] *Dependent Variable: work motivation*

***Table 5.*** *Model Summary*

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .717a | .513 | .485 | .80281 |

[a] *Predictors: (Constant), CHANGES AFFECT HOSPITAL, intrinsic_valence, MANAG.POSITION, YEARS IN THE SAME POSITION, INTENTION_LEAVE, GENDER, GRADUATION DEGREE, MARITAL STATUS, ORGANIS_STRUCTURE, expectancy, AGE, TYPE OF HOSPITAL, POSITION, TIME WORKING IN HOSPITAL, AREA OF WORK, extrinsic_valence, intrinsic_instrum, extrinsic_instrum*

The age seems to create some differences related with extrinsic instrumentality and intrinsic valence. While the young people valorise more the extrinsic instrumentality elements (getting good pay, getting monetary bonuses getting pay increases, having more opportunities for promotion) the elderly appreciate more the elements of intrinsic valence.

One of the results of these comparisons is related to the fact that there is not any difference in perception regarding the work motivation by age group.

The illiterate group of employees has the highest level of work motivation and they appreciate more the elements of intrinsic valence. At the opposite side, health employees with doctoral studies exhibit the lowest level of work motivation.

Regarding the experience in the hospitals, individuals with more than 10 years' experience in the same position are the most demotivated by extrinsic instrumentality elements (getting good pay, getting monetary bonuses getting pay increases, having more opportunities for promotion).

Regarding the marital status, the separated or divorced individuals are those the most demotivated in terms of expectancy and overall work motivation.

I found out also differences between doctors, nurses, administrative staff, support staff or helpers in terms of intrinsic valence and work motivation, revealing that the most motivated are the support staff, while the nurses are the most demotivated personnel.

Another interesting result of our study was the fact that the most motivated people are those from managerial and diagnostic area of work in terms of work motivation, intrinsic valence or extrinsic instrumentality.

Also people from horizontal organizational structure registered a higher level of overall work motivation and extrinsic instrumentality.

It is worth mentioning that there are not statistical significant differences between gender, work experience, and management position and the overall level of work motivation or the main factors identified from expectancy theory-expectancy, intrinsic valence, and extrinsic instrumentality (Table 6).

*Table 6.*

| | | expectancy | extrinsic_instrum | intrinsic_valence | work motivation |
|---|---|---|---|---|---|
| | | Mean | Mean | Mean | Mean |
| Type of hospital | Sig(t-test) | 0.23 | 0.83 | 0.01* | 0.00* |
| Gender | Sig(t-test) | 0.36 | 0.66 | 0.79 | 0.89 |
| Age | Sig(ANOVA) | 0.91 | 0.005* | 0.083*** | 0.184 |
| Graduation degree | Sig(ANOVA) | 0.65 | 0.12 | 0.063*** | 0.029** |
| Time working in hospital | Sig(ANOVA) | 0.77 | 0.31 | 0.28 | 0.17 |
| Years in the same position | Sig(ANOVA) | 0.93 | 0.08*** | 0.49 | 0.19 |
| Marital status | Sig(ANOVA) | 0.09*** | 0.96 | 0.13 | 0.079*** |
| Position | Sig(ANOVA) | 0.14 | 0.31 | 0.00* | 0.00* |
| Area of work | Sig(ANOVA) | 0.24 | 0.00* | 0.00* | 0.00* |
| Management position | Sig(t-test) | 0.39 | 0.76 | 0.65 | 0.97 |
| Organizational structure | Sig(ANOVA) | 0.00* | 0.00* | 0.24 | 0.00* |

## CONCLUSION

The findings of this study supported the validity of the modified expectancy theory model with five dimensions- expectancy, extrinsic and intrinsic instrumentality, extrinsic and intrinsic valence of employee motivation in health system in Jordan. The proposed expectancy theory model for motivation was tested using data from 325 hospital employees.

The empirical results pointed out the statistical significance of three of five components of Vroom expectancy theory, extrinsic instrumentality and intrinsic valence. For the overall level of work motivation manifest also a significant impact the type of hospital, graduation degree, and experience in the same position and also area of work.

For Jordanian hospital employees, the intrinsic valence is most appreciated followed by the expectancy.

Expectancy increases employee motivation by creating a sense of accomplishment, while intrinsic valence motivates employees to take more responsibility, making full use of their abilities and accomplishments. Expectancy and intrinsic valence are employee motivators. Extrinsic instrumentality showed no positive effect on work motivation.

When hospital employees perform well, and the intrinsic outcomes are controlled, expect good pay, monetary bonuses, and pay increases or promotions, the motivation of employees who decreases if they do not receive those extrinsic rewards. Results showed that intrinsic valence and expectancy contribute more to employee motivation than extrinsic instrumentality.

The main empirical results are that employees understand if they work hard, their performance and productivity will significantly improve, will be accomplished and can be viewed as an effective employee.

Since having a fully use their skills and knowledge in the workplace and a sense of accomplishment and a personal growth and development, taking responsibility, and having challenging work are good motivators for employees, managers should recognize employees who do well.

Still after all the lack of suitable plans and strategies to attract the young personnel from the government and the MOH.

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# ASSESSMENT OF INITIAL PATIENT VISITS TO A DENTAL CLINIC FOR OPTIMIZATION OF ORTHODONTIC CARE IN PATIENTS WITH PARTIAL ABSENCE OF TEETH

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**ABSTRACT** — Delayed patient visit to a dentist accounts for a deterioration of hygiene indices, resulting in partial or complete tooth loss. Studying the issue of the incidence of partial absence of teeth, as well as the organization and treatment of patients with this pathology, we found that quite often the provision of qualified care to patients with partial absence of teeth can become difficult due to the presence of some complications. Therefore, in this study, an analysis of the first patient visit to a dental clinic was carried out in order to optimize the quality of orthodontic care to patients with partial absence of teeth.

**KEYWORDS** — initial visit, a dental clinic, orthodontic care, referral, partial secondary edentia, organization of orthodontic care.

## INTRODUCTION

Russian society has been in the phase of modernization of industry, the economics and the social sphere. Without an active participation of civil society the solution of such critical problems would be impossible. [1]

Therefore, the Association of private dental clinics has been actively operating in the country along with the Dental Association of Russia for 20 years.

The transition to market relations in the field of medicine has led to the emergence of alternative forms of medical care through commercial dental medical organizations. In recent years, the network of such organizations has grown noticeably, and they currently provide a fairly significant proportion of medical care to the population. [2, 3, 4]

Thus, in the process of this study, there was a need to analyze the indicators of the first patient visit to private dental organizations in Moscow according to several criteria.

*Purpose of the study* is to conduct an analysis of the initial patient visit to dental clinics for optimizing orthodontic treatment of patients with partial absence of teeth.

## MATERIAL AND METHOD

Data analysis was carried out on the basis of 10 private dental clinics (PDC). The time period for the analysis of the initial patient visit to dental clinics was determined as — 2008–2018.

## RESULTS AND DISCUSSION

The dynamics of the number of initial patient referral to specialists at the PDC is visually reflected in the graph (Fig. 1). As it can be seen, throughout the analyzed time period, the largest part of the primary patient flow for medical care is distributed to dentists and dental therapists. Moreover, in the period of 2016, there was a general decline in patient flow in all areas of specialties.

We studied the distribution of patients according to initial visit to specialists at PDC, which is reflected in Table 1.

According to the analysis, it was found that the proportion of patients referring to dental therapists is 60.3–70.5% of the total patient flow. Of these, 45.3–61.8% is the patients who visited the clinic in the basis of voluntary health insurance (VMI) (Table 1).

The smallest proportion is made up of patients who initially refer to orthodontists — 1.3–4.2%. Of these, up to 3.5% are in patients who go to the clinic according to the VHI (Table 2).

In the process of analysis, a stable tendency was revealed: patients with partial absence of teeth most often get an appointment with an orthodontist in the direction of an orthopedic dentist, to whom, in turn, they are often referred by dental therapists. In this regard, an analysis of the patient referral was carried out: 1) from a dental therapist to an orthopedic dentist, 2) from an orthopedic dentist to an orthodontist (Table 3).

Thus, we can conclude that the specialty of a dental therapist is a key link at a dental organization. The majority of patients during their first visit to the PDC are accepted by a dental therapist, where they receive the necessary information and referral to the next specialist.

## CONCLUSION

Thus, the resulting comprehensive analysis of the initial patient access to dental clinics can be taken as a basis for optimizing the organization and provision

of orthodontic treatment to patients with partial absence of teeth.

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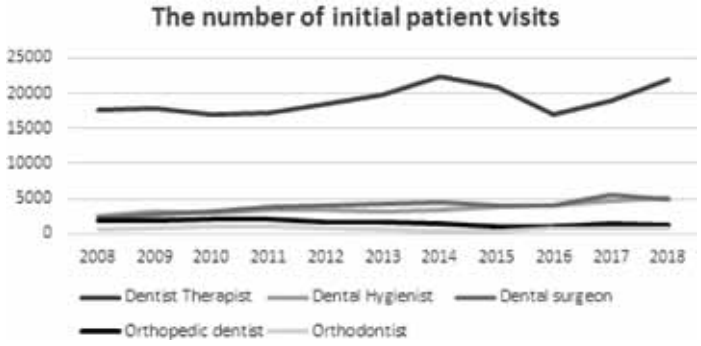


***Fig. 1.*** *The number of initial patient visits to specialists at PDC*

***Table 1.*** *Initial referral to specialists at PDC*

| Speciality | Analyzed time period | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | % Of general patient flow | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
| DentalTherapist | | 70,5 | 67,4 | 64,6 | 62,7 | 64,7 | 66,9 | 69,4 | 68,8 | 63,1 | 60,3 | 64,4 |
| Dental Hygienist | | 10,3 | 11,7 | 11,5 | 12,2 | 11,9 | 11,0 | 10,7 | 12,9 | 14,9 | 15,2 | 15,0 |
| Dental surgeon | | 9,6 | 10,5 | 12,0 | 13,8 | 14,4 | 14,4 | 14,1 | 13,5 | 15,1 | 17,3 | 14,5 |
| Orthopedic dentist | | 7,3 | 6,9 | 7,7 | 7,4 | 6,1 | 5,3 | 4,4 | 3,5 | 4,0 | 4,7 | 3,9 |
| Orthodontist | | 2,3 | 3,5 | 4,2 | 3,9 | 2,9 | 2,4 | 1,4 | 1,3 | 2,9 | 2,5 | 2,2 |

***Table 2.*** *Initial patient referral according to the VHI*

| Speciality | Analyzed time period | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | % Of general patient flow in the department | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
| Dental Therapist | | 53,6 | 55,6 | 59,1 | 61,8 | 60,2 | 54,5 | 48,2 | 46,9 | 45,3 | 50,8 | 51,9 |
| Dental Hygienist | | 45,1 | 42,8 | 43,4 | 43,2 | 39,3 | 42,4 | 49,1 | 57,8 | 60,8 | 65,0 | 75,5 |
| Dental surgeon | | 61,9 | 58,7 | 58,3 | 60,4 | 60,8 | 53,0 | 46,0 | 51,9 | 48,3 | 51,4 | 52,5 |
| Orthopedic dentist | | 12,2 | 6,1 | 7,7 | 7,1 | 7,1 | 6,5 | 3,9 | 5,7 | 3,5 | 2,7 | 1,8 |
| Orthodontist | | 3,5 | 1,9 | 0,9 | 1,3 | 1,0 | 1,1 | 0,7 | 0,3 | 0,1 | 0 | 0,3 |

***Table 3.*** *Patient Referral*

| Direction | Analyzed time period | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
| Dental Therapist ↓ Orthopedic dentist | 423 | 1094 | 2315 | 5468 | 7343 | 9346 | 12094 | 12602 | 11582 | 14022 | 12442 |
| Orthopedic dentist ↓ Orthodontist | NR | 31 | 108 | 203 | 252 | 162 | 132 | 138 | 188 | 155 | 103 |

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# ANALYSIS OF THE RESULTS OF THE TREATMENT OF VARIOUS FORMS OF GENDER IDENTITY DISORDERS IN MEN

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**ABSTRACT** — The medical records of patients with male transsexualism were studied, medical assistance was received at the Clinical and Diagnostic Center of Andrology and Transplantology. It was revealed that the availability of adequate measures for the prevention of suicides and the occurrence of problems of people with impaired self-identification (transgender people) leads to a biological and passport state in accordance with mental status. To develop an algorithm for complex therapy of specialists of various profiles [3].

**KEYWORDS** — igender identity, incomplete masculinization, violation of gender formation, hermaphroditism, male transsexualism, suicidal tendencies, gender correction.

The term *gender* is a complex of anatomical, physiological and biological characteristics of people, where a person is identified as a man or woman. The concept of "gender" is used to describe the socio-psychological criteria of personality. This concept includes such characteristics as biological gender, gender stereotypes, gender norms and gender identity [1]. Gender identity is one of the basic characteristics of a person and a product of a person's social adaptation. It begins by showing patterns of male and female behavior.

Naturally, in the family, there are standards that form ideas about one's own identity: gender behavior, self-esteem and its place in society [3]. Gender identity is finally formed in adolescence. Gender stereotypes and gender preferences [2].

In our scientific society, two models are indicated: human identity: bipolar and multipolar. The bipolar model is based on the idea of strict differentiation: on the basis of gender identity: men have only masculine qualities, and women have serious feminine qualities. A softer multipolar model that allows the existence of several options for gender identity within the same sex.

Thus, individuals have reliable inner sensations of being male or female. Science considers any violation of gender auto-identification of a person as a pathological condition. The most severe form of gender identity violation is transsexualism.

*Objective:*

To study the frequency of occurrence of psychogenic male transsexualism and to assess the compliance of the main criteria for sexual identification.

## MATERIAL AND METHODS

We studied the medical records of patients with a violation of gender identity and who received treatment at the Clinical and Diagnostic Center of Andrology and Transplantology, RUDN University, Moscow. Only 20 patients of male (passport) gender with violation of gender identity. In the work, standard examination methods were used to identify the patient's gender: genetic, gonadal, hormonal, phenotypic, psychological and legal.

## RESEARCH RESULTS AND DISCUSSION

Studied 20 cards of male patients. The analysis did not include patients with endogenous mental illnesses and organic brain diseases [4.]. The average age of transgender patients who applied to the Clinical Center was 27 ± 2 years, which corresponds to the active labor and reproductive period of a person. The appearance of the first symptoms of gender identity violations in childhood was noted by 11 patients: they repeatedly expressed their desire to be a girl to their parents, often changed into women's clothes and preferred to play with dolls.

The results showed an analysis of medical records that the genetic gender in all patients corresponded to normal digital parameters. We found a match in the gonadal and genetic sex in only 17 examined, which amounted to 85%. from the total. A standard hormonal study showed that in 15 out of 20 patients, the data are within normal limits and correspond to the gonadal form. Moreover, in all examined patients, the phenotypic gender corresponded to the hormonal and gonadal sex. Whereas in 8 patients (40%) the pheno-

typic gender did not coincide with the legal one. We found that the psychological gender in 15 patients (75%) was different from the genetic, gonadal, and phenotypic. It should be noted that the legal gender obtained at birth was retained by 11 subjects (55%). Of the 20 examined 8 patients (40%) had already changed their passport gender before contacting the Clinical Center. Medical records did not provide data on concomitant and hereditary diseases. Sex correction surgery was performed on 15 patients at the Clinical Center of Andrology and Transplantology. Surgical intervention was carried out according to the standard technique in several stages throughout the year. Of the 15 operated, only one patient experienced complications in the early postoperative period, which were successfully eliminated. All patients are satisfied with the results of gender reassignment surgery. The psychological state of patients (Table 1) was assessed as stably positive on some issues of the diagnostic scale (the diagnostic scale of the questionnaire *Masculinity, Femininity, and Gender Type of Personality* of the Russian analog of BSRI, 2010–2012).

***Table 1.*** *Dynamics of patient self-esteem*

| Masculinity Scale | Before Surgery | After Surgery |
|---|---|---|
| Courage | low | high |
| Willingness to take risks | low | high |
| Domination | low | high |
| Masculinity | mild | moderate |
| Leadership | low | high |
| A sense of self-sufficiency and confidence | low | high |
| Psychological satisfaction with the results of surgery | excitement | high |

However, two patients were forced to refuse sex reassignment surgery in accordance with the psychiatrist's opinion. One — in connection with suicidal tendencies and mental instability. Highly qualified psychiatric care was successfully provided to the second patient. However, even with the development of severe surgical complications, patients rarely regret the surgery performed to correct the sex.

## CONCLUSIONS

All medical measures in patients with pathology of sexual development should be regarded as interventions for health reasons since they prevent suicidal attempts. The moral component of the quality of life of patients improves markedly after surgery [5]. However, gender change does not completely solve all the problems of people with pathology of gender development, as new difficulties arise associated with the loss of previous social and physiological skills and adaptive experience to life in society. Patients who undergo surgery should undergo regular medical examinations in accordance with the guidelines recommended for their age. All stages of the examination, diagnosis, and treatment should be carried out in accordance with the International Medical Standards for Transgender People [6].

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# BENEFITS AND HARMS OF MOBILE DEVICES FOR HIGH SCHOOL STUDENTS

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**ABSTRACT** — It is well known that electromagnetic radiation from modern mobile devices has a negative effect on the central nervous system, especially for children. We studied the opinion of high school students about the impact of mobile devices on their bodies by questioning. It was revealed that students using mobile devices up to 7 hours a day note irritability, tearfulness, dissatisfaction with themselves and their academic performance is much lower than that of peers. It turned out that *Internet addiction* is observed more often in girls than in boys.

**KEYWORDS** — educational migration, youth health, mobile devices, radiation, Internet addiction, visual impairment, depression.

Modern society is focused on building a new model of the school, and as the main result involves the development of students' *gene* of independence in cognitive activity. Today, the established forms and methods of teaching schoolchildren require correction and new pedagogical decisions, taking into account the information society as a whole [4]. However, with the active introduction of all forms of electronic technology in the educational process, one should not forget about the information security of children. Today, a huge amount of information, both about the benefits and the dangers of mobile devices for children. Each parent has his own opinion on the use of tablets by children, or a categorical restriction, or time limits or complete freedom. Under the influence of EMR, absolutely all organs, and systems of the child's body fall. In children, often using cell phones, the processes of memorization and reproduction of information, sleep is disrupted [5]. According to statistics, from 2015 in the UK every 3rd child has his own tablet. Under the age of 15, 60% of children used a tablet computer at home.

However, the Parliamentary Assembly of the Council of Europe (PACE) recommends that all reasonable measures be taken to reduce the effects of electromagnetic radiation, especially radio frequencies from mobile phones, on children and young people who are most at risk of brain tumors [1]. Scientists from different countries asked the UN to formulate international standards for the safety of electromagnetic radiation.

On the recommendation of the Canadian Society of Pediatricians, there should be a restriction on the use of mobile devices to 2 hours a day for children 6 to 18 years old. In Russia, electronic textbooks have been actively introduced since 2015. The Ministry of Education and Science requires the content of electronic and paper textbooks to be consistent. However, according to the Russian sanitary standards, it is not recommended for children to use phones, smartphones, tablets. However, to ensure the information security of children, along with the prohibition of information products, it is necessary to promote the creation of conditions that ensure positive socialization and individualization of the child, his psychological well-being and positive worldview [2]. Researchers from the Russian center for electromagnetic safety argue that electromagnetic radiation from modern mobile devices has a negative effect on the central nervous system, especially children. In adolescence, gadgets carry the danger of the emergence of *Internet addiction*.

Internet addiction is a mental disorder in which a person is very obsessively willing to enter the global network and is not able to get out of it on time. [3]

Schoolchildren who regularly used tablets and smartphones differ from their peers in diffused attention, increased impulsivity. Their ability to self-regulation decreases. The regular use of smartphones and tablets takes a lot of time, reducing the time for physical activity. Naturally, such a way of life leads to a delay in the physical development of the child, and therefore his successes in school are quite low.

With prolonged use of electronic sensor devices in children, abnormal formation of muscle tissue is observed, and spinal curvature occurs. Most smartphones harm the eyes, as they contribute to the development of myopia. With the frequent use of mobile devices, children become closed or spend a lot of time alone, avoid contacts, both with their peers and their loved ones, including parents. Children begin to lie and skip classes at school. Turning to them with ordinary questions and requests causes an inadequate, sometimes

aggressive reaction. The purpose of the study: to identify the presence of *Internet addiction* in the 8th-grade students.

## MATERIAL AND METHODS

We studied the opinion of high school students on the impact of mobile devices on the body of the younger generation. The study involved only children of the same class. There are 20 children in total, 10 of them boys and 10 girls. The average age was 13.5–14 years. Students filled out forms at school anonymously and independently, without the influence of adults. The questionnaire included 18 questions: age, gender, from what age has access to mobile devices, what does it use for, Internet addiction, study, health, well-being, and other points.

## DISCUSSION

According to the age of access to a mobile device, two groups were identified. The first group — they had access to technology from 7 years old — 6 children, of which girls — 2, boys — 4. The second group — children had access from 10 years old — 14 schoolchildren, among them — 8 girls and 6 boys. In the first group, children use smartphones first for playing and watching video films, and then for learning. 3 out of 6 reported impaired vision, poor sleep, and fatigue (2 schoolchildren boys, 1 girl). Two are studying *satisfactorily*, and 4 students (3 boys and 1 girl) — *good*. The presence of *Internet addiction* was noted by 3 children, and mood swings, if they selected a mobile phone, were noted by all respondent children. Students in this group are ready to use a mobile device for an unlimited time. In the second group, 8 schoolchildren use mobile devices, first for playing, then for learning (5 girls and 3 boys). All of them noted the presence of *Internet addiction*, deterioration in visual acuity and rapid fatigue. 4 schoolchildren complain of headaches and poor sleep. They rated their studies *satisfactory*. It was revealed that students who use (6 children) mobile devices for learning, watching instructional videos are learning *good* and *excellent*. Deny *Internet addiction* in their own right. They can turn off mobile devices themselves.

It was revealed that *Internet addiction* is observed more often in girls than in boys. Headaches, fatigue and poor sleep are more often noted by girls, which is shown in Fig. 1. While visual impairment was detected in 11 schoolchildren, there are more girls among them.

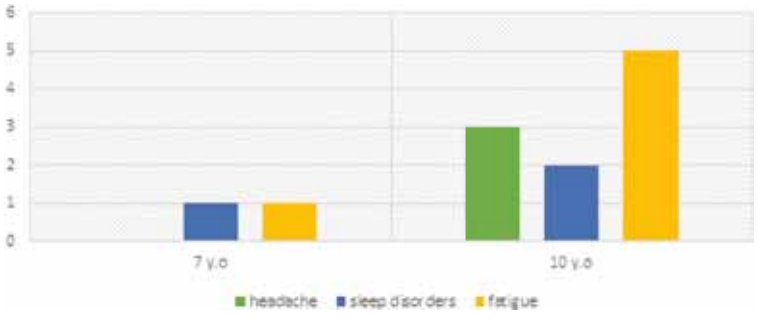


***Fig. 1.***

It was revealed that 12 students have access to mobile devices from 1 hour to 4 hours a day. While 8 students have access — 7 hours or more per day. The performance analysis showed that students who have limited access to mobile devices up to 4 hours a day study better, and their *Internet addiction* is less pronounced emotionally and brighter.

Studies have shown that students using mobile devices up to 7 hours a day report irritability, tearfulness, dissatisfaction with themselves and their academic performance is lower than that of their peers.

## CONCLUSIONS

1. Students are ready to use the mobile device for an unlimited time.
2. Early access to mobile devices (from the age of 7) contributes to the development of *Internet addiction*. The performance of this group is low.
3. The use of mobile devices for self-training does not particularly improve academic performance since, without the control of elders, children are distracted by other sites.
4. The long-term use of mobile devices worsens students' well-being.

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# STUDY OF THE MENSTRUAL CYCLE IN FOREIGN FIRST-YEAR STUDENTS OF RUDN UNIVERSITY

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**ABSTRACT** — Educational migration of young people is often accompanied by serious violations in human physiology. Almost all representatives of hot countries who have entered countries with a temperate and cold climate show changes in the menstrual cycle to one degree or another. The little-known culture of the new country also negatively affects the psycho-emotional state of foreign students. A study showed that all foreign students have menstrual irregularities. It also revealed a fluctuation in weight, which was reflected in the overall performance of students.

**KEYWORDS** — foreign students, menstrual cycle, entry, adaptation, academic performance, weight, countries, migration, stressful situations.

## INTRODUCTION

Over the past 50 years, the rate of increase in student flows has exceeded the rate of spread of higher education. According to UNESCO, the level of international student mobility has increased over the past 25 years by 300%. According to experts, the number of students studying abroad is 2.8 million, and by 2025 it will be 4.9 million. Getting into a foreign country, in a different culture, many young people experience discomfort, psychological stress and often get sick, which can lead to various complications. Unfortunately, some students return home without completing their education (1). Students who have moved from hot countries to countries with a more moderate, continental and sharply continental climate are worse at adaptation. Experience shows that even under the most favorable conditions of international contacts, when entering a new culture, many, as a rule, have various kinds of difficulties and problems. Often, representatives of different countries and cultures know little about each other, are guided by stereotypical ideas, have false and sometimes distorted, negative information about another culture and are biased towards it, which cannot but affect the length and complexity of their adaptation to another sociocultural environment. All this actualizes the problem of social adaptation of foreign students (2).

According to the observations of many gynecologists, stress and psycho-emotional experiences are often reflected in the menstrual cycle in the form of various disorders. Moreover, there are changes in the hormonal system of foreign students. It is no secret that psycho-emotional fluctuations can contribute to the launch of new diseases in the female body. According to the gynecologist Iev Daise, the risk group includes young active and practically healthy girls, in whom the body reacts to a large physical and psycho-emotional load, and possibly to excessive demands on themselves (3). Thus, a relationship was established between the stress state and hormonal imbalance.

## PURPOSE

To study changes in the menstrual cycle in foreign students of the first year of study at the university.

## OBJECTIVES

Identify changes in food culture; identify weight changes and study the psycho-emotional state of students.

## MATERIALS AND METHODS

To solve the tasks, we have developed a special questionnaire, consisting of 15 points, including such questions as age? Weight? The beginning of the menstrual cycle? Which country? Having sex, etc. The questions are designed in such a way that it is possible to identify the pattern of change in the menstrual cycle in stressful situations or to refute the relationship between them.

## RESULTS AND DISCUSSIONS.

The survey involved 43 students, 13 of them are studying at the preparatory faculty, and 30 in the first year. The distribution of female students by faculty, we presented in Fig. 1.

The study involved foreign students in their first year of residence in Russia. Survey results showed that 21 of one girl's weight increased from 6 to 17 kg, and 17 students lost weight from 4 to 20 kg. Only 5 girls showed a slight change in weight by an average of ± 1.2 kg. It should be noted that one foreign student of the Faculty of Economics (Colombia) lost 20 kg

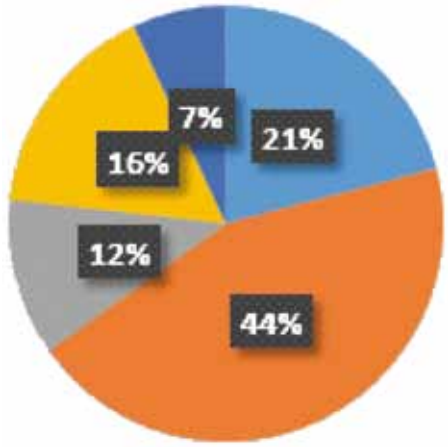


*Fig. 1.*

in weight, while a student of the Faculty of Medicine (North Caucasus) showed an increase in weight of up to 17 kg over 1 year. Also, according to the results of the survey, we found that 18 girls had a complete cessation of menstruation from 2 to 6 months. It was revealed that in 23 girls menstruation became more plentiful, painful and prolonged. Of all the examined, only 2 girls had no menstrual irregularities. Perhaps this is due to the fact that students took birth control drugs 1.5 years before moving to Russia. It turned out that the smallest violations of the menstrual cycle in students from neighboring countries compared with students from Latin America.

## RECOMMENDATIONS

1. It is necessary to first study the climatic and social characteristics of the country of entry in order to reduce the negative effects on the body of the educational and psycho-emotional load.
2. Before coming to colder countries, it is advisable to take medications to maintain immunity.
3. Parents conduct educational work with children on the food ethics of the child.

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# MORPHOMETRIC ANALYSIS OF AGE-RELATED CHANGES IN THE PYRAMIDAL NEURONS OF THE HUMAN PREFRONTAL CORTEX FROM 8 TO 21 YEARS

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**ABSTRACT** — The article is devoted to the study of age-related changes in the size of pyramidal neurons of the human prefrontal cortex in postnatal ontogenesis. Histological material was obtained from 42 left cerebral hemispheres of males aged 8 to 21 years who died as a result of injuries without brain damage. The material was divided into three age groups: 1 — children aged 8 to 12 years (the age period of the second childhood, 15 observations), 2 — adolescents aged 13 to 16 years (12 observations), young men aged 17 to 21 years (15 observations). Morphometric analysis of pyramidal neuron sizes was performed in the III3 sublayer of the prefrontal cortex in the frontal eye field 8, the speech field 45 (Broca zone) and in the field 10 on the lateral surface of the frontal pole. For this purpose, we used virtual images of frontal paraffin sections of the prefrontal cortex 10 microns thick, stained with cresyl violet on Nissl. In each field of each of the three age groups we measured the height and width of the basal part of bodies at least 3000 neurons. The body volume of each neuron was calculated using a formula to calculate the cone volume. In each field of the prefrontal cortex we also analyzed age-related changes in the percentage of small, medium and large neurons. For indicators of different age groups and different individuals we calculated the average, the error of the average and the confidence interval with the level of significance P=95% ($p<0.05$). It was found that the largest individual differences in the size of pyramid neurons were characteristic of children whose individual indicators differed from the average indicators of the whole age group by 18–26%. We found a significant increase in the average volume of pyramid neurons in the field of 10 in adolescents compared to children. We also showed that in young men the change in the number of neurons in the classes of large cells led to the appearance of single neurons of the largest size in the range from 6101 to 8100 $\mu m^3$, which accounted for 5–7% of the total number of neurons studied. The obtained results demonstrate significant age-related changes in the size of pyramid neurons of the external pyramidal layer in the fields of 8, 45 and 10 prefrontal cortex in men aged from 8 to 21 years.

**KEYWORDS** — human prefrontal cortex, pyramidal neurons, morphometry, postnatal ontogenesis.

## INTRODUCTION

The study of changes in the human cerebral cortex during ascending ontogenesis continues to be a topical problem in age-related neuromorphology. It is important to determine the degree and nature of age-related changes affecting the control systems of the brain. The leading role in these control systems is played by the prefrontal cortex, which participates in the implementation and control of the most complex forms of cognitive activity [1]. It is known that modern brain imaging methods do not yet allow studying the microstructural components of the cerebral cortex in living people so that it would be possible to trace intracortical structural changes at different stages of life. Histological examination of the human cerebral cortex using morphometric techniques provides this opportunity. Modern morphometric data indicate that in the prefrontal cortex of the left hemisphere the largest changes in pyramid neuron size are observed from birth to 2–3 years. By the age of 7, pyramid neuron sizes in the cerebral cortex of girls are approaching those of adult women, while in boys neuron sizes are still changing [2]. When studying the size of neurons, as a rule, the size of the profile field (median section) of neuronal bodies is analyzed, but not their volume [3]. However it is known that at growth of the sizes of three-dimensional object the size of its volume changes to a greater extent than the area of median section [4]. Body volume is an important quantitative characteristic of the metabolic and functional potential of the neuron.

## OBJECTIVE

The aim of the study was to study the age-related dynamics of changes in body volumes of pyramid neurons in the human prefrontal cortex at late stages of ascending ontogenesis.

## MATERIALS AND METHODS

42 left hemispheres of men aged 8 to 21 years who died from injuries unrelated to brain damage were investigated. Collection of sectional material was authorized by the Ethical Commission of the Institute of Developmental Physiology of the Russian Academy of Education (Protocol No. 3 of 23.05.1996) and was carried out in the forensic mortuaries of Moscow and

Moscow region. The material was divided into three age groups: 1 — children aged 8 to 12 years (the age period of the second childhood, 15 observations), 2 — adolescents aged 13 to 16 years (12 observations), young men aged 17 to 21 years (15 observations). The pieces of the prefrontal cortex for histological examination were taken in the frontal eye field 8, the speech field 45 (Brocae zone) and on the lateral surface of the frontal pole in field 10 according to the Atlas of cytoarchitectonics [5]. The material was fixed in 10% neutral formalin, dehydrated in alcohols of ascending concentration and poured into paraffin according to standard methods. Each 40th frontal section 10 μm thick was stained with Nissl cresyl violet. We used a computer morphometry method with Image Tools technology (National Institutes of Health, USA) and ImageExpert™ Gauge microobject geometric measurement program (NEXSYS, Russia), as well as a Biolam-15 LOMO® microscope with an integrated USB camera UCMOS01300KPA (Altami, Russia) for measurements in the external pyramidal layer of the cortex (III$^3$ sublayer) of the height (H), as well as the width of the basal part (a) bodies of neurons with clearly visible nucleus, nucleolus and cytoplasm. The volume of the conical cell body (V) for each pyramidal neuron was calculated by the formula:

$$V = \frac{1}{3}\pi H[\frac{a}{2}]^2$$

The sample size for each section was not less than 10 neurons, for each histological preparation — not less than 4 sections, for each individual — not less than 5 preparations, for each annual age interval - not less than 3 individuals, for each age group — not less than 3000 neurons in each of the studied fields. We determined 8 size groups to calculate the percentage of pyramidal neurons of different sizes. Two groups were assigned to small neurons: 1 — from 101 to 1100 μm$^3$, 2 — from 1101 to 2100 μm$^3$. Three groups were assigned to middle neurons: 3 — from 2101 to 3100 μm$^3$, 4 — from 3101 to 4100 μm$^3$, 5 — from 4101 to 5100 μm$^3$. The largest groups also included 3 groups: 6 — from 5101 to 6100 μm$^3$, 7 — from 6101 to 7100 μm$^3$ and 8 — from 7101 to 8100 μm$^3$. For indicators of different age groups and different individuals, the average value, the error of the average and the confidence interval with a significance level of P = 95% ($p < 0.05$) were calculated.

## RESULTS

In boys aged 8–12 years in the III$^3$ sublayer of the external pyramidal layer, the mean group indices of pyramid neuron volumes in fields 8 and 45 did not have significant differences (Table 1). In comparison with these fields in the field 10 of frontal pole the size of pyramid neurons was on the average 1.2 times less. Individual averages for different children within the same age group ranged in the field 8 from 1,646.5±88.7 to 2,681.4±142.9 μm$^3$, in the field 45 — from 1,696.9±84.2 to 2,610.5±126.6 μm$^3$, in the field 10 — from 1,503.3±78.6 to 2,488.4±118.5 μm$^3$. In adolescents 13–16 years old, the volume of pyramid neurons in fields 8 and 45 did not change on average in comparison with children of the second childhood period. In field 10, the sizes of neurons increased 1.1 times, however, despite a significant increase, they were 1.1 times smaller than in other fields of the same age group. Minimum average individual indices of pyramid neuron volumes in all investigated fields increased by 1.1–1.2 times in comparison with children aged 8–12 years. As a whole, individual indicators within the group of adolescents ranged in the field of 8 from 1910.6±95.4 to 2607.3±137.8 μm$^3$, in the field of 45 — from 1921.5±112.2 to 2344.8± 104.1 μm$^3$, in the field of 10 from 1832.0±89.3 to 2421.3±132.7 μm$^3$. In young men aged 17 to 21, the average size of pyramid neurons in all investigated fields of the prefrontal cortex remained stable and did not differ from those found in children and adolescents. The differences between the volumes of pyramidal neurons in field 10 and the remaining fields in young men were the same as in adolescents. Individual indicators within the group of young men ranged in the field of 8 from 2057.5±107.2 to 2714.0±152.6 μm$^3$, in the field of 45 — from 1930.19±91.8 to 2558.09±125.0 μm$^3$, in the field of 10 from 1838.0±96.4 to 2410.0±130.6 μm$^3$. The study of pyramid neuron distribution by size classes showed that in all age groups small neurons prevailed, the total content of which varied in children from 56 to 73%, in adolescents — 66–68%, in young men — 54–58%. In adolescents in the field 8 the redistribution of neuron sizes towards their increase occurred within the small cell classes, while the content of medium-sized neurons increased insignificantly (Fig. 1). In fields 45 and 10, the content of medium-sized neurons increased compared to children (Fig. 2, 3). The content of size classes 4 and 5 was 12–22% of the total neuron population. In young men, the content of small neurons in all fields changed insignificantly. However, the redistribution of the number of neurons within large cell classes led to the appearance of single neurons of the largest size in the range from 6101 to 8100 μm$^3$, which accounted for 5–7% of the total number of neurons.

## DISCUSSION

The results obtained show that significant changes in the size of pyramid neurons of the upper floor of the prefrontal cortex occur not only in the early stages

***Table 1.*** *Volume of pyramid neurons in the III³ sublayer of the human prefrontal cortex at different stages of postnatal ontogenesis (M+m) (mkm³)*

| Cortical area | Second childhood | Adolescents | Young men |
|---|---|---|---|
| Field 8 | 2243,9±45,2 | 2336,6±53,7 | 2351,2±56,8 |
| Field 45 | 2216,4±39,9 | 2241,6±32,6 | 2259,9±54,4 |
| Field 10 | 1889,6±34,3* | 2083,4±45,4*# | 2150,2±50,0^ |

*Differences are significant (at p<0,05) in comparison with:*
** other fields of the same age group; # same field previous age group; ^ field 8 in the same age group.*

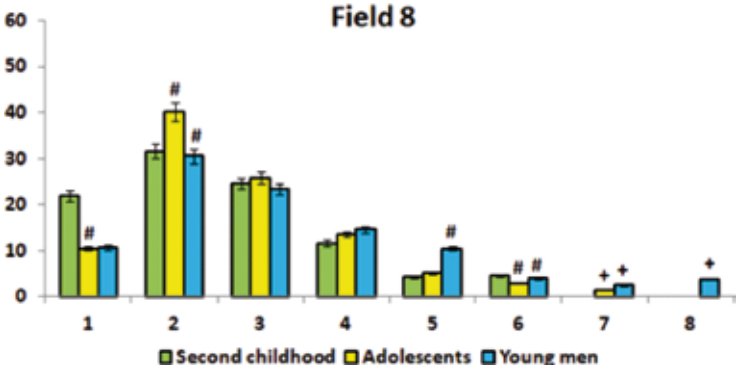


***Fig. 1.*** *Percentage of pyramidal neurons from different size classes in sublayer III3 of field 8*

***Here and on Fig. 2 and 3:*** *on the x-axis — neuronal size groups (1 — 101–1100 μm³, 2 — 1101–2100 μm³, 3 — 2101–3100 μm³, 4 — 3101–4100 μm³, 5 — 4101–5100 μm³, 6 — 5101–6100 μm³, 7 — 6101–7100 μm³ and 8 — 7101–8100 μm³); on the y-axis — neuronal percentage.*
*Green bars — children 8–12 years old, yellow bars — adolescents, blue bars — young men. The vertical segments represent the error of the mean. # — differences are significant (at p<0,05) in comparison with same field previous age group; + — emergence of the largest neurons.*

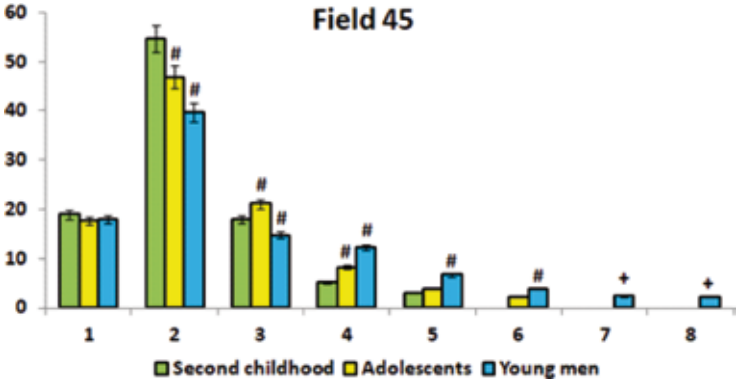


***Fig. 2.*** *Percentage of pyramidal neurons from different size classes in sublayer III³ of field 45*

of life, but also in adolescents and young men. The field 10 of the prefrontal cortex is one of the areas most late maturation in postnatal ontogenesis [6]. The significant increase of neuron sizes detected by us in field 10 on the lateral surface of the hemisphere in adolescents in comparison with children of 8–12 years old serves as an argument that microstructural transformations of the prefrontal cortex and its cortical-cortical connections do not end with children and continue in the puberty period. In adolescents, the importance of the frontal pole cortex increases for the realization of such functions as coordination of the sequence of actions in the time continuum, maintenance of working memory, control of emotional aspects of behavior, change of attitude to a specific type of activity [7, 8]. In this regard, in our opinion, the body volume of pyramidal neurons can be considered as one of the structural descriptors that allow estimating the level of morphofunctional cortical development in adolescents and young men. Studying the average size of pyramid neurons in individuals has shown that significant individual differences are observed in each of the age groups. There is an opinion that individual differences in the complex of morphological parameters in the population increase as they grow older. This process is seen as a consequence of the influence of not only hereditary but also environmental factors [9]. However, when analyzing the average group indicators of pyramid neuron volumes in the upper floor of the prefrontal cortex included in complex associative neural networks, we found that the most variable in terms of the studied parameter are neurons in the cortex not in young men but in children aged 8-12 years. Individual differences of neuronal sizes in the studied fields in children vary by ±18–26% from the average value of the whole age group. In adolescents, the

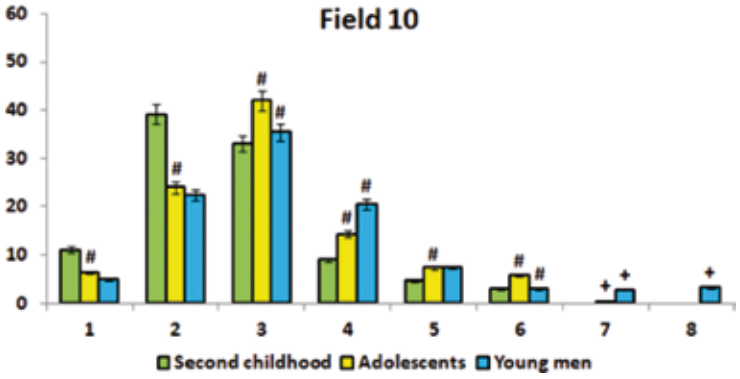


***Fig. 3.*** *Percentage of pyramidal neurons from different size classes in sublayer III³ of field 10*

range of individual variability is narrowed compared to the second childhood period. The variability of average individual neuronal volume in adolescents is ±5–18% of the average of the whole age group. The largest range of variability is found in the frontal eye field 8, the smallest — in the speech field 45. In young men there is *stabilization* of the range of neuronal size fluctuations in individuals. The average volume of neurons individually varies in all investigated fields of the prefrontal cortex by ± 12–15% of the mean group size. The results showed that not only children, but also adolescents and young men have a redistribution of neurons in size classes. This redistribution in different fields of the prefrontal cortex has specific features. However, the appearance of the largest pyramid neurons occurs in all fields in young men, which in our opinion is typical for the prefrontal cortex. Such neurons have particularly extensive receptive fields and can probably be regarded as polysensory multifunctional neurons with mixed selectivity [10]. It can be assumed that they are able to effectively engage in the activity of various functionally specialized neural networks, ensuring the implementation of the most complex cognitive processes involving the prefrontal cortex.

## CONCLUSION

The study demonstrates the possibilities of computational neuromorphology to determine age-specific features of the cerebral cortex microstructure at different stages of postnatal ontogenesis. Further perspective of applying quantitative approach to assessment of age-related changes and variants of structural organization of the cerebral cortex may be connected with improvement of noninvasive methods of human brain tissue visualization.

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# MICROWAVE DETECTION OF SKIN DIELECTRIC PROPERTIES IN SOME LABORATORY ANIMALS

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**ABSTRACT** — The purpose of this study was a comparative study of the dielectric properties of the integumentary tissues of rats and rabbits. The study allowed to develop standards of basic dielectric parameters and their species-specificity for Wistar rats and rabbits.

**KEYWORDS** — microwave sensing, skin, rat, rabbit.

Currently, there are numerous medical imaging technologies, but not all biological tissues are covered by their capabilities. So, despite the superficial localization, full visualization of the skin remains a problem [1, 3]. One of the solutions to this problem is to develop methods for assessing the dielectric properties of the skin [1–3]. In this regard, the purpose of this study was a comparative study of the dielectric properties of the integumentary tissues of rats and rabbits.

## MATERIAL AND METHODS

The dielectric permittivity and conductivity of the skin of 12 rabbits of the breed "Gray Giant" and 25 rats of the Wistar line were studied. The study in all animals was performed at a single point in the middle part of the back. Before the study, the hair in the study area was epilated. The dielectric properties of the skin were evaluated by near-field resonant microwave sensing using a software and hardware complex developed at the Institute of Applied Physics of the Russian Academy of Sciences (Nizhny Novgorod) [2]. The study was carried out with a single sensor with a depth of 5 mm. The data were processed in the package Statistica 6.1. All animal experiments were performed in according to the compliance with EC Directive 86/609/EEC.

## RESULTS

It is established that both studied parameters are species-specific (Fig. 1), and rabbits have both dielectric permittivity and skin conductivity significantly higher than rats ($p<0.05$). This, on the one hand, is due to the specific features of the structure of the skin and subcutaneous structures in the animals under consideration, and, on the other hand, may be due to the uneven thickness of the integumentary tissues in them. Interestingly, in humans, the absolute values of the parameters are significantly higher than in both animal species studied ($p<0.05$ for rats and rabbits).

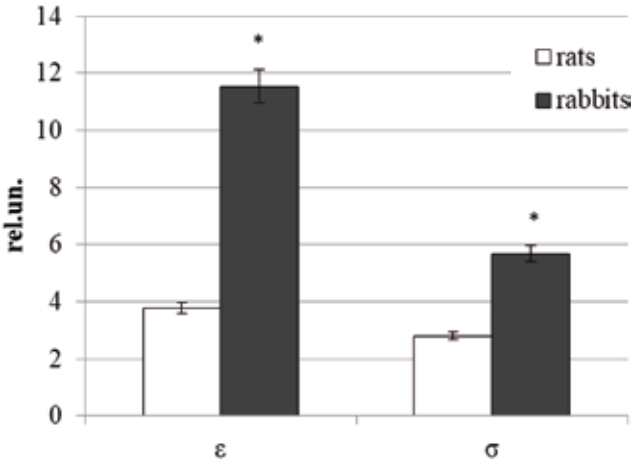


***Fig. 1.*** *The level of dielectric permittivity (ε) and conductivity of the skin in rats and rabbits ("*" — level of statistical significance of differences to rats $p<0,05$)*

## CONCLUSION

Thus, the study allowed to form standards of basic dielectric parameters for Wistar rats and rabbits of the breed "Gray Giant", as well as to demonstrate their species-specificity.

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# *ANTHROPOS – CAVASCREEN* DIAGNOSTIC EXPERT SYSTEM IN ESTIMATION OF HEMODYNAMICS STATE

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**ABSTRACT** — An innovative diagnostic complex has been created that allows a systematic approach to analyzing the performance of various blood circulation sections — the heart itself and its regulation (ECG), central and peripheral hemodynamics (according to the reogramme), skin circulation (up to 382 indicators). This allows for a qualitatively different level to assess the state of healthy individuals and patients in the prone and standing position, and to use these data for the diagnosis and correction of treatment.

**KEYWORDS** — Anthropos-cavascreen, hemodynamics, diagnostics.

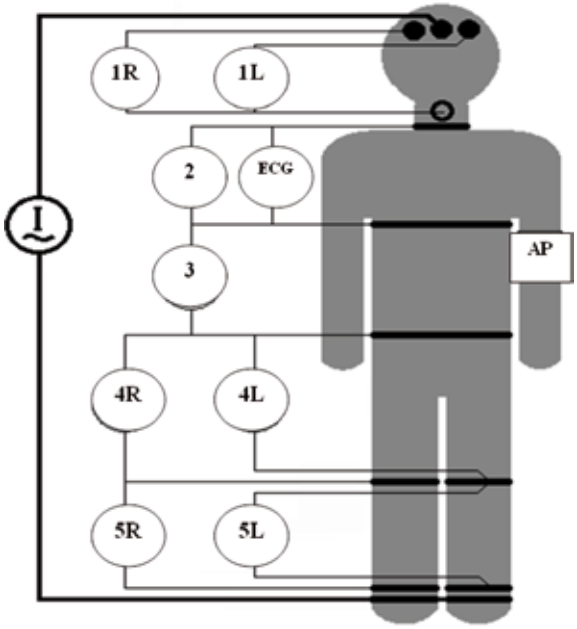


***Fig.1.*** *Scheme of tetrapolar superposition of current (I) electrodes and potential electrodes for rheographic registration of hemodynamic parameters. Designations on the connected system of potential electrodes: 1 — head, 2 — chest, 3 — abdomen, 4 — pelvis-thigh, 5 — Shin; R-right, L — left. AP-cuff measurement of blood pressure, ECG- electrocardiogram*

The most important factor in the development of medicine are innovative methods in the diagnostics and support of human health. This possibility is realized on the basis of the system assessment of hemodynamics according to the complex technique of tetrapolar thoracic and regional rheography developed by us with the use of the laboratory of medical expert systems *Anthropos systems lab.* (Vinnitsa, Ukraine) and the Institute of Medical Technology and Equipment ITAM. Zabrze, Poland)) hardware-software complex *ANTHROPOS-CAVASCREEN* (Fig. 1).

The research was carried out within the framework of the international project on the European Fund *EUREKA* (Eureka EU 2939 project dated 31.1.2003). On the basis of the experimental and clinical materials obtained by us, the optimal algorithm for the analysis of the thoracic reocardiocycle and peripheral rheograms is formed and justified.

In our complex the system and multilevel complex assessment based on basic laws of functioning of cardiovascular system, including features of regulation on hydrostatic (gravitational) factor of blood circulation at the person in standing position is used. The complex of direct and settlement hemodynamic indicators is analyzed. To analyze and evaluate the state of blood circulation, 130 measured and calculated indicators in the standing and lying position are used, as well as 102 related indicators with respect to their values according to the mandatory conditions of the study (standing-lying). Additionally, 20 indicators are determined for the samples *standing* and *lying down* with breath retention. In total, according to the conditions of the anthropophysiological study, up to 382 indicators are used in the diagnostic assessment of hemodynamic support of the somatic state.

## GENERAL CHARACTERISTICS OF COMPONENTS OF *ANTHROPOS-CAVASCREEN*:

— Implementation of multichannel synchronous registration of basic and differential rheograms

reflecting pulse blood flow of the brain on the left and right, lungs, abdominal hemodynamics, blood circulation of the pelvis and lower extremities (shins) symmetrically on the left and right.
— An electrocardiogram is recorded at the same time.
— Measurement of the basic impedance characteristic of the investigated hemodynamic blocks.
— Study of cutaneous blood flow and circulatory thermoregulation by measuring the electrical conductivity of the skin by a modified Nakatani technique.
— Cuff blood pressure measurement.
— Calculation of the main hemodynamic parameters.
— On the basis of anthropophysiologically oriented multiparameter analysis of the state of blood circulation in the standing and lying positions, a package of output documentation is automatically formed — a complete Protocol and a diagnostic conclusion.
— In the diagnostic conclusion in verbal and graphic form the system characteristic of a condition of cardiovascular system on the main hemodynamic mechanisms (volume — capacity — the pump function — a blood flow), as a whole and on the main blocks and components of blood circulation is given, and also all revealed hemodynamic syndromes separately on position of a body standing and lying are described.

## GENERAL FEATURES AND PURPOSE OF *ANTHROPOS-CAVASCREEN* TECHNOLOGY

The hardware-software complex and expert system is designed to diagnose the state of the cardiovascular system. Instrumental techniques used in the system (multichannel tetrapolar thoracic and regional rheography, electrometry of the skin by electrical conductivity, oscillometric measurement of blood pressure) are non-invasive and do not cause inconvenience to the patient.

The diagnostic concept of diagnostic expert system *Anthropos–Cavascreen* for the cardiovascular system on the basis of anthropological approach is considered as an anatomical and functional integrity of natural biological quality of man (bipedalism) and directly associated value of the gravitational factor in the circulation.

Computer hardware and software complex *Anthropos-Cavascreen* allows to simultaneously measure the parameters of the state of 8 hemodynamic blocks. Assessment of circulation in separate functional units (blood pressure, blood volume, the pumping function of the left and right heart, small and large circle circulation, arterial and venous blood circulation of the head left and right, abdomen, pelvis, thigh and lower leg left and right) is not isolated, but comprehensively and systematically in the context of the general state of blood circulation and other functional blocks. The study is carried out in two typical variants for man as an upright creature body positions (standing and lying). This takes into account the hemodynamic parameters of both postural conditions, as well as the associated characteristic of the condition *standing/lying*.

When analyzing the data obtained for each position of the body, we use sex and age ratios of the absolute values of direct and derived hemodynamic parameters, as well as percentages of these values in standing relative to their size in the supine position (standard model state).

The expert system *Anthropos-Cavascreen* on the basis of multiparameter comparison of the measured hemodynamic parameters with the *normative model* and the use of the algorithm of multilevel criteria and syndrome analysis forms an individual *state model*, which is described by the diagnostic conclusion. In conclusion, only syndromes are presented in descriptive (verbal) and graphic form, as functionally and clinically significant circulatory conditions, the group characteristic of which does not correspond to the *normative model*, but coincides with the hemodynamic profile of the *model of circulatory disorders*.

The expert system *Anthropos-Cavascreen* allows to carry out screening and dynamic diagnostics of cardiovascular system at early stages of violations of its condition, helps the doctor in decision-making on correction of the revealed changes, and also allows to monitor efficiency of the carried-out treatment.

Given the importance of optimal hemodynamic support of any somatic condition in the full range of *health-illness-disease*, diagnostic information obtained with the help of *Anthropos-Cavascreen*" is useful in the pre-medical and medical support of healthy, pregnant, patients of any nosological profile.

Computer hardware and software complex *Anthropos-Cavascreen* is designed for functional diagnostics departments, polyclinics, hospitals and institutions of health profile, insurance medicine, as well as to provide a workplace for a family doctor.

## CONCLUSION

The hardware and software expert system *ANTHROPOS-CAVASCREEN* allows a systematic approach to the analysis of indicators of various departments of blood circulation: the heart and its regulation (ECG), central and peripheral hemody-

namics (rheogram), skin circulation (up to 382 indicators). The use of the algorithm of multilevel criteria and syndrome analysis reveals an individual *state model*, including syndromes of functionally and clinically significant circulatory conditions, the group with the hemodynamic profile of the *model of circulatory disorders*. This allows to fully assess the condition of the examined persons in the lying and standing positions. Studies performed in more than 2,000 patients have shown the value of using these data for diagnosis and treatment correction. The research methodology of the hardware and software complex is protected by an international patent.

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# EVALUATION OF PERIPHERAL BLOOD INDICATORS AND CYTOGENETIC INDICATORS USING COPPER(I) COMPLEXES FOR BURNS

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**KEYWORDS** — burn, copper complexes, proliferative activity, chromosome aberrations, ploidy of cells , number of red, white blood cells, hemoglobin level.

## INTRODUCTION

Extensive deep burns cause a complex of peculiar pathological functional and morphological changes of internal organs and systems of the body. According to numerous literature data, a significant factor in further development of damage of tissues after burn injury is excessive activation of lipid peroxidation of cell membranes and the appearance of an excessive quantity of oxygen free radicals, generated by activated leukocytes, as well as those formed during tissue proteolysis [1, 2].

Burn injury also causes deep changes in hematological parameters. In case of blood flow through tissues during the burn period, we can view thermal damage and destruction of red blood cells with the release of free hemoglobin into the plasma [3, 4, 5].

Burn disease also causes a expressed leukocyte reaction, described by many researchers in clinic and during experiment [6, 7].

For tissue healing in burn cases, drugs that have anti-inflammatory, analgesic and regenerative properties are used [8]. In this field, metal-organic complexes based on copper and possessing high antioxidant activity are of special interest.

The copper biological role is diverse. Vital enzymes, performing complex functions in the body, comprise such a metal. Copper is the key component of the enzyme cytochrome oxidase, carrying out cellular respiration in all organs and tissues and is a constituent of vitamins, hormones and pigment substances. Copper has an impact on the synthesis of sex hormones, normalizes the work of the endocrine system, activates insulin [9].

The biogenous role of copper is participating in the processes of hematopoiesis. The trace element taking part in the synthesis of hemoglobin, carrying out the transfer of oxygen in the body, increases the speed of blood circulation. Copper takes part in the synthesis of collagen and elastin, supports skin turgor; without it connective tissue loses its resilience, bones and cartilage lose elasticity. Copper is also important for nerve tissue, it is a constituent part of the myelin sheaths of nerve cells isolating nerve fibers. Copper has an active participation in the metabolism of carbohydrates: activates the oxidation of glucose, slows down the destruction of glycogen in the liver. Copper is of great importance for the immune system. The metal neutralizes the toxins of microorganisms, prolongs the impact of antibacterial drugs [10, 11], reduces inflammatory reactions.

Copper derivatives are used for burns healing [12]. The use of copper sulphate determines a faster closure of the dermal wounds so the application of copper sulfate has been proposed in regenerative medicine [13].

According to literary sources and also our early studies [14, 15, 16, 17], several copper-based complexes are of low toxicity and expressed radioprotective properties.

In order to identify a possible positive effect on burns, we studied two copper(I) complexes, namely: $[Cu(PTA)_4]BF_4$ and $[Cu(PCN)(HBP_{z3})]$ PTA=1, 3, 5-triaza- 7-phosphaadamantane. PCN = tris (cyanoethyl) phosphine and $HBP_{z3}$ = trispyrazolylborate. Such compounds (hereinafter referred to as PTA and PCN) have been chosen because they have already demonstrated remarkable cytotoxic toward cancer cells both in vitro and in vivo tests [18]. Moreover as compound PTA is an homoleptic, water-soluble compound, whereas compound PCN is a mixed-ligand neutral complex insoluble in water (Fig. 1), we tried to correlate their therapeutic effect in case of thermal burns with their chemico-physical features.

## MATERIALS AND METHODS

The synthesis of copper(I) complexes $[[Cu(PTA)_4[BF_4]$ (PTA=PTA=1,3,5-Triaza-7-phosphadamantane) and $[HB(pz)_3Cu(PCN)]$

($HB(pz)_3$=tris(pyrazolyl)borate, PCN=tris (cyanoethyl)phospine was carried out according to published procedures [18, 19]

The in vivo experiments were performed on sexually mature white, outbred rats with an average weight of 180–200 g. All animal experiments were performed in according to the compliance with EC Directive 86/609/EEC.

Rats were divided into 4 groups: I — only with a thermal burn (clean burn); II — thermal burn with injection of the (I) complex PTA; III — thermal burn with injection of the Cu (I) complex PCN; IV — animals without burn (intact group)

On the epilated surface of the skin in the back of animals was applied thermal burn of III AB degree on 30% of the body surface. 30 minutes after the applied burn, Cu complexes of PTA and PCN were administered intraperitoneally to various groups of animals at a dose of 50 mg/kg in the form of an aqueous suspension. The control group consisted of animals with a clean burn. Injection was performed every 2 days during 14 days before the start of rejection of the wound scab.

The activity of these compounds was evaluated by survival, average life expectancy that showed the dynamics of death of experimental rats during a 30-day monitoring.

Visual monitoring of a burn wound was carried out. Observations were carried out during 60 days, when the wounds healed completely and were covered with coat (pelage).

For hematological analysis blood was taken from the tail vein at certain terms (on the 3, 7, 14 and 30$^{th}$ days). The following indicators were determined: blood coagulation time; the leukocyte number (according to the classical method with the help of the Goryaev camera); the hemoglobin level (hemoglobin was studied on the device *Mindray BA-88A*), red blood cells and platelets (was studied using an optical microscope at a magnification of x300).

For cytogenetic analysis (by the method of Ford-Wollam) the bone marrow was taken from the femur. Cytogenetic analysis was performed on an optical microscope. We studied the mitotic index (MI) with an increase of ×300, chromosomal aberrations (CHA) ×900, polyploid cells (PC) ×1440.

## RESULTS

On the 60$^{th}$ day after complete wound healing, visual monitoring showed that epithelial regeneration, fouling were more actively viewed in the group with intraperitoneal injection of PTA than in the control groups and PCN injection.

On the fifth day after the burn, when the rats received 3 injections of metal complexes, the analysis of

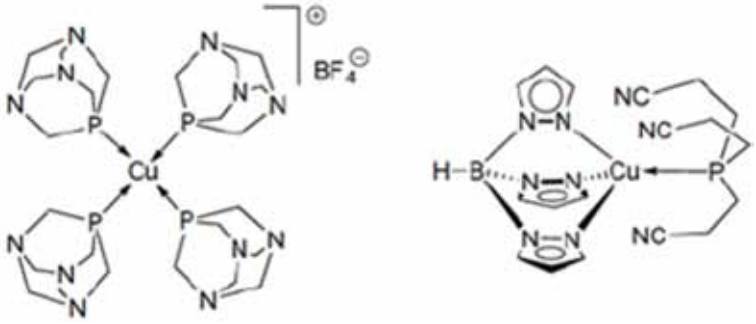


***Fig. 1.*** *Chemical structure of [Cu(PTA)$_4$] BF$_4$ (PTA) left and [Cu(PCN) (HBP$_{z3}$)] (PCN) right*

the karyotype showed that all cytogenetic indicators in three groups of experimental animals statistically significantly differ from the karyotype of intact individuals. When comparing the cytogenetic indices of both groups of rats with introduced copper complexes with control data, a slight variability of the parameters was observed without statistically significant shifts, as shown in the table 1.

As can be seen from the table, when comparing the cytogenetic parameters of the last term of the experiment of three experimental groups with the intact group, there was a tendency to increase the mitotic index (MI). In the control and PCN groups, this indicator is still significantly lower than normal, but in the PTA group it is closer to normal (the difference between the normal group and Burn + PTA is not significant). Aberrant chromosomes, mainly in the form of gaps, in the control and PCN groups are significantly higher than normal, and in the PTA group this indicator does not exceed a statistically significant level.

Comparison of the karyotypes of this period of study of the PCN and PTA groups with the control showed that the cytogenetic parameters of MI and PC of the PCN groups are significantly different. This means that, due to the combination of PTA, the indices MI and PC have a clear tendency to normalize.

Summing up the cytogenetic indices and visual monitoring criteria as well as the absence of animal death in the group with injection of the metal-organic complex PTA (vedi infra) we can conclude that this compound activates reparative processes, improving the cytogenetic status of experimental rats. In particular, it increases the proliferation of bone marrow cells, as a result of which the hematopoiesis of burnt animals improves.

Hematological parameters were analyzed in dynamics over the entire duration of the experiment and the results are shown in table 2.

As can be seen from table 2, the burn causes a significant change in the number of white blood cells

***Table 1.*** *Change of cytogenetic parameters in 4 groups after burn*

| terms after the study | 5th day after the burn | | | | 30th day after the burn | | |
|---|---|---|---|---|---|---|---|
| groups / indicators | intact group | control | Burn+PCN | Burn+PTA | control | Burn+PCN | Burn+PTA |
| MI% | 20,1±2,8 | 9,8±1,2<br>$P_1$<0.05 | 10,1±1,5<br>$P_1$<0.05<br>$P_2^1$>0.05 | 11,2±1,7<br>$P_1$<0.05<br>$P_2$>0.05 | 12,8±1,8<br>$P_1$<0.05 | 13,2±1,9<br>$P_1$<0.05<br>$P_2$>0.05 | 17,0±1,2<br>$P_1$>0.05<br>$P_2^1$<0.05 |
| CHA% | 3,0±0,22 | 4,4±0,42<br>$P_1$<0.05 | 4,6±0,44<br>$P_1$<0.05<br>$P_2$>0.05 | 4,1±0,39<br>$P_1$<0.05<br>$P_2$>0.05 | 4,2±0,48<br>$P_1$<0.05 | 4,3±0,42<br>$P_1$<0.05<br>$P_2$>0.05 | 3,8±0,4<br>$P_1$>0.05<br>$P_2$>0.05 |
| PC% | 0 | 4,0±0,38 | 3,9±0,4<br>$P_2$>0.05 | 3,2±0,36<br>$P_2$>0.05 | 3,3±0,36 | 2,9±0,31<br>$P_2$>0.05 | 2,0±0,24<br>$P_2$<0.05 |

$P_1$ — *The significance of differences in the performance of groups with PCN and PTA with the norm group*
$P_2^1$ — *The significance of differences in the performance of groups with PCN and PTA with the control group*

***Table 2.*** *Rat blood counts for a clean burn, PCN and PTA injection*

| indicators | days | Clean burns (control) | Burn+PCN | Burn+PTA |
|---|---|---|---|---|
| Blood coagulation time (seconds) | 3 | 415,0±7,63 | 413,8±47,75 | 340,0±35,46* |
| | 7 | 327,5±32,5 | 230±11,55* | 217,5±42,25* |
| | 14 | 360,0±34,64 | 150,0±20,31* | 207,4±12,53* |
| | 30 | 316.7±52.47 | 280.7±35,51 | 195,0±36.63* |
| Leukocyte ($x10^9$/l) | 3 | 8,3±0,59 | 9,5±1,6 | 7,5±1,2 |
| | 7 | 10,2±2,2 | 14,8±4,3 | 17,6±1,1* |
| | 14 | 8,8±0,7 | 9,3±2,2 | 11,7±0,7* |
| | 30 | 5,93±0,6 | 10,7±1,4* | 11,54±2.1* |
| Platelets (N/µl) | 3 | 588333,3±44378,42 | 568750±113933 | 489000±57649,8 |
| | 7 | 637500±2500 | 668333,3±64957,25 | 606250±48104,7 |
| | 14 | 495000±66583,28 | 392500±37052,89 | 405000±54815,71 |
| | 30 | 705000±5000 | 576666,7±71316,98 | 817000±43433,86* |
| red blood cells ($x10^{12}$/l) | 3 | 5,92±0,13 | 5,52±0,9 | 5,45±0,4 |
| | 7 | 3,13±0,1 | 3,2±0,15 | 3,88±0,35* |
| | 14 | 6,56±0,18 | 4,62±0,17* | 5,23±0,19* |
| | 30 | 6,38±1,9 | 6,0±0,8 | 5,62±0,26* |
| Hemoglobin (g/l) | 3 | 134,6±6,06 | 133,5±10,57 | 138,2±9,24 |
| | 7 | 136,5±5,5 | 107,3±11,39* | 97,3±1,2* |
| | 14 | 163,3±10,13 | 136,2±2,52* | 141,4±2,25* |
| | 30 | 161,3±1,76 | 140,3±4,97* | 139,2±3,39* |

* — *The significance of differences in the performance of groups with PCN and PTA with the control group*

in the blood of animals. So, on the 7th day after the injury in all groups there is an increase in the number of leukocytes, which indicates the course of reparative processes. The highest rates were obtained on the 7th day of the study, since at this time an infection joins the leukocyte reaction of the body. And if leukopenia is observed in rats from the control group at the end of the study, a tendency toward normalization is observed in groups with injection of compounds. On the 30th day, there was a significant difference in the level of leukocytes in the control group from groups with injection of PTA and PCN complexes.

By the 30th day, the level of leukocytes in groups of animals with burns+PTA and burns+PCN injection approaches the level of leukocytes in the normal group ($8.6\pm0.68 \cdot 10^9$/l).

Burn injury leading to inhibition of hematopoiesis is the cause of severe erythropenia and anemia. These two indicators in the early stages (7th day) of the study were significantly lower than the corresponding norms (erythrocytes: $6.2\pm0.35 \cdot 10^{12}$/l; hemoglobin; 158.0±14.6 g/l). As can be seen from the table, at the last observation periods (14th and 30th days), an increase in the number of red blood cells and a hemoglobin level. There was a significant difference between these indicators in the control group and the group with the PTA compound, which indicates a beneficial effect of this complex.

This conclusion is also confirmed when calculating the survival and average life expectancy of rats. Survival experiments were performed on 21 rats, 7 animals per group. Groups: Clean burn; PTA + burn and PCN + burn. An experiment to determine survival and average life expectancy showed that in the group of rats with the PTA complex, the indicators were significantly better (100% survival) than in animals with only burns (control), as shown in Table 3.

***Table 3.*** *Survival and average life expectancy of rats*

| Groups | Survivalc(%) | Average life expectancy in days |
|---|---|---|
| Control | 57 | 20,57 |
| Burns+PTA | 100 | 30 |
| Burns+PCN | 57 | 19,57 |

According to the equations and logarithmic regression curves describing the dynamics of survival and shown in Fig. 2, the survival of the group with the injection of the PCN complex and the control group is identical and there will be a further decline in this percentage in contrast to the group introduced with the PTA complex.

Based on the results of survival, life expectancy, cytogenetics and hematology, we can conclude that the PTA complex under study exhibits tangible healing properties. According to all observed criteria, the PTA complex showed beneficial effects on experimental animals.

## CONCLUSIONS

Basing on the survival results, average life expectancy, cytogenetic and hematological indicators, it can be concluded that studied complex PTA demonstrate noticeable healing properties.

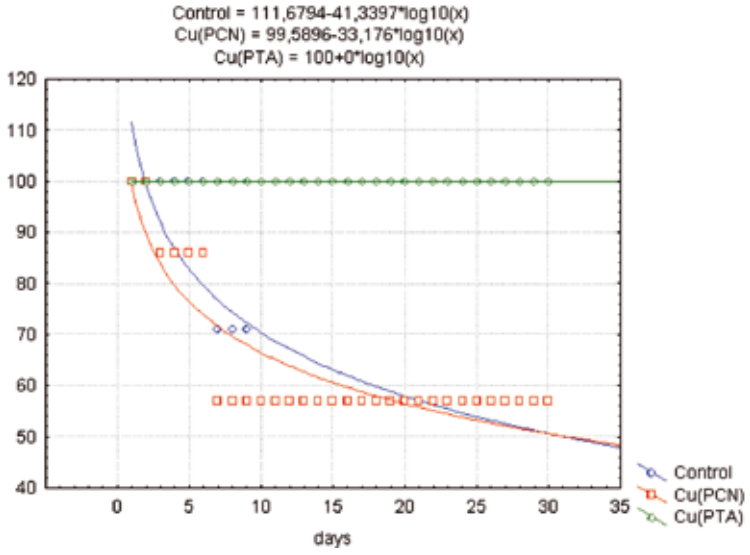


***Fig. 2.*** *Equations and logarithmic regression curves describing the dynamics of survival*

In the early stages of analyzes (days 3 and 7), both compounds mitigate the damaging effects of burn injury, but in the last periods of observation (days 14 and 30), the group with PTA injection has many test values: (blood counts) approached normal values.

Based on the results obtained, it can be assumed that the studied Cu-1 complexes effectively promote reparative processes in bone marrow cells and has a therapeutic effect on thermal burns (especially PTA). The results of this yet preliminary research require continuation and search for new effective means for treating burn surfaces.

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# STRUCTURE OF THE RENAL LYMPH NODE IN EXPERIMENTAL PROSTATE CARCINOGENESIS AND LASER PROSTATECTOMY

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**ABSTRACT** — A promising and developing area in oncology is the use of high-energy laser radiation. The structure of the prostate and renal lymph nodes of mice was studied on the 18th day of the experimental prostate tumor and after its instrumental and laser resection. On the 18th day of prostate tumor growth in mice, severe T-zone hyperplasia and sinus reaction were detected in the renal lymph nodes. On the 18th day after instrumental resection of the tumor, t-zone hyperplasia persists, and the transport function of the renal lymph nodes is partially restored. On the 18th day after resection of the tumor with high-energy ND:YAG laser radiation, with a wavelength of 1064 nm, a photostimulating effect was detected in the peripheral heating zone, which is expressed in the restoration of the structure of regional lymph nodes.

**KEYWORDS** — experimental prostate tumor, renal lymph nodes, prostatectomy, high-energy laser radiation.

## INTRODUCTION

During carcinogenesis, various stages of the immune response are disrupted, followed by its failure, immunological tolerance is developed, caused by an excess of tumor antigens, activation of suppressor T-lymphocytes and macrophages, and blocking of the effector link of the immunocompetent system by circulating tumor antigens, antibodies, and antigen-antibody immune complexes; [1, 2]. Radical prostatectomy is the optimal method of treating a malignant prostate tumor and eliminating the immunosuppressive effects of cancer on the body and in the early stages of the disease, when there are no metastases to the lymph nodes. One of the promising and developing areas of Oncology practice is the use of high-energy laser radiation used for dissection of tissues, hemostasis, evaporation of pathological formations of blood serum coagulation with local *hyalinization* of tissues [5]. An important condition for preventing postoperative recurrence and tumor metastasis is the structural and functional restoration of the regional lymphatic apparatus. The study of morphological transformations occurring in regional lymph nodes after resection of an experimental prostate tumor will assess the degree of recovery of their structural and functional organization and the state of the local immune response.

The purpose of our study was to identify structural changes in the regional lymph nodes of the prostate (renal) during its experimental tumor and after prostatectomy using an instrumental method and using high-energy laser radiation.

## RESEARCH MATERIAL AND METHODS

We used sexually Mature 14-week-old male NEA mice in the amount of 40 pieces (vivarium *Institute of Cytology and genetics* SB RAS, Novosibirsk). All experiments were performed in accordance with the principles of humanity set out in the European community Directive (86/609 / EC). An experimental model of prostate carcinogenesis was created by inoculating (under ether anesthesia) a diluted cell strain of the Ehrlich's transplanted ascitic tumor into the prostate parenchyma — 0.2 ml of ascitic fluid containing 500–550×$10^3$ atypical tumor cells [4]. The animals were divided into 4 groups of 10 individuals: 1 group — intact animals (control); 2 — animals on the 18th day of experimental carcinogenesis; 3 — animals on the 13th day of the experiment, with preliminary complete instrumental resection of the tumor on the 5th day of its growth. 4 — animals on the 13th day of the experiment, with preliminary full laser resection of the tumor on the 5th day of its growth. Prostatectomy was performed under ether anesthesia in compliance with the methods of asepsis and antiseptics: in the 3rd group by laparoscopic method using a microsurgical instrument, and in the 4th group using a flexible optical fiber emitter from an ND:YAG laser pulse radiation device, with a radiation wavelength of 1064 nm, pulse energy of 100 j/$cm^2$, with a pulse duration of 20 MS, and a frequency of 1 Hz. (Laura 50, *Lazerus* LLC, Russia): After prostatectomy, the material was collected on day 18 after the tumor was inoculated. For histological examination, after euthanasia, the prostate, tumor fragments, and renal lymph nodes were taken. According to the standard histological method, the material was wired, and longitudinal median histological sections were made with a thickness of 5–7 microns, which were stained with hematoxylin-eosin and Azur II-eosin. The preparations were studied using light

microscopes (Leica (Germany), MBS-10 (Russia) at magnification of 32, 400 and 1000 times. Morphometric of structural and functional zones of lymph nodes and tumor tissue was performed [7]. The results of the experiments were processed using standard methods of variation statistics, and the probability of reliability of differences was determined using the Student's criterion at $p<0.05$.

## RESULTS AND DISCUSSION

On the 5th day of induced carcinogenesis, a tumor node with a volume of 2 m 3 is formed in the prostate, consisting of polymorphic atypical cells. On the 18th day of prostate carcinogenesis, almost complete replacement of its structural components with these cells was found: the tumor parenchyma was 82.3±0.63%, the tumor stroma was 17.7±0.43%, and the stromal — parenchymal index was 0.22±0.01. Lymphoplasmocytic infiltration along the course of blood vessels, focal necrosis and hemorrhages were noted. Metastases on the 18th day of carcinogenesis were determined in the marginal and cerebral sinuses of the renal lymph nodes. In the renal lymph nodes on the 18th day of tumor growth, pronounced signs of paracortical hyperplasia were revealed — the T-dependent zone increased by 87% compared to the 1st group, the size of the brain cords decreased by 14%, and the brain sinuses — by 52%. In General, the size of the cortical substance of the lymph nodes increased by 74% in comparison with intact animals (control), and the area of the brain substance decreased by 16% — the cortical-brain index increased by 2.3 times in comparison with the control. The area of the B-dependent zone in the lymph nodes decreased by 10% compared to intact animals (Table 1).

On the 18th day of tumor growth, when developing a late stage of carcinogenesis, accompanied by metastasis (II–III stage), the redistribution of lymph flow and changing of structural specialization of the lymph nodes revealed marked paracortical hyperplasia — determined characteristic, a sinus reaction to the metastasis — reducing the size of the cerebral sinuses, and changes in the structural and functional specialization of lymph nodes and fragmented type to intermediate [3]. On the 13th day after the instrumental prostatectomy (prostatectomy was performed on the 5th day of tumor growth), only single atypical tumor cells were detected in the marginal and cerebral sinuses of the renal lymph nodes. In the lymph nodes after instrumental prostatectomy, compared with the group without removing the tumor, an increase in the size of the medulla and a decrease in the cortical area was revealed. The structural and functional organization of lymph nodes after prostatectomy indicates an increase in their transport potential, which is confirmed by a decrease in the cortical-brain index (Table 1). The structure of lymph nodes revealed a 12% decrease in the area of secondary and primary lymphoid nodules and paracortical zone (Table 1). It can be assumed that the path of lymph transport within the lymph nodes changes, which is confirmed by a reduction in the size of the marginal sinus and an increase in the area of the brain. On the 13th day after laser prostatectomy (prostatectomy was performed on the 5th day of tumor growth), atypical tumor cells were not detected in the marginal and cerebral sinuses of the renal lymph nodes. In the lymph nodes after laser prostatectomy, compared with the group without removing the tumor, an increase in the size of the medulla and a decrease in the cortical area was also revealed. in comparison with the group with instrumental prostatectomy, these changes are amplified (the size of the cortical substance decreases by 7%, and the brain substance increases by 4%). The structural and functional organization of lymph nodes after laser prostatectomy indicates an increase in their transport potential, which is confirmed by a decrease in the cortical-brain index, compared with the group with instrumental prostatectomy, this index decreases by 10% (Table 1) the structure of lymph nodes in comparison with the group without tumor removal, and in contrast to the group with instrumental correction, there was an increase in the area of secondary and primary lymphoid nodules (by 26% and 54%), a decrease in the area of the paracortical zone by 45% 9, and in comparison with the group with instrumental prostatectomy by 74%. The size of the marginal and cerebral sinuses in the lymph nodes during laser resection increases, in comparison with the group with instrumental resection. The data obtained indicate that the pathway of lymph transport within the lymph nodes changes in comparison with the group with instrumental prostatectomy.

## SUMMARY

The results obtained indicate that on the 18th day of observation, 13 days after instrumental removal of the prostate tumor in mice, structural transformations were detected in the kidney lymph nodes, which indicates activation of their transport function, persistent paracortical hyperplasia, and inhibition Of the b-link of the immune response (reduction of the area of secondary lymphoid nodules and brain cords). n the renal lymph nodes of mice, after instrumental removal of a prostate tumor, we found only a partial restoration of their structural and functional organization in comparison with intact animals, which indicates that their barrier-filtration function was suppressed after surgery. After laser resection is more complete restora-

***Table 1.*** *Sizes of structural and functional zones of renal lymph nodes in intact animals (control) in experimental prostate tumors on day 18 (EPT), after instrumental prostatectomy (EPT +PE), after laser prostatectomy (EPT +LPE) (M± m) %*

| Structural components of renal lymph nodes | Control | EPT | EPT + PE | EPT + LPE |
|---|---|---|---|---|
| Germinative center | 0,98±0,14 | 1,88±0,11 | 0,91±0,14 | 1,44±0,17•• |
| Corona | 1,3±0,14 | 1,9±0,13 | 1,18±0,11• | 3,33±0,19•• |
| Secondary lymphoid nodules | 2,28±0,06 | 3,78±0,07* | 2,09±0,1• | 4,77±0,07•• |
| Primary lymphoid nodules | 2,34±0,16 | 1,53±0,08* | 0,88±0,07• | 2,37±0,23•• |
| Interfollicular zone | 0,76±0,13 | 1,32± 0,1 | 0,76±0,11• | 2,93±0,15•• |
| Paracortical zone | 20,1±0,62 | 37,58±0,65* | 33,28±1,32• | 24,5±0,78•• |
| Brain cords | 46,67±2,95 | 40,33±0,47 | 39,55±2,15• | 41,86±2,1 |
| Brain sinuses | 23,1±1,56 | 11,22±0,36* | 20,86±1,1• | 21,2±0,73 |
| Capsula | 1,9±0,17 | 2,47±0,17* | 1,03±0,09• | 0,44±0,12•• |
| Marginal sinus | 2,72±0,19 | 1,65±0,12 | 1,53±0,09• | 1,8±0,17 |
| Trabeculas | 0,22±0,08 | 0,13±0,06 | 0,03±0,02• | 0,12±0,06•• |
| Cortical substance | 25,43±0,4 | 44,2±0,9* | 37,0±1,29• | 34,56±0,36•• |
| Brain substance | 69,73±1,15 | 51,55±0,91* | 60,41±1,62• | 63,08±0,66•• |
| B-dependent zone | 52,04±0,98 | 46,95±1,1* | 43,28±1,76 | 51,92±0,67•• |
| K \ M index | 0,37±0,01 | 0,86±0,02* | 0,61±0,02• | 0,55±0,02•• |

** — the differences are significant in comparison with the control at P<0,05.*
*• — differences are significant in comparison with the group on the 18th day of EPT at P< 0,05*
*•• — differences are significant in comparison with the group on the 18th day of EPT + LPE at P < 0,05*

tion of structural and functional organization of the renal lymph nodes, resulting in the reduction paracortical hyperplasia, activation of transport function and restore the sizes of b-dependent zones of the lymph nodes. As shown by the data we received earlier [6] in the pelvic lymph nodes of mice after laser prostatectomy, the restoration of structural and functional organization is also observed, and the study of their cell composition indicates pronounced processes of proliferation and blast transformation of lymphoid cells, activation of the macrophage reaction, which reflects the high activity of the local immune response after prostatectomy. Resection of an experimental prostate tumor, regardless of the method, leads to the restoration of the structural organization of the renal lymph nodes, which is probably the result of a decrease in local antigenic stimulation and endogenous intoxication after removal of the tumor.

Laser resection for prostate tumors is more effective in restoring the structural organization of regional lymph nodes to the prostate, which is expressed in normalization of the ratio of T-and B-dependent zones within the lymph nodes and activation of transport function (increase in the size of the marginal and cerebral sinuses). It can be assumed that high-energy laser radiation in the IR region of the spectrum during local thermal photodestruction of a prostate tumor has a local photostimulating effect in the peripheral heating zone on interstitial spaces, lymphatic capillaries and vessels, and lymph nodes due to absorption and scattering of radiation.

Exposure to the laser beam during evaporation and destruction of prostate tumor tissue is accompanied by the restoration of the structure of regional lymph nodes, which is an indicator of the activation of the local immune response, which is of important prognostic value in the postoperative period and at the stage of healing of the operating wound.

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# IN VIVO OPTICAL CLEARING OF HUMAN SKIN UNDER EFFECT OF SOME IMMERSION AGENTS

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**ABSTRACT** — Results of in vivo optical immersion clearing of human skin under the effect of aqueous solutions of a number of immersion agents (monosaccharides of ribose, glucose and fructose, as well as glycerol, a triatomic alcohol) were obtained with the use of the OCT method. Values of average velocity of scattering coefficient change, which were obtained through an averaged A-scan of the OCT signal in a derma region with the depth from 350 to 700 μm, were determined in order to evaluate the optical clearing efficiency. Good correlation was identified between the velocity of scattering coefficient change and the optical clearing potential value. Molecular modeling of interaction of a number of immersion clearing agents with collagen allowed to identify correlations between the optical clearing efficiency and the energy of intermolecular interaction.

## INTRODUCTION

Applying modern methods of photomedicine and biomedical optics for diagnosis and therapy of diseases is associated with difficulties arising due to the fact that skin and many other biological tissues have strong scattering in visible and near-infrared regions. This scattering occurs due to deflection index change at borders of different macromolecular structures, mostly on collagen fibers that are primarily responsible for light scattering of skin [1]. These difficulties can be overcome with injection of biocompatible molecular agents into the tissue, which to some extent stimulates its optical clearing [2, 3]. A lot of articles [4–10] present in vivo and in vitro experimental studies on clearing of different biological tissues, which indicates urgency of the issue. Papers [11–12] present studies on interaction of a number of immersion agents with collagen, conducted with the use of theoretical methods.

## EXPERIMENT METHODS AND RESULTS

Aqueous solutions (60%) of the following immersion agents were used to study optical clearing of skin: monosaccharides (ribose, glucose and fructose) and, for comparison, glycerol, a triatomic alcohol. The optical coherence tomography (OCT) was used to evaluate the effect of clearing properties of immersion liquids on skin in vivo experiments. Visualization was carried out with the use of an optical coherence tomograph Thorlabs OCP930SR (Thorlabs, USA) with the following parameters: radiation wave central length of 930 ± 5 nm., axial and lateral resolution of 6.2 and 9.6 μm. respectively (in the air), scan region length of 2 mm. (Fig. 1).

The measurements were carried out on a skin area of the back of a forearm. The scans were recorded prior to exposure to the immersion agents, then at 1-minute intervals during 40 minutes of exposure. Four volunteers were involved in the measurements, and a total of five experiments was carried out for each immersion agent.

The attenuation coefficient μt [15] was evaluated by the OCT scans skew on the basis of the single scattering model [13–14]. The figure presents analyzed areas of the OCT image, an averaged A-scan of the OCT signal of the human skin dermal layer in vivo (5 minutes after the application of 60% ribose solution on the surface) and an approximating curve, which was plotted with the use of the single scattering model. OCT signals were averaged by the A-scan over the whole scanning area. The scattering coefficient values were determined in the averaged A-scan region at the depth from 350 to 700 μm.

In the scope of this paper, values of the light scattering coefficient, obtained with the use of the averaged A-scan in the derma region with the depth from 350 to 700 μm, were determined in order to evaluate the efficiency of in vivo optical clearing of human skin.

Values of the module of average velocity of the scattering coefficient change at the time segment from 5 to 35 seconds were used for numerical expression of the skin optical clearing efficiency. These velocities are presented in the table as skew values in regression line equations. The molecular modeling was carried out according to the method, described in paper [11] (Table 1).

As the table shows, the energies of interaction of a collagen peptide molecule with molecules of different

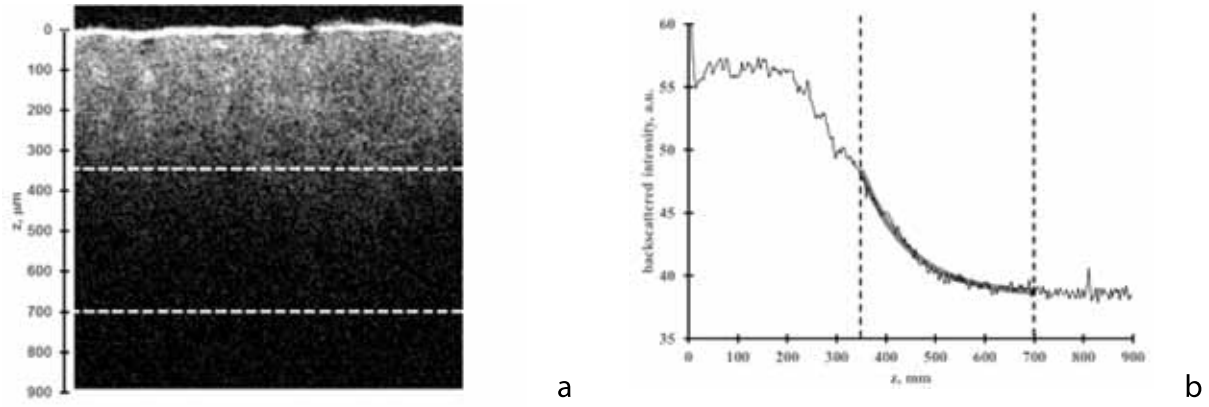


*Fig. 1. Measurements of the scattering coefficient μs in the derma region with the depth from 350 to 700 μm, based on the analysis of depth distribution of the averaged OCT signal with the use of the single scattering model; (a) is the in vivo fragment of the B-scan of skin, used to average the OCT signal, (b) is the depth distribution of the averaged OCT signal (thin curve) and the approximation result according to the single scattering model (thick curve). The dashed lines are borders of the regions where the value $\mu_s$ was estimated*

*Table 1. Lengths of hydrogen bonds (in angstroms), energies of inter-molecular inter-actions (in kJ/mol) between the fragments of collagen $(GPH)_3$ and different clearing agents, calculated with the use of the method PM6/B3LYP/6-31G(d), as well as experi-mental values of optical clearing velocity*

| Type of agent | Hydrogen bond lengths | DE | Efficiency of skin optical clearing |
|---|---|---|---|
| glycerol | 1.74; 1.91; 1.92; 1.93; 2.44 | -42.8 | 0.607 |
| ribose | 1.84; 1.90; 1.91; 1.95 | -80.9 | 0.789 |
| glucose | 1.68; 1.71; 1.84; 1.94 | -94.5 | 0.937 |
| fructose | 1.82; 1.84; 1.90; 1.96; 2.23 | -89.2 | 1.056 |

clearing agents, calculated with the quantum chemistry method, correlate well with the values of velocity of scattering coefficient change that were experimentally obtained within the present study.

It allows to speak of the fundamental importance of a post-diffusion stage, where collagen interacts with clearing agents and produces an effect on optical clearing of biological tissues. The study results allow to suggest that during the process of this interaction, a partial substitution of collagen-related water occurs. It leads to disturbance in a binding net of hydrogen bonds and, as a consequence, to a reversible process of collagen fibril dissolution, which, in its turn, lowers the value of their deflection index and equalizes it to the intercollagen medium. The higher collagen affinity of a clearing agent, the more effective is the process.

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# PREVALENCE OF RISK FACTORS, COMORBIDITY AND EMOTIONAL DISTURBANCES IN PATIENTS WITH MYOCARDIAL INFARCTION AND ATRIAL FIBRILLATION

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**ABSTRACT** — In patients with myocardial infarction and atrial fibrillation, the relationship of risk factors, the structure of comorbid conditions, and the severity of psychoemotional disorders were evaluated. 138 patients of the cardiology department were examined. Such prevailing risk factors as increased alcohol consumption, high salt intake, overweight combined with depressive disorders; a constant form of atrial fibrillation linked to nicotine addiction and associated with anxiety disorders were found in patients with myocardial infarction with a paroxysmal form of atrial fibrillation. These factors should be considered when choosing treatment and rehabilitation options.

**KEYWORDS** — myocardial infarction, atrial fibrillation, comorbid conditions, anxiety-depressive disorders.

## INTRODUCTION

The diagnosis and management of patients with comorbid pathology remains one of the most difficult tasks in clinical practice. Most patients with cardiovascular diseases in real medical practice are characterized by a combination of two or more diseases and conditions, that is, comorbidity [1, 2]. For the correct planning of treatment and prophylactic measures, it is necessary to carefully study not only the structure of risk factors and the frequency of synchronously occurring diseases in patients with myocardial infarction, but also the severity of emotional disorders in various forms of atrial fibrillation [3, 6].

*Objective*

to assess risk factors, the structure of comorbid conditions and the severity of psychoemotional disorders in patients with myocardial infarction with various forms of atrial fibrillation.

## MATERIALS AND METHODS

138 patients (63 men, 75 women) who were hospitalized in the cardiology department of the City Clinical Hospital No. 7 GBUZ with a diagnosis of myocardial infarction with atrial fibrillation were examined. Depending on the form of atrial fibrillation, the patients were divided into 2 groups: the 1st consisted of 83 (60,1%) patients with a paroxysmal form, the 2nd group — 55 (39,9%) with a constant form. The examination was carried out in the first three days of hospitalization of patients. Conducted: general clinical examination, the lipid spectrum of blood plasma (total cholesterol, low and high density lipoproteins, triglycerides; mmol/l) was determined while taking lipid-lowering drugs (atorvastatin at a dose of 40–80 mg/day).

To assess the emotional state, the HADS anxiety and depression questionnaire was used [7], which included 14 statements in 2 subscales: *anxiety* (odd points), *depression* (even points). Interpretation of the results was carried out by evaluating the total indicators of each subscale: 0–7 points — the absence of reliably expressed symptoms of anxiety / depression; 8–10 points — subclinically expressed anxiety/depression; 11 and above points — clinically expressed anxiety and depression.

For early identification of people at risk and alcohol abusers, we used the AUDIT test [4], developed in 1989 by the WHO working group. The test contains a series of 10 questions: three questions on consumption, four questions on addiction and 3 questions on problems related to alcohol consumption. To assess the degree of nicotine addiction, the Fagerstrom test [5, 8] was used, which determines the relationship between an individual score and the severity of manifestation of nicotine addiction. Interpretation of the test results: from 0 to 3 points — a low level of dependence, 4–5 points — an average level of dependence, 6–10 points — a high level of dependence.

When studying the consumption of table salt with food, the methodology recommended for epidemiological studies was used, which is based on the assessment of the use of sodium chloride with food in public canteens [9]. So, if people, judging by the survey, never add food, then this corresponds to the use of a small amount of table salt per day. In those cases

when the food is salted after the test, this corresponds to a moderate intake of table salt and if the food is salted without trying, then a conclusion was drawn about the increased use of sodium chloride.

Body mass index — (BMI) — a value that allows you to assess the degree of conformity of a person's weight to his height and, thereby, indirectly assess whether the mass is insufficient, normal or excess (obesity) in relation to established standards. The body mass index is calculated by the formula: BMI = $M/P^2$, where M is body weight, kg, P is height, m. Values and interpretation of BMI: 16 or less pronounced weight deficit; 16-18 insufficient (deficit) body weight; 18–25 norm; 25–30 overweight (obesity); 30–35 first degree obesity; 35–40 obesity of the second degree; 40 or more obesity of the third degree (morbid).

To analyze and evaluate the obtained data, standard methods of descriptive statistics were used: calculation of average values and standard deviation ($M \pm \sigma$) for a normal distribution. For comparison of groups, the Student t-test was used (for quantitative variables). The value of $p < 0.05$ was taken as the level of statistical significance. For statistical processing of the obtained results, Statistica version 10 programs were used.

## RESULTS

As can be seen from the data given in Table 1, in patients with a paroxysmal form of atrial fibrillation, an average degree of nicotine dependence predominates, then weak and high, but not very high. However, in patients with a constant form, a weak, high, and less often very high degree was more often recorded in the absence of an average degree of nicotine addiction.

In the analysis of adherence to alcohol (Table 2) it was found that, in patients with a paroxysmal form of atrial fibrillation, safe and dangerous use was more common. In patients with a constant form, in most cases, safe, then dangerous and less harmful use of alcohol was recorded. Alcohol dependence was not recorded in any group. The number of points was: 3,0±1,4 and 11,5±3,5 ($p < 0,001$) in patients with paroxysmal form and 5,5±1,5, 12,5±1,5 and 17,4±1,3 ($p < 0,001$) with a constant form of atrial fibrillation, respectively.

A study of the consumption of table salt with food among those examined with MI (Table 3) showed that moderate and high consumption is more often recorded among people with both paroxysmal and persistent forms of atrial fibrillation, and less often, low.

As can be seen from the data given in Table 4, in patients with myocardial infarction with a paroxysmal form of atrial fibrillation, overweight prevails compared with the constant form, while in patients with a constant form — obesity ($p = 0,006$; test $\chi^2$).

Thus, in patients with myocardial infarction with a paroxysmal form of atrial fibrillation, the structure of risk factors is dominated by an average degree of nicotine addiction, dangerous alcohol consumption, high salt intake and excess body weight, and with a constant form of atrial fibrillation, a mainly weak and high degree of nicotine addiction is recorded, harmful use of alcohol and obesity.

From the data presented in Table 5 it is seen that from concomitant pathologies in patients with a paroxysmal form, vascular diseases of the brain, endocrine system and gastrointestinal tract predominate ($p=0,013$; test $\chi^2$), while in patients with a constant form the frequency increases diseases of the brain, kidneys and endocrine system.

When studying lipid metabolism, in all patients with both constant and paroxysmal forms of atrial fibrillation while taking statins, the target values of the parameters of total cholesterol, LDL, and TG were not achieved.

So in patients with paroxysmal atrial fibrillation, the level of total cholesterol was 3,8 ± 1,03; LDL — 2,2±0,7; TG — 1,2±0,5; in patients with a constant form, respectively 4,09±1,03; 2,4±0,9; 1,2±0,6, which reflects the likelihood of progression of atherosclerosis and requires enhanced lipid-lowering therapy.

When studying anxiety disorders in patients with myocardial infarction with atrial fibrillation, it was found that in individuals with paroxysmal and persistent atrial fibrillation, no statistically significant changes were detected. As can be seen from Fig 1, in patients with myocardial infarction with a paroxysmal form of atrial fibrillation, in most cases there was no anxiety, then subclinical and less clinically severe anxiety was recorded. In patients with myocardial infarction with a constant form of atrial fibrillation, in contrast to persons with a paroxysmal form, the frequency of subclinical and clinically severe anxiety increased. In the 1st group, among persons with no anxiety, the level on the HADS scale was 3,59±2,0 points, with subclinically expressed anxiety — 8,9±0,8 points, with clinically expressed anxiety — 12,0±0,1 points; in patients of the 2nd group, respectively, 3,6±1,8; 8,8±0,7; 12,0±0,9 points.

When studying depressive disorders (Fig. 2), among patients of the 1st group, the frequency of subclinical and clinically severe depression was higher than in the 2nd group. In the first group, among people with no depression on the HADS scale, its level was 4,2±1,8 points, with subclinically expressed depression — 8,8±0,7 points, with clinically expressed depression — 12,5±0,5 points ; in the 2nd group, respectively — 3,7±2,0; 8,5±0,7; 13,0±0,1 points.

*Table 1.*

| Nicotine addiction | Atrial fibrillation | | | | | | |
|---|---|---|---|---|---|---|---|
| | Paroxysmal (n=19) | | | Constant (n=12) | | | p < |
| | n | % | Number of points | n | % | Number of points | |
| Low degree | 7 | 36,8% | 2,1 ± 0,7 | 5 | 41,6% | 3,6 ± 0,4 | - |
| Medium grade | 9 | 47,3% | 4,9 ± 0,2 | - | - | - | - |
| High degree | 3 | 15,7% | 6,95 ± 0,7 | 5 | 41,6% | 6,3 ± 0,4 | - |
| Very high | - | - | - | 2 | 16,7% | 9,0 ± 0,8 | - |

*Table 2.*

| Alcohol consumption | Atrial fibrillation | | | |
|---|---|---|---|---|
| | Paroxysmal (n=30) | | Constant (n=23) | |
| | n | % | n | % |
| Safe use | 22 | 73,3% | 16 | 69,5% |
| Dangerous use | 8 | 26,6% | 5 | 21,7% |
| Harmful use | - | | 2 | 8,6% |
| Alcohol addiction | - | - | - | - |

*Table 3.*

| Salt intake | Atrial fibrillation | | | | |
|---|---|---|---|---|---|
| | Paroxysmal (n=83) | | Constant (n=55) | | p < |
| | n | % | n | % | |
| Low | 9 | 10,8% | 5 | 9,0% | - |
| Moderate | 57 | 68,6% | 38 | 69,0% | - |
| High | 17 | 20,4% | 12 | 21,8% | - |

*Table 4.*

| BMI | Atrial fibrillation | | | |
|---|---|---|---|---|
| | Paroxysmal (n=83) | | Constant (n=55) | |
| | n | % | n | % |
| Normal | 23 | 27,7% | 14 | 25,4% |
| Excess | 44 | 53,0% | 17 | 30,9% |
| Obesity | 16 | 19,2% | 24 | 43,6% |

*Table 5.*

| Accompanying illnesses | Atrial fibrillation | | | |
|---|---|---|---|---|
| | Paroxysmal (n=83) | | Constant (n=55) | |
| | n | % | n | % |
| Respiratory diseases (COPD, bronchial asthma, pneumonia) | 10 | 12,0% | 6 | 10,9% |
| Endocrine Disease (Diabetes) | 22 | 26,5% | 18 | 32,7% |
| Gastrointestinal diseases (peptic ulcer, chronic gastritis) | 18 | 21,6% | 4 | 7,27% |
| Anemia | 8 | 9,6% | 3 | 5,45% |
| Vascular diseases of the brain (acute cerebrovascular accident, chronic cerebral ischemia) | 25 | 30,1% | 31 | 56,3% |
| Kidney disease (chronic pyelonephritis) | 7 | 8,4% | 8 | 14,5% |

Thus, in patients with a paroxysmal form of atrial fibrillation, the emotional burden is characterized by predominance of depressive disorders, and in the constant form, anxiety, which must be taken into account when constructing further rehabilitation programs.

## CONCLUSION

In patients with myocardial infarction with a paroxysmal form of atrial fibrillation, the predominant risk factors are: dangerous alcohol consumption, high salt intake and overweight combined with depressive disorders in the form of subclinical and clinical depression, and with a constant form of atrial fibrillation, a high degree of nicotinic dependence and mild anxiety disorders: subclinically and clinically severe anxiety, which must be taken into account when carrying out preventive, rehabilitation measures and the solution of expert issues.

*Conflict of interest*

All authors declare that there is no potential conflict of interest requiring disclosure in this article.

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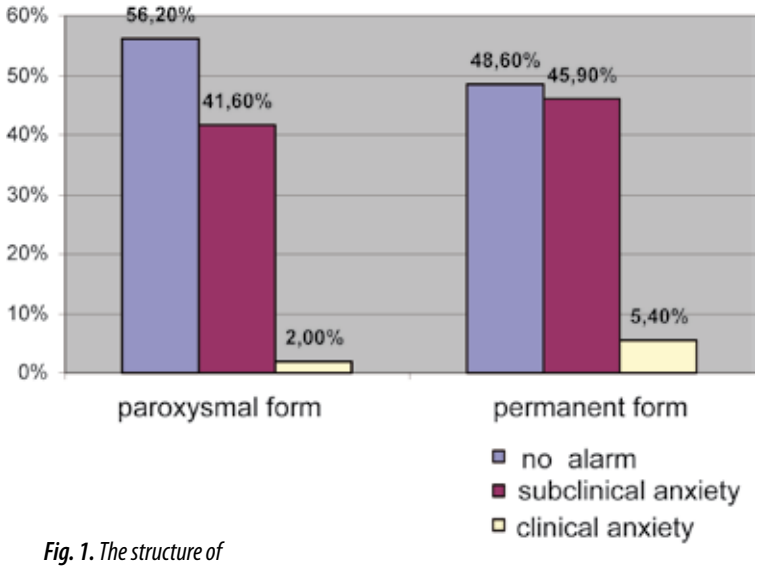


*Fig. 1. The structure of anxiety disorders in patients with myocardial infarction with atrial fibrillation*

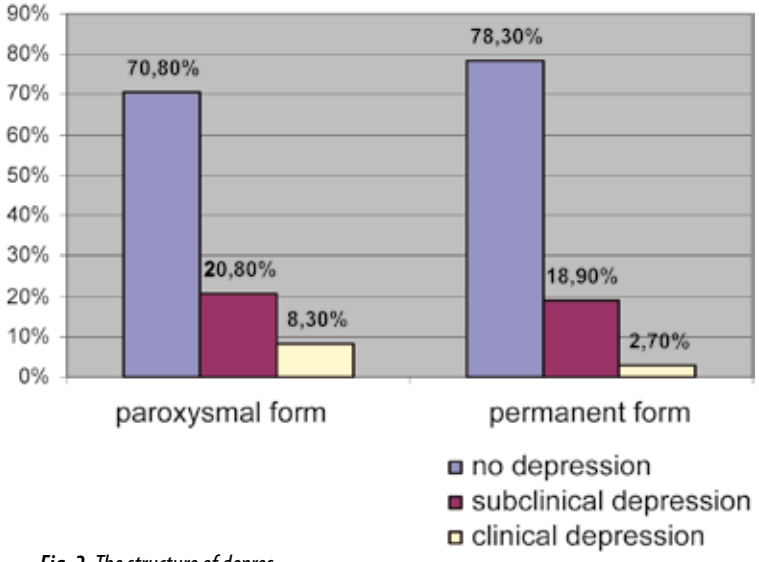


*Fig. 2. The structure of depressive disorders in patients with myocardial infarction with atrial fibrillation*

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# OPTIMAL CHOICE OF ANTIRETROVIRAL THERAPY REGIMEN INCLUDING PHOSPHAZIDE

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**ABSTRACT** — A clinical and laboratory study on selection, prescription and use of optimal antiretroviral therapy regimens for HIV patients was conducted. It was identified, that phosphazide has significant therapeutic efficacy and safety among nucleoside analog reverse-transcriptase inhibitors.

**KEYWORDS** — safety, phosphazide, HIV infection, therapy.

## INTRODUCTION

It is known that HIV infection is one of the most complex biomedical health problems in the world. The disease causes negative consequences, signs of an emergency and long-term problems, including death [1, 2]. In Russia, there is an annual increase in morbidity, social significance and epidemiological danger, which dictates the need of new approaches to HIV/AIDS retroactions including safe and effective drug usage. According to Russian guidelines, antiretroviral therapy (ART) is carried out using the combination of at least three drugs [3, 4].

To achieve the long-term therapeutic effect of ART, it is necessary to select treatment regimens with effective and safe drugs based on the objective principles of rational drug use.

Using the expert system *AntiHIV-1* which includes the elements of the *Rational Unified Process* (RUP) software methodology, optimal and safe treatment regimen, including a NRTI class drug — phosphazide, were selected.

## METHODOLOGY, MATERIALS AND RESEARCH METHODS

The medical expert system *AntiHIV-1* was created in 2017 on the basis of *Perm State Center for the Prevention and Control of AIDS and Infectious Diseases* by Federal State Budgetary Educational Institution of Higher Education *Perm State Pharmaceutical Academy* of the Ministry of Health of the Russian Federation with contribution from *Perm National Research Polytechnic University*.

Taking into account the criteria of *effectiveness* and *safety*, the safest drug of the class of nucleoside reverse transcriptase inhibitors (NRTIs) in ART regimens was determined.

## MAIN CONTENT OF THE STUDY AND ANALYSIS OF THE RESULTS

In the automatic information system *AntiHIV-1* for analysis of the choice and purpose of ART, 33 used antiretroviral drugs from six classes registered in the state register of medicines were included. 25 of them were monocomponent drugs and 8 were complex (two- and three-component), they were included into the pharmacotherapeutic group J05A *Direct-acting antiviral drugs* according to the Anatomical Therapeutic Chemical Classification (ATC) classification [5].

599 medical records of patients receiving ART on an outpatient basis were analyzed, which made it possible to identify side effects and draw conclusions about the toxicity of the drugs used.

ART regimen with phosphazide were the safest one. Phosphazide is the first Russian NRTI class drug that was synthesized in the laboratory of the Institute of Molecular Biology. V.A. Engelhardt RAS [6] (Fig. 1)

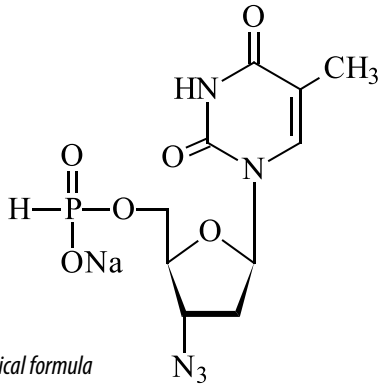


***Fig. 1.*** *Phosphazide chemical formula*

High anti-HIV activity of phosphazide against HIV-1 reproduction in cultures of H9, MOLT and MT-4 lymphoblastoid cells was established (Galegov, 1988) as well as low toxic effects on tissues and organs [7, 8, 9, 10].

We had also studied its safety and low toxicity in the schemes of perinatal chemoprophylaxis of mother-to-child HIV transmission, treatment of infection and prevention of parenteral infection of medical workers in the course of their duties earlier. [11–14].

As a result, ART regimens with the least number of undesirable side reactions (ADR) from organs and systems were identified — this is a combination of 2 NRTIs + AI — tenofovir + phosphazide + dolutegravir (73 (11.8%) of 617 ADR), while the combination of abacavir + phosphazide + dolutegravir potentially causes only 8 (1.3%) ADR, which are the same for all three drugs.

Among the alternative ART regimens, phosphazide + emtricitabine + fosamprenavir (52 (8.4%) of 617 ADR), phosphazide + emtricitabine + atazanavir, and phosphazide + emtricitabine + fosamprenavir / ritonavir with five (0.8%) ADR should be marked.

The analysis of the clinical laboratory diagnostics results, changing under the influence of antiretroviral therapy drugs, revealed ART regimens, the use of which causes the least effect on the change in laboratory parameters. These are the following drug combinations recommended in the Russian Federation: phosphazide + emtricitabine + fosamprenavir, phosphazide + emtricitabine + saquinavir / ritonavir, phosphazide + lamivudine + fosamprenavir, phosphazide + lamivudine + saquinavir / ritonavir.

Among monocomponent ART drugs, phosphazide is characterized by the least number of potential manifestations of ADR — 10 ADR(1.6%).

There should be noted such ART drug regimens that do not influence the indicators of clinico-laboratorial diagnostics (0 indicators of CLD (0.0%) out of 42) for the treatment of HIV infection: phosphazide + emtricitabine + atazanavir and phosphazide + lamivudine + fosamprenavir [15–17].

## CONCLUSION

As a result of the use of the AIS *AntiHIV-1*, the optimal ART regimens which have the least amount of side effects were determined. All schemes include a representative of NRTI class — phosphazide, which is registered and manufactured in Russia.

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# CORRELATION OF PERIPHERAL BLOOD PARAMETERS WITH RISK FACTORS FOR STAGE 3 ARTERIAL HYPERTENSION

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**ABSTRACT** — In order to assess the correlation of the main parameters of peripheral blood with risk factors (RFs) on a gender basis in patients with stage 3 hypertension (HTN) undergoing hypotensive therapy, 98 patients were examined. They were divided into 2 groups based on their gender (men — 45; women — 53). The following FRs were studied: age, disease duration, body mass index, blood lipid profile: total cholesterol, low-density lipoproteins, triglycerides; blood glucose, glomerular filtration rate (GFR, ml / min / 1.73 $m^2$). The main parameters of peripheral blood were studied: the number of erythrocytes, hemoglobin concentration, total white blood cell count, erythrocyte sedimentation rate. During the treatment, the systolic BP (SBP) was approximately 130 mm Hg, the diastolic BP (DBP) — 80 mm Hg. It has been established that blood parameters differ in men and women. It has been found that the total number of white blood cells in men directly correlates with the contents of triglycerides and blood glucose, and in women it is directly related to the level of triglycerides and GFR and inversely related with the blood glucose concentration. It can be assumed that the gender of patients determines the relationship between the RFs and peripheral blood parameters.

**KEYWORDS** — arterial hypertension, risk factors, gender, blood parameters.

Arterial hypertension (HTN) is considered to be a major risk factor (RF) for cardiovascular disease (CVD) causing the development of acute cerebral circulatory disorders, myocardial infarction, chronic heart and kidney failure which determine high mortality and disease prognosis of patients with this pathology [1, 5, 6]. Combinations of different RFs lead to the progression of HTN with subsequent malfunctioning of some of the organ systems. An example of this is the blood system. Some patients have erythrocytosis detected in the peripheral blood [2–4] or anemic syndrome of various severity [5, 7], while others have normal blood parameters. Analysis of the relationship of the RFs with the main parameters of peripheral blood in patients with Stage 3 HTN is of great scientific interest and importance.

*The aim of the study*

Is to evaluate the main parameters of peripheral blood and their correlation with the RFs on a gender basis in patients with Stage 3 HTN undergoing hypotensive therapy.

## MATERIAL AND METHODS

The study was conducted in accordance with the WMA Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and approved by the Ethics Committee of Tver State Medical University. The patients gave voluntary informed consent to be included in the study. The primary inclusion criterion for the participants was Stage 3 HTN. Patients with cancer, acute and chronic diseases in the acute stage, with Stage 3 chronic heart failure were excluded from the study.

We randomly examined 98 patients (men — 45, women — 53, average age — 64.45 years) with verified Stage 3 HTN undergoing treatment in Tver Regional Clinical Hospital. The patients were divided into 2 groups based on their gender (men — 45, average age — 63.5±9.12; women — 53, average age — 65.19±10.02). The following RFs were studied using the interview method, physical examination and analysis of laboratory investigationss: age, disease duration (DD, years), obesity (weight, kg), body mass index (BMI, kg/$m^2$), blood lipid profile: total cholesterol (TCh, mmol/l), low density lipoproteins (LDLs, mmol/l), triglycerides (TGs, mmol/l); blood glucose (BG, mmol/l), glomerular filtration rate (GFR, ml/min/1.73 $m^2$, according to the CKD-EPI and MDRD formulas). The main parameters of the participants' peripheral blood were assessed: the number of red blood cells (RBCs · $10^{12}$/L), hemoglobin concentration (HB, g/L), the total number of white blood cells (WBCs · $10^9$/L), erythrocyte sedimentation rate (ESR, mm/h). During the administered treatment, the systolic blood pressure (SBP) was approximately 130 mm Hg, the diastolic blood pressure (DBP) was 80 mm Hg.

Statistical data processing was carried out using the program package "Microsoft Excel", "Biostat-2007". The data is presented as M±SD. Significance evaluation of the differences was carried out by the one-factor variance analysis and Fisher criterion, correlation (r) was determined using Spearman's method. The correlation coefficient significance was determined by the correlation table.

## RESULTS

The two groups were comparable in age, number of subjects and examination methods. The peripheral blood parameters in the patients with Stage 3 HTN were within normal limits. Correlation analysis showed that in the men, the RBC count was inversely correlated with TCh and LDLs (r=-0.43, p=0.01, r=-0.51, p=0.001, respectively). The Hb concentration was directly correlated with weight, BMI (r=0.39, p=0.01, and r=0.40, p=0.01, respectively) and GFR (according to the CKD-EPI formula, r =0.295, p=0.05, and the MDRD formula, r=0.36, p=0.05). The ESR showed correlation with LDL concentration (r=0.41, p=0.01). The total WBC count was associated with the TGs and BG values (r=0.37, p=0.05, r=0.294, p=0.05 respectively).

In the women, the number of RBCs showed inverse correlation with age (r=-0.26, p=0.05), DD (r=-0.34, p=0.05), TCh (r=-0.31, p=0.05), TGs (r=-0.352, p=0.01) and there was a direct correlation with GFR (according to the MDRD formula, r=031, p=0.05).

The study showed evidence of inverse dependence of the HB concentration on the patients' age (r=-0.38, p=0.01) and DD (r=-0.34, p=0.05) and the GFR (according to the formula CKD-EPI r=-0.32, p=0.05, according to the formula MDRD r=-0.31, p=0.05). The ESR (r=0.30, p=0.05) directly correlated with the age. The total WBC count directly correlated with the TG (r=0.272, p=0.05) and GFR (according to the formula MDRD r=0.34, p=0.05) values and inversely correlated with the BG parameters (r=-0.29, p=0.05) and the values of systolic and diastolic BPs (r=-30, p=0.05, r=-30, p=0.05, respectively).

Overall, these results indicate that in the men and women with Stage 3 HTN, FRs showed a multidirectional correlation with the main parameters of peripheral blood. It can be noted that the decrease in RBCs and Hb in the men was observed with increased levels of TCh, LDLs and TGs. A decrease in GFR led to a decrease in Hb concentration. The ESR value grew with the increased LDL content.

In the female participants, with increasing age and DD, there was a decrease in the RBC count and Hb concentration. Like the male participants, they showed an increase in TCh and TGs and a decrease in the GFR which led to a decrease in the RBC count. The increased ESR values were caused by age and LDLs. It can be assumed that the decreased RBC count is associated with a decrease in their deformability, alongside with an increase in lipids, atherosclerosis progression, and changes in the RBC cytoskeleton during HTN [7].

In the men, an increase in TGs and BG led to an increase in the total WBC count. In the women, the total number of WBCs varied depending on the TG, BG and GFR values. They showed a decrease in the total number of WBCs with an increase in the SBP and DBP parameters, and an increase in the total number of WBCs was observed with a decrease in the GFR.

## CONCLUSION

Analysis of the correlation of peripheral blood parameters with RFs in Stage 3 HTN shows a focus on reducing RBCs and Hb and forming the anemic syndrome. Blood parameters in men and women differ. It has been found that the total WBC count in men directly correlates with TG and BG values, and in women directly correlates with the levels of TGs and GFR and inversely correlates with BG concentration. It can be assumed that the gender of patients is a vector that affects the relationship between the RFs and peripheral blood parameters. In men, an increase in TGs and BG led to an increase in the total WBC count. In women, the total number of WBCs varied depending on the values of TGs, BG and GFR. They showed a decrease in the total number of WBCs with an increase in SBP and DBP parameters, and an increase in the total number of WBCs was observed with a decrease in the GFR.

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# THORACIC EPIDURAL ANALGESIA FOR THE PREVENTION OF POST-ERCP PANCREATITIS: A RANDOMIZED STUDY OF 491 CASES

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**ABSTRACT** — Aim. To evaluate the effectiveness of thoracic epidural analgesia (TEA) for prevention of post-ERCP pancreatitis (PEP).
Materials and methods. Between 2015 and 2019, a randomized study of the results of endoscopic treatment in 491 patients was conducted. The first group of patients (N=247) received thoracic epidural analgesia during ERCP procedures, the patients of the second group (N=244) received a narcotic analgesic.
Results. In the first (TEA) group there were no cases of pancreatic necrosis and fatal outcome, in the second (control) group in 7 (2.9%) patients were diagnosed with this adverse event, of which 3 (1.2%) patients died. A statistically significant reduction in the incidence of PEP was found due to the use of epidural analgesia in all age categories ($p = 0.0004$-$0.0232$), in women ($p = 0.0000$) and men ($p = 0.0057$), patients with jaundice ($p = 0.0000$), with sphincter of Oddi dysfunction ($p = 0.0000$), with common bile duct stones ($p = 0.0004$), with tumor ($p = 0.0010$), after biliary sphincterotomy ($p = 0.0000$), biliary-stone extraction ($p = 0.0013$), naso-biliary drainage ($p = 0.0016$). The study has proved the effectiveness of thoracic epidural analgesia in patients with high risk of post-ERCP pancreatitis ($p = 0.0000$).
Conclusion. The use of thoracic epidural analgesia during therapeutic ERCP procedures is an effective method of preventing post-ERCP pancreatitis.

**KEYWORDS** — therapeutic ERCP, prevention of post-ERCP pancreatitis, thoracic epidural analgesia.

## INTRODUCTION

For more than 50 years ERCP procedures have been successfully used in the treatment of patients with benign and malignant diseases of hepatopancreatobiliary zone. Compared with surgery, endoscopic correction has significantly reduced the risk of adverse effects in a substantial number of patients with choledocholithiasis, sphincter of Oddi dysfunction, chronic calculous pancreatitis, tumors of the bile ducts and pancreas [1, 2, 3].

The improvement of endoscopic techniques, specifically those of performing ERCP procedures, and the use of pharmacological prophylaxis have significantly reduced the risk of adverse effects. However, it still can't be claimed that ERCP procedures present a completely safe intervention. According to many authors, the greatest cause for concern is the post-ERCP pancreatitis (PEP) [4, 5, 6, 7]. Numerous studies have shown that the PEP rate in the total sample reaches 10% and up to 40% in high risk patients [8, 9, 10, 11].

Since the moment ERCP procedures started to be used for treating patients the search for a universal and effective method of preventing PEP has been going on, but until now the problem has not been completely resolved [12, 13, 14, 15].

During the time we have been using ERCP procedures we have been actively implementing all available methods of PEP prevention, however the PEP rate has remained rather high. Based on his ample experience of using thoracic epidural analgesia (TEA) and the knowledge of its positive effects (good pain relief, increased perfusion in the area of regional block, the sphincter of Oddi relaxation), one of the authors of this article (M.I.T.) suggested applying it in therapeutic ERCP as a way to prevent PEP.

## MATERIALS AND METHODS

A prospective controlled parallel randomized study has been conducted. Initially, we decided that a clinically significant result of applying TEA should be considered reducing of PEP incidence by 50%.

The statistician of our clinic determined that to provide 80–90% of research power we needed a sample from two groups, comprising about 450–480 patients (used the Altman nomogram).

The study was approved by the Volgograd regional independent ethics committee (ref: 124/2007/12/24) and registered with ClinicalTrials.gov (NCT 01964066). All patients gave their written informed consent for participation in the study.

***Inclusion criteria:***

1. Patients with performed therapeutic ERCP;
2. The ERCP procedure was performed in a patient for the first time;
3. Prior to the ERCP procedure the patient didn't have any clinical signs of acute pancreatitis.

***Exclusion criteria:***

Development of complications during the ERCP procedure that required urgent surgical intervention (massive haemorrhage, Dormia basket avulsion and others).

Between January 2015 and December 2019 786 ERCP procedures were conducted. All the patients were hospitalized. In 53 (6.7%) patients had endoscopic intervention carried out for diagnostic purposes. In 528 (67.2%) cases, the intervention was performed for the first time; in 205 (26.1%) cases the patients already had ERCP procedures performed before. 27 of 528 (5.1%) patients were diagnosed with symptoms of acute pancreatitis before the intervention. One patient refused to participate in the experiment.

Preoperatively the subjects were randomly assigned (by using sealed envelopes — blind randomization) into two groups, 250 patients each.

The patients of the first group had TEA applied during the ERCP procedure; other methods of pain relief were applied to the patients of the second (control) group.

The first group (TEA group) of patients received the following premedication: atropine sulfate 0.5–1 mg, midazolamum 5 mg. Puncture and catheterization of the epidural space was carried out in accordance with the standard procedure at the level of ThVII–ThVIII vertebrae. Half an hour before performing ERCP ropivacainum 0.5% — 8–10 ml was injected into the epidural space.

The second group (control group) of patients received the following premedication: atropine sulfate 0.5–1 mg, midazolamum 5 mg, trimeperidinum 2% — 1 ml.

General anaesthesia with propofol 2 mg/kg with or without orotracheal intubation with a cuffed tube was used for high-risk patients considering their clinical status (i.e., age, patients with extremely poor health status (American Society of Anaesthesiologists (ASA IV)), prussic dementia and clinical presentation).

In the TEA group three patients were excluded from the experiment due to unsuccessful attempt to epidural catheterization (2 cases) and retroduodenal perforation (1 case). Six patients were excluded from the second group on account of massive haemorrhage (1 case), retroduodenal perforation (2 cases), Dormia basket avulsion (1 case), failed cannulation (2 cases), which required surgical intervention.

Ultimately, the treatment outcomes of 491 patients were analyzed: 247 patients in the first /TEA group and 244 patients in the second/control group.

After receiving ERCP procedures all the patients were admitted to the intensive care unit. The TEA group patients continued to receive epidural analgesia (ropivacainum 0.2% — 5 ml/h). The control group patients received non-narcotic analgesics (Ketorolacum 3% — 1 ml). All the patients from both groups received infusion therapy (crystalloids 10–15 ml/kg).

The variables documented for each case included the characteristics of the patients and the specifics of each procedure, as listed in Table 1. During the next day rounds at least three surgeons, who did not participate in the study, diagnosed the presence or absence of acute pancreatitis. Acute pancreatitis was diagnosed on the basis of the clinical picture (characteristic abdominal pain, nausea, vomiting, gastric stasis, tachycardia, etc.), laboratory data (hyperamylasemia, leukocytosis) and ultrasonoscopy results. The sphincter of Oddi dysfunction (SOD) was signaled by the common bile duct extension (more than 8 mm) in the absence of stones and tumors of the common bile duct or pancreas and/or difficult cannulation of choledochitis (more than 5 attempts). Biliary and/or pancreatic sphincter manometry was not used due to lack of equipment.

Procedural complexity was rated by an established grading scale. Grade 1 includes all standard biliary procedures; grade 2 includes large bile-duct stones extraction, hilar strictures and benign biliary strictures. The variables (demographic data, the nature of the disease, the results of laboratory and instrumental studies, the outcome, etc.) were introduced into researcher's database within 10 days after the intervention. Unfortunately, the public database of our clinic is only being generated at the moment.

Demographic characteristics of the patients are presented in Table 1. The average age of the patients in the study group was 58±1.0 years, in the control group — 62±1.0 years. The number of women and younger patients (under 65) was slightly larger in the TEA group: 66.0% vs 64.8% and 64.8% vs 53.7%, respectively. The study groups differed in some other variables. Patients with tumors (33.2% vs 36.5%, $p = 0.4460$) and jaundice (33.2% vs 38.1%, $p = 0.2554$) were slightly larger in the TEA group. At the same time, in the TEA group we more frequently observed patients with common bile duct stones (50.6% vs 42.2%, $p = 0.0622$), SOD (15.0% vs 9.0%, $p = 0.0522$), common bile duct stones and SOD (14.2% vs 9.0%, $p = 0.0747$), calculous cholecystitis (30.8% vs 29.5%, $p = 0.7608$). Since the TEA group was presented by younger patients, concomitant diseases were detected in 74.5% (184/247) patients in the TEA group and in 84.4% (206/244) patients in the control group ($p = 0.0065$). However, the number of patients with severe comorbidities (ASA IV) did not differ between the study groups ($p = 0.2573$); the majority of such patients were diagnosed with cardiovascular dis-

eases (73.9% [136/184] in the first group and 74.8% [154/206] in the second group). Other variables did not differ between the study groups.

To determine the statistical significance of differences between the study groups were used nonparametric tests. Each group was divided into subgroups differed by age, sex, nature of the disease and character of the intervention. The statistical processing was performed using the Mann-Whitney U-test and $\chi^2$ Pearson. The difference was considered significant at the significance level of more than 95% ($p < 0.05$). Analyses were performed with Statistica 10.0 (StatSoft Inc., USA).

## RESULTS AND DISCUSSION

A total of 491 therapeutic ERCP procedures were performed and documented over the period of 5 years. Depending on the nature of the disease different types of endoscopic procedures were used. The study groups somewhat differed on this indicator. In the TEA group the procedures of biliary sphincterotomy (79.4% vs 77.9%, p = 0.6886), balloon dilation (20.2% vs 18.0%, p = 0.5337), biliary-stone extraction (57.5% vs 52.5%, p = 0.2626) and lithotripsy (11.3% vs 9.4%, p = 0.4880) were performed slightly more often. In the second group, was statistically insignificantly more often performed was biliary-stent insertion (27.9% vs 23.1%, p = 0.2230). For the prevention of PEP in 15.8% of patients of the TEA group and 12.3% in the second group pancreatic stents (p = 0.2653) were installed. The study groups did not differ in the procedural complexity (Table 1).

During the time of this study 46 (9.4% [46/491]) cases of PEP were diagnosed in total; 89.1% (41/46) of total PEP cases were registered in the second group (Table 2). Thus, the incidence of PEP in the TEA group was 2.0% (5/247) while in the control group it was 16.8% (41/244) (p = 0.0000).

The absolute majority of PEP patients in both groups had a mild form of disease (80% [4/5] and 66% [27/41] observations, respectively) and we were able to arrest their clinical manifestations within three days. One patient (20%) from the TEA group, and 7 (17%) patients from the second group needed the continuation of intensive anti-pancreatic therapy up to 7 days. Taking into account the clinical picture and data from laboratory and instrumental tests 7 (2.9% [7/244]) patients in the control group were diagnosed with pancreatic necrosis. In all cases the symptoms of pancreatic necrosis developed rapidly and were characterized by total and subtotal lesion of the pancreas. 42.9% (3/7) of patients with pancreatic necrosis had an unfavorable outcome: two patients died from multiple organ failure syndrome and one patient from acute coronary syndrome.

Clinical and procedural predictors of PEP are shown in Table 3.

A statistically significant reduction in the incidence of PEP was found due to the use of epidural analgesia in all age categories (p = 0.0004-0.0232), in women (p = 0.0000) and men (p = 0.0057), patients with jaundice (p = 0.0000), with sphincter of Oddi dysfunction (p = 0.0000), with common bile duct stones (p = 0.0004), with tumor (p = 0.0010), after biliary sphincterotomy (p = 0.0000), biliary-stone extraction (p = 0.0013), naso-biliary drainage (p = 0.0016). Among the patients of the TEA group over 65, with tumors, with calculous pancreatitis with severe comorbidities (ASA III-IV), after the installation of biliary stents and lithotripsy there was not a single case of developing PEP. There was not a single death case in the TEA group. More frequently the postoperative period was accompanied by the development of PEP in women (10.3% [35/341]), younger patients (under 65) (10.3% [30/292]) and in patients with SOD (18.1% [21/116]). According to our data, these factors increased the risk of developing PEP. The patients who had a combination of these factors were considered at high risk for PEP.

Table 4 presents the data on the incidence of PEP in patients at high risk of developing this undesirable consequence.

During the entire time of using ERCP procedures we searched for methods of preventing the development of PEP. We conducted numerous investigations aimed at studying the preventive effect of different groups of medications (indomethacin, somatostatin, heparin, etc.) [16, 17]. For this purpose we proposed to use various tactics of endoscopic intervetions [18]. Nevertheless the development of PEP remained a major problem after therapeutic ERCP procedures [19].

The study has provided reliable data on the efficacy of applying TEA in therapeutic ERCP procedures in order to prevent the development of PEP. The study has demonstrated that the incidence of PEP was reduced from 16.8% to 2.0% of cases. In the TEA group all the PEP cases were of mild to moderate severity. The use of TEA helps to prevent the development of pancreatic necrosis and unfavourable outcome, which greatly increases the safety of applying therapeutic ERCP procedures to patients at high risk for PEP and severe comorbidities. Besides it is important to mention that the endoscopists noted that the use of TEA creates a more comfortable environment for their work.

No doubt this prevention method has its drawbacks. The main disadvantages, we believe, are the following: the necessity to engage a doctor who has mastered the technique of performing TEA; the

***Table 1.*** *Selected subject and procedural characteristics of patients*

| Variable | Total (% of total) | | p |
|---|---|---|---|
| | TEA group (N = 247) | Control group (N = 244) | |
| Subject | | | |
| Age | | | |
| 18–50 y | 67 (27.1) | 48 (19.7) | 0.0512 |
| 51–65 y | 93 (37.7) | 83 (34.0) | 0.4010 |
| 66–80 y | 66 (26.7) | 90 (36.9) | 0.0156* |
| >80 y | 21 (8.5) | 23 (9.4) | 0.7200 |
| Sex | | | |
| Women | 163 (66.0) | 158 (64.8) | 0.7732 |
| Context | | | |
| Jaundice | 82 (33.2) | 93 (38.1) | 0.2554 |
| Common bile duct stones | 125 (50.6) | 103 (42.2) | 0.0622 |
| SOD | 37 (15.0) | 22 (9.0) | 0.0522 |
| Common bile duct stones and SOD | 35 (14.2) | 22 (9.0) | 0.0747 |
| Tumor | 82 (33.2) | 89 (36.5) | 0.4460 |
| Calculous pancreatitis | 8 (3.2) | 8 (3.3) | 0.9802 |
| Prior cholecystectomy | 81 (32.8) | 75 (30.7) | 0.6247 |
| Calculous cholecystitis | 76 (30.8) | 72 (29.5) | 0.7608 |
| ASA grade | | | |
| IV | 13 (5.3) | 19 (7.8) | 0.2573 |
| III | 41 (16.6) | 40 (16.4) | 0.9510 |
| I and II | 193 (78.1) | 185 (75.8) | 0.5418 |
| Procedural | | | |
| Biliary sphincterotomy | 196 (79.4) | 190 (77.9) | 0.6886 |
| Balloon dilation | 50 (20.2) | 44 (18.0) | 0.5337 |
| Biliary-stone extraction | 142 (57.5) | 128 (52.5) | 0.2626 |
| Installation of biliary stent | 57 (23.1) | 68 (27.9) | 0.2230 |
| Lithotripsy | 28 (11.3) | 23 (9.4) | 0.4880 |
| Installation of pancreatic stent | 39 (15.8) | 30 (12.3) | 0.2653 |
| Naso-biliary drainage | 47 (19.0) | 54 (22.1) | 0.3951 |
| Difficulty gradew | | | |
| 2 | 83 (33.6) | 72 (29.5) | 0.3290 |
| 1 | 164 (66.4) | 172 (70.5) | |

***Note:*** **P < 0.05, statistically significant; ASA – American Society of Anaesthesiologists; SOD – sphincter of Oddi dysfunction.*

***Table 2.*** *Post-ERCP pancreatitis and severity*

| Group | Total (% of total procedures) | Severity (% of post-ERCP pancreatitis) | | Mortality (% of total procedures) |
|---|---|---|---|---|
| | | Mild/Moderate | Severe | |
| TEA group (N = 247) | 5 (2.0) | 5 (100) | 0 (0) | 0 (0) |
| Control group (N = 244) | 41 (16.8) | 34 (82.9) | 7 (17.1) | 3 (1.2) |
| p | 0.0000* | 0.0000* | 0.0073* | 0.0805 |

***Note:*** **P < 0.05, statistically significant.*

***Table 3.*** *Clinical and procedural predictors of post-ERCP pancreatitis*

| Variable | post-ERCP pancreatitis/total (% total of variable) | | p |
|---|---|---|---|
| | TEA group | Control group | |
| Clinical | | | |
| Age | | | |
| 18–50 y | 2/67 (3.0) | 12/48 (25.0) | 0.0004* |
| 51–65 y | 3/93 (3.2) | 13/83 (15.7) | 0.0042* |
| 66–80 y | 0/66 (0) | 11/90 (12.2) | 0.0032* |
| >80 y | 0/21 (0) | 5/23 (21.7) | 0.0232* |
| Sex | | | |
| Women | 4/163 (2.5) | 31/158 (19.6) | 0.0000* |
| Men | 1/84 (1.2) | 10/86 (11.6) | 0.0057* |
| Context | | | |
| Jaundice | 1/82 (1.2) | 20/93 (21.5) | 0.0000* |
| Common bile duct stones | 1/125 (0.8) | 12/103 (11.7) | 0.0004* |
| SOD | 1/37 (2.7) | 13/22 (59.1) | 0.0000* |
| Common bile duct stones and SOD | 3/35 (8.6) | 4/22 (18.2) | 0.2818 |
| Tumor | 0/82 (0) | 11/89 (12.4) | 0.0010* |
| Calculous pancreatitis | 0/8 (0) | 1/8 (12.5) | 0.3017 |
| Prior cholecystectomy | 4/81 (4.9) | 11/75 (14.7) | 0.0395* |
| Calculous cholecystitis | 1/76 (1.3) | 18/72 (25.0) | 0.0000* |
| ASA grade | | | |
| IV | 0/13 (0) | 1/19 (5.7) | 0.4007 |
| III | 0/41 (0) | 4/40 (10.0) | 0.0378* |
| I and II | 5/193 (2.6) | 36/185 (19.5) | 0.0000* |
| Procedural | | | |
| Biliary sphincterotomy | 3/196 (1.5) | 32/190 (16.8) | 0.0000* |
| Balloon dilation | 3/50 (6.0) | 5/44 (11.4) | 0.3524 |
| Biliary-stone extraction | 4/142 (2.8) | 17/128 (13.3) | 0.0013* |
| Installation of biliary stent | 0/57 (0) | 9/68 (13.2) | 0.0044* |
| Lithotripsy | 0/28 (0) | 3/23 (13.0) | 0.0489* |
| Installation of pancreatic stent | 0/39 (0) | 3/30 (10.0) | 0.0435* |
| Naso-biliary drainage | 2/47 (4.3) | 15/54 (27.8) | 0.0016* |

***Note:*** **P < 0.05, statistically significant.*

***Table 4.*** *Post-ERCP pancreatitis incidence in high-risk patients*

| Group | Total (post-ERCP pancreatitis) | Severity (% of total) | | |
|---|---|---|---|---|
| | | Mild | Moderate | Severe |
| TEA group (N = 46) | 46 (4) | 3 (6.5) | 1 (2.2) | 0 (0.0) |
| Control group (N = 24) | 24 (13) | 7 (29.2) | 4 (16.7) | 2 (8.3) |
| p | 0.0000* | 0.0003* | | 0.0470* |

***Note:*** **P < 0.05, statistically significant.*

invasiveness of the method (despite its safety); its limited application for patients with coagulopathies (e.g. patients with liver failure); its use limited only to hospitalized patients. There remain some unresolved issues. Not all patients undergoing therapeutic ERCP procedures are in need of TEA. Currently neither indications nor contraindications for using this method of preventing PEP have been identified. The need for TEA while performing general anaesthesia also remains unclear. These issues need to be addressed in further research.

The fact that the study included all patients meeting of the inclusion criteria, hospitalized in clinic for the last 5 years, and the sample size indicates the validity of the study.

## CONCLUSION

The use of thoracic epidural analgesia significantly reduces the incidence of post-ERCP pancreatitis in therapeutic ERCP procedures. The use of TEA during therapeutic ERCP procedures is an effective prevention method for patients at high risk of post-ERCP pancreatitis. In conclusion we would like to note that this study does not call into question the effectiveness of other prevention methods recommended by various authors, but rather complements them. As always, each patient requires an individual approach.

### *Conflict of interests*

The authors state that they have no conflict of interests.

### *Contributors*

MIT and VVM collected, analyzed, and interpreted data and made the figures. ASP did the literature review and collected data. AVE and YuIV collected data and made the figures. MIT and VVM interpreted and analysed the data. MIT, ASP, AVE, YuIV and VVM prepared the manuscript for submission.

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# CLINICAL RESULTS AND INDICATORS OF CYTOKINES IN THE TREATMENT OF PURULENT WOUNDS IN PATIENTS WITH DIABETES MELLITUS

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**ABSTRACT** — The authors provide a comparative assessment of the results of a clinical study of purulent wound healing and the profile of pro- and anti-inflammatory cytokines in 71 patients with type 2 diabetes mellitus. In group 1 (44), Biointegra ointment, lymphatic and NO-therapy were used. In 27 patients (group 2), comparable by sex and age, treatment was carried out by ultrasonic cavitation of wounds, dressings with Levomekol ointment and traditional intramuscular administration of a similar antibiotic and immune preparation. In the group 1, the general condition normalized on the 5–7$^{th}$ day, the level of glycemia decreased, the purulent process was localized within the damaged tissues and the imbalance in the cytokine profile was eliminated. In the group 2, positive dynamics was observed 4–5 days later than in the first group. The terms of treatment in the main group were 14.6±1.2, in the comparison group — 19.8±1.8 inpatient days.

**KEYWORDS** — Purulent wound, diabetes mellitus, wound healing, cytokines.

## INTRODUCTION

In the XXI century, there has been a steady increase in the number of patients with diabetes mellitus with purulent surgical infection. This is due to the annual increase in the registration of cases of diabetes and their doubling every 10 years [1].

In patients with diabetes, the healing of purulent wounds is characterized by a mild course of the phases of the wound process, which is associated with a violation of all types of metabolism. Surgical infection aggravates the clinical course of diabetes mellitus, insulin deficiency increases, followed by impaired function of the organs of the effector and regulatory systems. In diabetes mellitus, there is a deficiency of endogenous NO-universal messenger regulator [2].

The healing of purulent wounds depends largely on the effectiveness of local drug treatment [3, 4].

In the fight against purulent infections, the technique of lymphatic (direct and indirect) administration of antibiotics and immune preparations has not yet been properly evaluated.

However, exogenous NO and Biointegra ointment in combination with lymphatic therapy have not been used in the complex treatment of purulent wounds in patients with diabetes mellitus.

*The aim of the study* is to argue the feasibility of using exogenous NO, *Biointegra* ointment, and conducting indirect lymphotropic antibiotic and immunotherapy in the treatment of purulent wounds in patients with diabetes mellitus of the second type.

## MATERIALS AND METHODS

In the studied group of patients (24 people) with type 2 diabetes mellitus with purulent wounds of various origins, regional lymphatic therapy was carried out: 1 time per day with 48 hour intervals, departing 1cm from the edges of the wound on both sides from 4 points, in half the daily dose, ceftriaxone 1.0 was introduced diluted in 8ml of a 2% solution of lidocaine + 32 unitsoflidase, and after 5 minutes, in the same place, imunofan (0.05 g) was injected subcutaneously. Every day, afterwound cleaning, its surface was treated for 5 minutes with exogenous NO produced by the apparatus SKSV/NO-01 *Plazon* in the *stimulator* functioning mode. The wounds were treated with *Biointegra* ointment — (the patent name of the drug), which is *NanoZnHApAM-Antibiotic-PEG*, with the inclusion of a water-soluble antioxidant — ethylene polyglucol with a molecular weight of 400 to 1500 cu.

In the comparison group — 21 patients with a similar pathology, comparable by sex and age, the antibiotic and imunofan were administered in the traditional intramuscular manner, and local wound treatment was carried out with dressings with Levomekol ointment. All patients underwent correction of hyperglycemia in accordance with the prescription of an endocrinologist.The effectiveness of the treatment was evaluated clinically by examining laboratory and by biochemical blood parameters, qualitative and quantitative studies of microflora, cytograms of touch smear, pH-metry of wound exudate. Studies were performed at the beginning of treatment, on 3–5$^{th}$, 7–9$^{th}$ and 10–14$^{th}$ days. The concentration of cytokines was determined using immunoenzymometrictest systems (LLC *Cytokine*, St. Petersburg).

The assessment of the reliability of the average data obtained and the difference between them, the correlation coefficients were assessed by the Student criterion. Indicators were considered reliable at $p < 0.005$ and $p < 0.001$.

## RESULTS AND THEIR DISCUSSION

On admission, the general purulent infection prevailed in all patients, the blood glucose exceeded the norm by 2–3 times. The concentration of pro-inflammatory cytokines was: IL-1b — 399.16±16.7 pg/ml; IL-6 — 158.22±15.6 pg/ml; IL-8 — 147.12±12.8 pg/ml; FNO — 265.14±10.14 pg/ml; anti-inflammatory: IL-4 — 88.8±6.72 pg/ml; IL-10 — 194.6±12.2 pg/ml (N — for the listed cytokines — 0–50). In the study group, by the end of 5–7 days, the general condition normalized, the purulent process was localized within the damaged tissues, the activity of the wound microbiota was suppressed, the walls of the wounds were cleaned from necrotic plaque, islands of granulation tissue appeared, and a regenerative type of cell reaction was recorded in smears. By this time, there was a significant decrease in systemic production of IL-1b by 1.52 times ($p < 0.005$), IL-6 by 1.6 times ($p < 0.005$), IL-8 by 8.2 times ($p < 0.005$), IL-10 6.2 times ($p < 0.005$). The FNO content was significantly reduced (1.65±0.14 pg/ml, ($p < 0.005$).

By the end of 10–14 days, the clinical picture of the regeneration phase of the wound healing process prevailed in the wounds, the microbial colonization of the wound wall decreased by 3–4 orders of magnitude, and the concentration of pro- and anti-inflammatory cytokines in the blood serum, except for FNO, did not exceed the reference values.

In the comparison group, on 10–14$^{th}$ days from the start of treatment, such a significant clinical effect was not noted, the decrease in cytokine profile indicators exceeded the highest normal range from 10.2 to 23.4%. FNO of the study group amounted to 62.24±8.18 pg/ml ($p < 0.001$), in the comparison group — 88.64±9.16 pg/ml ($p < 0.005$).

## DISCUSSION

In the study group, it was much faster to eliminate the detrimental effect of the etiological factor, to optimize the components that contribute to the transition of the purulent wound process into the regeneration phase, which ultimately led to the elimination of the causes of the imbalance of some pro- and anti-inflammatory cytokines. The remaining concentration of the proinflammatory cytokine FNO in both groups of patients is a consequence of the systemic, specific immunobiological reaction characteristic of patients with diabetes mellitus [5].

## CONCLUSION

1. In the complex treatment of patients with diabetes mellitus and purulent wounds, regional antibiotic and immune therapy in combination with local wound treatment with Biointegra ointment and treatment with exogenous nitric oxide allow targeted, pathogenetically substantiated therapy of purulent wounds.
2. In the study group of patients, the quality of treatment improved, which ultimately led to a reduction in treatment time by an average of 5 days: in the study group, 14.6±1.2, in the comparison group — 19.8±1.8 inpatient days.

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# THE USE OF OXYGENATED WATER AND LYMPHATIC THERAPY IN THE TREATMENT OF POST-INJECTION PURULENT COMPLICATIONS IN DRUG ADDICTS

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**ABSTRACT** — We compared the results of treatment and multifunctional examination of 78 patients (study group) with parenteral drug addiction and post-injection purulent lesions of the soft tissues and vessels of the lower limbs. In the study group (47), we used oxygenated drugs (OxyEnergya) and indirect lymphotropic administration of drugs. Systemic oxidative therapy was carried out by oral administration of OxyEnergya 15ml twice a day. In the comparison group (31), patients received conventional treatment. In the study group, the proposed complex treatment algorithm provides a relatively earlier (3–7 days) onset of the clinical effect of treatment.

**KEYWORDS** — drug addiction, phlegmon, phlebitis, oxygenated water, lymphatic therapy.

## INTRODUCTION

In recent years, the contingent of patients with parenteral drug addiction has changed, which is associated with the intravenous administration of synthetic drug substitutes [1]. After short-term or 1-2-fold intravenous drug administration, postinjection phlebitis develops, which is often combined with paravasal purulent-inflammatory infiltrates or phlegmon [2]. In most cases, purulent foci are localized in a functionally dangerous zone — the ileo-inguinal region and are characterized by extensive lesions and a tendency to spread along the great vessels [].Local post-injection complications are often accompanied by the development of gross changes in the homeostasis system. The success of treatment will be determined by the effectiveness of the antimicrobial and local treatment of purulent wounds, elimination of dysfunction of regulatory and effector systems organs [3].

The aim of the study is to prove the appropriateness of using oxygenated water and indirect lymphotropic combined drug therapy in the treatment of modern drug addicts with post-injection purulent-inflammatory complications.

## MATERIALS AND METHODS

In 2017–2019, 78 patients were treated with parenteral drug addiction with purulent-inflammatory post-injection lesions of the soft tissues and veins of the upper third of the right (55) and left (23) thighs. There were 49 men and 29women, aged 18 to 44 years, who injected surrogates of synthetic drugs (analogue of amphetamine) into the veins of the inguinal region. To determine the nature of post-injection complications, ultrasound of soft tissues and ultrasound Doppler scanning of the main veins of the lower limbs were performed. To improve the blood rheological properties and regional blood flow, low molecular weight dextrans (rheopolyglucin, reftan) were introduced. Purulent foci were opened under intravenous anesthesia. The lower limb was-dressed in Bellersplints.

In the study group (35), we carried out indirect lymphotropic administration of drugs. Inthe first interdigital space of the foot, ceftriaxone 1.0 diluted in 4 ml of a 2% lidocaine solution + 32 edlidase was injected strictly subcutaneously with the needle pointing to the dorsum of the foot, and after 5 minutes, 50 mg of imunofan diluted in 5ml of isotonic solution of sodium chloride; fraxiparine in a dose of 0.6 ml was injected more proximally. This manipulation was carried out 1 time per day with 48 hour intervals. Management of purulent wounds with oxygenated medicinal compositions (*extempore*: Levomekol ointment was mixed in 1:1 combination with OxyEnergya). Systemic oxidative therapy was carried out by oral administration of OxyEnergya by15 ml twice a day. OxyEnergya is a highly purified water enriched with oxygen molecules in an amount of 250,000 ppm/l. OxyEnergya was given in the morning and evening *peros* in a volume of 30 ml.

In the comparison group (33), persons comparable by gender and age, had similar drugs administered by the traditional, intramuscular method, and their wounds were treated by dressings with Levomekol ointment.

The treatment results were evaluated clinically, by studying biochemical and laboratory blood parameters, bacteriological monitoring, including determination of microbial colonization of the wound wall, studying the cytokines profile, cytograms of wound contact preparation, pH measurement of wound

exudate.The studies were performed upon admission of patiens, then on the 3–5th, 7–9th and 11–13th days from the start of treatment.The data obtained were subjected to statistical processing by the STATISTICA 6.0 application software package. Indicatorswere considered reliable at $p < 0.05$ and $p < 0.01$.

## RESULTS, DISCUSSION

In 61 (78.2%) patients, phlebitis was accompanied by the formation of paravasalphlegmon, in 17 (21.8%) — femoral soft tissue infiltration. Inflammation was characterized by severe clinical course, hyperthermia (up to 39° C), leukocytosis (from 12.7 to $21.8 \cdot 10^9$/L), blood LII up to 5.6. The presence of abscess was confirmed by ultrasound examination. Ultrasound scanning of the veins revealed parietal inflammation without valve insufficiency of the veins of the lower extremity. Ultrasound scanning of the veins revealed parietal inflammation without valve insufficiency of the veins of the lower limbs. At inoculation for flora, a mixt infection was detected: Staphylococcus aureus in combination with gram-negative flora. In the first group of patients, the general condition normalized at the 5–7th day, the purulent process was localized within the damaged tissues. By the end of 7–9 days from the start of treatment, the cytological picture prevailed in the wound contact preparations, corresponding to the transition of the wound process to the phase of regeneration. By this period of treatment, the imbalance between pro- and anti-inflammatory cytokines was eliminated. On days 11–13, 17 patients had early secondary sutures; 5 had edges of their wound reduced with adhesive bandage strips. 13 patients had wound hiatus longer than 20 cm and it was closed in stages, starting from its corners (1–2 sutures) and so on for 3–5 days until the complete elimination of a wound defect. By the end of treatment,indicators of laboratory and biochemical blood tests were approaching the upper limit; LII was 1.8±0.2 ($p < 0.01$).The average hospital stay was 17.8±2.2 inpatient days.In the comparison group, the research results were significantly different, and the duration of treatment exceeded the one of the first group by 5–8 days.

In the study group, of the use of OxyEnergya and saturation of powerful collector of the inguinal lymphatic system with the antibiotic and immunomodulator contributes to a more rapid relief of local and general symptoms of purulent inflammation. Lymphatic therapy in combination with wound dressings saturated with oxygenated drug compositions allows targeted delivery of drugs to the lesion site[3, 4].

As a result, the terms of normalization of the general conditionand of elimination of homeostasis disorders are reduced by 1.5–2 times, the symptoms of thrombophlebitis are more quickly relieved, the purulent process is localized within the damaged tissues, and wound microbial flora activity is suppressed [5]. As a result, the conditions are optimized for the passage of the purulent wound process into the regeneration phase, and the inpatient treatment time is reduced by 5.2 ± 1.4 inpatient days.

## CONCLUSIONS

1. Post-injection purulent complications caused by synthetic surrogate drugs In modern patients with parenteral drug addiction are characterized by extensive damage of soft tissue. It proceeds according to the hyperergic type of inflammatory reaction with the development of an imbalance of pro- and anti-inflammatory cytokines.
2. Local and general use of OxyEnergya in combination with indirect lymphatic therapy improves the quality of care for this group of patients, and reduces the duration of inpatient treatment by an average of 5–7 days.

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# 5-YEAR EXPERIENCE OF MINIMALLY INVASIVE TREATMENT OF BAKER CYSTS IN CHILDREN IN CONDITIONS OF OUTPATIENT SURGERY CENTER

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**ABSTRACT** — The article deals with a method of treatment of Baker cysts in children by evacuation of cysts content followed by an orthopedic treatment, which has been carried out over 5 years in conditions of an outpatient surgery center.

**KEYWORDS** — Baker cysts in children, drainage, outpatient surgery center.

## INTRODUCTION

In modern surgical practice, the relevance of approaches and tactics for treatment of cyst Bakers have not yet been identified and do not have a unique protocol.

There are various methods of conservative and operational treatment of this pathology, starting from compresses with medicinal herbs, ending with a complete simultaneous excision of the cyst cavity.

## MATERIAL AND METHODS

360 children with Baker cysts aged 3 to 12 years underwent observation in our orthopedic center over the past 5 years. To each patient an ultrasound examination was assigned, education level identified as well as differential diagnostics with phlebectasis of the popliteal region was conducted. If the cyst is tense on palpation, its volume exceeds 10 $cm^3$ or an obvious cosmetic defect patients were offered a drainage treatment aiming at evacuating the contents of the cyst through a Brown catheter with subsequent washing of the cavity with 2% novocaine solution and application back plaster casts with a stiffener for a period of 14 days with restrictive home regimen and subsequent wearing of the knee orthosis for a period of 1 month.

If after an ultrasound examination the cyst volume does not exceed 10 $cm^3$, patients were prescribed a follow-up examination after 3 months with a control ultrasound checkup. In the event of a decrease in cyst volume, the patient remained under dynamic observation every 3 months, if the volume increased, we puncture treatment was performed according to the method described above.

Among 360 patients, puncture was performed in 76 children with a sex ratio: 67% boys, 33% girls.

After 3 months, increase in the cyst cavity was observed in 17 children.

Relapse in the near term — 5–7 weeks after a puncture in 3 patients (due to violation of the restrictive regime). Relapse in remote periods — 2–3 months after the puncture (resumption of active sports activities such as gymnastics, football, tennis) 5 children. Accordingly, to puncture treatment this algorithm of actions was employed only in 25.83% of cases.

## CONCLUSIONS

The obtained results, in our opinion, determine this technique as a priority, enabling to avoid the operative intervention and the introduction of cytostatics in the paraarticular region.

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# OFF-PUMP CORONARY ARTERY BYPASS GRAFTING IN PATIENTS WITH OBESITY: COMBINED ANESTHESIA VERSUS TOTAL INTRAVENOUS ANESTHESIA

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**ABSTRACT** — Many researchers attribute obesity to an independent risk factor for perioperative complications of off-pump coronary artery bypass grafting (off-pump CABG).
AIM. To conduct a comparative analysis of the early postoperative complications of off-pump CABG in obesity patients with with various types of anesthetic benefits.
MATERIALS AND METHODS. A randomized study of the results of surgical treatment was carried out in obesity patients with coronary heart disease performing pump CABG.
The study included 197 patients. The study group (n = 98) included patients who underwent combined anesthesia (with thoracic epidural analgesia (TEA)), and patients in the control group (n = 99) underwent total intravenous anesthesia (with opioids).
RESULTS. The use of combined anesthesia (with TEA) in patients with obesity significantly reduced the risk of developing new onset of renal dysfunction (p = 0.0180), respiratory complications (p = 0.0177), atrial and ventricular arrhythmias (p = 0.0029). We were less likely to diagnose other complications in patients of the study group, compared with patients in the control group: acute coronary syndrome (1.0% versus 3.0%, p = 0.3173), multiple organ failure syndrome (1.0% versus 3.0%, p = 0.3173), local infectious complications (1.0% versus 6.1%, p = 0.0561). An uncomplicated early postoperative period was observed in 89.8% of patients in the study group and in 52.5% of patients in the control group (p = 0.0000).
CONCLUSION. The use of combined anesthesia (with TEA) for off-pump CABG in patients with obesity reduces the risk of early postoperative complications, duration of hospitalization and stay in an intensive care unit.

**KEYWORDS** — off-pump coronary artery bypass grafting, prevention of complication, obesity, thoracic epidural analgesia.

## INTRODUCTION

Despite significant progress in the development of cardiac surgery associated with the advent of high-tech equipment and modern supplies, to date, coronary artery bypass grafting (CABG) is one of the most commonly used surgical methods for the treatment of patients with coronary heart disease (IHD) [1, 2, 3].

But this surgical intervention in obese patients is associated with certain difficulties in surgical access, which often increases the time and trauma of the operation [4, 5]. Some researchers attribute obesity to an independent risk factor for the development of perioperative complications of CABG due to unfavorable hormonal levels, metabolic disorders of glucose, lipids and purines, and changes in the hemostatic system [4, 5].

For a long time, studies are ongoing to reduce injuries of myocardial revascularization in patients of this category. It was possible to expand indications for CABG operations on a working heart (off-pump CABG), which would eliminate the risks associated with cardiopulmonary bypass [6, 7]. But this tactic does not always bring the desired result in patients with obesity due to the often low contractile function of the left ventricle and multivascular damage to the coronary arteries [7]. In this regard, the search for new approaches to reducing the risk of complications after an off-pump CABG in patients of this category has not lost its relevance [8, 9, 10, 11].

In this regard, the aim of this study was a comparative analysis of the incidence of postoperative complications of off-pump CABG in patients with obesity with different types of anesthetic benefits.

## MATERIALS AND METHODS

We conducted a randomized controlled trial of the results of surgical treatment of coronary heart disease in 200 patients with obesity who underwent coronary artery bypass grafting without cardiopulmonary bypass (off-pump CABG), from January 2015 to December 2019 at the bases of the Department of Anesthesiology and Resuscitation of Volgograd State Medical University. The type of anesthesiological aid was determined with a randomizing sign: combined (general anesthesia combined with thoracic epidural analgesia (TEA)) or total intravenous anesthesia. Randomization was carried out by the method of computer random sequence of numbers. Inclusion criterion: patients with obesity who underwent off-pump CABG. Exclusion criteria: performed on-pump CABG or there were absolute contraindications for TEA. Three patients were excluded from the study who underwent

on-pump CABG due to clinical need. As a result, the study included the results of treatment of 197 patients.

The study was approved by the Volgograd Regional Independent Ethics Committee (IRB 00005839 IORG 0004900 [ref: 118/2014/12/05]). All patients received voluntary written informed consent to participate in the study and publish the results.

For the diagnosis of obesity, a body mass index (BMI) of ≥30 kg/m$^2$ was used. All subjects are divided into two groups. In the study group patients (n = 98), combined anesthesia was used as an anesthetic aid: intravenous infusion of a propofol solution of 3–4 mg/kg × hour, in combination with high thoracic epidural analgesia, which provided sensory block at the level Th I-X vertebrae. Epidural continuous infusion of solutions ropivacaine 0.3–0.5% — 6–7 ml/h with fentanyl 0.004–0.006 mg/ml was carried out. Puncture and catheterization of the epidural space was carried out 1 day before the operation. In patients of the control group (n = 99), total intravenous anesthesia was used: intravenous infusion of propofol 3–4 mg/kg × hour in combination with continuous infusion of fentanyl solution 0.006–0.008 mg/kg × hour. Induction of anesthesia was carried out by bolus intravenous injection of a solution of propofol (2 mg/kg), muscle relaxation was provided by depolarizing (solution of suxometonium chloride 1–1.5 mg/kg) and non-depolarizing (solution of pipecuronium bromide 0.04–0.06 mg/kg) muscle relaxants. Solution of fentanyl (0.004–0.006 mg/kg) was additionally bolus injected into the most traumatic stages of the operation (sternotomy, thoracotomy, cardiac enucleation).

In the early postoperative period, epidural analgesia continued for 72 hours in patients of the study group, and narcotic analgesics were used in patients of the control group. In all studied patients, postoperative analgesia was supplemented with the use of non-steroidal anti-inflammatory drugs (lornoxicam 8 mg × 2 times a day or ketorolac 30 mg × 3 times a day). In the postoperative period, the diagnosis of acute coronary syndrome (ACS) took into account patient complaints, the appearance or expansion of zones of hypokinesis (according to echocardiography), an increase in ischemic changes on the electrocardiography, an increase in markers of myocardial necrosis (creatine phosphokinase-MB, troponin-T). The syndrome of multiple organ failure was established with failure in three or more body systems. New onset renal dysfunction was established with an increase in blood plasma creatinitis by 2 mg/dl or more. Atrial and ventricular arrhythmias were considered if they lasted 24 hours or more. Respiratory complications were recorded when confirmed by X-ray data.

As shown in Table 1, according to demographic and operational data, the comparison groups were comparable (by sex and age, duration of surgery and the number of shunts imposed, patients' comorbid state ($p > 0.05$)).

All findings were processed by means of variation statistics methods using the STATISTICA 10.0 software. The statistical processing was performed using the Mann-Whitney U-test and $\chi^2$ Pearson. The difference was considered significant at the significance level of more than 95% ($p < 0.05$).

## RESULTS AND DISCUSSION

Patients in the control group required longer invasive respiratory support than patients in the study group (5.3 ± 0.8 vs 3.6 ± 0.9 hours ($p = 0.0274$)). In the study group there were significantly more patients who did not need invasive respiratory support (8.2% vs 1.0% in the control group ($p = 0.0162$)) and significantly fewer patients with invasive respiratory support lasting more than 6 hours (14.3% versus 28.3% in the control group ($p = 0.0165$)). In the early postoperative period, patients of the control group had a shorter duration of adrenergic agonist therapy (AAT), but this decrease was not significant ($p = 0.5715$).

Researchers compared other postoperative parameters of the study groups (Table 1). It was found that the use of combined anesthesia (with TEA) in obese patients significantly reduced the risk of developing new onset renal dysfunction ($p = 0.0180$), respiratory complications ($p = 0.0177$), atrial and ventricular arrhythmias ($p = 0.0029$). In patients with the study group, there was one case of the development of ventilator-associated pneumonia, and in the control group this complication was recorded in eight patients. We were less likely to diagnose other complications in patients of the study group, compared with patients in the control group: acute coronary syndrome (1.0% vs 3.0%, $p = 0.3173$), multiple organ failure syndrome (1.0% versus 3.0%, $p = 0.3173$), local infectious complications (1.0% vs 6.1%, $p = 0.0561$). An uncomplicated early postoperative period was observed in 89.8% of patients in the study group and in 52.5% of patients in the control group ($p = 0.0000$).

The use of combined anesthesia reduced the median time from surgery to discharge from the hospital by 51.7 h. In the study group, as compared to the control group (215.8 h in control and 164.1 in study group $p = 0.0419$). The treatment time in the intensive care unit also significantly decreased (65.6 h in control and 44.2 h in study group ($p = 0.0229$)).

Hospital mortality in the study group and in the control group was 1.0% (1/98) and 2.0% (2/99),

***Table 1.*** *Comparison of patient demographics and various operative and postoperative parameters*

| Study parameters | Study group (n = 98) | Control group (n = 99) | P |
|---|---|---|---|
| Demographic profile: | | | |
| Male , n (%) | 54 (55,1) | 56 (56,6) | 0,8361 |
| Age (mean±SD) | 62,1±8,3 | 61,8±9,1 | 0,4931 |
| ≤ 65 лет, n (%) | 52 (53,1) | 58 (58,6) | 0,4350 |
| > 65 лет, n (%) | 46 (46,9) | 41 (41,4) | |
| BMI (mean±SD) | 34,1±3,3 | 35,8±3,1 | 0,3718 |
| Hypertension, n (%) | 58 (59,2) | 61 (61,6) | 0.7271 |
| DM, n (%) | 44 (44,9) | 50 (50,5) | 0,4308 |
| COPD, n (%) | 14 (14,3) | 12 (12,1) | 0,6536 |
| Renal dysfunction, n (%) | 8 (8,2) | 6 (6,1) | 0,5658 |
| CCI, n (%) | 27 (27,6) | 32 (32,3) | 0,4647 |
| Operative parameters: | | | |
| Operation duration (mean±SD) | 259,3±72,4 | 254,6±68,3 | 0,7185 |
| Bypass 1, n (%) | 8 (8,2) | 11 (11,1) | 0,4834 |
| Bypass 2, n (%) | 69 (70,4) | 65 (65,7) | 0,4746 |
| Bypass 3, n (%) | 21 (21,4) | 23 (23,2) | 0.7612 |
| Postoperative parameters: | | | |
| Extubation, h, (mean±SD) | 3,6±0,9 | 5,3±0,8 | 0,0274* |
| No ventilation, n (%) | 8 (8,2) | 1 (1,0) | 0,0162* |
| Up to 3 hours, n (%) | 18(18,4) | 6(6,1) | 0,0083* |
| 3-6 hours, n (%) | 58(59,2) | 64 (64,6) | 0,4298 |
| More than 6 hours, n (%) | 14(14,3) | 28(28,3) | 0,0165* |
| AAT, h, (mean±SD) | 13,3±7,6 | 12,7±6,7 | 0,5715 |
| No therapy, n (%) | 12 (12,2) | 10(10,1) | 0,6329 |
| Up to 6 hours, n (%) | 26 (26,5) | 28 (28,3) | 0,7828 |
| 6-12 hours, n (%) | 32 (32,7) | 37 (37,4) | 0,4874 |
| More than 12 hours, n (%) | 28 (28,6) | 24 (24,2) | 0,4907 |
| New onset renal dysfunction, n (%) | 2 (2,0) | 10 (10,1) | 0,0180* |
| ACS, n (%) | 1 (1,0) | 3 (3,0) | 0,3173 |
| Respiratory complications, n (%) | 1 (1,0) | 8 (8,1) | 0,0177* |
| Atrial and ventricular arrhythmias, n (%) | 4 (4,1) | 17 (17,2) | 0,0029* |
| Multiple organ failure syndrome, n (%) | 1 (1,0) | 3 (3,0) | 0,3173 |
| Local infectious complications, n (%) | 1 (1,0) | 6 (6,1) | 0,0561 |
| ICU stay, h (mean±SD) | 44,2±6,4 | 65,6±7,3 | 0,0229* |
| Hospital stay, h (mean±SD) | 164,1±31,3 | 215,8±37,1 | 0,0419* |
| Mortality, n (%) | 1 (1,0) | 2 (2,0) | 0,5667 |

***Note:*** ** P<0.05, statistically significant; ICU — Intensive Care Unit; BMI — Body mass index; DM — Diabetes mellitus; COPD — Chronic obstructive pulmonary disease; CCI — Chronic cerebral ischemia; AAT — Adrenergic agonist therapy; ACS — Acute coronary syndrome; SD — Standard deviation.*

respectively. The cause of death was multiple organ failure syndrome in 100% of cases.

Patients in the control group had higher intraoperative consumption of narcotic analgesics and intravenous anesthetics (by 36.7% and 29.6%, respectively). This affected the lengthening of the required time for invasive respiratory support, which was accompanied by an increase in the incidence of ventilator-associated pneumonia in the early postoperative period.

The decrease in the incidence of postoperative complications associated with the use of TEA can be explained by a more effective decrease in the severity of the operational stress response and endothelial dysfunction, improved perfusion of the operative zone

and the prokinetic effects of TEA, and an increase in the quality of postoperative analgesia. A significant decrease in the incidence of respiratory complications, atrial and ventricular arrhythmias in patients of the study group is probably due to a decrease in the duration of invasive respiratory support (due to a decrease in the dose of narcotic analgesics) and sympathetic blockade accompanying TEA.

Due to the small sample size of this study, in some cases there were no statistically significant differences in patients in the incidence of the most common complications of CABG. In this regard, for inclusion in the wide clinical practice of the proposed method, confirmation of the results by large randomized trials is required.

## CONCLUSION

The use of combined anesthesia (with TEA) for off-pump CABG in patients with obesity reduces the risk of early postoperative complications, the duration of hospitalization and the duration of treatment in the intensive care unit.

## CONFLICT OF INTERESTS.

The authors state that they have no conflict of interests.

*Contributors*

MIT and AMS collected, analysed, and interpreted data and made the figures. ASP did the literature review and collected data. AVE and YuIV collected data and made the figures. MIT and SMS interpreted and analysed the data. MIT, ASP, AVE, SMS, YuIV and AMS prepared the manuscript for submission.

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# THE ROLE OF ACUTE PHASE PROTEINS IN ASSESSING THE SEVERITY OF THE CONDITION IN PATIENTS WITH PERFORATED GASTRODUODENAL ULCERS

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**ABSTRACT** — Perforated gastroduodenal ulcers are a serious disease of adults and children requiring emergency surgical care. In this article we consider the role of acute phase proteins in assessing the severity of the condition in patients (adults and children) with perforated gastroduodenal ulcers.

**KEYWORDS** — gastroduodenal ulcers, children, adults, acute phase proteins, perforated ulcer, C-reactive protein, alpha 2-macroglobulin, pregnancy-associated alpha2-glycoprotein.

## INTRODUCTION

In clinical medicine there are problems that remain relevant, despite the achievements of med-ical science and practice.

The urgency of the problem of treatment of perforated gastroduodenal ulcers is due to the high incidence of peptic ulcer disease, frequent complications by perforation of ulcers and a variety of therapeutic and tactical settings [4, 6, 7]. Despite the achievements of pharmacotherapy of peptic ulcer disease, there is little reason to hope for a significant reduction in the number of patients with perforation of ulcers. This is explained, first of all, by the fact that in a significant number of patients with peptic ulcer perforation of the ulcer occurs against the background of asymptomatic course of the disease or when the clinical picture is erased. Among young people and adolescents, this number reaches 50% [4, 5, 7]. Such patients, of course, do not receive preventive treatment. In addition, in some patients with gastroduodenal ulcers, conservative treatment is in-effective and when the courses of drug therapy are interrupted, they develop complications of peptic ulcer disease, including perforation of the ulcer [3, 4]. In some patients, prophylactic treatment courses is difficult due to social reasons. Thus, it can be assumed that surgical treat-ment of perforated ulcers in the near future will occupy a significant place in emergency surgery of the abdominal cavity [1, 3, 5, 7]. It is known that the occurrence of any acute inflammatory process is accompanied by an acute-phase response of the body. Acute phase response is a com-plex of local and systemic reactions mediated by various mediators-cytokines, prostaglandins, kinins, hormones. The amplitude and nature of the response depend on the activity of the process [2, 3, 4, 5, 7]. It is proved that the acute phase response is accompanied by an increase in the content of certain groups of blood proteins (acute phase proteins — APPs), the concentration of which changes in response to inflammation, trauma and other pathological effects [2, 4, 7].

### *Aim*

Determination of diagnostic significance of minor proteins (C-reactive protein — CRP, alpha2-macroglobulin α2M, pregnancy-associated alpha2-glycoprotein α2-PAG) in perforated gastro-duodenal ulcers.

## MATERIALS AND METHODS

79 patients (adults and children) with perforated gastroduodenal ulcers were delivered to the surgical Department of *N.N. Silitscheva Regional Pediatric Clinical Hospital* and *S.M. Kirov Municipal clinical hospital № 3* in Astrakhan. Among them, 16 of the patients (20,4%) were admitted up to 24 hours from the onset of the disease, whereas 63 (79,6%) of patients were ad-mitted later than 24 hours. Late admission to the hospital in most cases was explained by the de-lay in patients seeking medical care. More often they were elderly people with atypical clinical picture of ulcer perforation, as well as young people and adolescents with a tendency to subside pain due to covered perforation. 83% of patients with gastroduodenal perforations were 16 to 60 years old. The ratio of males to females is 1:10. Perforations of acute ulcers without a history were noted in 19% of cases. 79 patients with perforated gastroduodenal ulcers aged 16 to 74 years who were on treatment were examined.

The dynamics of the disease was evaluated on the basis of clinical symptoms and objective indicators

of endogenous intoxication. The complex of clinical studies included: General analysis of blood and urine biochemical analyses (residual nitrogen and urea of blood, aminotransferases, creatinine, alkaline phosphatase, amylase of blood and urine, water-electrolyte composition), determined by standard methods.

Concentrations of C-reactive protein (CRP), alpha2-macroglobulin (α2M), pregnancy-related alpha2-glycoprotein (α2-PAG) were studied in the blood serum of patients on admission, immediately on the day of surgery and again 3–5 days after surgery, before discharge, by immuno-diffusion analysis (mg/l). The average donor indicators were determined in 82 healthy individuals aged 16 to 70 years. The obtained results were processed with the help of statistical analysis package Statistica 6, SPSS V 10.0.5, programs "STATLAND", "EXCEL-97", "Basic Statistical" taking into account standard methods of variational statistics, including calculation of the Student's t-criterion to assess the reliability of differences. The data are presented as M±m, signifi-cant differences were discussed at t≤ 0,001.

## RESULTS AND DISCUSSIONS

In the serum of patients with perforated gastroduodenal ulcers before treatment, an increase in the level of CRP up to 120 mg/l was noted in 73%, α2-PAG-up to 160.3 mg/l in 56,%, α2M — up to 1280 mg/l in 56,% of patients. At the end of treatment (including surgery), a decrease in the level of these three proteins is recorded. Table 1 clearly shows the difference in the content of α2-PAG, CRP, α2M in serum before treatment and after.

Thus, minor proteins can serve as biomarkers of the intensity of the inflammatory process in a number of pathological conditions. Their determination in patients in critical condition is not only of clinical and diagnostic importance, but also allows to assess the severity of the condition of patients, the adequacy and effectiveness of therapy, as well as timely predict the likelihood of complications.

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***Table 1.*** *Detection and concentration frequency (M±m) CRP, α2-PAG, α2M, in blood serum of donors and patients with perforated ulcer on receipt and discharge*

| Reactant protein (identification method) | PU n=42 | | donors n=80 |
|---|---|---|---|
| | before | after | |
| CRP (IDA) | 73,41% | 76,34% | 3,33% |
| Serum, mg / l | 120±14,5* | 20,1±9,4* | 0,7±0,4 |
| α2-PAG , (IDA) | 56,34% | 48,04%* | 7,77% |
| Serum, mg / l | 160,3±10,5 | 40,0±6,67 | 3,5±1,09 |
| α2M, (IDA) | 100% | 100% | 100% |
| Serum, mg / l | 1280±166 | 320±52 | 1033±267 |

***Note:*** ** — reliability of differences between groups of patients with control (donors).*

Thus, the concentration of CRP is reduced by 6, α2-PAG by 4, α2M by 3 times. The concentration of the studied proteins in serum correlates with their concentration in exudate (Table 2).

***Table 2.*** *Detection frequency and concentration of CRP, α2-PAG, α2M exudate of patients with perforated ulcer on receipt and discharge*

| APPs(IDA) | n=42 | |
|---|---|---|
| | before | after |
| CRP: frequency of detection. ( %) | 54,05% | 45,94% |
| concentration, mg / l | 160±26,6* | 40±19,7* |
| α2-PAG: frequency of detection. ( %) | 44,5% | 38,3% |
| concentration, mg / l | 160±16,6* | 60±19,7* |
| α2M: frequency of detection. ( %) | 100% | 100% |
| concentration, mg / l | 160±18* | 40,2±12 |

***Note:*** ** — P — reliability of differences before and after treatment.*

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# THE BACTERIOPHAGES IN THE TREATMENT OF PERITONITIS OF APPENDICULAR ORIGIN

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**ABSTRACT** — Due to development of laparoscopic techniques for the surgical treatment of acute appendicitis, the problem of the occurrence of early postoperative complications has not changed at present, which makes it necessary to carry out preventive measures. In the present study, one of the most frequent complications of acute appendicitis, peritonitis, has been modeled on the example of a biological model, with the aim of developing a method of preventive measures. The group of authors considered antibiotic prophylaxis, as well as an alternative method of preventive perioperative bacteriophage therapy. The evaluations method was based on the study of the clinical picture of the course of peritonitis in experimental animals, the pathomorphological and histological examination of the sectional peritoneum. As the result of the study, the authors did not reveal a significant difference in the methods of perioperative prophylaxis of complications of acute appendicitis, which makes possible to conduct monotherapy with bacteriophages, which is a promising direction in the face of ever increasing antibiotic resistance to antibacterial chemotherapy drugs.

**KEYWORDS** — acute appendicitis, peritonitis, bacteriophages, perioperative bacteriophage therapy.

Among acute surgical diseases of the abdominal organs, acute appendicitis is one of the most common. The incidence of acute appendicitis is approximately equal in all countries of the world and rates between 4 and 5 cases per 1000 people per year. The patients mortality with acute appendicitis according to different authors, varies from 0.14% to 0.5%, while for older people it reaches 4.6%, exceeding the average statistics in 10 times [1]. The number of early infectious complications after appendectomy, according to various sources, rates from 4 to 20% and practically did not decrease due to the use of laparoscopic surgical equipment. The problem of postoperative appendectomy complications remains relevant and require the search for ways to prevent these complications [2, 3, 4]. One of preventions type is bacteriophage therapy. According to some authors, bacteriophages have great potential in the fight against pathogenic microorganisms [5, 6, 7].

*The purpose of the study* was to study the possibility of improving the surgical treatment results of peritonitis, the most common complication of acute appendicitis, by reducing the number of postoperative complications of infectious genesis.

The problem was solved in the experiment by comparative assessment of the conservative fragment results of simulated peritonitis treatment using antibiotic therapy and combination therapy with bacteriophages.

## MATERIALS AND METHODS

Studies were performed on 47 non-linear white rats weighing 200–250 g.

To simulate peritonitis was used infection of the abdominal cavity the museum strain of E. Coli 25922.

The immunodeficiency state of experimental animals was caused by limiting calorie intake for 5 days. The rats abdominal hair was shaved and the surface of the stomach was extracted with a 70% alcohol solution. Then the abdominal wall was pierced perpendicularly at the base of the skin fold, then the needle was passed along the fold and the suspension of the E. coli museum strain was injected with 10 billion microns. bodies per 100 g of rat mass in two ml of physiological saline.

The studied laboratory animals were divided into three groups. The first group (control) contains 3 animals. Rats received no treatment.

The second group contains 20 animals. Rats received treatment in the form of a single intraperitoneal administration of Cefipim at the rate of 100 milligrams per kg body mass in two ml of physiological saline.

The third group contains 20 animals. Rats received treatment in the form of a single intraperitoneal injection of 2.5 ml of Sextophagus.

The animals were removed from the experiment on days 3, 7 and 14 by overdosing an anesthetic drug (in accordance with the principles of humane treatment of laboratory animals).

Evaluation of the results was carried out according to the clinical picture, the state of the abdominal cavity and the macroscopic and histological (with hematoxylin and eosin staining) examination of the preparations of the intestine and parietal peritoneum.

## RESULTS

On the first day of the experiment, there was no significant change in the clinical picture in animals.

There was observed lethargy, appetite was not modified.

On the second day of the experiment, 38 animals began to manifest a general clinical picture of peritonitis: hypodynamism, lethargy, animals tried not to leave the corners of the cell, ruffled hair, rapid breathing, and loose stools were noted. There was a sharp decrease in appetite.

By the third day, a similar clinical picture developed in 45 animals. Two animals showed no signs of an inflammatory reaction of the body. On the third day, two animals were withdrawn from experiments with sampling material. At autopsy, one to three ml of fibrinous-purulent peritoneal exudate was found in the abdominal cavity of rats. The inside of the abdominal wall was reddened, dull with fibrin overlay. Separate small focal hemorrhages were noted on the intestinal mesentery. The loops of the intestines were swollen, in some places, the intestine looked edematous, and the vascular pattern of the intestinal wall seemed strengthened. Histological examination of the sectional material revealed focal and diffuse accumulations of neutrophilic leukocytes between the muscle fibers of the intestinal wall with signs of necrosis, pronounced venous congestion, stromal edema, and perivascular leukocyte infiltration. On the fifth day, three rats from the control group died; in the section, they showed signs of diffuse purulent peritonitis with single perforations of the intestinal loops. On the seventh day, half (10) rats from the second and third groups were removed from the experiment.

In rats of the second group, there was a slight swelling of the intestinal walls, injection of the mesenteric vessels. Histologically, a pronounced neutrophilic infiltration and a moderate macrophage reaction were detected in the walls. The edema of the stroma of the walls and their venous plethora remained.

The third group rats, a similar picture was observed. Histologically determined diffuse leukocyte infiltration of the intestinal walls with a large number of macrophages.

During comparing the results of treatment of experimental peritonitis in rats of the second group (sanitation with an antibiotic solution) and the third group (sanitation with a bacteriophage) on the seventh day, no significant morphological changes in the intestinal walls were detected. At the same time, the impression was made that in the last group the recovery processes in the gut were more actively.

On the fourteenth day, the remaining animals were withdrawn from the experiment.

In rats of the second group, the state of the abdominal cavity for this observation period was close to normal; in half of the cases, a moderate adhesion process was noted. Histological examination showed signs of residual inflammation, noticeable venous congestion, moderate infiltration of the intestinal walls with neutrophilic leukocytes, and a large number of macrophages.

The third group rats, macroscopic signs of peritonitis were also stopped, small adhesions of the peritoneum were noted. Histologically, an insignificant neutrophilic reaction with a small number of macrophages remained in the intestinal wall. The structure of the peritoneal cover was close to normal.

Finaly treated rats with the antibiotic, by the end of the observation period, residual signs of inflammation of the intestinal wall remained, and in rats treated with the bacteriophage had of the peritoneum structure of the intestine was closer to normal.

## CONCLUSIONS

Thus, our experimental studies have revealed quite satisfactory results of monotherapy by bacteriophage for experimental peritonitis. Phages in comparison with antibiotics have no less therapeutic efficacy. According to morphological data, the inflammatory process in the abdominal cavity stopped through phages rather quickly and at the same time there is a tendency to scale back the inflammation more quickly than with antibiotic treatment.

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# ASPECTS OF THE ETIOLOGY OF EXTRAORGANIC RETROPERITONEAL CYSTS

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**ABSTRACT** — Etiology of primary extraorganic retroperitoneal cysts is most often a disorder of embryonic development. The most common causes of secondary cysts are trauma and surgical interventions in the past. We analyzed 28 case histories of patients with extraorganic retroperitoneal cysts. After surgical removal 13 cysts turned out to be primary, other 15 — secondary cystic formations. Malignant condition was found in 2 primary cysts. We came to the conclusion that primary extraorganic retroperitoneal cysts develop due to impaired embryonic development and can be divided into enteric, bronchogenic, urogenital, dermoid, mesothelial and lymphatic cysts. The etiology of secondary cysts is determined by the presence of a history of abdomen or back trauma, as well as the surgery that was performed in the past by laparotomy or retroperitoneal access.

**KEYWORDS** — extraorganic retroperitoneal cyst, primary and secondary cyst, embryonic development, trauma, surgery.

## INTRODUCTION

The question of the occurrence of extraorganic retroperitoneal cysts (EORC), despite the increase in their incidence in recent decades, is poorly understood and is addressed only by single researchers, who describe mainly single observations of this pathology [1, 2, 3, 4, 5]. The lack of a unified classification of the EORC lies at the heart of a methodological problem that leaves a number of issues unresolved.

Etiology of primary cysts is most often a disorder of embryonic development [6]. The most common causes of secondary EORC are trauma noted by patients at different times of life, or any manipulations during surgical interventions on the organs of the abdominal cavity and (or) retroperitoneal space [7, 8]. Sometimes the cause can be an inflammatory disease of the retroperitoneal organs, such as acute pancreatitis [8, 9].

The basis of this study includes unresolved issues that determine and clarify the causes of true and false EORC.

## MATERIALS AND METHODS

We analyzed 28 case histories of patients who were treated at the Tver Regional Oncology Center from 2010 to 2017. All patients underwent surgery to remove retroperitoneal extraorganic cyst.

## RESULTS

On a histological examination of 28 preparations, 13 cysts turned out to be true (primary), the wall of which was lined with various types of epithelium: 8 — stratified squamous (dermoid cyst), 2 — single-row cubic (mesothelial cyst), 1 — multilayer ciliary prismatic (bronchogenic cyst), 1 — cylindrical epithelium intestinal type (enteric cyst), 1 — transitional (urogenital cyst). It should be noted that atypical cells are detected in the wall of two true cysts. In one case a highly differentiated intestinal adenocarcinoma was determined, in another — cancer in situ in the transitional epithelium.

15 cystic formations were recognized as false (secondary), because they did not contain epithelial lining. Their wall was represented by fibrous tissue. At a histological examination of the walls of the false EORC, atypical cells were not detected.

From the history of life it is known that the abdomen trauma was noted in 9 patients with secondary EORC (60%). 5 patients with false cysts (33%) and 1 patient with a true cyst (8%) underwent surgery in the past by laparotomic or retroperitoneal access.

## CONCLUSION

Based on the results of the study and the analysis of literature data we came to the conclusion that primary extraorganic retroperitoneal cysts develop due to impaired embryonic development and can be divided into enteric, bronchogenic, urogenital, dermoid, mesothelial and lymphatic cysts. The etiology of secondary retroperitoneal extraorganic cysts, in contrast to true cysts, is determined by the presence of a history of abdomen or back trauma, as well as the surgery that was performed in the past by laparotomy or retroperitoneal access.

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# ANALYSIS OF MICROFLORA IN MODERN OUTPATIENT CLINIC

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**ABSTRACT** — Antibiotic resistance is a global problem of modern medicine. In the research a microflora of out-patient department visitors in 2018–2019 was examined. It was revealed that the most often microbes were Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli. The dynamics of bacterial resistance to antibiotics was also analyzed. The multiple bacterial resistance to antibiotics were detected. The data show a rapid resistance genes spread among non-hospital strains, which necessitates constant monitoring of antibiotic sensitivity in order to develop the right tactics to combat antibiotic resistance.

**KEYWORDS** — antibiotics, bacterial resistance, outpatient clinic.

## INTRODUCTION

Antibiotics has opened a new era in the treatment of infectious diseases. Due to widespread of antibiotics anew infectious diseases are now emerging that could not be treated with antibacterial drugs. Microbes adapted to antibacterial drugs and developed special protective mechanisms [1]. Antibiotic resistance has been defined by the World Health Organization as a global problem that requires immediate joint action to solve it [2].

## MATERIALS AND METHODS

To study the results of microbiological examination of the materials obtained in the outpatient department of State Clinical Hospital No.7 (Tver, Russia) in order to get condition of extra-hospital bacterial resistance. 280 results of microbiological examination of pharynx, nose, eyes, wounds and ears Bodydischarge, as well as sputum and urine were processed.The bacterial resistance to antibiotics were to was also analyzed. The results of microbiological examination subjected to statistical analysis.

## RESULTS

In total 12 species of pathogens were detected. The study revealed that in case of outpatient infection, the most frequentwere Staphylococcus aureus (24.6%), Streptococcus pyogenes (16.1%), pathogenic Escherichia coli (20.0%).

The resistance of Escherichia coli strains to 3rd generation Cephalosporins was 30.9% and to 4th generation Cephalosporins 28.8%. Compared to the data of 2010–2011 there is a significant increase in the resistance of Escherichia coli to antibiotics of Cephalosporin series [3]. In comparison with the data of 2010–2011 we noted a massive increase in the resistance of Escherichia coli to Aminoglycosides from 0.3% to 56%, and to Gentamicin — 10.0% to 66.7%. If in 2010–2011 there was an absolute sensitivity to Imipenem, at present 33.3% of resistant strains have been identified. Resistance to Amoxiclav has decreased from 41.7% to 35.7% compared to 2010–2011, which may be associated with growth of antibiotic resistance [3, 4].

The most common pathogen of extra-hospital infections, Staphylococcus aureus, is characterized by low resistance to 3rd and 4th generation of Cephalosporins and to Ciprofloxacin (3.1%). However, high resistance to amikacin (65%) has been detected, and is expected to be high against Amoxicillin/Clavulanate (66.7%), due to its widespread use in the treatment of most non-hospital bacterial infections [5].

Etiologically, Klebsiella pneumoniae ranks second in prevalence among the agents of extra-hospital infections of the Enterobacteriaceae group. Strains of Klebsiella pneumoniae showed a high level of resistance to inhibitor-proof Penicillin (Amoxicillin/Clavulanate) 52.6%, 4th generation Cephalosporin (Cephepin) 30.8%, 3rd generation Cephalosporins (Cefotaxime and Ceftriaxone 19% and 21.4%, respectively). 42.9% of the selected crops were insensitive to Amikacin. Carbapeneme-resistant (Imipenem) were 20% of obtained isolates. The 3rd generation of Cephalosporin (Cephoperazone/Sulbactam) was the most active against Klebsiella pneumoniae.

Enterobacter is one of the most difficult groups for β-lactam antibiotics. Among all isolated strains of Enterobacter aerogenes 25% of Cephalosporin-resistant strains and 36.4% of cultures insensitive to Cephoperazone have been identified. Also in our study, 100% of Enterobacter aerogenes strains were found to be sensitive to imipenem. Due to the absolute activity of Imipenem and inhibitor-proof Cephalosporins, preparations of these groups can be recommended for treatment of infection caused by Enterobacter aerogenes.

Evaluation of the resistance results of Staphylococcus epidermidis showed a high level of resistance to Amoxicillin/Clavulanate (42.9%), Imipenem (57.1%),

4th generation unprotected Cephalosporins (30%), and 3rd generation (22.2% to Ceftriaxone and 25% to Cefotaxime). Absolute insensitivity to 2nd generation Fluoroquinolones (Ofloxacin and Norfloxacin) and 50% resistance to Ciprofloxacin have been detected.

In our study, 50% of Pseudomonas aeruginosa strains were found to be completely resistant to imipenem, and not a single strain showing sensitivity to Carbapeneme group antibiotics. To prevent the risks associated with the increase and spread of resistance to the antibiotics of the surveillance group, it is necessary to limit the use of Imipenem in the treatment of diseases caused by Pseudomonas aeruginosa.

## CONCLUSIONS

The spectrum of dominant species in 2018–2019 identified during the sampling of the outpatient clinic included gram-negative Escherichia coli, Klebsiella pneumoniae and gram-positive Staphylococcus aureus, Streptococcus pyogenes microorganisms, among which strains with multiple resistance to antibiotics were detected. The data indicate a rapid resistance genes spread among non-hospital strains, which necessitates constant monitoring of antibiotic sensitivity in order to develop the right tactics to combat antibiotic resistance.

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# EFFECT OF THE INTERLEUKIN-1B -511 C/T GENE POLYMORPHISM ON THE COURSE OF DUODENAL ULCER AND EROSIVE GASTRODUODENITIS IN CHILDREN

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**ABSTRACT** — The effect of the interleukin-1β (IL1β, IL-1β)-511 c/t gene polymorphism on the characters of the pattern and the course of erosive gastroduodenitis (EG) and duodenal ulcer (DU) in children was studied. It was proved that the T\T genotype is predisposing to the development of duodenal ulcer and is associated with the onset of the disease at an early age. Associations of the C\T genotype with a typical phenotype of diseases were found while the C\C genotype is associated with a high significance of the genetic factor in the development of the disease.

**KEYWORDS** — duodenal ulcer (DU), erosive gastroduodenitis (EG), children, -511 c/t polymorphism, gene, IL-1β.

## INTRODUCTION

Today the duodenal ulcer and the erosive gastroduodenitis are a multifactorial systemic disease with a polygenic inheritance. Currently, the study of the genetic basis of the immune response in duodenal disease in children, particularly the polymorphisms of IL-1β genes, allows expanding the etiopathogenetic ideas about the disease and identifying genetic risk factors for certain complications and course options which can promote a personalized approach to the treatment of diseases [1, 2]. The study was aimed to evaluate the effect of the interleukin-1β-511 c/t gene polymorphism on the course of duodenal ulcer and erosive gastroduodenitis in children.

## MATERIALS AND METHODS

100 patients with gastroduodenal erosions and ulcers (the main group) were examined: 46 children with the duodenal disease (1st subgroup) and 56 children with the erosive gastroduodenitis (2nd subgroup). The mean age of diagnosing was 8.14 ± 0.25 years (3–17 years). The control group for genetic research included 100 healthy residents of Astrakhan. To perform molecular genetic analysis the total DNA was extracted from whole blood samples using the standard phenol-chloroform extraction method. Genotyping of polymorphic markers of the studied gene was carried out using polymerase chain reaction and analysis of restriction fragment length polymorphism. Statistical analysis was performed using the Statistica for Windows software package.

## RESULTS AND DISCUSSION

When analyzing the frequencies of the T\T, C\T, C\C genotypes and the T and C alleles of IL1β (-511c/) there were no significant differences between the control and the main groups. Thus, there is no association between the T\T, C\T, C\C genotypes and the C and T alleles of the IL1β (-511c/t) gene polymorphism with erosive and ulcerative lesions of the gastrointestinal tract. There were no significant differences in the occurrence of C T alleles and T\T, C\T, C\C genotypes of IL1β (-511c/t) gene polymorphism in the control group and patients of the first subgroup, as well as in the control group and patients of the second subgroup ($\chi^2 = 0.846$, df2; $p = 0.655$ and $\chi^2 = 3.119$, df2; $p = 0.211$, respectively).

According to the data the T\T genotype is *predisposing* to the development of duodenal ulcer in children among the cohort of patients with gastroduodenal erosions and ulcers (Table 1). According to the data it was found that patients of the first subgroup with the C\C genotype had more often a genetic predisposition than those ones with the combination of the T\T + C\T genotypes ($\chi^2 = 4.221$; df1; $p = 0.040$; OR = 4.583 (CI 1.254–16.748 )). No significant differences between the alleles in the study group were found ($\chi^2c = 0.915$; df1; $p = 0.339$).

It was found that the C\C genotype is *protective* for the development of erosive gastroduodenitis in children under 12 age (Table 2) while the T\T genotype is *predisposing* to the development of duodenal ulcer in young children (that is up to 12 years) in relation to patients of the older age group (Table 3).

We have analyzed the effect of genotypes and alleles of IL1β (-511c/t) gene polymorphism on the phenotypic manifestations of diseases in the patient group (Table 4) and in isolation in children of the first and second subgroups. It was found that the C\T genotype is *predisposing* to a typical disease pattern

***Table 1.*** *Distribution of genotype and allele frequencies of IL1β (-511c/t) in children of the first and second subgroups*

| Subgroup / genotype | DU n=46 | EG n=54 | $\chi^2$ (df); p $\chi^2$ = 5,553, df2; p = 0,063 |
|---|---|---|---|
| T\T | 8 (17,4%) | 2 (3,7%) | $\chi^2$ = 3,762; df1; p=0,053<br>Fisher test 0,04076; p < 0,05<br>OR=5,474 (CI 1,100–27,247) |
| C\T | 20 (43,5%) | 24 (44,4%) | $\chi^2$ = 0,009; df1; p = 0,923 |
| C\C | 18 (39,1%) | 28 (51,9%) | $\chi^2$ = 1,618; df1; p = 0,204 |
| alleles | n= 66 | n=78 | |
| T | 28 (42,4%) | 26 (33,3%) | $\chi^2$ = 1,261; df 1; p=0,262 |
| C | 38 (57,6%) | 52 (66,7%) | |

***Table 2.*** *Distribution of genotype and allele frequencies of IL1β (-511c/t) gene polymorphism in children with erosive gastroduodenitis depending on age*

| age / genotype | children under 12 age n=24 | children over 12 years old n=30 | $\chi^2$ (df1); p |
|---|---|---|---|
| T\T | 2 (8,3%) | 0 (0%) | ---------- |
| C\T | 14 (58,4%) | 10 (33,3%) | $\chi^2$ = 3,375; df1; p =0,067 |
| C\C | 8 (33,3%) | 20 (66,7%) | $\chi^2$ = 4,674; df1; p =0,031<br>OR = 0,250 (CI 0,080–0,781) |
| alleles | n=38 | n=40 | |
| T | 16 (42,1%) | 10 (25,0%) | $\chi^2$ = 2,566; df 1; p = 0,110 |
| C | 22 (57,9%) | 30 (75,0%) | |

***Table 3.*** *Distribution of genotype and allele frequencies of IL1β (-511c/t) gene polymorphism in children of the first subgroup depending on age*

| age / genotype | children under 12 years old n=6 | children over 12 years old n=40 | $\chi^2$ (df); p<br>$\chi^2$ = 12,693; df 2; p = 0,002 (p<0,01) |
|---|---|---|---|
| T\T | 4 (66,7%) | 4 (10,0%) | $\chi^2$ = 11,661 ; p < 0,001<br>OR = 18,000 (CI 2,468–131,290) |
| C\T | 0 (0%) | 20 (50,0%) | ---------- |
| C\C | 2 (33,3%) | 16 (40,0%) | $\chi^2$ = 0,097; p =0,756<br>Fisher test 1,00000, p >0,05 |
| alleles | n=6 | n=60 | |
| T | 4 (66,7%) | 24 (40,0%) | $\chi^2$ = 1,588; df 1; p = 0,208<br>Fisher test 0,38874, p>0,05 |
| C | 2 (33,3%) | 36 (60,0%) | |

both in children of the main group (OR = 4.352 (CI 1.841–10.292) and in patients with duodenal ulcer (OR = 4.200 (CI 1.132–15.587)) and with erosive gastroduodenitis (OR = 4.583 (CI 1.442–14.571)) in isolation. At the same time, the C\C genotype appears as *protective* (OR = 0.314 (CI 0.133–0.744)) for the development of the classic pattern of the disease and is reliably associated with the erased symptoms of the disease in children of the main group. There were no significant phenotypic differences between the C and T alleles in the pattern between patients with duodenal ulcer ($\chi^2$ = 0.512; p = 0.475) and erosive gastroduodenitis ($\chi^2$ = 1.257; p = 0.263).

It was found statistical differences in the frequency of the T\T, C\T and T\T genotypes of IL1β (-511c/t) gene polymorphism in the frequency of Helicobacter pylori in the main group and in children with duodenal ulcer. The protective effect of the T\T genotype on the development of HP infection in children of the first subgroup was proved ($\chi^2$ = 20 583; df2; p <0.001; OR = 3 182 (CI 0.721–14 047)) (Table 5).

## CONCLUSION

During the study, it was examined the effect of the IL1β -511 c/t gene polymorphism on the characters of the pattern and the course of erosive gastroduo-

***Table 4.*** *Phenotypic variant of the set of symptoms in patients with duodenal ulcer and erosive gastroduodenitis with different alleles and genotypes of IL1β (-511c/t) gene polymorphism*

| Diagnosis / genotype | DU + EG (n=100) | | $\chi^2$ (df); p |
|---|---|---|---|
| | typical (n= 38) | atypical (n= 62) | $\chi^2$ = 11,863; df 2; p = 0,003 |
| T\T | 2 (5,3%) | 8 (12,9%) | $\chi^2$ = 0,979; df1; p = 0,372 |
| C\T | 25 (65,8%) | 19 (30,6%) | $\chi^2$ = 11,810; df1; p < 0,001<br>OR = 4,352 (CI 1,841–10,292) |
| C\C | 11 (28,9%) | 35 (56,5%) | $\chi^2$ = 7,175; df1 ;p = 0,008<br>OR = 0,314 (CI 0,133-0,744) |
| alleles | typical (n= 63) | atypical (n= 81) | |
| T | 27 (42,9%) | 27 (33,3%) | $\chi^2$ = 1,371; df1; p = 0,242 |
| C | 36(57,1%) | 54 (66,7%) | |

***Table 5.*** *Helicobacter pylori frequency in children with duodenal ulcer and erosive gastroduodenitis with different alleles and genotypes of IL1β (-511c/t) gene polymorphism*

| genotype | DU + EG | | DU | | EG | |
|---|---|---|---|---|---|---|
| | identified n=25 | not identified n=75 | identified n=9 | not identified n=37 | identified n=16 | not identified n=38 |
| T\T | 6 (24,0%) | 4(5,3%) | 6 (66,7%) | 2 (5,4%) | 0 (0%) | 2 (5,3%) |
| C\T | 8(32,0%) | 36 (48,0%) | 0 (0%) | 20 (54,1%) | 8 (50,0%) | 16 (42,1%) |
| C\C | 11(44,0%) | 35 (50,7%) | 3 (33,3%) | 15 (40,5%) | 8 (50,0%) | 20 (52,6%) |
| $\chi^2$ (df); p | $\chi^2$ = 7,653; df 2;<br>p = 0,022 | | $\chi^2$ = 20,583; df 2;<br>p <0,001<br>OR =3,182 (CI 0,721 – 14,047) | | $\chi^2$ = 1,015, df 2;<br>p = 0,602 | |
| alleles | identified n=33 | not identified n=111 | identified n=9 | not identified n=57 | identified n=24 | not identified n=54 |
| T | 14 (42,4%) | 40 (36,0%) | 6 (66,7%) | 22 (38,6%) | 8 (33,3%) | 18 (33,3%) |
| C | 19 (57,6%) | 71 (63,9%) | 3 (33,3%) | 35 (61,4%) | 16(66,7%) | 36 (66,7%) |
| $\chi^2$ (df); p | $\chi^2$ = 0,443; df 1; p= 0,506 | | $\chi^2$ = 1,490; df 1; p =0,223 | | $\chi^2$ = 0,068, df 1; p = 0,795 | |

denitis and duodenal ulcer in children. It is proved that the T\T genotype is predisposing for the development of the duodenal ulcer and is associated with the onset of the disease at an early age and HP infection. Associations of the C\T genotype with a typical phenotype of diseases were identified while the C\C genotype is associated with a high significance of the genetic factor in the development of the disease. Thus, the study of the genotypic basis of duodenal ulcer and erosive gastroduodenitis in children is an important task, the solution of which will promote the development of fundamental ideas about the pathogenesis of the disease and the formation of a personalized approach to treating patients.

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# EFFECT OF THE GENETIC VARIABILITY OF METALLOPROTEINASE 9 RS3918242435 GENE POLYMOR-PHISM ON THE COURSE AND OUTCOME OF BRONCHOPULMONARY DYSPLASIA IN CHILDREN

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**ABSTRACT** — The effect of polymorphism in matrix metalloproteinase 9 (MMP-9) rs3918242435 gene on the course and outcome of bronchopulmonary dysplasia (BPD) in children was evaluated. The study proved that despite of association of genotype CC with a short-term respiratory support, it increases the incidence of bronchial obstructive syndrome on the background of the respiratory infections in children, as well as the risk of infection of the respiratory tract with gram-negative microflora and is associated with a long-term therapy with inhaled glucocorticosteroids (ICS).

**KEYWORDS** — bronchopulmonary dysplasia, children, polymorphism, MMP-9.

## INTRODUCTION

In recent years, many studies on the genetic basis of bronchial diseases in children proved the participation of hereditary factors in the development of the disease [3]. As a result of the search for single-nucleotide polymorphic substitutions with the expected phenotypic effect in the promoter and intron regions, a number of MMP gene polymorphisms, particularly polymorphism in metalloproteinase 9 rs3918242435, were identified using bioinformatics methods [2]. As known, MMP-9 (gelatinase-B) is one of the enzymes engaged in remodeling of extracellular matrix, mobilization of matrix-related growth factors, and cytokine processing [1]. To assess the effect of the genetic variability of MMP-9 rs3918242435 gene polymorphism on the course and outcomes of BPD we have analyzed the associations of the clinical manifestations of the disease with polymorphic variants of this gene, with a study of the frequency of the studied polymorphism in samples of patients with bronchopulmonary dysplasia and healthy donors.

## MATERIALS AND METHODS

It has been examined 106 patients suffering from bronchopulmonary dysplasia. Molecular genetic studies of the MMP-9 gene polymorphism were carried out by the method of polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP). The following parameters in patients with various alleles and genotypes were analyzed: gender, duration and nature of respiratory support, severity of BPD, outcomes of the disease, frequency and severity of bronchial obstruction syndrome, level of treatment, lung function according to bronchophonogram or spirography, sputum culture results, mass growth index, comorbidities. Statistical analysis of the data was carried out using Data Studio software, STATISTICA 6.0 application software package.

## RESULTS AND DISCUSSION

During the study, there were no significant differences in the frequencies of C and T alleles and C\C, C\T and T\T genotypes in MMP-9 rs3918242435 polymorphism in the control group and in patients with BPD ($\chi^2 = 5.257$, $p = 0.073$; $df = 2$). When assessing the distribution of alleles and genotypes in relation to severity, statistical significant differences were also not found ($\chi^2 = 389$, ($p = 0.421$); $df = 4$). At the same time the analysis of statistical data showed gender differences in the distribution of genotypes in MMP-9 rs3918242435 polymorphism: C\C genotype was significantly more common in girls in the main group of patients (Table 1).

It was proved that CC genotype of MMP-9 gene polymorphism is predisposing for short-term mechanical ventilation ($\chi^2 = 7.185$ ($p = 0.008$)), $df = 1$ OR = 5,000 (CI 1.574–15.880), at the same time the genotype is protective in regard to long-term mechanical ventilation (more than 1 month) (OR = 0.510 (CI 0.104–0.768)). The study of the effect of MMP-9 rs3918242435 gene polymorphism on outcomes of bronchopulmonary dysplasia in children, particularly, the frequency of recovery or the formation of a chronic bronchopul-monary dysplasia, did not reveal statistically significant differences between C\C, C\T, T\T genotypes ($\chi^2 = 1.820$ , ($p = 0.403$), $df = 2$) and also

***Table 1.*** *Distribution of genotype and allele frequencies of MMP-9 rs3918242435 polymorphism with respect to gender in children with BPD*

| gender / genotypes | boys (n=76) | girls (n=30) | $\chi^2$ ; p<br>$\chi^2$C\C-T\C-T\T = 7.439; p <0,05; p=0,025; df=2 |
|---|---|---|---|
| C\C | 56 (73,7%) | 28 (93,3%) | $\chi^2$ = 5,049 (p=0,025), df=1<br>OR=0,200 (CI 0,044–0,917) |
| C\T | 16 (21%) | 0 | |
| T\T | 4 (5,3%) | 2(6,7%) | $\chi^2$ = 0,079 (p=0,779), df=1 |
| alleles | (n=92) | (n=30) | |
| C | 72 (78,3%) | 28 (93,3%) | $\chi^2$ = 0,09811 (p=0,063), df=1 |

between C and T alleles ($\chi^2$ = 1.35 (p = 0.873), df = 1). According to the statistical data, no associations were found between the polymorphism of MMP9 gene and the frequency of acute respiratory viral diseases (ARVI), as well as the first episodes of ARVI up to a year ($\chi^2$ = 0.092, p = 0.955, df = 2).

In accordance with the data in Table 2, the C\C genotype of MMP-9 polymorphism is a predisposing genotype for the development of bronchial obstruction syndrome in children with respiratory infection ($\chi^2$ = 16.133 (p <0.001), df = 1 OR = 7,200 (CI 2.550–20.333)), while the combined effect of C\T and T\T genotypes has a protective effect on this ground ($\chi^2$ = 6.318, p = 0.012; OR = 0.216 (CI 0.071–0.662); df = 1; $\chi^2$ = 7.038, p = 0.008, OR = 0.125 (CI 0.021–0.731).

With the genetic variability of MMP-9 rs3918242435 gene polymorphism, there were statistically significant differences for different genotypes influencing on the nature of the microbiota of the respiratory tract in children with BPD. Gram-negative bacteria (P.aeruginosa, Klebsiella, E. coli) were often found in patients with C\C genotype ($\chi^2$ = 9.708, p = 0.008, df = 2), while the T\T genotype was predisposing to gram-positive bacteria ($\chi^2$ = 9.373, p = 0.010, df = 2). (Table 3)

Analysis of the results showed that C\C genotype is predisposing to prolonged use of ICS in children with BPD, while the representatives of C\T and T\T genotypes have to use ICS in 11.6 and 4.7% of cases (Table 4).

***Table 2.*** *Association of alleles and genotypes of polymorphism of MMP-9 with the development of bronchial obstruction syndrome (BOS)affected by ARVI in children with BPD*

| BOS / genotypes | available (n=82) | absent (n=24) | $\chi^2$ ; p<br>$\chi^2$C\C-T\C-T\T = 14,167; (p<0,001); df=2 |
|---|---|---|---|
| C\C | 72(87,8%) | 12 (50%) | $\chi^2$ = 16,133 (p<0,001), df=1<br>OR=7,200 (CI 2,550– 20,333) |
| C \T | 8 (9,8%) | 8 (33,3%) | $\chi^2$ = 6,318 (p=0,012) df=1<br>OR=0,216 (CI 0,071– 0,662) |
| T\T | 2 (2,4%) | 4 (16,7%) | $\chi^2$ = 7,038 (p=0,008), df=1<br>OR=0,125 (CI 0,021– 0,731) |
| alleles | n=90 | n=32 | |
| C | 80(88,9%) | 20 (62,5%) | $\chi^2$ = 11,122, (p<0,001), df=1<br>OR=4,800 (CI 1,816–12,685) |

The study of lung function is one of the most important criteria for the diagnosis of respiratory tract diseases when assessing their severity and degree of effectiveness of therapy. According to statistical analysis, no association of the influence of the genotypes and alleles of MMP-9 gene with the level of respiratory tract damage, particularly the upper, middle and lower ones, was detected. ($\chi^2$ = 4.713, p = 0.095; df = 2).

## CONCLUSION

The study proved that despite the association of C\C genotype of the matrix metalloproteinase 9 (MMP-9) rs3918242435 gene polymorphism with short-term respiratory support it increases the incidence of bronchial obstructive syndrome affected by respiratory infections in children, the risk of infection of the respiratory tract with gram-negative microflora

***Table 3.*** *Association of genotypes and allele frequencies of MMP-9 rs3918242435 gene polymorphism of microbiota of the bronchial apparatus in children with BPD*

| bacteria / genotypes | gram-positive (n=12) | gram-negative (n=50) | No significant microflora (n=44) | χ2 ; p<br>χ2G\G-T\G-T\T= 19,290; p < 0,01; (p<0,001); df=4 |
|---|---|---|---|---|
| C\C | 6(50%) | 44 (88%) | 30(68,2%) | χ2 = 9,708, (p=0,008), df=2 |
| C \T | 2 (16,7,6%) | 2 (4%) | 12 (27,3%) | χ2 = 9,917, (p=0,008), df=2 |
| T\T | 4 (33,3%) | 4(8%) | 2 (4,5%) | χ2 = 9.373 (p=0,010), df=2 |
| alleles | n=14 | n=52 | n=56 | |
| C | 8 (57,1%) | 46 (88,5%) | 42 (75%) | χ2 = 7,291 (p=0,027), df=2 |

***Table 4.****The effect of MMP-9 rs3918242435 gene polymorphism on the duration of ICS use*

| duration / genotypes | constantly (n=86) | episodically (n=20) | χ2 ; p<br>χ2C\C-T\C-T\T = 5,601; p <0,05; (p=0,061); df=2 |
|---|---|---|---|
| C\C | 72(83,7%) | 12 (60%) | χ2 = 5,551; (p=0,019); df=1<br>OR=3,429 (ДИ 1,185– 9,917) |
| C \T | 10(11,6%) | 6 (30%) | χ2 = 4,274 (p=0,039,), df=1 |
| T\T | 4 (4,7%) | 2 (10%) | χ2 = 0,31609 (p=0,352), df=1 |
| alleles | n=72 | n=50 | |
| C | 58(80,6%) | 42 (84%) | χ2 = 0,81129 (p=0,627), df=1 |
| T | 14(19,4%) | 8 (16%) | |

and is associated with the need for long-term use of ICS. This genotype leads to an increase in the level of MMP which affects the activity of inflammation, the degradation of collagen with the involvement of the neutrophils of inflammation. [1, 2].

Based on the above, the analysis of polymorphism of the metalloproteinase 9 rs3918242435 gene is useful for predicting the course of bronchopulmonary dysplasia in premature infants and the formation of a personalized approach to their treatment.

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# EXPERIENCE OF LONG-TERM OMALIZUMAB TREATMENT FOR PEDIATRIC ASTHMA IN ASTRAKHAN REGION

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**ABSTRACT** — The efficacy of the addition of the genetically engineered drug Omalizumab in complex anti-inflammatory therapy in children with moderate-to-severe uncontrolled bronchial asthma (BA) living in the Astrakhan region was evaluated. In the study, it was proved that the recombinant humanized monoclonal antibodies (IgG1) — Omalizumab (Xolair) leads to a sharp decrease in the frequency of exacerbations, reduces the dose of inhaled glucocorticosteroids (ICS), which characterizes gaining control over bronchial asthma and improving the quality of life in patients.

**KEYWORDS** — bronchial asthma, children, Omalizumab (Xolair).

## INTRODUCTION

Today, the high growth rate of the urbanization of the population, the deep introduction of biologically unsafe products into the diet, massive air pollution trigger an increase allergic diseases in childhood, including bronchial asthma. According to the Guideline (GINA 2019), in order to achieve control in patients with moderate to severe form of BA, if the use of medium or high doses ICS plus long-acting β2-agonists (LABA) and/or leukotriene modifiers (LM) is not effective, it is suggested to add a genetically engineered drug anti-IgE therapy of Omalizumab (Xolair). Based on the central role of immunoglobulins E in the genesis of inflammation of bronchial asthma in children, it can be regarded as the most successful target for pathogenetic therapy [1, 2].

## OBJECTIVE

This study evaluates the efficacy of Omalizumab in baseline treatment of children with moderate-to-severe bronchial asthma in Astrakhan.

## MATERIALS AND METHODS

The study enrolled 14 patients age 6 to 17 years (mean age 10.8 + 2.1 years) with bronchial asthma in baseline treatment with Omalizumab.

According to modern international consensus documents (GINA, 2019), the diagnosis of Bronchial Asthma was verified based on the bronchodilator reversibility test or airway hyperresponsiveness in combination with a characteristic clinical performance, laboratory findings and the presence of atopy. The research was carried out on the basis of the analysis of medical documentation, a survey of patients, as well as their parents according to the developed questionnaire. The questionnaire consisted of three blocks of questions. The first block contained the patient's passport data and clinical and anamnestic features of the disease (degree of severity and duration of BA, the presence of comorbid allergic pathology, the frequency and intensity of symptoms, the level of treatment to relieve exacerbations, the degree of tolerance of physical and emotional stress, lung function measures and Asthma Control Test results) before Xolair therapy. The second block was aimed at identifying the side-effects of the drug, with the refinement of local and general adverse reactions. The third section of the questionnaire included questions characterizing the course of the disease and the degree of control in patients receiving the genetically engineered drug Omalizumab, specifying the dosage and duration of administration.

All patients were reviewed once a month and received the prescribed dose of the drug in the Pulmonology Department of the State Budgetary Institution of Health Care of Astrakhan Region Regional Children's Clinical Hospital named after N.N. Silischeva in Astrakhan. Monthly, it was monitored patients' general clinical indicators of blood and urine, the level of total immunoglobulin E, carried out functional breathing test and filled in tests–questionnaires to objectify the patient's subjective attitude to his/her disease (ACT test: scores of 20 or more were classified as well-controlled asthma, less than 19 points as not-well controlled).

## RESULTS AND DISCUSSION

The examined cohort was consisted of 7 boys and 7 girls. The age of patients is presented as follows: 6–10 years — 6 children, 11–14 years — 5 children, 15 and more years — 3 children. The duration of treatment of bronchial asthma before addition of Xolair in baseline anti-inflammatory therapy was up to 8 years in 8 children; from 8 to 10 years — in 3 patients; more than 10

years — in 3 patients. Taking into account the combination of clinical features and functional indicators 12 children form 14 patients were diagnosed with severe bronchial asthma, 2 patients — moderate asthma. As a baseline therapy, 12 patients received a fixed high-dose ICS plus LABA (1000 mcg of fluticasone propionate or budesonide 720 mcg) and plus leukotriene modifiers or long-acting M-anticholinergics. Two patients with a moderate disease, anti-inflammatory therapy was represented by a combination of ICS/LABA (in moderate therapeutic doses of ICS) plus AM.

The frequency of daily and nocturnal symptoms before omelizumab add-on ranged from 2 times a week to daily. At the same time, exacerbations requiring medical assistance, including in-hospital, were observed in 8 patients once in a month and in 6 patients more than 2 times a month. 78.5% from 100% of responders were required a short-term course of treatment with systemic corticosteroids 3 or more times a year to relief attacks. Exercise intolerance and sharp limitation of emotional stress were common in all patients. When assessing the level of control according to the Asthma Control Test, asthma was interpreted as uncontrolled in all children (the total number of points varied from 8 to 16). It should be noted the high compliance to therapy in families of patients (strict adherence to hypoallergenic life and the recommendations of the attending physician) and the correct technique for applying an individual inhaler by the patient. The following co-existing allergic diseases were identified: atopic dermatitis in 5 patients, year-round allergic rhinitis in 11 patients, drug allergy in 5 children, food allergy in 11 children.

Given the lack of control over the disease during the baseline anti-inflammatory therapy of 4 and 5 steps, as well as the high adherence to therapy of patients' families according to federal clinical guidelines for the treatment of bronchial asthma in children, the genetically engineered drug Omalizumab (Xolair) was added to the therapy. Dosing was determined for each individual patient according to the dosing table based on the initial level of immunoglobulins E and the patient's body weight. 7 patients were receiving 150 mcg of Omalizumab; 1 patient — 225 mcg; 6 children — 300 mcg. The drug was administered subcutaneously 1 time in 4 weeks. Following administration of the drug, the following local and general adverse reactions were noted. In 4 children, mild headache and dizziness were noted, in 4 children, slight hyperemia and edema were observed at the injection site. According to the manufacture's recommendations, these side-effects of the drug are not a contraindication for further therapy. Therefore, Xolair administration was continued. One child had an anaphylactic reaction in the form of acute urticaria following the first administration of Omalizumab, so the drug was canceled and the patient was excluded from further observation.

At the time of the study, Xolair was used from 6 months to 4 years. For 6 months, Xolair was a component of baseline anti-inflammatory therapy in 1 patient, from 6 to 18 months — in 7 patients, 2 children received Omalizumab for 2 years and 3 children for more than 3 years. The results of the study indicate that 69.2% (n = 9) of patients achieved stable control of the disease: relief of both nocturne and daily attacks (within a few months to a year), satisfactory exercise tolerance and low interest in short-acting β2 agonists. 4 (30.8%) patients had partial control of the disease: daily and nocturne symptoms of a mild degree 1–2 times per month. 2 out of 3 patients had a restriction of physical activity, which was more associated with parental hyper-care than with persistent bronchial hyperresponsiveness associated with physical activity. Asthma Control Test results show the disease control, which are ranged from 18 to 25 points in all patients.

With regular Omalizumab treatment, the basline anti-inflammatory therapy in 11 patients (84.6%) was stepped down by reducing ICS dose due to long-lasting drug remission and a high level of disease control. Thus, if before Xolair therapy 12 children had been receiving high-dose ICS therapy, 2 children — medium dose ICS, then, with genetically engineered drug add-on 10 children reduced ICS to medium dose, 2 children — to low dose ICS. One patient continued to receive high dose of inhaled hormones to achieve disease control. When analyzing the lung function measures all patients had a significant increase in the level of FEV1.

## CONCLUSION

The study results indicate that the recombinant humanized monoclonal antibodies (IgG1) — Omalizumab (Xolair) in complex of baseline anti-inflammatory therapy in children with moderate-to-severe bronchial asthma leads to a sharp decrease in the frequency of exacerbations and emergence department visits, reduces the dose of inhaled (ICS), increase lung function which characterizes gaining control over bronchial asthma and improving the quality of life in patients.

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# GENETIC ASPECTS OF INFLAMMATION IN CHILDREN WITH BRONCHIAL ASTHMA IN ASTRAKHAN REGION

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**ABSTRACT** — The search for genetic markers that control the key links in the pathogenesis of bronchial asthma is relevant. Identification of the association of polymorphic loci of candidate genes with a risk of developing severe forms of bronchial asthma in children is regarded as most promising. A frequent change in the structure of genes is associated with the single nucleotide polymorphisms, which affect the phenotype of the disease and determine differences in the clinical manifestations of the same nosological entity.

**KEYWORDS** — asthma, children, gene polymorphism, genotypes, alleles, cytokines, inflammation.

## BACKGROUND

Bronchial asthma (BA) is a phenotypically heterogeneous disease that is difficult in the timely diagnosis of this disease especially in children. A number of authors note a significant increase in the prevalence of asthma in children over the past 25 years [1,4,5]. A study of the genetic aspects of asthma in Russia was focused on studying the polymorphism of interleukin ligand and receptor genes, assessment of their expression. The results confirmed the important role of the genetic component in controlling inflammation in bronchial asthma. Currently, great successes have been achieved in the study of the pathogenesis of bronchial asthma, however, many stages of the formation and modification of the course of this disease are controversial and not entirely clear. Perhaps the lack of adequate control over the course of the disease is due to the peculiarities of the endogenous regulation of cell-cell interactions carried out by cytokines — regulators of both non-specific inflammatory processes and the allergen-specific immune response of the *cellular* and *humoral* types [7, 10].

Among a large number of candidate genes for BA and atopy, the attention of researchers is largely attracted to the IL-4 gene. It is often called the *critical cytokine of inflammation* [3, 6, 8, 9]. Studies of its already known polymorphisms related to BA and atopy as well as the search for new mutations of this gene are of great interest [5, 7, 8, 11].

*Objective* is to analyze the IL-4 gene polymorphisms at C-590T gene in children with bronchial asthma of Astrakhan population, to study the associations of this gene polymorphism with some clinical and anamnestic indicators.

## MATERIALS AND METHODS

Study was prospective full-design. The population of children living in the territory of the Astrakhan region was examined. The control group was represented by conditionally healthy children in the amount of 182 people. The second group of children with bronchial asthma consisted of 174 people. The diagnosis of asthma and its severity was made in accordance with the criteria of international documents, the national treatment program and strategies for bronchial asthma in children. Children with a previous history of at least 1-year history of the disease were examined.

For molecular genetic analysis, the total DNA was isolated from whole blood using the standard phenol-chloroform extraction method. Genotyping of polymorphic markers of the studied genes carried out by polymerase chain reaction (PCR) and restriction fragment length polymorphism analysis (RFLP analysis). The Pearson's chi-squared test ($\chi^2$) with Yates correction for continuity was used to test correspondence of genotype distribution to the expected one under Hardy-Weinberg equilibrium (HWE), comparison of genotype and allele frequencies, assessment of allele bonds of genes.

## RESULTS AND DISCUSSION

The study of C-590T polymorphism of the IL-4 gene in conditionally healthy children showed the prevalence of the genotypes C/C and C/T (36.2% and 53.9%, respectively) over the genotype T/T (9.9%), the mutant C allele dominated and was in 58.6% of children, and the wild T allele was in 41.4%. Statistical analysis did not show any significant differences in the frequencies of alleles and genotypes between the control group and children with acute obstructive and recurrent bronchitis. Thus, the C-590T polymorphism of the IL-4 gene is not associated with the occurrence of these nosologic entities (Table 1).

We have analyzed the effect of this polymorphism on the occurrence of viral infections, on early bron-

***Table 1.*** *Distribution of genotypes and allele frequencies of IL-4 gene polymorphism at C-590T gene in groups of conditionally healthy children, and patients with acute obstructive bronchitis and recurrent bronchitis*

| Genotypes | 1. Control group: conditionally healthy (n=91) | 2. Acute obstructive bronchitis (n=54) | 3. Recurrent bronchitis (n=72) |
|---|---|---|---|
| T/T | 9 (9,9%) | 5 (9,3%) | 4 (5,5%) |
| C/T | 49 (53,9%) | 27 (50%) | 39 (54,2%) |
| C/C | 33 (36,2%) | 22 (40,7%) | 29 (40,3%) |
| $\chi^2$; p | | 1–2<br>$\chi^2$ = 0,289; p>0,05; P=0,866; df=2 | 1–3<br>$\chi^2$ = 1.118; p > 0,05; P=0,572; df=2 |
| Alleles | n=140 | n=81 | n=111 |
| T | 58 (41,4%) | 32 (39,5%) | 43 (38,7%) |
| C | 82 (58,6%) | 49 (60,5%) | 68 (61,3%) |
| $\chi^2$; p | | $\chi^2$ = 0,079 p>0,05 (p=0,780), df=1 | $\chi^2$ = 0,186 p>0,05 (p=0,667), df=1 |

cho-obstructive syndrome development, the possibility of allergic diseases in patients and have monitored a family allergic history in children of the examined groups.

In the study, we found that the genotype C/C in patients with acute obstructive bronchitis is predisposing to frequent respiratory diseases of the upper respiratory tract (Fisher criterion 0.04304 p <0.05, df = 1, OR = 3.971 (CI 1.096–14.379 )), while the genotype C/T has a protective effect.

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# STRUCTURE AND DYNAMICS OF ROTATORY SUBLUXATION OF THE CERVICAL SPINE IN CHILDREN

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**ABSTRACT** — Rotational subluxations of C1-C2 vertebrae in children is a common pathology causing acute torticollis syndrome and destabilizing the child and his family. The number of recurrent cases has increased, which requires the study and development of preventive measures. An analysis of the incidence dynamics was carried out in 2010-2018. Some clinical and radiological features of the process, seasonality, age, gender prevalence were also studied.

**KEYWORDS** — Rotational subluxation of C1-C2 vertebrae, dynamics, age features, seasonality.

Most common among cervical spine anomalies in children are rotational subluxations in the C1–C2 segment, which are usually accompanied by symptoms of severe pain and unilateral torticollis (A. Gubin, 2010, ClarkCh.R. 2005). In the last decade frequency of pathology has been steadily increasing (A . Kurkin, 2011; P. Gencpinara M. Erkan, 2015). This fact raises many questions and discussions, and, in our opinion, requires close examination. On the background of rapidly developing highly evidence-based medicine, a clinical-statistical analysis remains as a necessary basic tool, enabling to obtain a reliable analysis of the regional incidence and to develop preventive measures.

*Objective*

To identify the structure and dynamics of the incidence of cervical rotational subluxations in children in the Astrakhan region.

## METHODS

The medical documentation of children who attended the traumatology department of the Regional Silishcheva Children's Clinical Hospital in period from 2010 to 2018 with symptoms of acute pain in the cervical spine and forced head position. The research materials were:

— results of a history and clinical examination of patients, including questionnaire data;
— call registers, stationary and outpatient cards;
— results of instrumental examination methods — radiography, computed tomography with 3-D reconstruction, magnetic resonance imaging.

At the same time, the parameters of growth, weight, age, seasonality of admission, and the frequency of calls were distinguished. The features of the x-ray picture in a certain group of patients were described. The data obtained were processed by statistical methods in order to identify patterns within the framework of a specific study.

The results of the study and their discussion: According to the data obtained in the trauma and orthopedic department of the Silishcheva Children's Regional Clinical Hospital for the period from 2010 to 2018. 4397 children with acute torticollis syndrome were admitted, which amounts t 17.8% of the total number of children with injuries during the same period. The number of children with the studied pathology increased annually (Fig. 1).

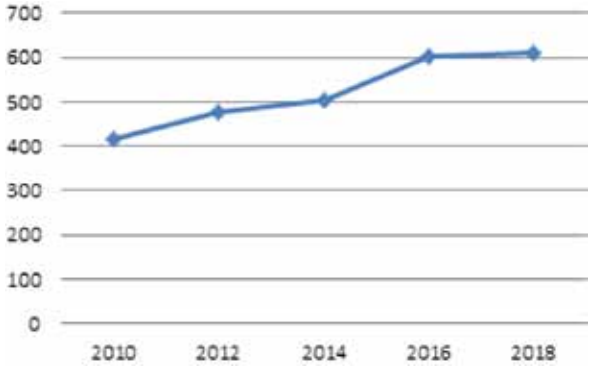


***Fig.1.*** *The dynamics of treatment with symptoms of acute pain in the cervical spine and a forced head position during the period of 2010–2018*

In order to clarify the diagnosis, all children underwent radiation instrumental examination. Radiography in 2 projections was performed with 100% of applicants. Computer tomography in 3D-format was performed with 72% of children. A clinical diagnosis

was made after the examination. Analysis of patients by age and gender characteristics in 2017–2018 is given in (Fig. 2). The predominance of boys aged 11–15 years is established.

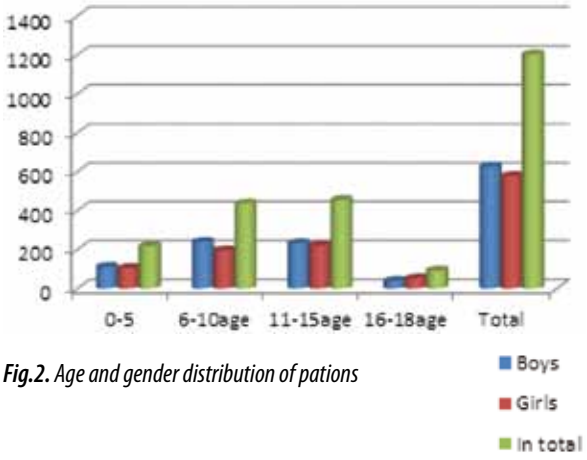


*Fig.2. Age and gender distribution of pations*

Acute and relapsing torticollis syndrome, according to the questionnaire, most often occurred at home (67%), at school (22%), places of sports (9%), and also on the street (2%) (Fig. 3)

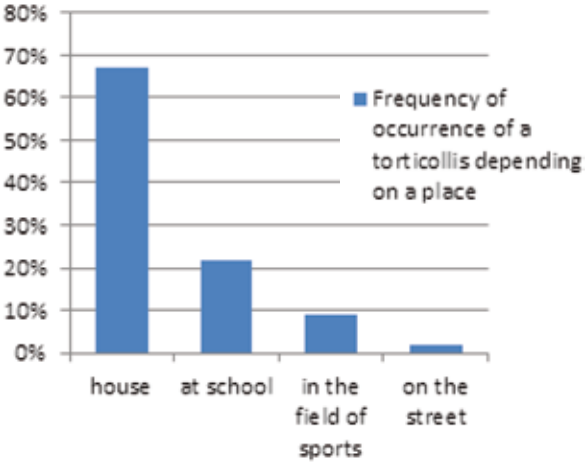


*Fig. 3. Torticollis frequency depending on the place of occurrence*

We believe that this is a confirmation of the non-traumatic nature of the pathology, because such condition most often occurred after sleep with relaxed skeleton muscles.

The most common answer to the question about the mechanism of the tinnitus syndrome occurrence was *during a quick turn of the head* after a night's sleep. In second place in frequency are sports. It should be noted that children indicated such sports as wrestling, athletics, rhythmic gymnastics, and dance sports. It was also revealed that the duration of sports in the above-mentioned species does not significantly affect the incidence rate. The results of a study of the seasonal occurrence of rotational subluxations of C1–C2 vertebrae, which we studied in 2017–2018, showed the following (Fig. 4):

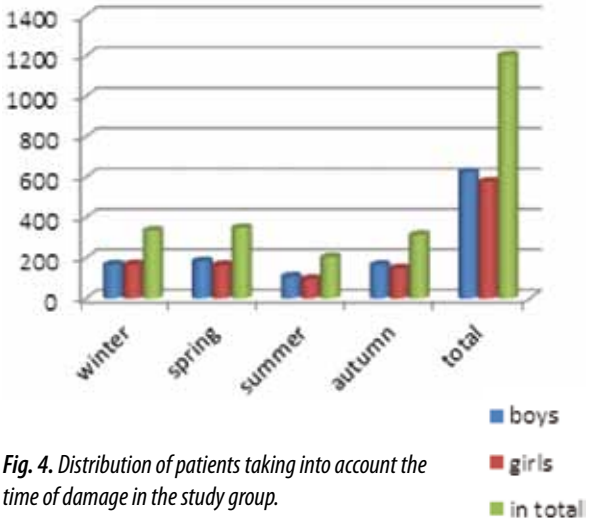


*Fig. 4. Distribution of patients taking into account the time of damage in the study group.*

Reduction in the incidence in the summer, which can be explained by a decrease in the static load in children was reliably established.

To study the features of the skeleton, somatometric studies were carried out, which showed a slight excess of the height-to-weight ratio when compared with standard centile tables, as well as a decrease in the average chest volume, which indicates the predominance of asthenic physique among children with rotational subluxations of C1–C2 vertebrae.

We suggest the presence of a relationship between asthenic physique and insufficient development of the ligamentous apparatus (systemic dysplasia of the connective tissue, syndrome of hypermobility joints) and the occurrence of rotational subluxations of C1–C2 vertebrae.

To this date, the results of radiation methods of examination have been studied in 144 children who applied in 2018–2019, while certain dysplastic symptoms were revealed in 68 patients (47%). In all children an adjustment of cervical lordosis was observed. Asymmetry of the joint spaces was detected in 30 (20.8%) children. Hypoplasia and underdevelopment of the posterior arch of the C1 vertebra was observed in 25 (17.4%) children. A CT scan of the sagittal plane al-

lowed us to detect an increase in the distance between the C1 and C2 vertebrae along the anterior contour in 15 (10.4%) children, as well as the deformation and underdevelopment of the contours of the transverse canal of the vertebral artery C1 of the vertebra. Delayed development of the ossification center at the odontoid apex C2 and underdevelopment of the side walls of the vertebra foramen in the transverse processes C1 of the vertebra is observed in almost half of the children. In most cases (n = 46), combinations of two or more components were revealed.

## CONCLUSIONS

An analysis of the dynamics of the incidence of rotational subluxations in the cervical spine in children of Astrakhan region indicates a progressive increase over the past ten years with an annual average increase of 4.3%. The study of incidence of rotational subluxations of C1–C2 vertebrae in children in Astrakhan region has revealed that 11–15 years old boys had a higher prevalence in the spring-autumn period.

Somatometric indicators for children with rotational subluxations of C1–C2 vertebrae indicate the predominance of asthenic body type.

The results of radiographic examination confirm the presence of dysplasia of the cervical spine in children with rotational subluxations of C1–C2 vertebrae.

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# THE SPECIFICS OF OCULAR PROSTHETICS IN PATIENTS WITH DIABETES MELLITUS

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**ABSTRACT** — Aim. To study the effect of pH on the conjunctival cavity.
Materials and methods. All patients underwent the following studies: Biomicroscopy of the conjunctival cavity, evaluation of the cosmetic effect of prosthetics, sensation and comfort, and bacterial culture of the discharge.
The results of the study. As a result of the study, it was found that patients using ocular prostheses with concomitant diabetes mellitus have a pH shift in the conjunctival cavity to the alkaline side, which will lead to partial inflammatory reactions of the conjunctival cavity, resulting in a decrease in the desired cosmetic effect
Conclusion. Diabetic patients require a lot of attention and a more thorough approach to meeting the conditions for normalizing the pH of the conjunctival cavity, and the terms of replacing the prosthesis, as a result, achieving a good cosmetic effect.

**KEYWORDS** — ocular prosthetics, anophthalmia, diabetes mellitus.

## INTRODUCTION

Every year in Russia, from 7.5 to 8 thousand enucleations are performed, according to the Ministry of Health of the Russian Federation from 1999.

More than 450,000 patients in the Russian Federation need eye prosthetics, while the prevalence of anophthalmus reaches 24.47 per 10,000 population (Lavrentieva, 2013; Federal clinical guidelines, 2015).

The only method of medical and social rehabilitation of people with anophthalmus, to date, remains eye prosthetics (Perfilieva et al.,2014; Perfilieva et al.,2015, p. 120).

Cosmetic and functional cosmetic results of ocular prosthetics depend on a combination of factors such as compliance with patient hygiene rules and timely replacement of prostheses(Perfilieva et al.,2014; Perfilieva et al.,2015, p. 120).

Diabetes affects five percent of the world's population. Another twenty-five percent are carriers of the disease. The significance of this disease in the world is growing, according to forecasts, by 2030, diabetes will become the seventh leading cause of death in the world(Roglic et al.,2005, p. 2130).

## MATERIALS AND METHODS

The work is carried out at the Department of Ophthalmology of the RUDN University and at the Center for Eye Prosthetics of Moscow from September 2018 to the present.

Under our supervision, there were 100 patients aged 8 to 82 years. Patients were divided into two groups: the first group (control group) — patients with anophthalmus and without diabetes mellitus (50 people; 100%), the second group (study group) — patients with anophthalmus complicated by diabetes mellitus (50 people; 100%,). All patients underwent the following studies: Biomicroscopy of the conjunctival cavity, evaluation of the cosmetic effect of prosthetics, sensation and comfort, and bacterial culture of the discharge. The material was processed statistically using computer programs based on the Excel.

## RESULTS

The results of our study when studying the condition of the acid-base balance of the conjunctival cavity showed: in the control group — 37 patients (37 eyes, 74%) the pH is 7.0–7.5, in 13 patients (13 eyes, 26%) the pH is 8,0–8.5, and in the second study group in 8 patients (8 eyes, 16%), the pH is 8.0–8.5, in 23 patients (23 eyes, 46%), the pH is 9.0–9,5, in 19 patients (19 eyes, 38%), the pH is 10.0–11. (Table 1).

***Table 1.*** *pH Measurement of the conjunctival cavity*

| № | Patientgroups, n, % | PH | | | |
|---|---|---|---|---|---|
| | | 7-7,5 | 8-8,5 | 9-9,5 | 10-11 |
| 1 | 1st group, n=50 (100%) | 37 (74%) | 13(26%) | - | - |
| 2 | 2nd group, n =50 (100%) | - | 8 (16%) | 23 (46%) | 19 (38%) |

In the study group, frequent inflammatory processes in the conjunctival cavity were noted, and staphylococcus aureus was found during bacterial culture that urgent treatment was required urgent treatment especially in those patients with high PH, while in the control group patients did not show frequent inflammatory reactions. In 90% of the control group, the bacterial culture was sterile (Fig. 1).

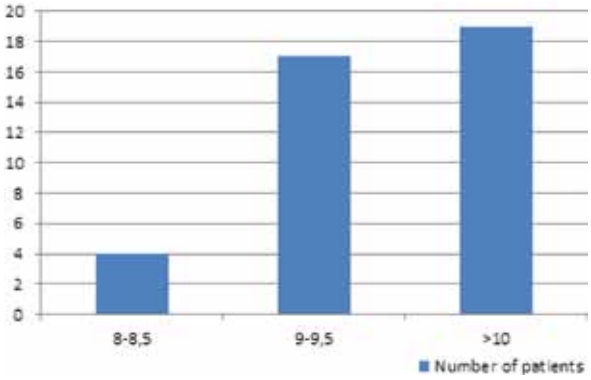


***Fig. 1.*** *The frequency of inflammatory reactions in patients with diabetes, depending on the pH of the connective cavity*

Patients using ocular prostheses with a concomitant disease with diabetes mellitus, which comply with the terms of replacement of the ocular prosthesis (1 year for a glass prosthesis and two years for a plastic prosthesis), have less inflammatory reactions in the conjunctival cavity and a better cosmetic effect, but worse than in patients without diabetes.

## DISCUSSION

On the territory of the Russian Federation, more than 450,000 patients require ocular prosthetics (Lavrentieva, 2013; Federal clinical guidelines, 2015), among them there are patients with diabetes mellitus, who have their own characteristics that affect the results of ocular prosthetics, and therefore, the problem of ocular prosthetics in patients with concomitant diabetes is relevant and requires special attention. In patients using ocular prostheses, the pH of the conjunctival cavity is normal or shifted to the alkaline side, among them patients with diabetes mellitus whose pH is shifted not only to the weak, but also to the more aggressive alkaline side, which leads to frequent inflammatory reactions in the conjunctival cavity and the appearance of Staphylococcus aureus, which requires immediate treatment, and frequent inflammatory reactions of the conjunctival cavity in these patients leads to a decrease in the desired cosmetic effect obtained from ocular prosthetics, therefore, normalization of the pH of the conjunctival cavity and timely replacement of the ocular prosthesis are some of the important conditions for preventing inflammatory reactions of the conjunctival cavity and obtaining the desired cosmetic effect from ocular prosthetics.

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# URIC ACID AS A RISK FACTOR FOR CATARACTS IN PATIENTS WITH GOUT

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**ABSTRACT** — Aim. To determine the concentration of uric acid in body fluids and its relationship with the development of cataract.
Methods. The study included 170 patients with male cataracts, aged 30 to 75 years, who were divided into two groups: the first group (control) — patients without gout 60 patients (60 eyes), the second group (study) — patients with cataract complicated by gout 110 patients (110 eyes). All patients signed an informed consent to participate in the study and the processing of personal data. In addition to standard ophthalmic research methods, all patients were also determined: the level of uric acid in the blood serum, in the tear and in the moisture of the anterior chamber. The diagnosis of gout is established by signs of ACR/EULAR (2015). Microsoft Excel 2019 and Statistic 20. These parameters allow you to analyze deviations from the normal, a comparison of two independent groups using the non-parametric Mann-Whitney test. Data were median (25%; 75% percentile). Differences at which $p < 0.05$ are considered statistically significant.
Results. The concentration of uric acid in biological fluids in patients of the study group was significantly increased compared with patients in the control group ($p < 0.0001$)
Conclusions. In patients with cataracts and with concomitant gout disease, an increase in the concentration of uric acid is observed not only in the blood, but also in the tear and moisture of the anterior chamber, which may be a risk factor for the development of cataracts. Measuring the concentration of uric acid in body fluids can be a useful tool for monitoring the health status and condition of eye tissues.

**KEYWORDS** — cataract, uric acid, gout.

## INTRODUCTION

Uric acid is the end product of the exchange of purine bases. In normal concentrations, one of its functions is to provide effective antioxidant ability. Elevated plasma uric acid levels can lead to gout and are associated with coronary heart disease, diabetes, and renal failure (Boscia et al., 2000). One reason for this may be that uric acid may act as a prooxidant. It is known that antioxidants under certain conditions are able to act as prooxidants — substances with opposite properties that are detrimental to cells. The eye is vulnerable to oxidative stress.

According to some authors (Bunin et al., 1973), changes in the composition of the aqueous humor of the anterior chamber with the formation of abnormal metabolites leads to destructive changes in eye tissue, including cataracts.

## MATERIALS AND METHODS

The study included 170 patients with male cataracts, aged 30 to 75 years, who were divided into two groups: the first group (control) — patients without gout 60 patients (60 eyes), the second group (study) — patients with cataract complicated by gout 110 patients (110 eyes). All patients signed an informed consent to participate in the study and the processing of personal data. In addition to standard ophthalmic research methods, all patients were also determined: the level of uric acid in the blood serum, in the tear and in the moisture of the anterior chamber. Gout was diagnosed using ACR/EULAR (2015) criteria. The material was processed statistically using computer programs Microsoft Excel 2019 and Statistic 20. Since the distribution of the parameters of the studied sample deviates from normal, the comparison of two independent groups was carried out using the non-parametric Mann-Whitney test. Data were presented as median (25%; 75% percentile). Differences at which $p < 0.05$ were considered statistically significant.

Samples of tear fluid, aqueous humor and blood serum were taken from patients undergoing cataract phacoemulsification. A 30 µl tear fluid sample was collected in the morning before surgery atraumatically from the lower lateral lacrimal meniscus with a capillary tube (5–25 µl; Roche Diagnostics GmbH, Vienna, Austria). After centrifugation, the samples were transferred to plastic microtubes and stored at -70° C until measurements were made by high performance liquid chromatography (HPLC). Moisture of the anterior chamber was obtained by transcortineal paracentesis of the anterior chamber with a 28 gauge needle connected to an insulin syringe. 100 ml of a moisture sample of the anterior chamber were taken from each patient. Samples were immediately transferred to the laboratory, centrifuged at 1500 g for 10 minutes, and stored at -70° C until use. Uric acid in the tear and in the moisture of the anterior chamber was determined by chromatographic method with electrochemical (EC) detection. The chromatograph (model HP 1100; USA) was equipped with a binary pump, an automatic

sample injection system, and an ESA Coulochem Model 5200A with a model 5011 analytical cell. Data was introduced in Chem Station version 8.04. All injections were performed in duplicate.

## RESULTS

In all patients of the control and study groups, the level of uric acid in the blood serum, in daily urine, in the tear and in the moisture of the anterior chamber (MIC) was determined (Table 1).

The concentration of uric acid in various media in patients of the study group was significantly increased compared with patients in the control group (p <0.0001) (Tabl. 1).

***Table 1.*** *The concentration of uric acid in various environments in the control and study groups*

| The concentration of uric acid in various environments | Control group | Study group | P |
|---|---|---|---|
| In the blood, μmol/l | 277.0 (251.0-304.3)[2] | 697.55 (426.7-801.65)[2] | < 0.0001[1] |
| In a tear, mcg/ml | 10.9 (10.6-11.3)[2] | 23,65 (17.2-27.6)[2] | < 0.0001[1] |
| In the MIC, mcg/ml | 8.0 (7.7-8.3)[2] | 19.15 (11.925-23.025)[2] | < 0.0001[1] |

***Note:*** *1 — Mann-Whitney criteria are used for statistical analysis; 2 — median (25% quartile, 75% quartile)*

## DISCUSSION

Uric acid is the end product of the exchange of purine bases. In normal concentrations, one of its functions is to provide effective antioxidant ability (Cutler, 1984). It was shown that in vivo urates are components of the main extracellular and intracellular antioxidant mechanisms (Yu, 1994). Uric acid is present not only in serum or plasma, but also in sweat, nasal and bronchial fluids. (Housley et al., 1995; Choy et al., 2000; Huang et al., 2002). Elevated plasma uric acid levels can lead to gout and are associated with coronary heart disease, diabetes, and renal failure (Lehto et al 1998). One reason for this may be that uric acid can act as a prooxidant and participate in oxidative stress. It is known that antioxidants under certain conditions are able to act as prooxidants — substances with opposite properties that are detrimental to cells.

The eye is vulnerable to oxidative stress. It has been argued that oxidative mechanisms play an important role in the pathogenesis of cataracts (Boscia et al., 2000; Aksoy & Keles, 2001). An increased risk of cataract was found with an increase in serum uric acid levels (Durant et al., 2006).

Our study showed that with gout, elevated uric acid levels not only in blood serum, but also in the tear and moisture of the anterior chamber, which can be a risk factor for cataracts.

The composition of the tear fluid is of interest because tears are the first barrier protecting the cornea from oxidative damage by photodynamic reactions and toxic chemicals (Gogia et al., 1998; Rose et al., 1998). Water humor also protects the eye tissue from changes caused by light, to which the lens and retina are especially sensitive.

Measuring the concentration of uric acid in body fluids can be a useful tool for monitoring the health status and condition of eye tissues. Further research is needed to confirm our findings.

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# DEPOSITS OF URIC ACID CRYSTALS IN THE OCULAR STRUCTURES OF PATIENTS WITH GOAT

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**ABSTRACT** — Aim. To study the features of eye manifestations with gout.
Methods. The study included 170 male patients with cataracts, aged 30 to 75 years, who were divided into two groups: the first group (control) — 60 patients without gout (100%), the second group (study) — 110 patients with cataract accompanied by gout (100%). In addition to standard ophthalmic testing, the level of uric acid in blood serum, in a tear and in the vagina of the anterior chamber was studied in all patients. These parameters allow to analyze deviations from the normal, a comparison of two independent groups using the non-parametric Mann-Whitney test. Data were median (25%; 75% percentile). Differences at which $p < 0.05$ are considered statistically significant.
Results. In the study group, deposits of uric acid crystals on the surface of the eye structures were found in 14 (13%) patients.
Conclusions. 15-year or more experience with gout associated with its regular therapy and prolonged hyperuricemia leads to an elevated level of uric acid in the tear and in the moisture of the anterior chamber and development of sodium monourate crystals and microtofuses on the ocular surface.

**KEYWORDS** — cataract, uric acid, gout, hyperuricemia, tophi.

## INTRODUCTION

Ophthalmic tophi for gout can be found on the conjunctiva, upper eyelid, lateral palpebral fissure, sclera, cornea, orbit, iris, lens and anterior chamber of the eye in patients with gout (Morris & Fleming, 2003; Ferry et al., 1985; Topping et al., 2003; Coassin et al., 2006; Lo et al., 2005). Corneal tophi was found in the epithelium and stroma of the cornea (Slansky & Kubara, 1968; Fishman & Sunderman, 1966). Monosodium urate crystals were confirmed in the cornea using polarized light microscopy (Bernad et al., 2006; Sarma et al., 2010), and a histopathological study confirmed gouty tophi in one of the latest studies (Sarma et al., 2010). Although ocular manifestations of gout have been reported, most of them are reports of isolated cases. The pathogenetic and clinical features of the ophthalmic manifestations of gout are still not well understood.

## MATERIALS AND METHODS

The study was carried out at the Department of Ophthalmology of the RUDN University and at the Department of Ophthalmology at the Sin State Medical University named after Sino, Dushanbe.

The study included 170 patients with male cataracts, aged 30 to 75 years, who were divided into two groups: the first group (control) — patients without gout 60 patients (100%), the second group (study) — patients with cataract complicated gout 110 patients (100%). All patients signed an informed consent to participate in the study and the processing of personal data.

The exclusion criteria from the study were: glaucoma, history of surgery and eye injuries, general diseases (autoimmune, diabetes mellitus), coronary heart disease, chronic renal failure.

In addition to standard studies of ophthalmic methods, all patients were also determined: the level of uric acid in blood serum, in a tear and in the vagina of the anterior chamber. The diagnosis of gout is established by signs of ACR/EULAR (2015). Microsoft Excel 2019 and Statistic 20. These parameters allow you to analyze deviations from the normal, a comparison of two independent groups using the non-parametric Mann-Whitney test. Data were median (25%; 75% percentile). Differences at which $p < 0.05$ are considered statistically significant.

## RESULTS

Deposition of uric acid crystals on the surface of the eye.

In the control group, no changes were found in the form of deposition of uric acid crystals on the surface of the eye structures.

In the study group, deposits of uric acid crystals on the surface of the eye structures were found in 14 (13%) patients. On the cornea in 3 (2.7%) patients, deposits were found in the epithelium and superficial stroma of the cornea, the crystals had an irregular shape, each measuring about 0.2 × 04 mm, separated by a transparent ring-shaped zone of high density. Fluorescein staining of the deposits was negative. There were no clinical signs of inflammation in or around the crystals.

Uric acid crystals were found in the sclera in 3 (2.7%) patients, chalky-white irregularly shaped, approximately 2 × 3 mm in size, separated from the other sclera by a transparent ring-shaped zone of high density. No clinical signs of inflammation were found in or around the crystals.

Gonioscopy revealed translucent material in 2 (1.8%) patients of the study group in the lower part of the anterior chamber angle.

Numerous transparent gelatinous deposits were found on the surface of the iris and on the edge of the pupil of 2 (1.8%) patients.

On the conjunctiva of the eyeball in 4 (3.6%) patients, clusters of refractory and cuboid subconjunctival crystals were found, each approximately 1 mm in the bulbar conjunctiva near the upper and lower limbs, separated from the cornea by a clean zone. There were no clinical signs of inflammation in or around the crystals.

In patients of the study group with the presence of crystalline deposits on the structures of the eyes, multiple tophi of the auricle, massive tophi in the area of the elbow joints, joints of the hands and feet were observed. The duration of gout disease was more than 15 years. These patients did not receive regular therapeutic treatment for gout.

In all patients of the control and study groups, the level of uric acid in the blood serum, in daily urine, in the tear and in the moisture of the anterior chamber (MIC) was determined (Tabl. 1).

***Table 1.*** *The concentration of uric acid in various environments in the control and study groups.*

| The concentration of uric acid in various environments | Control group | Study group | P |
|---|---|---|---|
| In the blood, μmol/l | 277.0 (251.0-304.3)[2] | 697.55 (426.7-801.65)[2] | < 0.0001[1] |
| In a tear, mcg/ml | 10.9 (10.6-11.3)[2] | 23,65 (17.2-27.6)[2] | < 0.0001[1] |
| In the MIC, mcg/ml | 8.0 (7.7-8.3)[2] | 19.15 (11.925-23.025)[2] | < 0.0001[1] |

***Note:*** *1- Mann-Whitney criteria are used for statistical analysis; 2 — median (25% quartile, 75% quartile)*

The concentration of uric acid in various media in patients of the study group was significantly increased compared with patients in the control group (p <0.0001) (Tabl. 1).

## DISCUSSION

A large number of epidemiological studies show that in recent years the incidence of gout has been increasing. But despite this, little attention is paid to eye complications caused by gout. With an increase in the level of uric acid in blood serum> 360 μmol/l, it saturates biological fluids, which leads to its crystallization in the form of monosodium salt when the super-saturation point is reached. Clinically, this is manifested by the formation of t tophi. Tophi are nodules formed during the deposition of sodium monourate in tissues, during which a slow epitaxial growth of crystals occurs with the formation of crystalline structures.

In the eye, precipitation of urate crystals has been described in the eyelids, tarsal plates, conjunctiva, cornea, sclera, tendons of extraocular muscles, orbit, lens, anterior chamber (Morris & Fleming, 2003; Topping et al., 2003; Martinez-Cordero et al., 1986; Slansky & Kubara, 1968; Fishman & Sunderman, 1966; Margo, 2004). Eye structures may be a weaker solvent for sodium monourate than plasma; with hyperuricemia, urate becomes oversaturated, especially at lower temperatures. With prolonged hyperuricemia, urate crystals and micro tophi develop in the eye structures.

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# FLATFOOT CHARACTERISTICS IN SCHOOLCHILDREN DUE TO THEIR CONSTITUTIONAL TYPE FEATURES

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**ABSTRACT** — The article offers the results of an anthropometric study of the foot sole (plantography) in schoolchildren, as well as analyzes the dependence that flatfoot features on the body constitution type.

**KEYWORDS** — flatfoot, anthropometry, schoolchildren, constitutional type, plantography.

## INTRODUCTION

Mobility plays a very important part in human life nowadays. Living one's life up to the fullest potential implies constant movement, which, in turn, involves health and proper musculoskeletal functioning [3, 6, 7]. The issue of flatfoot has always been in the focus of researchers since it results in fatigue when walking, pain in the feet, knees, hips and lower back, back-pain, and impaired posture [1, 2, 4, 5]. Despite a rather wide scatter in the respective figures, most authors agree that this disease is common and affects various groups of the population, especially students. In this regard, studying the correlation of constitutional types and changes in the feet arch in schoolers appears an urgent issue.

Morphological studies require not only a qualitative description of the object studied, yet also a detailed account of its quantitative features [8, 10, 13]. Traditional instrumental and high-tech anthropometric methods, if employed, allow identifying the qualitative and quantitative morphological features of the somatotype, their age- or gender-related, physiological or pathological variability, which, in turn, would offer a chance for an objective and reliable evaluation of the basic anatomical features [9, 11, 12, 14].

*Aim of study:*

to identify the patterns of flatfoot in schoolchildren related to the body constitution type.

## MATERIALS AND METHODS

The study was carried out in the Medicine & Biological School, City of Saratov (Russia) among students aged 12–17 and attending grades 6–11. The study involved 145 school students. The anthropometric evaluation was carried out following the generally accepted methodology (V.S. Speransky, V.N. Nikolenko, etc.) employing a standard set of anthropometric tools: a measuring tape (cloth; in centimeters; step — 1 mm), electronic medical scales and a plastic height meter (step — 1 cm). The plantographic study was carried out based on the anthropometric points on the foot sole, which were marked on their graphic prints.

*Research Methodology:*

— draw a line from the center of the heel print to the interdigital space of the third and fourth toes;
— identify the most protruding points on the inner contour of the foot in the front and heel areas and connect them (tangent AK);
— from the center of the tangent, recover the perpendicular to the intersection with the first line;
— divide the resulting segment into three equal parts. Numbering starts from the inside of the print to the outside. I degree flatfoot — the inner contour of the print falls within the first interval; II degree flatfoot — the inner contour of the print belongs to the second interval; III degree flatfoot — the inner contour lies within the third interval.

*Transverse flatfoot detection*

— on the foot print, we identify the most prominent points on the inner and outer sides of the forefoot – points A and B, corresponding to the heads of the 1st and 5th metatarsal bones, and connect them together;
— through point B on the print outer side, and the most prominent heel point, draw a tangent to which we restore the perpendicular running from point D — the extreme rear point of the heel print, thus getting point E;
— place point P on the most prominent edge of the big (or second) toe. DP is the print length.

— multiply the length of the DP segment by 0.16 and measure it from point E along the BE line. This is point C. CE = 0.16 · DP;
— from point C we recover the perpendicular to the BE line. CC¢ is the middle calcaneal axis;
— cut the CC¢ segment in half, which offers us point F — the middle calcaneal point;
— cut the AB segment in half and get point Z;
— connect points F and Z thus getting the conditional foot axis;
— from points A and B, draw lines AN and BR parallel to FZ (the conditional foot axis);
— from points A and B, draw lines AP and BQ through the extreme front points of the 1st and the 5th toes.

Normally, the angle at the first toe (NAP angle) is below 18°, while the angle at the fifth toe (QBR angle) is less than 12° (Fig. 1).

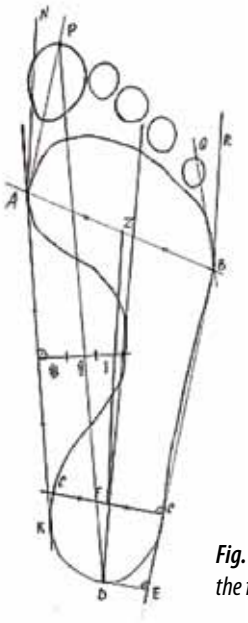

*Fig. 1. Anthropometric points of the sole of the foot for plantography*

The work implied identifying the body type. The classifications employed here were those by Chernorutsky, Shevkunenko, as well as Vervek index.

1. Chernorutsky identifies 3 body types: asthenic, normosthenic and hypersthenic. To classify a certain person's type involves calculating a numerical index, or Pignet index, which is based on the formula below:

$$I = L - (M + R)$$

$L$ — body length (cm), $M$ — body mass (kg), $R$ — chest circumference (cm).

Depending on the numbers obtained, there are 3 types of body to be described:

Asthenic at $I > 30$, normostenic $10 < I < 30$ and hypersthenic $I < 10$ types. The lower the numerical index, the larger the body.

2. Shevkunenko mentions brachymorphic, mesomorphic and dolichomorphic body types. The criterion is the ratio of the shoulders width to the length of the entire body. (Less than 22 — dolichomorphism, 22–33 — mesomorphism, above 33 — brachymorphism).

3. Besides, attributing to a particular type can be done through Vervek body mass-to-length index. This is a specific indicator of the harmony of growth. In healthy children, it does not change over age and is calculated by the formula below:

$$\frac{L}{2P + R}$$

$L$ — body length (cm), $P$ — weight (kg), $R$ — chest circumference (cm). Normally, the index value varies from 0.85 to 1.25. These are the limits for the mesomorphic body type. The index of 0.85 and below indicates that the child is delayed in growth; in case it is above 1.25, this is considered to be a sign of dolichomorphism and the predominance of growth in length.

The participants within this study had many indicators examined, namely height, weight, epigastric angle, chest circumference, shoulder width.

To process the obtained data, the RuleMarker program version 2.3 was used (JSC IT Ltd., St. Petersburg, 1992); application package for statistical data processing Statgraphics 4.0; 1D and 2D programs — elementary statistics; Microsoft Excel for Windows 2000 (Microsoft Corp.). Differences in indicators were considered significant at $p < 0.05$.

## ORIGINAL DATA

Based on the classification by Chernorutsky, the students were divided into 3 groups: asthenics (44.8%), normosthenics (48.1%), hypersthenics (7.1%) (Fig. 2).

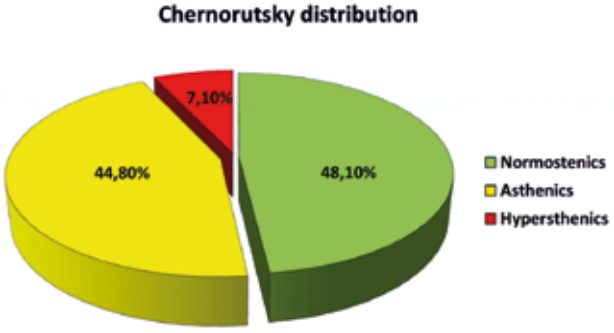


*Fig. 2. Distribution by somatic types (%): normostenics, asthenics, hypersthenics*

Following the classification by Shevkunenko, only schoolers with mesomorphic (93.7%) and dolichomorphic body types (6.3%) were identified among the study participants (Fig. 3).

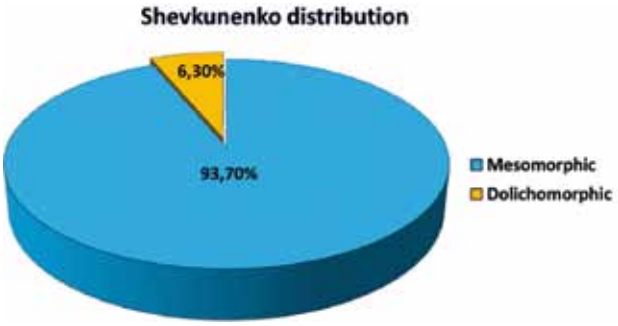


***Fig. 3.*** *Distribution of the examined by body type (%): mesomorphic, dolichomorphic*

In most observations (62.2%), the Vervek index fell within the range of 1.25–0.85 units, which indicates harmonious development; 37.8% of the observations in the group revealed delay (index below 0.75 units), while no tall students were observed in this sample (1.35–1.25 units) (Fig. 4).

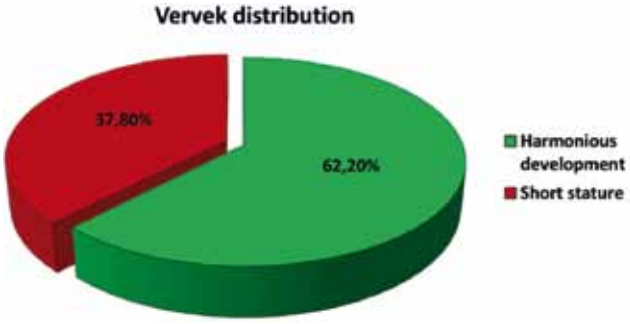


***Fig. 4.*** *The occurrence of harmonious development (%): harmonious development, short stature*

Table 1 shows the results for all the students involved in the study.

The weight of the students varied from 34 to 84 kg, the average of that being 55.4 kg; the variability for this feature was average (16.5%). This is the highest indicator of the variability coefficient of all the features taken into account. The average height was 166.17 cm. In general, this feature varies from 140 to 190 cm. The variability coefficient was low (5.16%). The chest circumference varied from 65 to 103 cm, the variability is low (7.15%), which is slightly above that of the height variability. The average value feature was 82.05 cm. The shoulder width was within the range of 34–51, the variability was low (7.69%), the average value — 40.88 cm.

Tables 2 and 3 present the results of a survey involving high school students of 2 age groups: youth and adolescents. The average weight for the students in the youth group was 55.94 kg, which is 1.8 kg above the average weight of those belonging to the adolescent group. This feature in the first group (adolescents) is more variable than in the other (youth), the coefficient in the 1st case was 18.84%, in the second — 14.48%. In the adolescent group, the feature ranged from 34 to 84 kg, in the group of young students — from 41 to 76 kg. The boundaries of the feature in the first group were reliably wider than in the second. The height of adolescent students ranged from 140 to 183 cm, among the youth — from 152 to 190 cm. The height variability coefficient for the adolescents, as in the case with the weight, was 0.25% higher. The average height in the group of adolescents was 162.61 cm, which is 5.39 cm below the average height in the group of the youth (168 cm).

The chest circumference in the adolescents ranged from 64 to 103 cm, and among the young students — from 64 to 97 cm. The variability coefficient for this feature in the first group was 7.86%, which is 1.35% above that in the second one, where it was 6.51%. The average value of this feature in the second group was higher than in the first group exceeding it by 0.91 cm. The shoulder width in the group of adolescents ranged from 35 to 51 cm, in the youth group it fell between 34 and 48 cm. The variability coefficient was 7.43% in the first group and 7.68% in the second. The average value of this feature for the young students was slightly lower compared to the adolescents and was 40.43 cm and 41.51 cm, respectively.

Tables 4 and 5 present the results investigating the morphometric features of girls and boys. The average weight for the girls was 53.46 kg, the feature was less variable (coefficient — 14.44%). In young men, the variability coefficient was 18.56% (average variability). The average height for the girls was below that in boys by 6.13 cm (164.14 cm). The same feature for the girls ranged from 150 to 177, for boys — from 140 to 190. The respective variability coefficient in the boys' group was 6.02% (low variability), which is 2.28% above than the coefficient in the group of the girls. The average chest circumference in girls was smaller than in boys by 1.39 cm (82.0 cm). The feature variability in the boys' group was 1.54 times higher than in the group of girls. The feature limits in the young men were wider than in the girls, 64–106 cm and 71–97 cm, respectively. The shoulder width ranged from 38 to 51 among the boys, and from 34 to 49 — among the girls. The variability

***Table 1.*** *Morphometric features of the entire study population*

| Parameters | Variational and statistical indicators | | | |
|---|---|---|---|---|
| | M±m | Min–max | δ | CV% |
| Weight | 55,4±0,81 | 34–84 | 9,14 | 16,5 |
| Height | 166,17±0,76 | 140–190 | 8,58 | 5,16 |
| Chest circumference | 82,05±0,52 | 64–103 | 5,87 | 7,15 |
| Shoulder width | 40,88±0,2 | 34–51 | 3,14 | 7,69 |

***Table 2.*** *Morphometric features of the adolescent students*

| Parameters | Variational and statistical indicators | | | |
|---|---|---|---|---|
| | M±m | Min–max | δ | CV% |
| Weight | 54,14±1,34 | 34–84 | 10,2 | 18,84 |
| Height | 162,61±0,66 | 140–183 | 8,4 | 5,17 |
| Chest circumference | 81,56±0,84 | 64–103 | 6,41 | 7,86 |
| Shoulder width | 41,51±0,4 | 35–51 | 3,08 | 7,43 |

***Table 3.*** *Morphometric features of the students falling in the group of youth*

| Parameters | Variational and statistical indicators | | | |
|---|---|---|---|---|
| | M±m | Min–max | δ | CV% |
| Weight | 55,94±0,96 | 41–76 | 8,10 | 14,48 |
| Height | 168±0,98 | 152–190 | 8,27 | 4,92 |
| Chest circumference | 82,47±0,64 | 64–97 | 5,37 | 6,51 |
| Shoulder width | 40,43±0,37 | 34–48 | 3,11 | 7,68 |

***Table 4.*** *Morphometric features of girls*

| Parameters | Variational and statistical indicators | | | |
|---|---|---|---|---|
| | M±m | Min–max | δ | CV% |
| Weight | 53,46±0,87 | 38–80 | 7,72 | 14,44 |
| Height | 164,14±0,7 | 150–177 | 6,14 | 3,74 |
| Chest circumference | 82,0±0,56 | 71–97 | 4,86 | 5,90 |
| Shoulder width | 39,86±0,32 | 34–49 | 2,81 | 7,05 |

***Table 5.*** *Morphometric features of boys*

| Parameters | Variational and statistical indicators | | | |
|---|---|---|---|---|
| | M±m | Min–max | δ | CV% |
| Weight | 58,77±1,42 | 34–96 | 10,91 | 18,56 |
| Height | 170,27±0,79 | 140–190 | 10,25 | 6,02 |
| Chest circumference | 83,39±0,83 | 64–106 | 7,59 | 9,10 |
| Shoulder width | 43,23±0,46 | 38–51 | 3,02 | 6,96 |

in the first case was 6.96%, in the second — 7.05%. The average value in the group of boys was higher than in the group of girls by 3.37 cm.

In order to identify a link between the body constitution and flatfoot, the groups of participants featuring different types of structure, were similar in the number. The comparative data on the foot archas per each type can be seen from Table 6.

Table 6 shows that among asthenics and hypersthenics, 3 out of 10 students have healthy foot arches with no change, which is not much less than among normostenics (4 out of 10). Among the normostenics, in turn, combined flatfoot occurs more often (3 out of 10) than among hypersthenics (2 out of 10) and 3 times more often than in case with asthenics (1 out of 10). According to the study, a change in the longitudinal foot arch is more common among asthenics (3 out of 10), which is 3 times above normostenics (1 out of 10) and 1.6 times above hypersthenics (2 out of 10). In turn, changed transverse foot arch in asthenics and hypersthenics reveal similar occurrence (3 out of 10), which is slightly higher than in normostenics (2 out of 10).

A survey was held among the participants to identify possible causes. For that, the students had to indicate (if present) not only a previously diagnosed flatfoot, yet also talked about their preference of high-heeled shoes (Fig. 5).

## CONCLUSION

Analyzing the obtained data, we can say that the incidence of flatfoot reveals some insignificant dependence on the general body structure. 71.8% of the students aged 12–18 years revealed changes in the foot arch. The share of change observed in the foot arch

*Table 6. Ratio of students with change observed in the foot arch, and those with no change, per each body constitution type*

| Type of flat feet | Asthenics | Normostenics | Hypersthenics |
|---|---|---|---|
| Transverse | 30% | 20% | 30% |
| Longitudinal | 30% | 10% | 20% |
| Combined | 10% | 30% | 20% |
| Healthy | 30% | 40% | 30% |


*Fig. 5. Footwear preference based on the survey*

among girls is higher than among boys (girls — 77.3%; boys — 60.0%), which could be explained by their lifestyle.

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# MODERN X-RAY DIAGNOSTICS POTENTIAL IN STUDYING MORPHOLOGICAL FEATURES OF THE TEMPORAL BONE MANDIBULAR FOSSA

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**ABSTRACT** — Based on the data obtained through panoramic radiograph analysis and cone-beam computed tomograms involving 213 patients (21–35 y.o.) featuring physiological occlusion and various gnathic and dental types of dental arches, a method has been developed to allow identifying the index of temporomandibular joints' articular fossae, taken as the ratio of the sagittal and the vertical sizes. The study revealed that in case of physiological occlusion there are three major types of the temporal bone articular fossa to be identified: dolichotemporal — *short* and *high*; brachytemporal — *long* and *low*; mesotemporal — *proportional*. It has been proven that with different physiological occlusions, the average type of the articular fossa is typical of those with mesognathic normodontic, brachygnathic macrodontic, and dolichognathic microdontic dental arches, while the articular fossa index is 1.84±0.21, 1.74±0.13 and 1.82±0.24, respectively. The systematization of the data from morphometric studies suggests that in case of physiological retrusion, the articular fossa value index is significantly lower compared to the average type of the articular fossa, whereas it is statistically higher in case we observe protrusion.

**KEYWORDS** — temporomandibular joint, temporal bone articular fossa, cone-beam computed tomography, front teeth physiological protrusion, front teeth physiological retrusion, dental arches.

## INTRODUCTION

Subject to epidemiological studies held by the World Health Organization in more than twenty economically prosperous countries of Europe, Asia and America, there is a very high incidence of temporomandibular joint (TMJ) issues in people of mature age. Clinical TMJ pathologies combined with chewing muscles parafunction, reduce significantly the patients' life quality due to the disabling effect they work on the chewing apparatus, and reveal low efficiency when treated through conservative methods [10, 35, 42, 51]. The temporomandibular joint dysfunction shows significant prevalence, polyetiology, progressive course, as well as a high relapse rate. The combination of the features typical of this disease places it among a number of urgent issues of higher significance in general medical, while the diversity of concepts and approaches to analyzing the TMJ dysfunction etiopathogenesis stirs a lot of interest among those committed to search for highly reliable diagnostic methods, specifically when it comes to the preclinical manifestations stage [17, 41, 68].

Difficulties in diagnosing and treating TMJ diseases are due to not only the lack of a clear understanding of etiopathogenesis, yet could be also accounted for by the extremely diverse clinical image of dysfunctional disorders [2, 16, 36, 50, 54].

Diagnostic issues are taken separately from the holistic view on the status of the dentofacial system as a whole, where TMJ is one of the major elements [3, 14, 30, 49, 61].

The quality and the long-term positive effect of treating dentition issues are the main goal of applied dentistry. The current progress stage in certain areas of clinical dentistry reveals a significant increase in the role of anthropometric, morphological, genetic and functional research methods. When talking about solving priority research and practical problems, we can hardly overestimate the role of the concept implying combined use of diagnostic methods as the basis of an integrated population strategy, which involves a detailed study of the TMJ functional pathology [5–7, 13, 22–24, 29, 32, 38–40].

The TMJ morphology gets quite serious attention in clinical orthodontics and prosthetic dentistry [15, 19, 45, 52]. The location of the joint bone elements is decisive for the lower jaw biomechanics, proof to that being data from various morphometric and functional studies [9, 37, 56, 60].

Currently, it is clinical, instrumental, radiological, graphical, and functional methods that are employed to diagnose TMJ dysfunction, whereas the most reliable of the methods in question include the axiography system, electromyography, computed tomography and magnetic resonance imaging [64, 69].

When examining the TMJ in patients undergoing orthodontic treatment for certain teeth and dentition issues, no pronounced structural changes were detected. At the same time, there was an obvious need for the joint X-ray examination in each case, since some pathology symptoms may manifest at the stage of treatment [20, 26–28, 55, 66].

It is worth noting the works by experts talking about the effect that the front teeth location (protrusive or retrusive) has on the TMJ morphology, as well as on the dependence that the front teeth topography has on the type of dental arches in people with physiological occlusion [8, 18, 33, 47, 58, 63, 65].

There have been signs of sexual dimorphism in teeth and dental arches identified for various physiological and pathological occlusions [11, 31, 46, 57, 62].

A key role in the etiopathogenesis of TMJ issues is assigned to anomalies, maxillofacial deformations [4, 21, 53, 67].

When deciphering teleroentgenograms of patients with TMJ dysfunction, the following indicators are mandatory: the facial and inclinational angles (by Schwartz); the occlusal plane inclination angle; the incisors inclinational angles; the angles showing the chin position and the apical bases of the jaws; the lower jaw head inclination angle in the sagittal plane; the ratio of the lower jaw branches and body size [43].

Based on the teleroentgenogram analysis in the lateral projection, the authors mention the following as the predictors of violated articulation of the lower jaw: prominent sagittal occlusal Spee curve, a multidirectional change in the upper and lower occlusal angles, a tendency to *zeroing* the difference between the angles of the sagittal articular and incisal sagittal angles [34, 44].

The authors note the features of the mandibular joint in people with defects in dental arches of various lengths, including full adentia, as well as the reason for graphic reproduction of dental arches taking into account individual TMJ features, as well as those of the craniofacial unit as a whole [1, 12, 25, 48, 59].

The available research literature offers no data on the TMJ articular fossa morphology in patients with various dental arches and the front teeth position (protrusion, retrusion), which constituted the aim of this study.

*Aim of study:* to identify the linear parameters, the index values of the TMJ articular fossae in people with various physiological occlusions, and reveal the dependence of the articular fossa shape on the type of dental arch.

## MATERIALS AND METHODS

Cone-beam computed tomography was employed for a morphometric study of TMJ in 213 patients (97 males, 116 females; median 29.3 ± 3.4) aged 21–35 years featuring various types of physiological occlusion with no sign of muscle & articular dysfunction. Computed tomography was performed on a Planmeca ProMax® 3D Plus cone-beam computed tomograph with a cephalostat. The data were processed using the Romexis Viewer software package, which allows obtaining, processing, storing, and export 2D and 3D images in the conventional medical universal DICOM file formats. Scanning parameters: voxel size — 200 microns; pixel size — 200 microns; 3D exposure time — 9–33 sec; reconstruction time in 3D mode — 2-30 sec; focal spot size — 0.5 mm; rotation step — 1 mm; step through the slice reconstruction — 1 mm; slice — 0.2 mm.

Physiological occlusion was identified in case of detecting six *Andrews* occlusion keys. The dental arch type (dental, gnathic) was identified in view of the modern classifications. The dental index was determined through the length of the dental arch, which was calculated as the sum of the crown widths (mesial-distal diameters) of 14 teeth (not taking into account the variable third permanent molars) (Fig. 1).

The sum of the crown widths of the 14 upper teeth lying within the range of 111–118 mm revealed the normodontia dental arch type. An arch length below 111 mm revealed microdontia, while macrodontia was observed in case the value went above 118 mm. Thus, the major dental types of the upper dental arches were determined as normodontia, macrodontia and microdontia (Fig. 2).

To determine the gnathic type of the dental arch, two main and relatively stable indicators were used — the size of the teeth and the width of the upper dental arch between the second molars. The measuring points of the second molars were located on the vertices of the vestibular distal tubercles near the occlusal contour of the crowns (Fig. 3).

The ratio of the crown widths half-sum of the 14 teeth to the width of the upper dental arch was indicative of the dental index of the arch, which determined its gnathic type. In case of index values within 0.9–0.97, the type of the dental arches was referred to as mesognathic. The index value below 0.9 was attributed to the brachygnathic type, while a value above 0.97 — to the dolichognathic type of dental arches (Fig. 4).

The morphometric study of TMJ used tomograms of the right and left sides with subsequent data analysis. For convenience, we used a technique for identifying the vertical and the sagittal size selecting three major types of the articular fossa.

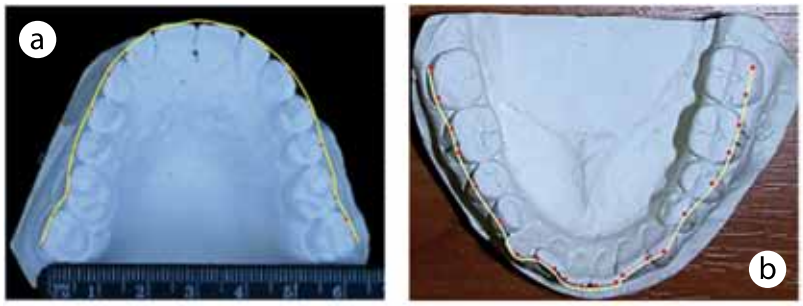


***Fig. 1.*** *Photographs of plaster models of the upper jaw (a) and lower jaw (b) with plotted contours of the tooth vestibular arc*

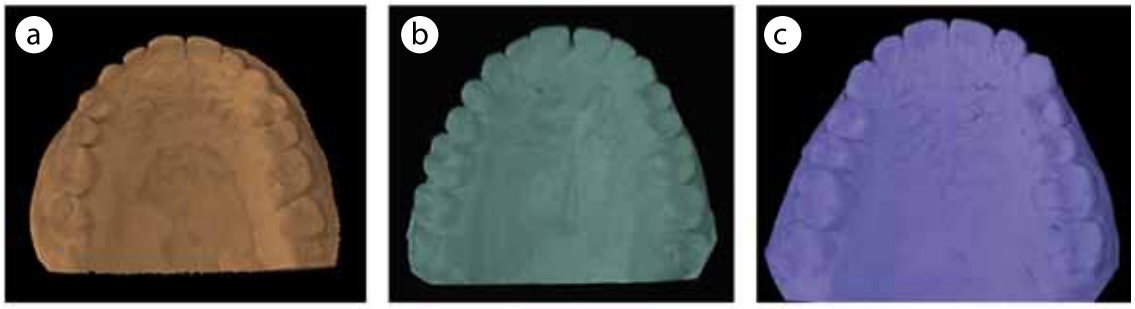


***Fig. 2.*** *Upper jaw cast model images featuring microdontism (a), normodontism (b) and macrodontism (c)*


***Fig. 3.*** *Width, depth and diagonal of the dental arches of the maxilla (a) and lower (b) jaw*

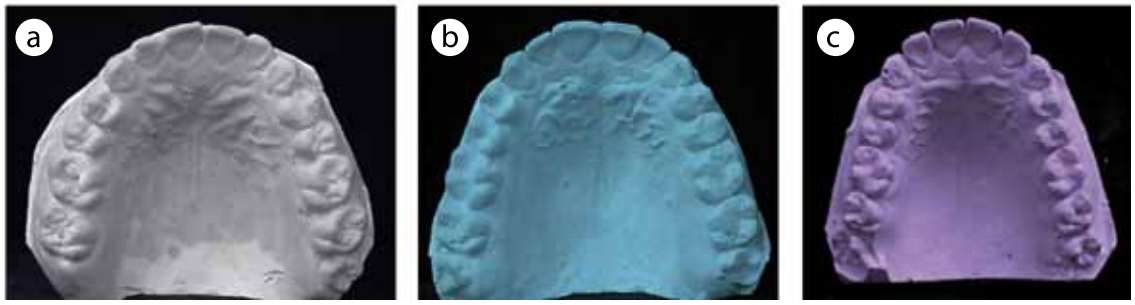


***Fig. 4.*** *Upper jaw cast model images with brachygnathic (a), mesognathic (b) and dolichognathic (c) dental arches*

### *Morphometric study methods*

The major anthropometric points were placed on the TMJ tomograms in the sagittal projection: A was a point on the lower edge of the external auditory canal; B was the point located on the articular tubercle slope; C was the top point of the articular fossa. Further, the lines were constructed: a horizontal line connecting the lower edge of the external auditory meatus (A) with the point located on the articular tubercle slope (B); a vertical line (CD), running down from the articular fossa top (C) perpendicular to the horizontal AB line. The sagittal (EB) and vertical (CD) sizes of

the articular fossa were measured, followed with identifying the articular fossa index taken as the ratio of the sagittal size to the vertical one (Fig. 5).

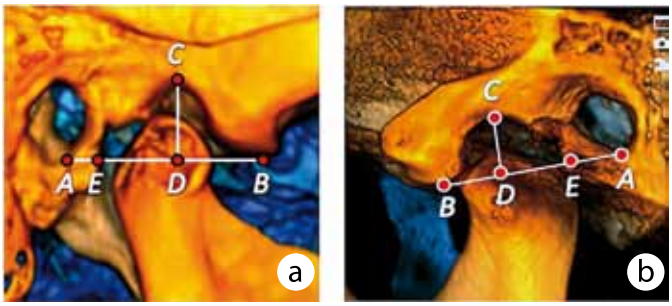


***Fig. 5.*** *The major reference points for measuring the linear parameters of the temporomandibular joint articular fossa on a CT scan: a — on the right, b — on the left.*

The shape of the mandibular (articular) fossa of the temporal bone was identified through the index value: dolichotemporal — *short* and *high*; brachytemporal — *long* and *low*; *mesotemporal — proportional*.

For statistical processing of the obtained data, the software products STATISTICA 8.0 and SPSS 22.0 (StatSoft, USA) were used. For each feature, the arithmetic mean value and the arithmetic mean error were identified. When establishing the significance difference between the average values from the counter-lateral sides, the Student t-test was identified. To identify the difference significance between the average parameters through comparing variances, we employed analysis of variance (ANOVA). The value of $p \leq 0.05$ was taken as the critical significance level.

## RESULTS AND DISCUSSION

The sagittal dimensions of the articular fossa of people with different physiological occlusions varied from 15.70 mm to 20.74 mm, while the articular fossa height was less susceptible to fluctuations, and the values ranged from 8.12 mm to 10.04 mm. The data obtained allowed calculating the articular fossa index for the mesotemporal type — 48.59 ± 1.82%. A decrease in the sagittal (less than 15.70 mm) sizes and an increase in the fossa height (beyond 10.04 mm) were considered as the dolichotemporal (*short* and *high*) type of the articular fossa (index value — 56.65 ± 2.12%). At the same time, an increase in the anteroposterior size exceeding 20.74 mm and a decrease in its height below 8.12 mm was defined as the brachytemporal (*long* and *low*) articular fossa (index value — 35.29 ± 1.74 %).

Table 1 offers a view on the morphometric parameters of the mandibular (articular) fossa of the temporal bone for various types of (dental, gnathic) dental arches.

Morphometric studies showed that people with normodont dental arches had the variability of the articular fossa size both in the sagittal and vertical planes. The smallest sagittal sizes were observed in people with brachygnathia (14.79 ± 1.37 mm), while the largest ones – in dolichognathia cases (22.12 ± 1.19 mm, $p \leq 0.05$). The vertical parameters had differences, too, and people with dolichognathia had a height of the articular fossa (8.93 ± 0.76 mm) that was significantly smaller than in cases with brachygnathia (12.53 ± 0.49 mm). The obtained data makes it obvious that the dental arch type affects the shape of the articular fossa. However, no such regularity was revealed through the analysis of the indicated gnathic types with macro-, normo-, and microdontism. People with macrodontism, for instance, had no difference in the sagittal sizes in cases of meso- and dolichognathia. This applies to the vertical dimensional parameters of the articular fossa as well. In case of microdental dental arches, a similar pattern was revealed with brachy- and mesognathia. No attempt to detect a link between the articular fossa shape and the gnathic types of dental arches (taking into account odontometric indicators) yielded any fruit.

Despite the numerous gnathic and dental types of dental arches, we have shown a certain pattern, which is due to the front teeth location. The research data indicate that the magnitude of the inter-incisal angle for different types of (dental, gnathic) dental arches is not the same. The incisors protrusive position and a decrease in the incisal angle are observed in people with mesognathy and macrodontism, and can also be found in patients falling into the group of dolichognathic dental arches with normo- and macrodontism. There is every reason to note that the shape of the articular fossa for these types of (dental, gnathic) dental arches is *long* and *low*, whereas the articular fossa index (the ratio of the sagittal to the vertical size) was 2.40 ± 0.22 for the mesognathic macrodont type; in case of the dolichognathic normodont type — 2.48 ± 0.27; for the dolichognathic macrodont type — 2.41 ± 0.19 (Fig. 6).

We have found that people with the retrusive position of the incisors and increased sizes of the incisal angle, the articular fossa shape in the sagittal direction is *short* and *high*, and therefore, the articular fossa index is significantly lower than in people with the protrusive position of the front group teeth. In case of the brachygnathic normodont type of dental arches, for instance, the articular fossa index was 1.18 ± 0.16,

***Table 1.*** *Morphometric parameters of the temporal bone articular fossa for various types of (dental, gnathic) dental arches, (M ± m), (mm), (p ≤ 0.05)*

| Physiological options for dental arches | Parameters of the articular fossa: | | |
|---|---|---|---|
| | Sagittal parameters | Vertical parameters | Ratio |
| Mesognathia, normodontism | 18,34±1,26 | 9,96±0,58 | 1,84±0,21 |
| Brachygnathia, normodontism | 14,79±1,37 | 12,53±0,49 | 1,18±0,16 |
| Dolichognathia, normodontism | 22,12±1,19 | 8,93±0,76 | 2,48±0,27 |
| Mesognathia, macrodontism | 21,28±1,14 | 8,87±0,36 | 2,40±0,22 |
| Brachygnathia, macrodontism | 18,59±1,13 | 10,67±0,88 | 1,74±0,13 |
| Dolichognathia, macrodontism | 21,71±1,23 | 9,01±0,74 | 2,41±0,19 |
| Mesognathia, microdontism | 15,03±1,02 | 13,07±1,04 | 1,15±0,19 |
| Brachygnathia, microdontism | 15,21±1,12 | 12,28±0,64 | 1,24±0,11 |
| Dolichognathia, microdontism | 17,96±1,08 | 9,87±0,89 | 1,82±0,24 |

in the case of the brachygnathic microdont type — 1.24 ± 0.11, and in the mesognathic microdont type — 1.15 ± 0.19 (Fig. 7).

The study outcomes show that in case of the incisors protrusive position, the shape of the articular fossa is significantly different from the articular fossa shape with the front teeth retrusion.

Note to be made that the incisors position affects the lower jaw biomechanics, and is reflected in the morphology of the temporomandibular joint major elements. Patients with averaged values of the incisal angle, for instance, had the ratio of sagittal sizes to the articular fossa height for the mesognathic normodont dental arches equal to 1.84 ± 0.21, for the brachygnathic macrodont type — 1.74 ± 0.13, and in case of the dolichognathic microdont type — 1.82 ± 0.24 (Fig. 8).

Systematizing morphometric data from the TMJ computed tomograms of patients with physiological occlusion and various types (dental, gnathic) dental arches allows distinguishing three major shapes of the mandibular (articular) fossa of the temporal bone: *dolichotemporal — short* and *high*; *brachytemporal — long* and *low*; *mesotemporal – proportional* (Fig. 9).

The above-described examination of the temporomandibular joint based on modern methods of X-ray should be mandatory in a clinic for orthopedic dentistry and orthodontics involving comprehensive examination, selecting the treatment tactics in patients with dentofacial anomalies, as well as evaluating the effectiveness of the dental treatment (rehabilitation).

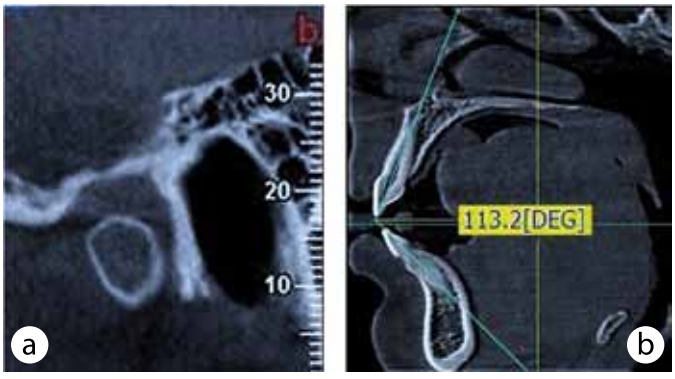


***Fig. 6.*** *Brachytemporal articular fossa (a) tomograms in the protrusive position (b) of the medial incisors*

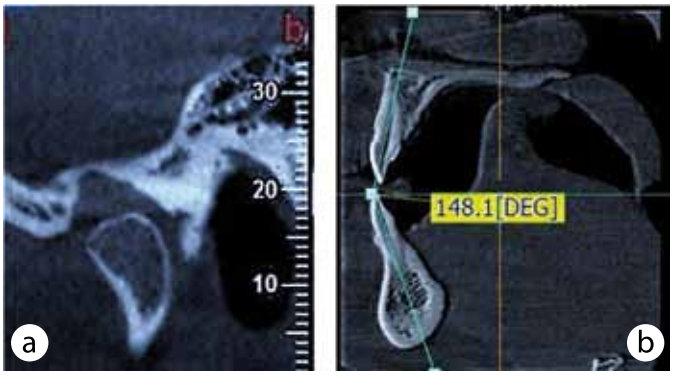


***Fig. 7.*** *Dolichotemporal articular fossa (a) tomograms in the retrusive position (b) of the medial incisors*

## CONCLUSIONS

1. The obtained results prove a link between the temporal bone mandibular (articular) fossa shape and various types of (gnathic, dental) dental arches. The type (brachy-, meso-, dolichotemporal) of the temporomandibular joint articular fossa is expressed as index values through the ratio of the sagittal and vertical size values.

2. A decrease in the interdental angle size at physiological protrusion of the front teeth is associated with

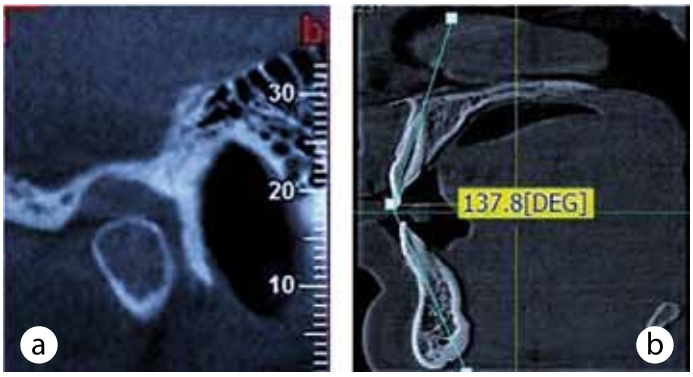


***Fig. 8.*** *Mesotemporal articular fossa (a) tomogram with the mesotrusive position (b) of the medial incisors.*

a significant dominance of the sagittal sizes over the vertical ones, which determines the articular fossa shape (in terms of the visual expression) as *long* and *low*. The brachytemporal type of the articular fossa is to be observed in people with mesognathia and macrodontism, as well as in patients with dolichognathic dental arches with normo- and macrodontism.

3. Increased interdental angle with the retrusive front teeth is associated by a decrease in the articular fossa index, if compared with the protrusive incisors indicators, thus visually setting the articular fossa shape as *short* and *high*. The dolichotemporal type of the articular fossa is predominant in people with mesognathy and microdontism, as well as in patients with brachygnathic types of dental arches with normo- and microdontism.

4. The averaged interincisal angle values in the mesotrusive position of the front teeth visualize the shape of the articular fossa as *proportional*. The mesotemporal type of the articular fossa can be observed in people with mesognathy and normodontism, as well as in patients with the brachygnathic macrodont and dolichognathic microdont dental arches.

5. Cone-beam computed tomography, which features its own specifics, high sensitivity, and low radiation exposure, allows obtaining the most comprehensive diagnostic data regarding the morphostructural status of the temporomandibular joint hard tissues. Improving the algorithms for visualization and analysis of the temporomandibular joint bone structures, taking into account the patient's individual features, would allow standardizing dental research methods as well as modifying the conventional systems for analyz-

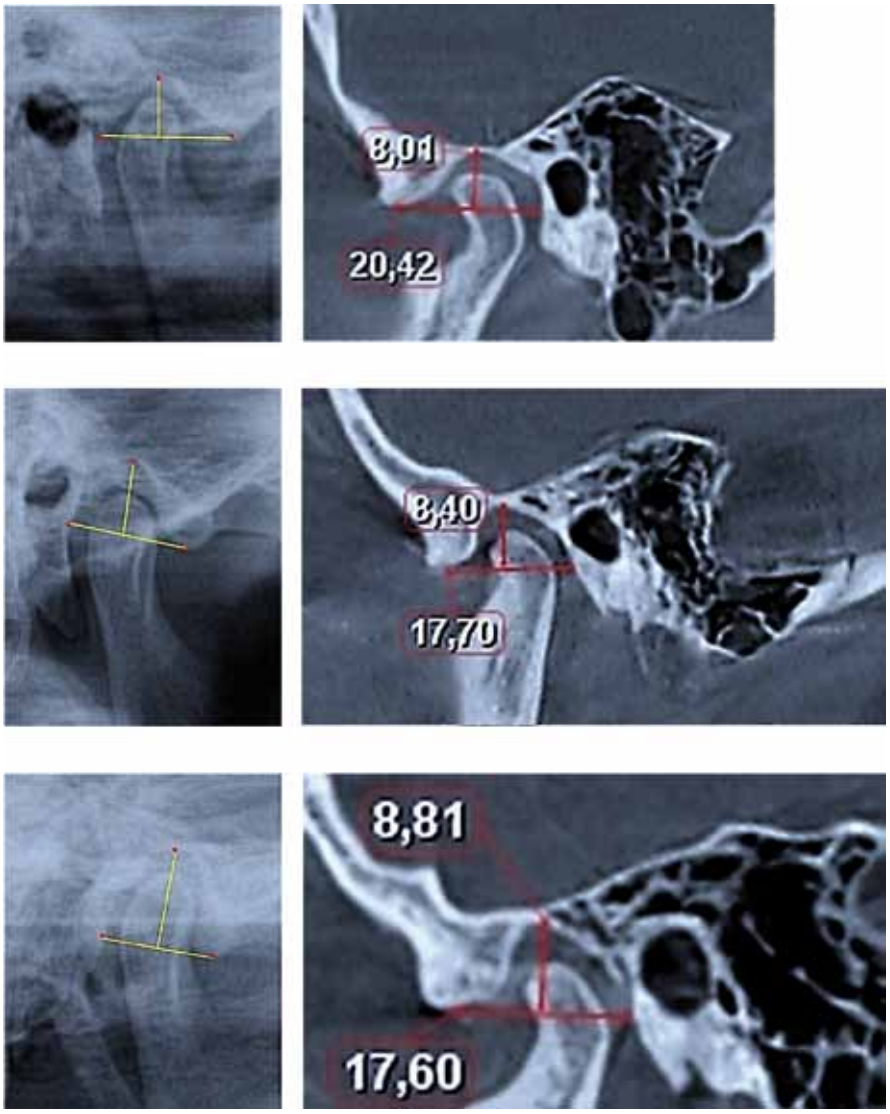


***Fig. 9.*** *X-ray image (a, c, e) and tomogram (b, d, f) of the TMJ in people with physiological occlusion and protrusive (a-b), mesotrusive (c-d) and retrusive (e-f) position of the front teeth*

ing and interpreting data obtained for the reliable diagnostics of patients revealing dentoalveolar anomalies and deformations.

6. The inclusion of the averaged index values of the temporal bone articular fossa for various types of dental arches in people with physiological occlusion in the *Clinical protocols for diagnostics and orthodontic treatment of dentoalveolar anomalies in outpatient settings* would reduce significantly the time orthodontist has to spend through clinical examination and setting the diagnosis, achieve a stable long-term treatment result, increase the efficiency of occlusal disorders diagnostics, identify the presence (absence) of maxillofacial gnathic pathology, and minimize the risk of complications.

7. The potential of further detailed investigation into the etiopathogenetic mechanisms of the temporomandibular joint dysfunction can be explained by the research-proven range of diagnostic capacities of modern dentistry, as well as by the development of highly reliable digital diagnostics technologies.

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# STRUCTURAL ARRANGEMENT OF THE TEMPOROMANDIBULAR JOINT IN VIEW OF THE CONSTITUTIONAL ANATOMY

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**ABSTRACT** — Based on the data obtained through panoramic roentgenograms, cone beam computed tomograms from 297 people featuring various somatotypes, orthognathic bite, and no sign of dentoalveolar pathology, we identified the morphometric parameters for the temporal bone mandibular (articular) fossa, and for the lower jaw head, followed with calculation of index values and the temporomandibular joint temporal congruent index. Depending on the linear and index values of the articular fossa, the patients were diagnosed with a brachio-, meso- and dolichotemporal type of the temporomandibular joint. The articular fossa index value (48.59 ± 1.82%) of the mesotemporal type indicates a double prevalence of the anterio-posterior parameter over the vertical one; a decrease in the index down to 35.29 ± 1.74% for the brachytemporal type means a more significant reduction in the articular fossa vertical size (*long* and *low*); an increase in the index up to 56.65 ± 2.12% of the dolichotemporal type points at an increase in the articular fossa vertical parameters (*short* and *high*). Regardless of the articular fossa type, in case of the orthognathic bite, the lower jaw head has been proven to occupy no more than 56.33% of the temporomandibular joint volume, evidence to that being the congruency index value. Analysis of constitutional types suggests the predominance of patients with the asthenic type of physique (56.6 ± 4.3%) over those with a normosthenic (27.3% + 2.9%) and a hypersthenic ones (16.1 ± 2.3%). Further study of the issues related to the temporomandibular joint individual variability in people with different types of body constitution will allow customizing the approach to therapy & prevention measures, as well as it would make help predict the treatment outcomes for patients with muscle & joint dysfunction.

**KEYWORDS** — temporomandibular joint, individual typological variability, constitutional anatomy, cone beam computed tomography, physiological occlusion.

## INTRODUCTION

Unresolved issues involving the structural arrangement (morphology, topography) and the temporomandibular joint (TMJ) functions, the spatial location in the skull and the relationship with other areas of the craniofacial complex, as well as the specific features of pathology diagnostics — all these are within the research and clinical focus. The data published on the issue is ambiguous, which is another proof to lack of clearly defined ideas concerning the TMJ anatomy, physiology in terms of gender differences, age-related changes, dentofacial system diseases, as well as constitutional (somatotypic) features [6, 35, 41, 51, 55, 58]. Experts claim that the supporting teeth apparatus, the chewing muscles and the TMJ constitute an interconnected functional unit that has stable self-regulation involving all the active components and ensuring effective operation of the entire dentition. The highly coordinated activity of the TMJ elements, taken as a complex anatomical unit, is regulated by the central nervous system through the muscle contractile activity, and is manifested by the balance of the left and right joints, and the presence of not only articulating (rotational) yet also translational movements along with pronounced adaptive & compensatory capacity in the joint [1, 13, 34, 42, 47–49, 54, 57, 60].

The epidemiological studies carried out in Russia reveal that the prevalence of structural and functional pathology of TMJ in the adult population reaches 89.4%, in young people — 61.3%, second only to dental caries and periodontal diseases. Despite the high incidence, TMJ diseases fall within the most complex and poorly studied groups of human pathology, while the respective issues implying improved methods of complex diagnostics, treatment and rehabilitation are extremely urgent and important in modern dentistry [52].

One of the key factors that determines the biochemical body features, and, therefore, the specifics of the constitution (body type), is the mesoderm parenchyma (mesenchyme). Depending on the quality and volume of the connective tissue found in the body, the following constitutional types have been identified (A. Bogomolets, 1926): asthenic — with tender and thin connective tissue dominating; fibrous — featuring the prevalence of dense and fibrous connective

tissue; pasty — with quaggy and edematous connective tissue prevailing; lipomatous — with abundant fat tissue (adipose degeneration). The somatotype is the result of the morphological parameters, which points at a particular body constitution type (Nikityuk B.A., 1995).

Experts have established a close link between the body reactivity, the metabolic intensity, the immune and endocrine status on the one hand, and body type on the other. The introduction of the population-centric somatotyping scheme, which is commonly observed in preventive medicine and clinical practice, is due to the sensitivity in assessing the individual development and the metabolic process rates; the simplicity of the method requiring a minimum number of anthropometric measurements; the proven link between clinically significant features and the somatotype; potential use of an individual-typological approach when analyzing the major values, as well as the established *physiological norm* of signs taking into account the body type and the racial and ethnic background [3–5, 8, 10, 12, 16, 19, 36, 46, 51, 56, 63].

Constitutional morphological diagnostics belongs to the research field of both theoretical and applied medicine. Currently, apart from the conventional anatomical and anthropometric approaches, there are also advanced high-tech research methods available, which allow proper evaluation of individual morphological features. Further research in clinical medicine is to be focused not only on the genetic predisposition in case of certain diseases observed in various morphological body constitutions, yet also on the fact that a particular body type can be viewed as a favorable factor, which may be indicative of a sufficient adjustment potential and lower likelihood of developing certain pathologies [2, 7, 9, 11, 15, 18, 20, 24, 27, 32, 38–40].

TMJ histomorphological studies helped identify five physiological structures (*norms*) (Petrosov Yu.A., 2007). Option one is a combination of a deep mandibular fossa with a well-developed lower jaw head. Option two is a small head of the lower jaw combined with a narrow and deep mandibular fossa. A third option is a combination of a well-developed lower jaw head with a narrow and deep mandibular fossa. Option four implies a small head of the lower jaw combined with a mandibular fossa that is flattened and wide. And another option is a combination of a well-developed lower jaw head with a shallow and wide mandibular fossa. The TMJ type that matches the first option is considered the standard *norm*, while the remaining ones are viewed as potentially sensitive to the development of morphofunctional disorders.

Morphologists and dentists take specific interest in data on the anatomical and topographic structure of TMJ elements at the stages of the craniofacial complex development. Research literature offers description of the relationship between the position of the lower jaw head and facial morphology. People with a vertical growth type of the facial part have been identified as featuring disturbed position of the lower jaw head much more often than persons with the horizontal growth type [17, 22, 26, 33, 53, 65]. X-ray diagnostic methods analysis indicates that a decrease in the anterior articular space is typical of the vertical type of facial growth, and, on the contrary, an increase in the anterior articular space is to be observed with the vertical type of growth [14, 21, 23, 25, 28, 29, 43–45, 61, 64].

The difficulty studying the temporomandibular joint can be accounted for by its small size, different density of the elements, the proximity to the skull base, later manifestation of clinical and diagnostic symptoms of dysfunction with a long latent period, as well as by low reliability of the methods like tomography, panoramic radiography, orthopantomography, contrast arthrography, which is due to the technology specifics [30, 37].

Employing methods for TMJ visualization using cone beam computed tomography and magnetic resonance imaging taken as advanced, high-tech, precision X-ray diagnostics methods, allows obtaining high-resolution 3D images; identifying the bone and soft tissue element status (articular disc, joint ligaments), as well as to studying their movement through function; conducting densitometric and planimetric studies; registering angular parameters to select proper diagnostics and treatment for patients with congenital and/or acquired maxillofacial pathologies [31].

Research works propose methods for measuring the temporal bone articular fossa and the lower jaw articular heads, which allow estimating the joint space size and the articular head location at different positions of the lower jaw [59, 62]. The available literature offers no account of index values that determine the ratio of the TMJ articular head and articular fossae size in people with physiological occlusion, as well as there is no data on the congruence of the major elements of the joint. Besides, there is no sufficient data on the link between the patient's body type and TMJ individual features, which was the purpose of this present study.

*Aim of study:*
to identify the linear parameters, the index values of the temporomandibular joint elements in people with the permanent teeth orthognathic bite and different body constitution types.

## MATERIALS AND METHODS

A clinical and X-ray examination of the temporomandibular joint was performed involving 297 people

(143 males, 154 females; median age 27.4 ± 2.1) in their first adulthood period, with complete dentition, orthognathic bite, and no sign of muscle & articular dysfunction. Following the age periodization scheme recommended by the VII All-Union Conference on Age Morphology, Physiology and Biochemistry (Moscow, 1965), the first period of adulthood for males is 22–35, while for females it is 21–35.

X-ray methods for the temporomandibular joint examination included panoramic radiography and cone beam computed tomography. The panoramic study was carried out on RayscanSymphonyAlpha 3D X-ray machine (South Korea) in the panoramic shooting software TEMPOROMANDIBULAR JOINT LATERAL PROJECTION (open, closed). The outcomes were processed using RayScanver. 2.0.0.0 offering the option of receiving, processing and storing data in the DICOM3.0-compatible format. The features of the panoramic shooting were: voxel size — 140–230 μm; magnification — 1.3; sensor — CMOS; focal spot — 0.5 mm; time — 2–14 s; panoramic image size — 148 mm; detector resolution — 630 × 1024 pixels. We used radiographs to evaluate the temporomandibular joint elements location at different positions of the lower jaw (closing in the usual occlusion, closing with the lower jaw forward, closing with the lower jaw down). Fig. 1 offers a view on the temporomandibular joint radiographs in the lateral projection.

***Basic linear dimensions measuring method***. The radiographs of the temporomandibular joint in the lateral projection get marked with the major anthropometric landmarks — the greatest convexity point of the articular tubercle; the point located on the lower edge of the external auditory meatus; the top point of the articular head. Further, the length of the articular fossa (head) was measured — between the greatest convexity points of the articular tubercle and the point located on the lower edge of the external auditory meatus, as well as the height of the articular fossa (head) in the vertical direction — between the articular head upper point and the point shaped by the intersection of the perpendicular and the horizontal lines (Fig. 2).

The computed tomography scanning of the temporomandibular joint was performed on a PaX-i3D SC cone beam tomograph with a FOV cephalostat (17×15 cm) (VATECH Global, South Korea). The results were processed using the following software products: dental graphic program SimPlant (Materialize Dental, Belgium) — for simultaneous viewing of axial, transverse (cross-section), panoramic sections; Viewer™ (Windows) software — for archiving, viewing, and importing data; EzDent-I™ (VATECH) software for obtaining, processing, storing, and exporting data in the DICOM JPG universal medical file formats; the diagnostic software Ez 3D-I™ (VATECH) — for three-dimensional (3D) and multiplanar reconstruction. Scan parameters — voxel size — 0.12/0.2/0.3 mm; time — 5.9 s in LowDose/UltraLowDose mode; scanning area size (FOV) — 12×9 cm; rotation step — 1 mm; reconstruction step — 1 mm; section thickness — 1 mm (Fig. 3, 4).

We believe that the following should be pointed out as the advantages of cone beam computed tomography with pre-panoramic radiography while studying the temporomandibular joint: precision; reduced radiation exposure; high-definition images of bone articular elements; imaging of bone articular surfaces in all planes; lack of projection distortions and overlays; visualization (in view of the change degree in contrast and brightness) of the hypertrophy signs of the masticatory muscles, which is necessary to establish the muscle involvement in case of dysfunctional disorders. The identified anthropometric marks allowed calculating the index of the articular (mandibular) fossa as a ratio of height to length. In a similar way, the index of the articular head (lower jaw head) was calculated as the ratio of height to length, expressed in per cent. We believe that when dealing with the dependence between the dimensional parameters of the articular head and articular fossa, there is some reasonable research and applied value in assessing the temporomandibular joint. For this purpose, we have proposed a congruency indicator based on the ratio calculation of the joint head module to the joint fossa module. In this case, the module is calculated as the half-sum of the height to the width of the element in question.

The articular fossa module is taken as 100%. In addition, the marked points allow us to measure linear dimensions in absolute terms and, most importantly, to determine relative indicators, among which the articular fossa index appears reasonable. The articular fossa index is a relative value, which does not require scaling of the joint elements regarding absolute values. A computed increase in the radiographs size when calculating the relative index only increases the statistical reliability of the research results. Systematizing the studied anthropometric parameters makes it obvious that the articular fossa index should be used to interpret the research data and prove the reliability of the proposed classification for the articular fossa — dolichotemporal, mesotemporal and brachytemporal.

The assessment of body types was carried out by determining the height-to-weight value (HWV) following the formula below:

$$HWV = (P / L) \times 100\%;$$

where P is body weight (kg), L is body length (cm).

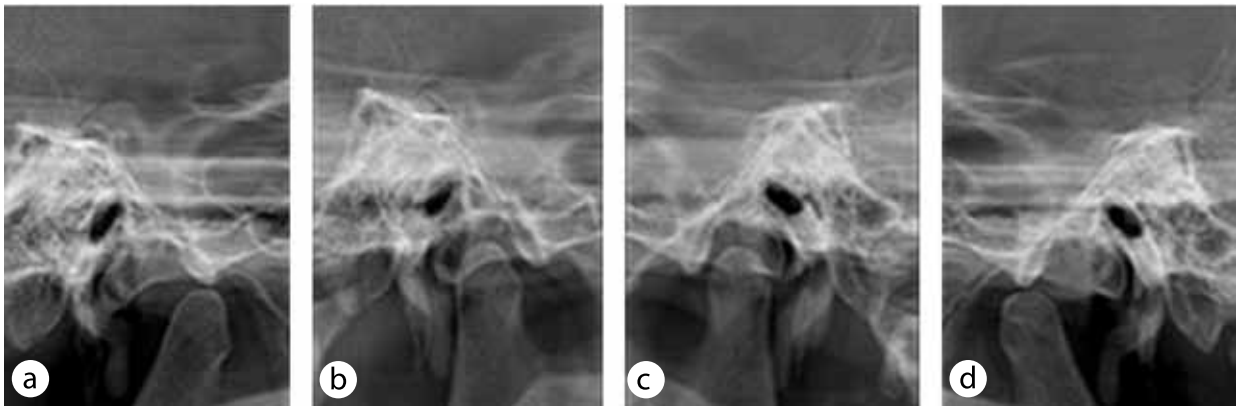


***Fig. 1.*** *Temporomandibular joint radiographs in the lateral projection: a — position open to the right, b — position closed to the right, c — position closed to the left, d — position open to the left*

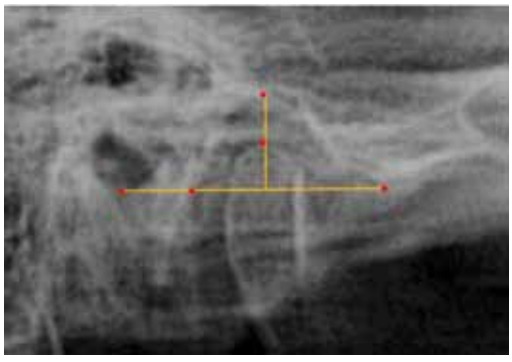

***Fig. 2.*** *Measuring the basic linear dimensions on the temporomandibular joint radiograph on the right*

The normosthenic (lysomorphic) type of body constitution fell within the HWV values of 37–40%. The asthenic (dolichomorphic) somatotype was identified at HWV value of below 37%, while the hypersthenic (brachymorphic) type was observed at an increase in the HWV beyond the regular values.

For statistical processing of the obtained data, the software products STATISTICA 8.0 and SPSS 22.0 (StatSoft, USA) were used. For each feature, the arithmetic mean value and the arithmetic mean error were identified. When establishing the significance difference between the average values from the counter-lateral sides, the Student t-test was identified. To identify the difference significance between the average parameters through comparing variances, we employed analysis of variance (ANOVA). The value of $p \leq 0.05$ was taken as the critical significance level.

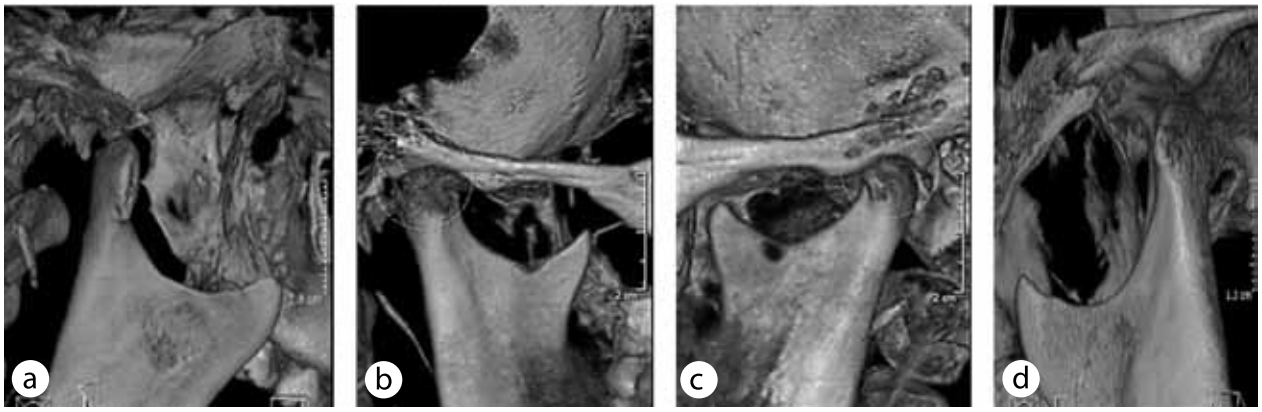


***Fig. 3.*** *The temporomandibular joint image obtained through a CT scan in the open position (a — right, d — left) and closed (b — right, c — left)*

## RESULTS AND DISCUSSION

The preliminary measurements results for the articular fossa in the patients revealed that the average anteroposterior size was 18.02 ± 0.54 mm; the articular fossa height of the temporal bone was 8.56 ± 0.27 mm, while the average index of the articular fossa was at

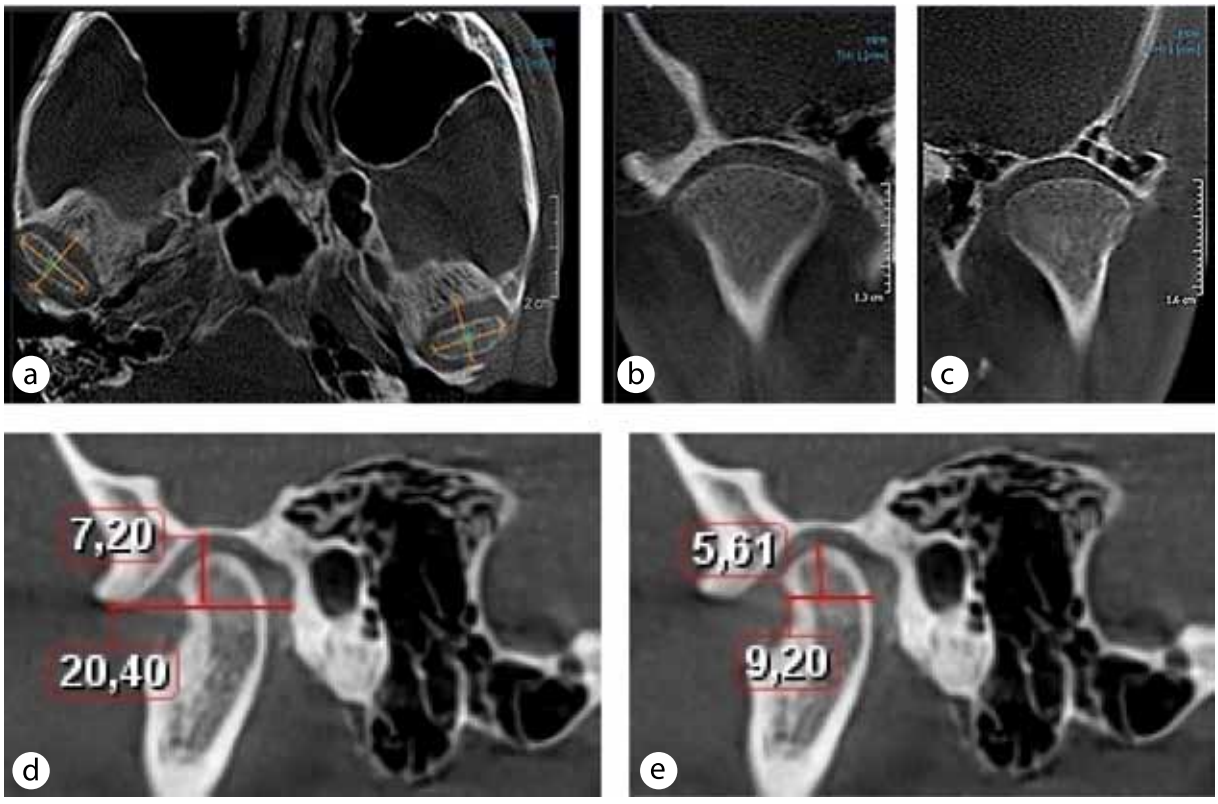


***Fig. 4.*** *The temporomandibular joint image in axial (a), coronary right (b), coronary left (c) and sagittal left projections with the mandibular fossa sizes (d) and the lower jaw head (e)*

47.50 ± 2.08%. Given the statistical data in identifying the confidence limits, going beyond the triple of the representativeness error, offered reasonable grounds for division of the articular fossa by the brachy-, meso- or dolicho-temporal type with a probability of 99.7%. In this regard, the articular fossa is equated to the brachytemporal type with an index below 41%, and the dolichotemporal type — with an index above 54%. Therefore, the articular fossa shape in the brachytemporal type is defined as long and low, whereas in the dolichotemporal type — as short and high.

Table 1 contains the morphometric parameters and index values of the major bone elements for various types of the temporomandibular joint.

A comparative assessment of the morphometric parameters and the index values of the bone elements under study (mandibular fossa, the lower jaw head) for various types of TMJ allows us to identify the presence of statistically significant differences based on our classification.

An analysis of the results of the study (Table 1) offers ground to argue that in case of the brachytemporal type of the temporomandibular joint, the mandibular fossa dimensions in the anteroposterior direction prevail over the vertical parameters (Fig. 5).

For patients with the brachytemporal type of the temporomandibular joint, the articular fossa index was 35.29 ± 1.74%, the fossa module was 13.82 ± 0.54 mm, the articular head module was 6.81 ± 0.23 mm, and the congruence was 49.35 ± 0.77%.

In people with the mesotemporal temporomandibular joint, the mandibular fossa parameters in the anteroposterior direction prevail over the vertical dimensions, too. However, the articular fossa index is significantly higher (48.59 ± 1.82%) than in people with the brachytemporal type (35.29 ± 1.74%) (Fig. 6).

For patients with the mesotemporal type of the temporomandibular joint, the fossa module was 13.15 ± 0.43 mm, the articular head module was 6.99 ± 0.33 mm, and the congruence was 53.19 ± 0.89%.

In people with the dolichotemporal type of the temporomandibular joint, the articular fossa index (56.65 ± 2.12%) exceeded the respective values for the brachytemporal (35.29 ± 1.74%) and mesotemporal (48.59 ± 1.82%) joint types, which visually defined the joint as *high* and *short* (Fig. 7).

For patients with the dolichotemporal type of the temporomandibular joint, the fossa module

***Table 1.*** *Morphometric parameters and index values of the main bone elements for various types of the temporomandibular joint, (M ± m)*

| Morphometric parameters, index values (units) | Types of temporomandibular joint | | |
|---|---|---|---|
| | Brachytemporal | Mesotemporal | Dolichotemporal |
| Pit Width, (mm) | 20,42±0,36* | 17,69±0,41 | 16,01±0,32* |
| Pit Height, (mm) | 7,21±0,89* | 8,61±0,55 | 8,95±0,57* |
| Pit module, (mm) | 13,82±0,54* | 13,15±0,43 | 12,48±0,39* |
| Fossa index, (%) | 35,29±1,74* | 48,59±1,82 | 56,65±2,12* |
| Head Width, (mm) | 8,82±0,31* | 9,02±0,44 | 7,46±0,28* |
| Head Height, (mm) | 4,79±0,19* | 4,97±0,51 | 4,48±0,37* |
| Head module, (mm) | 6,81±0,23* | 6,99±0,33 | 5,97±0,27* |
| Head Index, (%) | 54,42±0,83* | 55,09±0,91 | 60,05±1,37* |
| Congruence, (%) | 49,35±0,77* | 53,19±0,89 | 55,39±0,94* |

***Note:*** ** — statistically significant in relation to the morphometric parameters and index values of patients with the mesotemporal type of the temporomandibular joint ($p \leq 0.05$).*

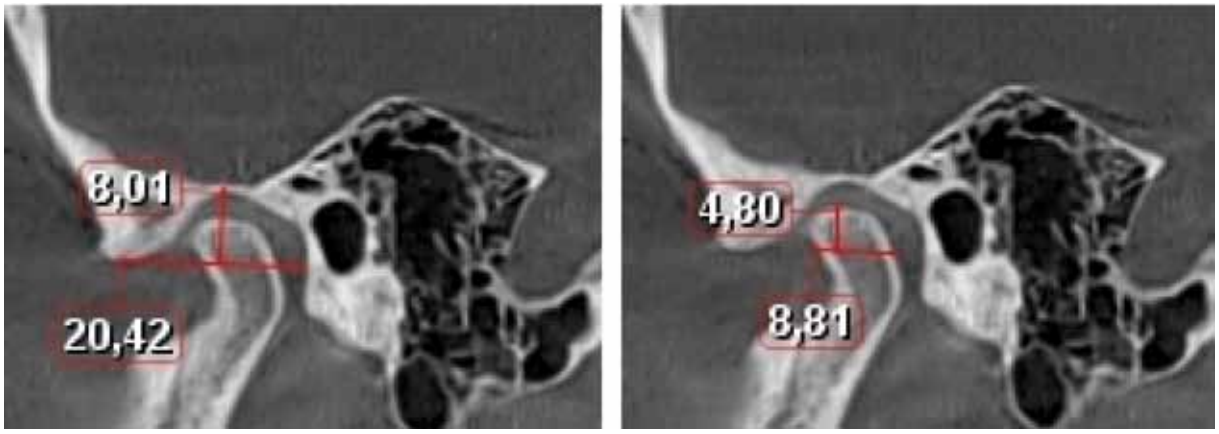


***Fig. 5.*** *Brachytemporal temporomandibular joint tomographic image featuring the sizes of the mandibular fossa (a) and of the lower jaw head (b).*

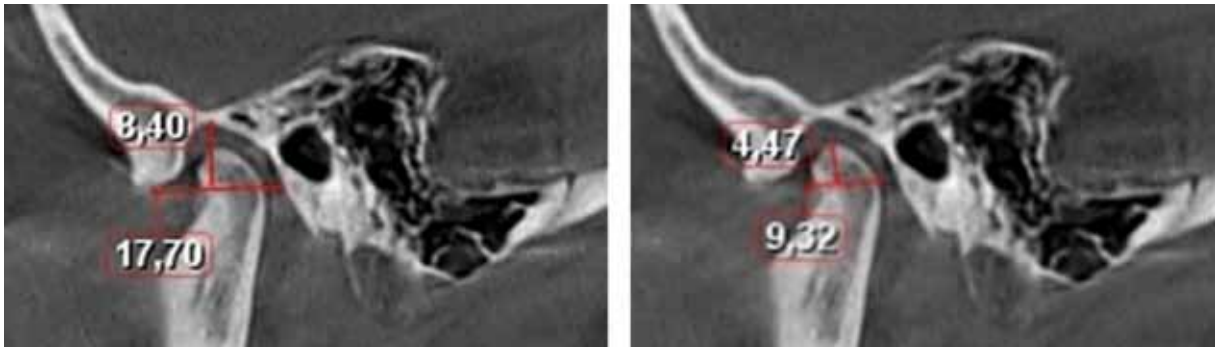


***Fig. 6.*** *Tomographic image of the mesotemporal temporomandibular joint with the sizes of the mandibular fossa (a) and the lower jaw head (b).*

size was 12.48 ± 0.39 mm, the articular head module was 5.97 ± 0.27 mm, and the congruence value was 55.39 ± 0.94%.

We have proven that in case of physiological occlusion, the studied TMJ morphometric values are statistically significant. There are serious grounds,

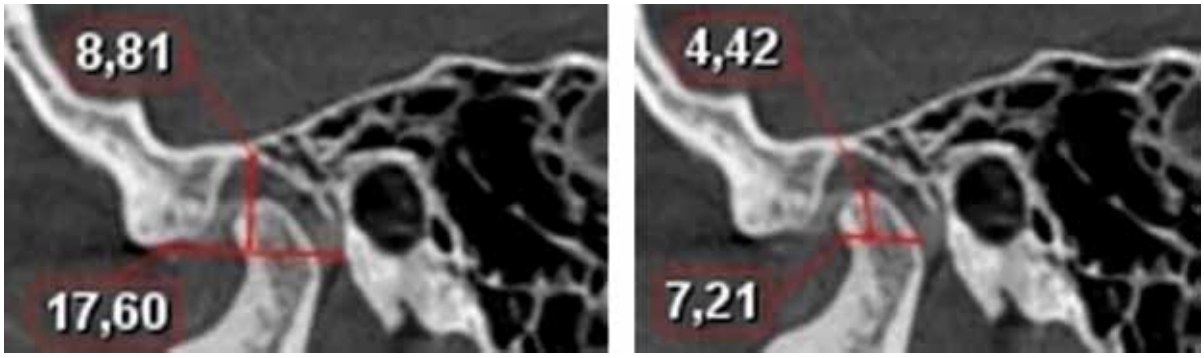


***Fig. 7.*** *Tomographic image of the dolichotemporal temporomandibular joint with the size of the mandibular fossa (a) and the lower jaw head (b)*

which allow claiming that in case of abnormal (pathological) bites, there are changes occurring not to the articular surface dimensions, yet also extending to the intraarticular topography.

The patients' individual typological differences were distributed as follows: asthenics (dolichomorphic body type) accounted for the majority – 168 (56.6 ± 4.3%) patients; normostenics (lysomorphic constitution type) – 81 (27.3% + 2.9%) persons; hypersthenics (brachymorphic body type) – 48 (16.1 ± 2.3%) of the patients examined. Taking into account and identifying the patient's body constitution features will further allow a new perspective when approaching the TMJ morphology issues, identifying predisposing factors in the occurrence of TMJ functional disorders, forecasting the TMJ dysfunction course in the early stages, as well as customizing treatment.

In view of the above, a comparative analysis of the meaning that the X-ray diagnostics methods have for the dentofacial system reveals that panoramic radiography is a reliable method helping visualize the TMJ bone elements status, which also allows identifying pathology (odontogenic, non-odontogenic), as well as related changes in the jaw bone structures. The data obtained through panoramic radiography does not always offer reliable information concerning the TMJ morphology, yet, this method is of high diagnostic value in terms of identifying significant destructive changes in the joint bone components. This is due to the fact that the overlay of the zygomatic arch X-ray image and the skull base on the mandibular (articular) fossa of the temporal bone and the lower jaw articular process on the orthopantomograms complicates significantly the identification of the initial (early) morphological changes in the TMJ bone structures. Unlike panoramic radiographic examination, cone beam computed tomography (through designing multiplanar reconstructions in oblique, sagittal, axial and coronary projections with different slice thickness) offers proper visualization of the temporomandibular joint bone elements, while the possibility of holding examinations with the mouth closed and open allows reliable evaluation of its functional status.

## CONCLUSIONS

1. The proposed methods for measuring the morphometric parameters of the temporomandibular joint with an orthognathic bite, taken as offering precision, high reliability and diagnostically significance, may be recommended for identifying maxillofacial anatomical and topographic features. Each of the methods is of a particular clinical and diagnostic significance, while other calculation methods can be employed as complementary (choice options) at the stage of the comprehensive examination and the tactics choice for treating patients with craniofacial anomalies (deformations), in order to increase efficiency and ensure optimal treatment (rehabilitation) outcomes.
2. The key indicator to classify a temporomandibular joint as belonging to a certain (brachy-, meso-, dolichotemporal) type is the individual feature of the temporal bone mandibular (articular) fossa, which is expressed in linear (absolute) sizes and index (relative) values.
3. For the mesotemporal type of the temporomandibular joint, the articular fossa index varies within 50%, which in linear dimensions indicates a double prevalence of the anteroposterior parameter over the vertical one. In case of the brachytemporal type, a decrease in the vertical size of the articular fossa is observed, which is expressed in the index decrease for the articular fossa (down to 35%). The dolichotemporal type, on the contrary, features an increase in the vertical parameters with a corresponding increase in the articular fossa index values by more than 56%.

4. With the orthognathic bite and a complete set of permanent teeth, there was the size variability of the lower jaw articular heads identified. However, there was no statistically significant difference in the major linear parameters observed. Following the structural options for the lower jaw head shape (according to Yu.A. Gladilin, 1969), oval-shaped heads (171 patients — 57.8%) are more common than cone-shaped (81 people — 27.4%) and bean-shaped (44 people — 14.8%) heads.
5. Regardless of the type (brachy-, meso-, dolichotemporal) of the temporal bone mandibular fossa with the orthognathic bite and a complete set of permanent teeth, the lower jaw head occupies no more than 56% of the joint volume, evidence to that being the temporomandibular joint congruency index.
6. The diagnostic efficiency parameters (sensitivity, specificity, accuracy) of the X-ray diagnostics methods employed to study of the temporomandibular joint structures include: for orthopantomography – 58.3%, 65.9%, 78.4%; for cone beam computed tomography — 93.1%, 95.7%, 94.2%, respectively.
7. Orthopantomography, which allows obtaining a planar image of the dentition elements, is one of the easy-to-perform, affordable, and relatively reliable X-ray diagnostics methods for the temporomandibular joint. Adding cone-beam computed tomography with panoramic radiography can be recommended for checking the preliminary diagnosis and planning the diagnostics and treatment tactics when dealing with patients suffering from temporomandibular joint issues.
8. A significant drawback of panoramic radiography, when examining the temporomandibular joint, is lack of option for obtaining statistically reliable information regarding the spatial relationship of the lower jaw head and the nearest anatomical structures — the temporal bone mandibular (articular) fossa and the articular tubercle.
9. Cone-beam computed tomography, as a specific and highly sensitive method used for spatial diagnostics of morphological, traumatic, degenerative lesions, as well as for changes in the temporomandibular joint bone structures, does not allow full visualization of disorders of the cartilage, muscle and soft tissue components. Due to the polyethiological nature of muscle & joint dysfunction, comprehensive diagnostics should be based on a combined use of computed tomography and magnetic resonance imaging, which would allow obtaining high-quality images of all the temporomandibular joint elements thus helping identify pathology in the early stages, and design effective pathogenetic schemes for comprehensive treatment.
10. The individual differences detected via X-ray methods in patients with physiological occlusion and various types of temporomandibular joint serve another ground for employing customized values through diagnostics of patients with dentoalveolar anomalies and deformities. There is an obvious need for further detailed and specified study into issues related to constitutionally genetic predisposition that may trigger temporomandibular joint pathology, and it may help identify prognostic factors, increase the efficiency while reducing the treatment time, as well as the risk of negative long-term effects (complications).

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# COMPARATIVE EVALUATION OF VASCULAR ENDOTHELIUM MICROCIRCULATION PARAMETERS AND FUNCTIONAL CONDITION IN PATIENTS WITH GENERALIZED PERIODONTITIS OF CHRONIC AND RAPIDLY-PROGRESSIVE COURSE

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**ABSTRACT** — The article offers a view at the results of a survey involving patients with generalized periodontitis of a rapidly progressive course compared with patients suffering from generalized periodontitis of a chronic course using laser Doppler flowmetry with identification of blood flow speed indicators and the level of endothelial factors expression. The data obtained shows that the imbalance between the development of vasodilators and vasoconstrictors towards an increase in the latter is a manifestation of vascular endothelial dysfunction of the periodontal complex, and, in our opinion, leads to a rapid progress of inflammation in it.

**KEYWORDS** — generalized periodontitis of chronic and rapidly progressive course, laser Doppler flowmetry, vascular endothelial dysfunction.

## INTRODUCTION

Inflammatory periodont diseases are a serious issue faced by dentistry nowadays, which is due to the multifactor etiology, the complex pathogenesis, short effect of most therapeutic measures. At the same time, aggressive periodontitis is increasingly common, in particular, rapidly progressive periodontitis (RPP), which has an almost continuously recurring course. RPP develops within 3–5 years, sometimes over several months, leading to a generalization of the process, severe inflammation, bleeding, bad breath, alveolar processes bone tissue lysis, loss of teeth, with frequent exacerbations and short remissions [1, 2, 6]. Given the polyethiological cause behind RPP, its treatment involves significant difficulties, which include greater resistance to interventions, and, accordingly, longer treatment with poorer outcomes [5, 10–15].

Bacterial invasion plays a leading role in the pathogenesis of aggressive types of periodontitis; however, antibiotic ethiotropic therapy of periodontitis does not offer long-term remission or complete recovery, which indicates involvement of some other, no less important mechanisms behind the development of the pathology, which include disorders in the periodontal microcirculation system [4, 7, 8, 9]. There are some works available focusing on the status of the hemostasis system microcirculatory component (the functional activity of red blood cells, platelets and thrombotic resistance of the vascular wall endothelium) in patients with RPP, which contribute to understanding the RPP pathogenesis mechanisms and the role that microcirculatory disorders play in the progression of this disease, which might serve a criterion for evaluating the effectiveness of the available therapeutic measures [3].

*Aim of study:*
to carry out comparative assessment of microcirculation parameters and the functional state of the vascular wall endothelium in patients with generalized periodontitis of a chronic and rapidly progressing course.

## MATERIAL AND METHODS

Laser Doppler flowmetry was used to study blood flow speed indicators as well as the level of endothelial factors expression in patients with rapidly progressing generalized periodontitis (main group, n = 20) compared to patients with chronic generalized periodontitis (comparison group, n = 20); the control group of basically healthy individuals included 20 people. The following indicators of the periodontal tissues microcirculation were studied: M — arithmetic mean value of the microcirculation index (PF unit); $\sigma$ — the root-mean-square deviation of the blood flow fluctuations amplitude from the arithmetic mean value (PF unit); Kv — variation coefficient (%).

Statistical processing of the results was carried out through parametric and non-parametric analysis using the "Statistica 8.0 for Windows" (StatSoft-Russia) and

Microsoft OfficeExelle 2007 software packages. The differences between the samples were evaluated with the Student t-test (in case of normal distribution of variables) and Mann-Whitney U-criterion (in case of lack of data coherence with normal distribution). The relationship between quantitative traits was studied using the Pearson correlation coefficient or the Spearman rank correlation coefficient, the critical significance level of p being at <0.05.

## RESULTS AND DISCUSSION

The obtained results showed that patients, both the comparison group and the main group, revealed significant changes in the functional state of the periodontal tissues microvasculature. The changes were primarily associated with disturbed peripheral tissue perfusion and a decrease in the vasomotor activity of microvessels, which was reflected in a significant decrease in the average perfusion rate to 14.06 ± 0.74 PF units. in patients with generalized periodontitis of a chronic course, and 12.01 ± 0.50 PF units — in patients with rapidly progressive periodontitis (p <0.05), a decrease in the perfusion index mean square deviation was to 1.17 ± 0.14 PF units and 1.01 ± 0.03 PF units; variation coefficient — to 10.55 ± 0.53% and 8.92 ± 0.40%, respectively.

Therefore, in case of generalized periodontitis, regardless of the course, there was disturbed periodontal tissues microcirculation identified, which featured pathological dilatation of the vessels, an increase in their permeability with the development of perivascular edema, impaired transcapillary metabolism and, as a consequence, the development of gum tissue hypoxia. The indicated pattern of microcirculatory disorders was more severe in patients with generalized periodontitis of a rapidly progressive course. A consequence of these microcirculatory disorders was a decrease in the rate of capillary blood flow, as well as in the number of functioning capillaries (due to a significant perfusion rate decrease) and vascular depletion of the periodontal tissues microvasculature.

The changes observed in periodontal tissues microcirculation in patients of the studied groups are directly related to changes in the vascular wall endothelium functioning as well as to a significant imbalance of bioactive substances secreted by it. The data obtained showed that, compared with the control group of virtually healthy individuals, patients with generalized periodontitis had statistically significantly reduced content of endothelial nitric oxide synthase (eNOS) and nitrite ions in the blood plasma, whose total concentration has been generally accepted as an indicator to be employed when assessing the eNOS activity and the nitric oxide production in the vascular endothelium.

In our study, patients of both groups showed an increase in the concentration of bioactive substances with vasoconstrictor activity — dimethylarginine (ADMA) and endothelin (1-38, big) along with a functional deficit of a group of substances featuring a vasodilating function (eNOS, nitrite ions) (see Table 1).

## CONCLUSION

In view a the above, the imbalance between the vasodilators and vasoconstrictors development leaning towards an increase in the latter is undoubtedly a manifestation of vascular periodontal endothelial dysfunction, and, as we see it, leads to rapid progress of the inflammatory development in it. This idea is enforced with statistically significant differences demonstrated by these indicators if matched against the control group's values, compared with patients of the comparison group and the main group (p <0.05). Besides, there was a statistically significant difference observed between these indicators in patients with generalized periodontitis of chronic and that of rapidly progressing course (p <0.05).

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***Table 1.*** *The functional status of vascular wall endothelium in patients of the studied groups*

| Duration of observation | eNOS, pg / ml | nitrites, mcg / ml | 1-38, big, pmol / l | ADMA, μmol / L |
|---|---|---|---|---|
| Control Group, n = 20 | 443,01 ± 2,07 | 0,74 ± 0,20 | 0,87 ± 0,06 | 0,38 ± 0,12 |
| Comparison group, n = 20 | 380,22 ± 3,33* | 0,55 ± 0,08* | 0,96 ± 0,06* | 0,50 ± 0,09* |
| Main group, n = 20 | 374,12 ± 3,03# | 0,45 ± 0,05# | 1,1 ± 0,08# | 0,59 ± 0,11# |

***Note.*** ** — statistically significant differences with the respective indicator in the group of healthy individuals; # — statistically significant differences with the respective indicator in the comparison group (U — Mann-Whitney test, p <0.05).*

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# CORRELATION BETWEEN MANDIBULAR ARCH WIDTH AND THE PARAMETERS OF THE SKULL

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**ABSTRACT** — 110 certified male skull samples were studied to identify the relationship between mandibular arch width and skull type. This can facilitate the determination of a physiological norm and avoidance of diagnostic and treatment errors.

## INTRODUCTION

For appropriate diagnosis and devising an adequate and rational treatment plan, it is essential to perform linear measurements of dental arches to establish correlations between arch width and skull type. Data on dimensions of dental arches obtained from skull samples might give more insight into their structure and correlation with skull type, which is of importance for both comparative basic medical research and personalized medicine.

## MATERIALS AND METHODS

We analyzed 110 certified male skull samples to identify the relationship between mandibular arch width and skull type. The cranial, or cephalic index was referred to as the ratio of the transverse to the longitudinal diameters of the skull: mesocephalic skull type 42 samples, brachycephalic skull type 36 samples and dolichocephalic skull type 32 samples.

Measurements of the vestibular and lingual surfaces of dental arches showed that the arches width was lesser than cranial vault width and cranial base width and did not depend on the skull type ($p < 0.001$; $r = +0.73$). It was revealed that the upper face height of all samples was greater than mandibular arch width vestibular surfaces at the level of the canines and premolars ($p < 0.001$; $r = +0.46 – +0.52$). The height of the dentoalveolar part of the upper jaw was statistically significantly inferior to the dental arches width at all measurement levels ($p < 0.001$; $r = +0.23$).

## CONCLUSION

The study of the relationship between dental arch widths and skull type is required for adequate interpretation of the studied values. This can assist in determining physiological norm more specifically, thus resulting in a decline of potential diagnostic and treatment errors in patients with dentofacial deformities.

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# PROLIFERATION OF HISTAMINE AND SEROTONIN IN MAST CELLS OF PATIENTS WITH INFLAMMATORY PERIODONTAL DISEASE IN THE COURSE OF TREATMENT

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**ABSTRACT** — The purpose of this study was to examine the indicators of cell proliferation, apoptosis, as well as the quantitative features of histamine and serotonin producing gum mast cells in patients with chronic gingivitis and periodontitis through the treatment dynamics. The study has shown that gingivitis is associated with hyperplasia and hyperfunction of the gum mast cells general population producing histamine, as well as with an increase in cell proliferation. Periodontitis revealed an increase in apoptosis, a decrease in periodontal proliferation due to hyperplasia and hyperfunction of the total mast cell population secreting histamine and serotonin.

**KEYWORDS** — gingivitis, periodontitis, proliferation, apoptosis, cell renewal, mast cells, histamine, serotonin.

## INTRODUCTION

Modern studies [1–8] reveal that the general pathomorphological pattern that determines the course and prognosis of any chronic process, including periodont inflammatory diseases, is due to the intensity of cell renewal processes, which can be employed both for early diagnosis of the disease, and to for developing its forecast. The involvement of mast cells in inflammation regulation and tissues proliferation explains the increased interest that researchers take in studying their role in periodont inflammatory diseases [10–16]. There is still lack of research in terms of studying quantitative features and functional organization of gum mast cells producing histamine and serotonin, if compared with the status of gum epithelial cells renewal in the pathogenesis of periodont inflammatory diseases [9].

*Aim of study:* to investigate the cell renewal of gum epithelial cells and the quantitative specifics of gum mast cells producing histamine and serotonin in patients with chronic gingivitis and periodontitis through the treatment dynamics.

## MATERIAL AND METHODS

The study involved 80 patients with chronic catarrhal gingivitis (CCG); 50 patients with mild chronic generalized periodontitis (CGP); the comparison group included 20 patients with intact periodont. All the patients underwent a comprehensive clinical and instrumental examination with their following indicators identified: OHI-s (Green J.C., Vermillion J.R., 1964); PMA (Parma, 1960); X-ray examination of the dentition. The periodontal tissues were studied through gum biopsy specimens (obtained with the patients' consent) during curettage and tooth extraction following orthodontic indications. Mast cells were identified with toluidine blue staining preceded by hydrochloric acid hydrolysis (reaction of *hidden* metachromasia). To verify histamine and serotonin producing gum mast cells (MC), commercial antibodies to serotonin (Dianova, Gamburg, Germany, 1:100) and histamine (Sigma, St. Louis, USA, titer 1:100) were used as primary antibodies. Monoclonal murine antibodies were used to the Ki-67 proliferating cell marker (Sigma, St. Louis, USA, titer 1:200). To identify apoptotic nuclei, the method of impregnation was used. The number of expressing cells was counted in 30 fields of view, and at the indicated magnigication, the numerical data was counted as per 1 $mm^2$ using the Video Test-Morphology 4.0 application morphometric software package.

The obtained outcomes were processed using Statistica version 8.0. The verification of quantitative numerical indicators for compliance with the normal distribution was performed using the Shapiro-Francia criterion. To test the hypotheses about the difference in the average values of normally distributed characteristics, Student and Fisher criteria were used, to identify differences in other values, the Mann-Whitney, Wilcoxon rank criteria were used.

## RESULTS AND DISCUSSION

The patients with gingivitis and periodontitis complained of bleeding gums, slight soreness, and halitosis. An objective examination determined hyperemia, swelling, and bleeding gums. The level of individual hygiene and inflammation in cases of gingivitis (OHI-s 2.94 ± 0.021); PMA (35.2 ± 1.2%) and periodontitis (OHI-s 3.25 ± 0.013); PMA (42.2 ± 1.7%) revealed no significant differences. Morphological and immunohistochemical studies revealed that the intact periodont had the general MC population indicators (9.2 ± 0.5), MC-histamine (7.6 ± 0.5), MC-serotonin (5.4 ± 0, 54). Gingivitis is associated with hyperplasia of the general population of gum MC (11.8 ± 0.7) and histamine producing MC (11.7 ± 0.6). The development of CGP featured an increase in the quantitative density of the total MC population (14.5 ± 0.6) with hyperplasia of MC cells producing both histamine (14.2 ± 0.6) and serotonin (13.2 ± 0.6). An electron microscopy study revealed signs of varying intensity MC degranulation, which is equivalent to an increase in their functional activity in both gingivitis and periodontitis. There was a direct correlation observed between the quantitative density of gum MC producing histamine and the PMA index for gingivitis and periodontitis (r = 0.64 and r = 0.69, respectively), between the number of serotonin producing MC and PMA in CP (r = 0.72).

The immunohistochemical study of the gums in healthy people in the periodontal epithelium revealed low values of proliferative (Ki-67 9.53 ± 0.19) and apoptotic activity (Iapt0.38 ± 0.04). In HCG cases, the proliferation and apoptosis indices do not change significantly (Ki-67 9.53 ± 0.19; Iapt 0.38 ± 0.04), which pointed at high compensatory capacity of the epithelium at this stage of the disease. CGP was found to have an expression increase (Ki-67 = 28.88 ± 1.42) and a low apoptosis rate (Iapt 0.54 ± 0.03). These results suggest that the basis of HCG and CGP morphogenesis belongs to disturbed renewal of epithelial cells. Catarrhal gingivitis is characterized by activated proliferation, while chronic periodontitis – by an increase in apoptosis activity with a decrease in cell proliferation. The dissociation between the proliferation and apopotosis activity in patients with CGP causes low cell renewal and an increase in degenerative processes in periodontal tissues. Hyperplasia of serotonin-producing mast cells leads to reduced gum regeneration. For instance, in case of CGP, hyperplasia of serotonin-producing gum MC is accompanied by an increase in apoptotic activity and a decrease in proliferation in the marginal gum epithelium, which is confirmed by a direct correlation between the number of MC with apoptosis indices (r = 0.75), and an invert correlation with Ki-67 (r = -0.57).

The conservative therapy led to restored periodontal structure in the patients involved. The results of morphofunctional studies prove that restoration of the structural and functional features of the periodont is achieved only a month after therapy. Patients with CCG, 14 days into the treatment revealed normalized quantitative density of the general population of periodontal MC (8.1 ± 0.3), MC-serotonin (5.1 ± 0.5), MC-histamine (7.9 ± 0.2). In patients with CGP, the number of the total population of gum MC (12.5 ± 0.3), and the number of serotonin producing gum MC (9.1 ± 0.4) remained slightly elevated and improved only a month after the therapy (MC serotonin 5.7 ± 0.4). In the group of patients with CGP, two weeks after therapy, a significant increase in the Ki-67 index was observed, if compared with the same value before the treatment. The activity of gum epithelial cells apoptosis decreased slightly, not to reach the values observed in the control group, though. One month after treatment, the patients with CGP featured improved cell renewal of gum epithelial cells.

## CONCLUSION

The leading factors in the occurrence and progression of inflammatory periodont diseases include deteriorated oral hygiene, changed neurohumoral regulation of periodont disease associated with mast cell hyperplasia, impaired gum epithelial cell renewal. The results obtained here suggest that chronic gingivitis features activated proliferation, hyperplasia and hyperfunction of the general population of gum mast cells producing histamine. The typical features of mild chronic periodontitis include increased apoptosis activity, decreased cell proliferation due to hyperplasia, and hyperfunction of the total mast cell population secreting histamine and serotonin.

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# HEMOMICROCIRCULATION OF THE ORAL MUCOSA AS AN EFFICIENCY INDICATOR OF LOCAL TREATMENT AND PREVENTING COMPLICATIONS FROM RADIATION AND CHEMOTHERAPY FOR HEAD AND NECK MALIGNANCIES

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**ABSTRACT** — Background: Mucositis is a common and severe complication of anti-tumour therapy. The use of plant-derived drugs in patients with malignant neoplasms of the oral mucosa and maxillofacial area according to a certain group of dental risks shows good results and can be considered as one of the promising methods for the prevention and treatment of mucositis. One of the methods confirming the effectiveness of the local treatment is the determination of hemomicrocirculation in the tissues of the oral mucosa.
Objectives: To determine the state of hemomicrocirculation in the tissues of oral mucosa in patients with oropharyngeal squamous cell carcinoma at different stages of anti-tumour therapy, as well as during the application of different methods for local treatment of oral mucositis.
Materials and Methods: From January 2017 to May 2018, in the Department of Radiotherapy of the National Medical Research Radiological Centre (NMRRC) of the Russian Federation, the microcirculatory parameter (MP) of hemomicrocirculation was determined in 69 patients diagnosed with oropharyngeal squamous cell carcinoma.
Results: In group I, hemomicrocirculation was higher at all measurement points than in group II. Clinical manifestations of oral mucositis in group I develop later than in group II and correspond to the maximum value of hemomicrocirculation in each group.
Conclusions: The results confirm that the use of long-acting plant-derived drugs is more effective than traditional oral irrigation with chamomile decoction and oleotherapy for the prevention and treatment of oral mucositis: Decrease in microcirculation indicators of group I (using the drugs) is 7.4% less than one of group II (not using the drugs); $p < 0.04$.

**KEYWORDS** — mucositis, hemomicrocirculation, long-acting plant-derived drugs.

## BACKGROUND

From 2017 to 2018, on the basis of the National Medical Research Radiological Centre (Ministry of Health of Russia), we determined the microcirculatory parameter (MP) of oral mucosa in four randomly selected points in 69 patients with oropharyngeal squamous cell carcinoma before radiotherapy at its various stages and after radiotherapy in the background of the local treatment of mucositis with the use of long-acting plant-derived drugs. The results showed their effectiveness for the prevention and treatment of oral mucositis, compared with common methods of irrigation cleansing to oral cavity with chamomile decoction and oleotherapy. The results also revealed the dependence of hemomicrocirculation in oral mucosa in patients with oropharyngeal squamous cell carcinoma on the severity of clinical manifestations of mucositis.

Cancer incidence continues to grow steadily, according to both Russian statistics and global indicators[4, 5]. An increase in the incidence of malignant neoplasms of the oral mucosa in Russia over the past 10 years has amounted to more than 30% [5].

Squamous cell carcinoma of varying degrees of differentiation is the predominant morphological variant among tumours of the oral mucosa. Certain sensitivity of these tumours to radiation and drug exposure, as well as primary neglect of the process and difficulty in performing surgical interventions made it necessary to use chemotherapy and radiotherapy that are sometimes the only forms of treatment for the above pathology [8].

Optimisation of chemotherapy regimens and use of conformal radiotherapy in the treatment of oropharyngeal squamous cell carcinoma decreased the frequency of its relapses and increased the average life expectancy of patients [14]. However, the frequency of occurrence of related complications such as, infectious, hemorrhagic, destructive, erosive-ulcerative and necrotic changes of the mucous membranes (mucositis), including in the oral cavity, remains at a high enough level. According to the European Society for Medical Oncology, the incidence of grade III–IV mucositis on the WHO scale reaches 85% among patients

receiving radiotherapy for the head and neck, but all patients who have received treatment have one or the other degree of mucositis [15].

Radiation mucositis, one of the most severe and often documented complications of anti-tumour therapy, can be the beginning of the development of severe enteropathy and often, the cause of death [16]. The development of mucositis leads to the interruption of the routes of ongoing anti-cancer treatment, thereby reducing its effectiveness, adversely affecting the prognosis of the disease [17]. Additionally, mucositis significantly increases the cost of treatment, the duration of hospitalisation and cost of medicines.

Much attention is paid to the study of the mechanisms of development of radiation and chemotherapeutic injuries of the oral mucosa in the treatment of cancer and oncohematological patients [6, 7, 9, 10, 11].

Currently, the main pathogenetic theory of the development of oral mucositis is the S. Sonis concept [9], divided into five stages of mucositis development: 1) initiation; 2) primary damage; 3) generation and amplification of signals; 4) ulceration; 5) healing.

According to literary sources [2], the study of the regulation of the microcirculation system in the tissues of oral mucosa allows the evaluation of functional changes' role, development of therapeutic interventions and determination of their effectiveness.

In a number of publications [1, 3, 4, 12], the vascular factor is brought to the forefront in the pathogenesis of radiation injuries of the oral mucosa; a change in vascular permeability leads to hypoxia and impaired trophism of irradiated tissues with subsequent structural degradation of the oral mucosa.

In connection with the above, the determination of blood microcirculation parameters in the tissues of oral mucosa in patients receiving radiation and/or chemoradiation therapy is of great scientific and practical interest.

## OBJECTIVE

To determine the state of hemomicrocirculation in the tissues of oral mucosa in patients with oropharyngeal squamous cell carcinoma at different stages of anti-tumour therapy, as well as during the application of different methods for local treatment of oral mucositis.

## MATERIALS AND METHODS

The inclusion criteria for this study includes patients who were diagnosed with oropharyngeal squamous cell carcinoma and aged 18–75. From January 2017 to May 2018, in the Department of Radiotherapy of the FSBI NMRRC of the Russian Federation, the MP of hemomicrocirculation was determined in 69 patients diagnosed with oropharyngeal squamous cell carcinoma.

The average age of patients was 54 years; 62% were men (42) and 38% women (27).

All patients had morphologically confirmed diagnosis of oropharyngeal squamous cell carcinoma.

Localisation was dominated by tongue injuries (32%), bottom of the mouth (20%) and oropharynx (24%). Among other sites of injury were lips, cheeks, and the alveolar bone on the lower jaw.

In majority of patients, the stage of disease T2N0M0 (39%), T3N0M0 (16%), or T3 N1M0 (20%) was established.

Burdened somatic history was observed in almost all patients over 50 years. In 32 patients (64%), associated chronic diseases were noted (asthma, chronic obstructive pulmonary disease and diabetes, pathology of the gastrointestinal tract). Most patients (78%) had more than one pathology.

Anti-tumour therapy in patients with oropharyngeal squamous cell carcinoma was carried out according to the standards of treatment for malignant neoplasms. At the first stage, patients underwent radiation treatment due to their refusal from surgical treatment or the presence of contraindications for surgical treatment. Remote radiotherapy was used in a separate version. Radiotherapy was delivered using a linear accelerator Clinac C2100 (Varían) in the bremsstrahlung mode with a photon energy of 6 MV.

Patients were divided into two groups, based on their voluntary consent to follow the recommendations of the dentist and to use prescribed treatment regimens for the prevention and treatment of oral mucositis.

Group I included 45 patients, who used prescribed by a dentist long-acting plant derived drugs *Tonsinal* (1 sachet contains water-soluble extracts of Hypericum herb, calendula flowers, yarrow grass, licorice root, rose hips, sea salt, decamethoxin, citric acid, lactose) and plate *CM-1* (1 sachet contains hypericum herb extracts, yarrow, sage, vitamin C, gelatin) for the prevention and treatment of oral mucositis in the background of anti-tumour therapy. These drugs are known as herbal medicines in Russia. The method of treatment included the use of drugs not only for their intended purpose and recommendations, but also daily oral care in the dental clinic: irrigation of the oral cavity with *Tonsinal* solution (1 powder per 300 ml of water) with the addition of 1 tsp. olive oil 4–6 times per day, as well as the application of plates *CM-1* on the mucosa of the cheeks on the right and left sides, twice every day for three to four hours. The total number of hours of direct exposure to oral mucosa was seven to eight hours.

Group II comprised 24 patients, who used oral irrigation with chamomile decoction (essential oils, resins, carotenoids, organic acids, flavonoids, phytosterol, choline, as well as vitamins B1, B2 and carotene) and vegetable oil (castor oil) for the prevention and treatment of oral mucositis in the background of the anti-tumour therapy.

The determination of the MP of hemomicrocirculation was carried out before radiotherapy, as well as at its stages with a total tumor dose of 8–18 Gy, 20–28 Gy, 30–38 Gy, 40 or more Gy at four randomly selected points: A — alveolar mucosa (near the gums) in the area of teeth 31 and 41; B — lower lip mucosa in the projection of the attachment site of the bridle; C — cheek mucosa in the projection of teeth 16, 17; D — mucosa of the bottom of the mouth in the projection of the attachment site of the tongue frenulum. The study was conducted with the help of the LAKK-M apparatus (second version), using a laser Doppler flowmetry (LDF) on the basis of FSBI NMRRC of the Russian Federation.

MP determines the dynamic characteristics of the microcirculation of blood — the change in blood flow (tissue perfusion) per unit time in the studied tissue volume of about 1 $mm^3$ in relative perfusion units *pf*. The LDF signal has a constant and a time-variable component, associated with the tone of the microvessels. The stationary component of the tone is due to the constant component of MP, while the variable component comprises active factors controlling the regulation of the vessel lumen, mediated by endothelial, neurogenic and myogenic mechanisms.

Given the small number of observations, statistical processing was carried out using the sign test (a non-parametric method).

In our study, ethical approval was obtained from the Ethics Committee of Institute of Medicine, Peoples' Friendship University of Russia (No. 0212), Moscow, Russia.

## RESULTS AND DISCUSSION

The results of determining the MP of hemomicrocirculation are presented in Table 1 and Fig. 1, 2.

As shown in table 1, the rate of MP in patients in groups I and II before radiotherapy is higher than after radiotherapy, at all points of measurement. This is explained by the effect of radiotherapy on vascular mechanisms and atrophy of vascular endothelium cells under the effect of radiotherapy, corresponding to literary sources. At the same time, in group I at point A, hemomicrocirculation indicators decrease by 49.6% compared with the baseline. In contrast to group II, indicators at point A decrease by 57.0%, $p < 0.04$.

At points B, hemomicrocirculation indicators decrease by 64.9% compared with the baseline. In contrast to group II, indicators at point B decrease by 90.2%, $p < 0.03$.

At points C, hemomicrocirculation indicators decrease by 5.8% compared with the baseline. In contrast to group II, indicators at point C decrease by 34.4%, $p < 0.04$.

At points D, hemomicrocirculation indicators decrease by 44.05% compared with the baseline. In contrast to group II, indicators at point D decrease by 54.1%, $p = 0.0678$.

At each measurement point, the difference is from 10 to 30%. These indicators confirm the effectiveness of the local treatment with the use of long-acting drugs in group I.

Figure 1 shows that MP in patients in groups I and II varies in different ways throughout the radiotherapy phase.

In group I, microcirculation indicators increase to a maximum point achieved with a dose of 20–28 Gy, on average corresponding to the first clinical manifestations of oral mucositis in patients of this group (hyperemia, mucosal edema), with subsequent decrease to 49.6% from the initial indicators. In group II, microcirculation indicators increase to a maximum point with a dose of 8–18 Gy, on average corresponding to the first clinical manifestations of oral mucositis in patients of this sub-group, with subsequent decrease to 57% from the initial indicators.

## CONCLUSION

The results confirm that the use of long-acting plant-derived drugs is more effective than traditional oral irrigation with chamomile decoction and oleotherapy for the prevention and treatment of oral mucositis: Decrease in microcirculation indicators in group I (using the drugs) is 7.4% less than one group II (not using the drugs); $p < 0.04$.

The dependence of the onset of clinical manifestations of mucositis on the maximum MP of hemomicrocirculation indicators reflects the possibility of considering hemomicrocirculation as a predictive factor for the development of mucositis.

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***Table 1.*** *The results of measuring MP in patients with squamous cell carcinoma in the background of radiation and/or chemotherapeutic therapy (M is the average MP value in the group. δ is the standard deviation)*

| MP | Localisation of measurements | | | |
|---|---|---|---|---|
| | Alveolar mucosa (near the gums) in the area of teeth 31. 41 (Point A) M. δ | Lower lip mucosa in the projection of the attachment site of the bridle (Point B) M. δ | Cheek mucosa in the projection of teeth 16. 17 (Point C) M. δ | Mucosa of the bottom of the mouth in the projection of the attachment site of the tongue frenulum (Point D) M. δ |
| Group I | | | | |
| Before therapy | 38.8 ± 3.68 | 15.4 ± 3.3 | 34 ± 1.9 | 37.5 ± 5.6 |
| 8–18 Gy | 38.0 ± 1.9 | 28.3 ± 1.1 | 37.5 ± 5.65 | 35.6 ± 1.1 |
| 20–28 Gy | 40.25 ± 5.15 | 41.4 ± 13.4 | 36.15 ± 4.65 | 48.2 ± 8.7 |
| 30–38 Gy | 39.3 ± 1.1 | 45.4 ± 1.1 | 45.4 ± 1.1 | 48.7 ± 1.1 |
| ≥ 40 Gy | 19.6 ± 0.01 | 5.4 ± 1.1 | 32.0 ± 0.01 | 22.3 ± 0.01 |
| Group II | | | | |
| Before therapy | 35.8 ± 0.01 | 24.5 ± 7.0 | 34.0 ± 1.9 | 33.6 ± 0.01 |
| 8–18 Gy | 43.6 ± 9.3 | 42.8 ± 13.7 | 45.4 ± 1.1 | 69.4 ± 26.7 |
| 20–28 Gy | 32.7±0.01 | 36.8 ± 1.2 | 32.0 ± 0.01 | 47.85 ± 15.1 |
| 30–38 Gy | 28.8±3.68 | 18.3 ± 0.01 | 32.0 ± 0.01 | 47.85 ± 15.1 |
| ≥ 40 Gy | 15.4 ± 3.3 | 2.4 ± 1.1 | 22.3 ± 0.01 | 15.4 ± 3.3 |

***Fig. 1.***

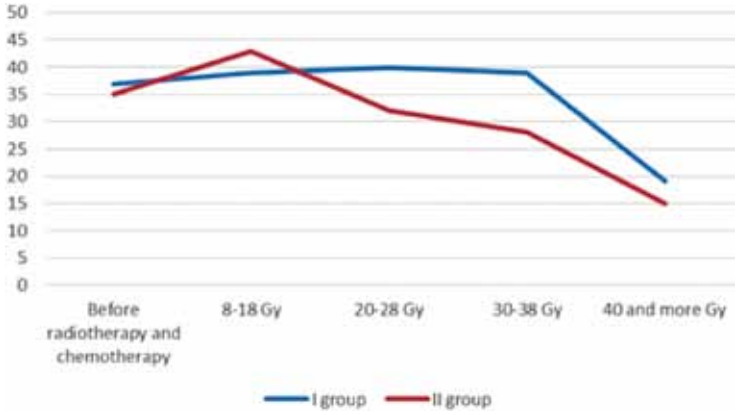


***Fig. 2.*** *Dynamic change in MP at point A (periodontal region in the projection of teeth 31, 41) in patients with oropharyngeal squamous cell carcinoma using long-acting drugs (group I) and patients using chamomile decoction and oleotherapy for oral irrigation (group II). The ordinate axis shows MP*

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